QUALITY IN SPORT
eISSN 2450-3118 · Open Access · Peer-reviewed
apcz.umk.pl/QS Nicolaus Copernicus University in Toruń

IDZIK, Kamil, KAWA, Michał, GACZOŁ, Agnieszka, GRZYBOWSKA, Dominika, KOPCIŃSKA, Paulina, PIOTROWSKA, Gabriela, GRZYB-KURNIK, Weronika, KURNIK, Michał, URBAŚ, Aleksander, KILIAN, Tomasz, MORTKA, Magdalena and BEDNARZ, Hubert. Safety of the Use of Psychiatric Medications in Pregnant Patients. A Review of Current Medical Knowledge. Quality in Sport. 2026;71:73983. https://doi.org/10.12775/QS.2026.71.73983

ARTICLE TIMELINE
Received: 04.07.2026. Accepted: 01.08.2026. Published: 31.08.2026.

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). © The Authors 2026.

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Safety of the Use of Psychiatric Medications in Pregnant Patients. A Review of Current Medical Knowledge

Kamil Idzik [KI]

Murcki Hospital in Katowice, Poland

kamilidzik99@gmail.com

https://orcid.org/0009-0000-7532-9255

Michał Kawa [MK]

Murcki Hospital in Katowice, Poland

michal.kawa2000@gmail.com

https://orcid.org/0009-0001-8083-291X

Agnieszka Gaczoł [AG]

Gabriel Narutowicz Municipal Specialist Hospital in Kraków, Poland

agnieszkagaczol1@gmail.com

https://orcid.org/0009-0008-9020-7123

Dominika Grzybowska [DG]

St. Luke's Provincial Hospital in Tarnow, Poland

dominikagrzybowska996@gmail.com

https://orcid.org/0009-0002-0599-8896

Paulina Kopcińska [PK]

Gabriel Narutowicz Municipal Specialist Hospital in Kraków, Poland

pjkopcinska@gmail.com

https://orcid.org/0009-0006-1495-1968

Gabriela Piotrowska [GP]

Gabriel Narutowicz Municipal Specialist Hospital in Kraków, Poland

piotrowskagabi24@gmail.com

https://orcid.org/0009-0009-1283-7135

Weronika Grzyb-Kurnik [WG]

Megrez Provincial Multi-Specialist Hospital Limited Liability Company in Tychy, Poland

wrgrzyb@gmail.com

https://orcid.org/0009-0001-7622-281X

Michał Kurnik [MKU]

Megrez Provincial Multi-Specialist Hospital in Tychy, Poland

michalkurnik95@gmail.com

https://orcid.org/0009-0008-4791-0630

Aleksander Urbaś [AU]

Murcki Hospital in Katowice, Poland

urbas41@gmail.com

https://orcid.org/0009-0004-5347-7192

Tomasz Kilian [TK]

Murcki Hospital in Katowice, Poland

kilianowskipl@gmail.com

https://orcid.org/0009-0000-3161-6914

Magdalena Mortka [MKO]
Medical University of Lublin, Poland
magdalenamortka2@gmail.com
https://orcid.org/0009-0009-0403-0008

Hubert Bednarz [HB]
Medical University of Lublin, Poland
hubertb7809@gmail.com
https://orcid.org/0009-0003-1639-0699

ABSTRACT

Pregnancy is a period of increased vulnerability to mental disorders and therapeutic challenges. Depression affects 10--15% of pregnant women, anxiety disorders up to 20%, and bipolar disorder 1--2% of women of reproductive age. Discontinuation of mood stabilizers is associated with up to a twofold increase in the risk of relapse. Untreated disorders increase the risk of obstetric and neonatal complications as well as suicide.

This paper is a narrative review of the literature from 2020--2025 (PubMed/MEDLINE, Embase, PsycINFO) concerning the safety of psychiatric medications during pregnancy. SSRIs, SNRIs, TCAs, antipsychotics, mood stabilizers, and benzodiazepines were discussed, taking into account the risk of congenital malformations, neonatal outcomes, and child development. Among the agents considered relatively safe were sertraline, haloperidol, quetiapine, and lamotrigine; valproate and paroxetine are contraindicated; data for some drugs remain limited.

The importance of an individualized risk--benefit analysis, use of the lowest effective dose, avoidance of polytherapy, and planning of perinatal care was emphasized. ECT was indicated as an alternative option. Discontinuation of treatment in severe disorders is not recommended.

Keywords: pregnancy, psychiatric medications, pharmacotherapy safety, SSRI, antipsychotics, mood stabilizers, benzodiazepines

1. INTRODUCTION

Pregnancy and the postpartum period constitute an exceptionally sensitive time in a woman's life, during which rapid hormonal, neuroendocrine, and psychosocial changes may both reveal latent mental disorders and significantly worsen the course of already existing illnesses. The issue of mental health in pregnant women is a challenge of enormous epidemiological scale. A systematic review and meta-analysis of 128 systematic reviews conducted by Grigoriadis et al. showed that the overall mean prevalence of perinatal depression is 26.3%, with antenatal depression at 28.5% and postpartum depression at 27.6%. These values are significantly higher among women belonging to groups of special concern, such as women experiencing domestic violence, living in poverty, or burdened with chronic somatic illnesses. [2]

Anxiety disorders, often co-occurring with depression, affect up to 20% of pregnant women, and exacerbations of obsessive-compulsive disorder (OCD) during pregnancy and the postpartum period are commonly described in the literature. The perceived risk of medication use during pregnancy causes many women to discontinue pharmacotherapy immediately after becoming aware of the pregnancy, which leads to recurrence of symptoms at a particularly critical moment—both for fetal organogenesis and for the woman's adaptation to the maternal role. The COVID-19 pandemic highlighted the scale of the problem: a global review with meta-analysis published in 2024 showed that during this specific period the prevalence of antenatal depression reached 29%, postpartum depression 26%, and prenatal anxiety 31%. These data emphasize that mental disorders in pregnancy constitute a serious global public health issue. [5][20]

Bipolar disorder affects 1--2% of women of reproductive age and is characterized by a particularly high risk of relapse during the perinatal period. In a meta-analysis including more than 3,000 patients with bipolar disorder, the postpartum relapse rate was as high as 35%. Discontinuation of mood stabilizers is associated with a twofold increase in relapse risk and a shorter time to the next episode compared with continuation of treatment. Importantly, this risk applies equally to manic and depressive phases. The immediate postpartum period is particularly critical for women with bipolar I disorder: the risk of mania and postpartum psychosis reaches 23% after the first delivery. Postpartum psychosis, although rare (incidence 1--2/1000 deliveries in the general population), is in women with bipolar disorder a phenomenon requiring mandatory psychiatric treatment, often including hospitalization. [3]

Women with schizophrenia are burdened with a significantly higher risk of adverse perinatal outcomes. A meta-analysis by Li et al. (2023), including studies from 2001--2022, showed that cesarean section accounted for 26.0% of deliveries, labor induction for 24.0%, low birth weight for 7.8%, and preterm birth for 9.1% among women with schizophrenia. The risk of congenital malformations in the offspring was 5.4%, and neonatal risk was assessed as significantly higher than in the general population. Importantly, some of these complications result from the disease itself and its impact on the mother's health-related behavior, not exclusively from pharmacotherapy. Women with schizophrenia are less likely to use regular prenatal care and more likely to smoke tobacco and use psychoactive substances. [4]

Particularly important is the fact that untreated mental disorders themselves constitute a risk factor for the fetus and the mother. Women with uncontrolled psychotic or affective symptoms are more likely to use alcohol, psychoactive substances, and tobacco, while at the same time neglecting prenatal care and proper nutrition. Depression during pregnancy increases the risk of preterm birth, low birth weight, and disturbances in mother--child bonding. Nutritional deficiencies resulting from appetite disturbances associated with mental illness may lead to deficiencies in folic acid, iron, and omega-3 fatty acids—substances of crucial importance for the development of the fetal nervous system. In women with bipolar disorder not treated pharmacologically, newborns demonstrated a significantly smaller head circumference compared with children of treated mothers, which is interpreted as a sign of impaired neurogenesis in the hypercortisolemic environment of depression. [3][5]

A meta-analysis by Etchecopar-Etchart et al. (2024), including 14 population-based cohort studies from 6 countries (47,954 women with bipolar disorder and 11,896,577 women without psychiatric diagnoses), showed that pregnant women with bipolar disorder are exposed to an increased risk of gestational diabetes (OR 1.46; 95% CI 1.06--2.03), pregnancy-induced hypertension (OR 1.19; 95% CI 1.02--1.40), antepartum hemorrhage (OR 2.02; 95% CI 1.30--3.13), cesarean section (OR 1.35; 95% CI 1.26--1.45), and postpartum hemorrhage (OR 1.39; 95% CI 1.20--1.62). The newborns of these women were burdened with a higher risk of prematurity (OR 1.49; 95% CI 1.29--1.72), low birth weight (OR 1.54; 95% CI 1.19--1.99), and congenital malformations (OR 1.29; 95% CI 1.09--1.53). These findings emphasize how profound the impact of psychiatric illness itself is on perinatal outcomes, independently of pharmacotherapy. [1]

The issue of cure or remission of mental disorders during pregnancy is complex. Some women experience an improvement in mental state during pregnancy—this particularly concerns anxiety disorders, where a change in life perspective and focus on pregnancy may temporarily alleviate symptoms. However, for depression and bipolar disorder, pregnancy does not constitute a protective factor—on the contrary, hormonal changes (a rapid increase, followed by a drop, in progesterone and estrogen levels) may intensify symptoms. The risk of relapse in the postpartum period is independent of the course of pregnancy and results primarily from the abrupt neuroendocrinological change after delivery. [3][5]

The clinician is therefore faced with a clinical dilemma of particular ethical weight: how to balance the potential risk of fetal exposure to psychotropic medications against the real risk resulting from the mother's untreated mental illness. Standard recommendations—the use of the lowest effective doses, avoidance of polytherapy, and preference for substances with a documented safety profile—are widely accepted; however, their practical implementation requires familiarity with current data from the literature. The aim of this paper is to systematically discuss and compare the data concerning the safety of the main groups of psychiatric medications used during pregnancy, published after 2020, with particular emphasis on the clinical implications for perinatal pharmacotherapy.

2. METHODOLOGY

This paper is a narrative review of the literature. The PubMed/MEDLINE, Embase, and PsycINFO databases were searched using the following keywords and their combinations (in English): pregnancy, psychiatric medication, antidepressants, SSRI, SNRI, tricyclic antidepressants, antipsychotics, second generation antipsychotics, first generation antipsychotics, mood stabilizers, benzodiazepines, lithium, valproate, lamotrigine, carbamazepine, safety, teratogenicity, congenital malformations, neonatal outcomes, perinatal, neurodevelopmental outcomes, ECT, electroconvulsive therapy. A time filter limited the search to the years 2020--2025. Exceptionally, selected studies published before 2020 were included because they constitute fundamental points of reference for current clinical guidelines (including Patorno et al. 2017; Huybrechts et al. 2016).

The inclusion criteria comprised: (1) original observational studies (cohort and case-control) concerning pregnancy outcomes in women using psychiatric medications during pregnancy; (2) systematic reviews and meta-analyses assessing obstetric or neonatal outcomes; and (3) clinical guidelines of scientific societies based on systematic reviews (ACOG, AAN, AES,

RANZCP). Excluded from the review were case reports (series below 10 cases), studies available exclusively in conference abstract form without a published full text, animal-only studies, and studies in which it was not possible to distinguish data concerning exposure during pregnancy from exposure outside pregnancy.

The methodological quality of primary studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies and the AMSTAR-2 tool for meta-analyses and systematic reviews. The data presented in the paper were synthesized narratively, divided into pharmacological groups and individual substances. Where numerical data were available (risk estimates, odds ratios with confidence intervals), they were cited directly from the primary literature. Given the high heterogeneity of the available data and the fact that this paper is a narrative review rather than a meta-analysis, pooled effect estimates were not calculated.

The main endpoints discussed in the paper included: (1) risk of major congenital malformations (MCM), defined as structural defects diagnosed at birth or in the first year of life, requiring treatment or leading to significant disability; (2) organ-specific malformations (cardiac defects, neural tube defects, cleft palate and lip, genitourinary defects); (3) obstetric outcomes (preterm birth, low birth weight, cesarean section, spontaneous miscarriage, stillbirth); (4) neonatal outcomes (neonatal adaptation syndrome, persistent pulmonary hypertension of the newborn [PPHN], withdrawal symptoms, hypotonia, hypoglycemia); and (5) long-term neurodevelopmental outcomes (intelligence quotient [IQ], autism spectrum disorder [ASD], ADHD, speech and language disorders).

In this paper, the convention of citing absolute risk as the number of cases per 1,000 exposed was adopted, which facilitates clinical interpretation of the results and the assessment of absolute, rather than merely relative, differences in risk. Terms such as “safe,” “favorable safety profile,” or “drug of choice” are used in this paper only in a relative sense—they indicate that the available scientific evidence did not demonstrate a significant increase in risk or that the increase was smaller than for other substances in the same class, and not that the substance is devoid of any risk for the fetus or mother.

3. RESULTS

3.1. Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin--Norepinephrine Reuptake Inhibitors (SNRIs)

SSRIs are the most commonly used group of psychotropic medications among pregnant women worldwide and constitute the first-line treatment in the pharmacotherapy of depression and anxiety disorders. It is estimated that in high-income countries 2--4% of pregnant women use SSRIs, and this proportion has increased over successive decades. An umbrella review of 51 meta-analyses published by Brunet-Gouet et al. (2022) showed that use of SSRIs as a class is associated with a statistically significant increase in the risk of major congenital malformations overall (8 meta-analyses), cardiac defects (11 meta-analyses), preterm birth (8 meta-analyses), neonatal adaptation symptoms (8 meta-analyses), and persistent pulmonary hypertension of the newborn (PPHN; 3 meta-analyses). However, the effect sizes were small or modest, and the risk of systematic bias—including so-called indication bias—was assessed as high in all included meta-analyses. [5][6]

Within the SSRI group, particular attention has been paid to paroxetine and fluoxetine. Numerous meta-analyses have consistently found an increased risk of cardiac defects with paroxetine use—especially atrial and ventricular septal defects—and, to a lesser extent, fluoxetine. The association of paroxetine with the risk of cardiac defects is one of the most consistently confirmed findings in the literature on the safety of psychiatric medications during pregnancy, recurring across all major cohort studies and meta-analyses from 2020--2025. In contrast, evidence suggesting an increased risk of congenital malformations overall for sertraline is inconclusive: individual studies described associations with isolated cardiac septal defects or craniosynostosis, but these findings were not consistently confirmed in analyses of higher methodological quality. Sertraline remains the drug of choice among SSRIs during pregnancy because of the best balance between safety profile and documented efficacy. [6]

The risk of PPHN associated with exposure to SSRIs and SNRIs has been the subject of numerous analyses. A meta-analysis evaluating more than 156,000 exposed women demonstrated a significant increase in the risk of PPHN with exposure to SSRIs/SNRIs in any trimester (OR 1.82; 95% CI 1.31--2.54; $I^2 = 72\%$) and with exposure after the 20th week of

pregnancy (OR 2.08; 95% CI 1.44--3.01; I^2 = 76%). Despite the statistical significance, the absolute risk difference remains small: the estimated incidence of PPHN in exposed newborns is approximately 2.9/1000 live births compared with 1/1000 in the general population. In clinical assessment, this risk should therefore be weighed against the consequences of untreated perinatal depression, whose effects on the fetus—through oxidative stress, elevated cortisol concentrations, and vasoactive substances crossing the placenta—may themselves increase the risk of PPHN. [6][7]

Symptoms of neonatal adaptation syndrome (NAS) described after SSRI exposure in the third trimester include irritability, increased or decreased muscle tone, feeding difficulties, seizures, and respiratory disturbances. According to most authors, they result from serotonergic toxicity rather than a withdrawal syndrome and resolve spontaneously within 1--2 weeks without permanent consequences. Data from the population-based cohort study by Nörby et al. (2023), covering all births in Sweden from 2006--2013 (n = 5,632), confirmed a higher risk of delayed neonatal adaptation after SSRI exposure in the third trimester; however, it was emphasized that hospitalization of newborns in intensive care units was rare (below 3% of those exposed). Furu et al. (2023), analyzing a Norwegian population cohort, confirmed these results. [6][7][8]

The issue of autism spectrum disorder (ASD) risk in children prenatally exposed to SSRIs is controversial and unresolved. An umbrella review from 2022 showed equivocal results—some meta-analyses described a moderate increase in ASD risk, whereas others did not confirm this association after accounting for familial psychiatric burden as a confounding variable. A multicenter cohort study from the ECHO program published in 2023 (n = 3,129 mother--child pairs) found that after adjustment for treatment indication, the association between prenatal antidepressant exposure and ASD disappeared, suggesting that the observed signal may result from the mother's genetic burden of illness rather than from a direct effect of pharmacotherapy. For ADHD, meta-analyses did not find a significant increase in risk after prenatal SSRI exposure. These findings have important clinical implications—they argue against discontinuing antidepressants during pregnancy solely because of concern about ASD risk in the offspring. [6][9]

3.1.1. Serotonin--Norepinephrine Reuptake Inhibitors (SNRIs)

Data concerning venlafaxine and duloxetine during pregnancy are less numerous than for SSRIs. An umbrella review from 2022 showed that SNRIs as a class are associated with a

similar increase in the risk of PPHN and neonatal adaptation symptoms as SSRIs. For venlafaxine, more pronounced withdrawal symptoms in the newborn have been described because of the drug's short half-life—therefore, in the third trimester, switching venlafaxine to sertraline is considered as a substance associated with a less pronounced withdrawal effect. There are no data indicating a significantly higher risk of major congenital malformations for SNRIs compared with SSRIs; however, the number of high-quality studies remains limited. Data concerning duloxetine are particularly sparse—available pregnancy registries include in total no more than several hundred exposed women, which is insufficient for a reliable assessment of teratogenic risk. [6][7]

3.1.2. Tricyclic Antidepressants (TCAs)

Tricyclic antidepressants (amitriptyline, clomipramine, imipramine, nortriptyline) are used less often than SSRIs because of a less favorable tolerability profile and a higher risk of cardiotoxicity and drug interactions; however, they remain in clinical use in women with depression resistant to SSRIs, pain disorders, or co-occurring insomnia. An umbrella review from 2022 did not demonstrate a statistically significant increase in the risk of major congenital malformations for TCAs as a group. Historical data from 1990--2010 concerning amitriptyline and nortriptyline did not suggest an increased MCM risk compared with the general population, but they were characterized by low methodological quality [10]. The strong anticholinergic effect of TCAs may be associated with neonatal adaptation disturbances (tachycardia, constipation, urinary retention, dryness of the skin and mucous membranes). In the case of TCA exposure in the third trimester, it is recommended to monitor the newborn for anticholinergic and withdrawal symptoms for a minimum of 48 hours. [6][10]

3.2. Typical and Atypical Antipsychotics

The use of antipsychotic medications during pregnancy has increased steadily over the last two decades, mainly due to the broader use of atypical antipsychotics (second-generation antipsychotics, SGA). It is estimated that in Western countries about 1--2% of pregnant women use antipsychotic medications, with SGAs surpassing typical antipsychotics in frequency of use. Indications include schizophrenia and other psychotic disorders, bipolar disorder (manic phase, maintenance of remission), severe depression with a psychotic component, and— increasingly, although off-label in many countries—anxiety disorders and insomnia. This latter tendency raises controversy because of the lack of adequate safety data for non-psychotic indications. [11]

The meta-analysis and systematic review by Quinn et al. (2026), covering more than 10 million pregnancies from 12 countries (12 studies meeting the inclusion criteria), showed that exposure to antipsychotic medications during pregnancy is associated with a borderline, statistically non-significant tendency toward an increased risk of major congenital malformations (OR 1.27; 95% CI 0.996--1.624; $p = 0.054$; $I^2 = 53\%$) [12]. After limiting the analysis exclusively to SGAs, this association disappeared (OR 1.16; 95% CI 0.78--1.72; $p = 0.47$). In contrast, exposure to antipsychotic medications was significantly associated with an increased risk of preterm birth (OR 1.35; 95% CI 1.13--1.62; $p < 0.01$; $I^2 = 70\%$). The authors emphasized that even after statistical adjustment, a residual effect of the underlying disease as a confounding variable cannot be excluded. [12]

3.2.1. Atypical Antipsychotics—Detailed Data

Quetiapine is the most commonly used atypical antipsychotic during pregnancy, which results both from its broad indication profile and from the widely available data from pregnancy registries. Data from the Medicaid database covering more than 4,000 exposed pregnancies did not show, after adjustment for confounding factors, a significant increase in the risk of congenital malformations overall (RR 1.01; 95% CI 0.88--1.17) or cardiac defects (RR 1.07; 95% CI 0.85--1.35) [5]. The Massachusetts General Hospital pregnancy registry for atypical antipsychotics (n = 155) recorded only 1.29% malformations in newborns exposed to quetiapine. These findings were confirmed in a prospective study from 2023, in which no teratogenic pattern for quetiapine was identified. Quetiapine is considered the drug of choice among atypical antipsychotics during pregnancy when such treatment is clinically indicated. Its sedative and anxiolytic effects make it particularly useful in manic episodes with agitation and in schizophrenia with predominant aggression. [5][11][12]

Olanzapine demonstrates an inconsistent safety profile in the available data. The Finnish population-based cohort analysis by Ellfolk et al. (2021), including 3,478 pregnancies exposed to SGAs and more than 1.27 million unexposed pregnancies, showed that olanzapine was the only SGA significantly associated with an increased risk of major congenital malformations overall (OR 2.12; 95% CI 1.19--3.76) and musculoskeletal malformations (OR 3.71; 95% CI 1.35--10.1). However, earlier studies, including a review of the Eli Lilly internal database covering 610 pregnancies, did not show an increase in risk above 3--5% malformations in exposed children. The discrepancy in results is probably partly explained by differences in the definition of exposure and malformations and in the way adjustment for

treatment indication was performed. Ellfolk et al. recommend limiting the use of olanzapine during pregnancy to situations in which safer alternatives are ineffective. [5][13]

Risperidone shows a potential teratogenic signal in several independent studies. The Medicaid database analysis by Huybrechts et al., including 1,566 exposed pregnancies, showed a significant increase in the risk of congenital malformations overall (RR 1.26; 95% CI 1.02--1.56) and cardiac defects (RR 1.26; 95% CI 0.88--1.81) after adjustment for confounding factors. Risperidone and its active metabolite paliperidone are not considered first-line drugs in pregnancy—if a patient is treated with risperidone before pregnancy and responds well to it, the decision to change medication must take into account the risk of psychiatric destabilization. [5][11]

Aripiprazole is one of the more commonly used atypical antipsychotics during pregnancy, particularly in bipolar disorder as augmentation to antidepressants. Data from the analysis by Huybrechts et al. (1,756 exposed pregnancies) did not show a significant increase in the risk of congenital malformations after adjustment for confounding factors. A study from the National Pregnancy Registry for Atypical Antipsychotics (n = 158 exposed) found no increased risk of malformations compared with the control group. Aripiprazole demonstrates reduced plasma concentrations in the third trimester due to pregnancy-induced CYP2D6 and CYP3A4 induction, which may require a dose increase. After delivery, dose reduction is necessary to avoid toxicity. [5][12]

Clozapine is used exclusively in treatment-resistant schizophrenia and rarely during pregnancy. Population data from Finland showed a malformation rate of 3.77% among 106 exposed pregnancies (OR 2.00; 95% CI 0.30--13.35), which did not reach statistical significance because of the small sample size. However, cases of agranulocytosis in the newborn have been described (necessitating blood count monitoring every 1--2 weeks during the first 6 months of the newborn’s life), as well as floppy baby syndrome, neonatal seizures, and macrocephaly. Clozapine should be used during pregnancy only when no safer alternative exists, and hematological monitoring of both mother and newborn is absolutely necessary. [5][13]

3.2.2. Typical Antipsychotics (First Generation)

Typical antipsychotics—haloperidol, chlorpromazine, and perphenazine—have the longest documented safety profile in pregnancy among antipsychotic drugs, resulting from many

decades of clinical use. Several large cohort studies and registry analyses have not demonstrated a significant increase in the risk of major congenital malformations for this group as a whole. ACOG guidelines indicate typical antipsychotics as the drugs with the best documented safety data in pregnancy, emphasizing their many-decades-long history of use in the absence of a consistent teratogenic signal. Haloperidol has been associated in some reports with shorter gestational age and lower birth weight; however, these findings were confounded by concomitant maternal smoking and psychoactive substance use. Haloperidol is particularly useful in acute states of agitation and psychosis requiring rapid intervention, including in emergency departments and psychiatric wards. [5][11]

Regardless of antipsychotic class, newborns exposed in the third trimester have documented extrapyramidal symptoms (hypertonia, hypokinesia, tremor) or anticholinergic symptoms requiring observation in the neonatal ward. These changes are generally transient and resolve spontaneously within 1--2 weeks. An Australian registry demonstrated that 37% of newborns exposed to antipsychotic medications exhibited some degree of respiratory disturbance at birth, and nearly half were admitted to a neonatal unit, which correlated with higher doses or concomitant use of mood stabilizers. This indicates the need for routine planning of neonatal observation in a neonatal unit in cases of exposure to antipsychotic medications in the third trimester. [5][12]

3.3. Mood Stabilizers

3.3.1. Lithium

Lithium is the first-line drug for the prevention of bipolar disorder relapse and one of the few psychiatric medications with documented efficacy in preventing postpartum relapse. Historically, its use in pregnancy raised concerns because of early registry reports suggesting a very high risk of Ebstein's anomaly (a tricuspid valve defect). The meta-analysis by Patorno et al. (2017), which remains a reference point for clinical recommendations, showed that the absolute risk of cardiac defects after first-trimester lithium exposure is 2.1--2.4% compared with 1.5% in the control population (RR 1.65; 95% CI 1.02--2.68), and the risk of Ebstein's anomaly is 0.6 to 0.9/1000 exposed. This value is several times higher than the population baseline (0.05--0.1/1000 births), but is still absolutely rare and markedly lower than the values reported in early registry reports from the 1970s. The clinical implications regarding lithium

monitoring during pregnancy and perinatal risk assessment were updated by Malhi et al. (2022). [3][14]

A key clinical issue in the use of lithium during pregnancy is variability in serum concentrations resulting from increased renal clearance during pregnancy (an increase in GFR by approximately 50%) and a rapid reversal of this trend after delivery, which may lead to lithium toxicity in the first days postpartum. Weekly or biweekly monitoring of serum lithium concentrations is recommended in the third trimester, and the target therapeutic concentration should be maintained at the lower limit of the therapeutic range (0.5--0.8 mEq/L). Neonatal lithium toxicity takes the form of floppy baby syndrome, respiratory disturbances, bradycardia, heart murmur, and transient motor disturbances. Neonatal toxicity is proportional to the maternal lithium concentration immediately before delivery. Malhi et al. (2022) recommend reducing the lithium dose by 20--30% in the week preceding the planned due date and intensive monitoring of concentrations during the first 2 weeks postpartum. [3][14]

3.3.2. Lamotrigine

Lamotrigine stands out among mood stabilizers because of its favorable safety profile during pregnancy and is the first-line drug in the pharmacotherapy of bipolar disorder during pregnancy, especially for depressive phases and maintenance of remission. The 2024 AAN/AES guidelines, summarizing a systematic review including studies up to 2022, showed that the risk of major congenital malformations with lamotrigine monotherapy is 30.7/1000 (95% CI 25.4--36.4), which is comparable to the risk for levetiracetam (34.8/1000) and significantly lower than for valproate (96.7/1000). For neural tube defects, the risk for lamotrigine is 3.4/1000, compared with 14.3/1000 for valproate. [3][15]

An important clinical limitation of lamotrigine use is the substantial decline in its serum concentration during pregnancy—resulting from estrogen-induced induction of the UGT1A4 enzyme—reaching 40--70% of baseline values. This fact requires active concentration monitoring and systematic dose increases during pregnancy, followed by gradual dose reduction after delivery to avoid toxicity (rash, ataxia, diplopia). Hasser et al. (2024) recommend weekly monitoring of lamotrigine concentrations throughout the third trimester, with dose adjustment according to the results. In neurodevelopmental studies, lamotrigine demonstrated a significantly higher global IQ in the offspring compared with valproate (mean IQ 105.8 vs. 93.9; $p = 0.05$) in the MONEAD study. The risk of ASD in children exposed to lamotrigine (14.5/1000) is significantly lower than for valproate (41.9/1000). [3][15]

3.3.3. Sodium Valproate

Sodium valproate is a substance with a documented, markedly unfavorable safety profile during pregnancy and is an absolutely non-recommended first-line treatment in women of reproductive age. The 2024 AAN/AES guidelines formulate a MUST AVOID recommendation category: clinicians must avoid the use of valproate in women of reproductive age whenever clinically feasible. Since 2018, the European Medicines Agency (EMA) has introduced successive restrictions on the use of valproate in pregnant women and women of reproductive age. [15]

The risk of major congenital malformations with valproate monotherapy is 96.7/1000 (95% CI 80.4--114.2)—more than three times higher than the risk for lamotrigine and carbamazepine. Specific defects include neural tube defects (open spina bifida, anencephaly)—14.3/1000 (95% CI 9.5--20.1), cardiac defects—25.1/1000, genitourinary defects—12.4/1000, and the risk of craniosynostosis and limb defects. The risk of malformations increases significantly at doses above 800--1000 mg/day. Standard folic acid supplementation does not protect against the teratogenic effects of valproate. The mechanism of teratogenicity includes inhibition of histone deacetylases (HDAC) and disruption of morphogenetic gene expression, which constitutes an epigenetic mechanism of teratogenicity not observed with other psychiatric medications. [15][16]

Valproate is also associated with serious adverse neurodevelopmental effects: the risk of autism spectrum disorder was 41.9/1000—the highest among all analyzed substances, significantly higher than for lamotrigine (14.5/1000) or levetiracetam (11.3/1000). The meta-analysis by Veroniki et al. (2021) confirmed a significant increase in ASD risk after prenatal valproate exposure (RR 2.9; 95% CI 2.0--4.2), independently of treatment indication. The NEAD study showed that children exposed to valproate in utero had lower IQ scores and performed worse in reading, working memory, and attention compared with children exposed to other antiepileptic medications. [15][16][17]

3.3.4. Carbamazepine

Carbamazepine is used during pregnancy both as a mood stabilizer in bipolar disorder and as an antiepileptic drug. Its safety profile is considerably more favorable than that of valproate. The risk of major congenital malformations with carbamazepine monotherapy is 43.7/1000 (95% CI 35.7--52.6), i.e., about 4.4%, slightly above the population background (2--3%). For

neural tube defects, the risk is 5.6/1000 (95% CI 2.6--9.7)—higher than for lamotrigine (3.4/1000), but markedly lower than for valproate (14.3/1000). Carbamazepine induces CYP3A4 enzymes, which accelerates the metabolism of oral contraceptives, other psychiatric medications, and vitamin K, increasing the potential risk of bleeding in the newborn. The 2024 AAN guidelines recommend preferring lamotrigine, levetiracetam, or oxcarbazepine when they are clinically adequate. [14][15]

3.4. Benzodiazepines

Benzodiazepines are used during pregnancy mainly in the treatment of anxiety disorders, sleep disorders, acute agitation, and as adjunctive medications in manic or psychotic episodes. Historical concerns about the teratogenicity of benzodiazepines focused on the risk of cleft palate, described in early, methodologically weak studies from the 1970s. More recent reviews from 2020--2024, including clearly larger cohorts, have largely excluded a significant risk of congenital malformations for benzodiazepines used in typical clinical doses. The 2024 AAN guidelines for clonazepam (in monotherapy) showed a malformation risk of 30.2/1000—comparable to lamotrigine and levetiracetam. [15]

However, exposure to benzodiazepines, especially long-acting ones (diazepam, clonazepam), in the third trimester is associated with significant neonatal risk, including neonatal withdrawal syndrome (seizures, tremor, hyperreflexia, tachycardia, vomiting) and floppy baby syndrome (hypotonia, hypothermia, apnea, sucking disturbances). These symptoms result from accumulation of benzodiazepines and their metabolites in fetal tissues due to the immaturity of the neonatal enzymatic system and the long half-life of the parent substance and its metabolites. The duration of symptoms correlates with the half-life of the benzodiazepine used and may range from several days to several weeks. [18]

The systematic review by Grigoriadis et al. (2020), including 21 cohort studies, found that benzodiazepine exposure is associated with a significant increase in the risk of preterm birth (OR 1.84; 95% CI 1.44--2.34) and low birth weight (OR 1.43; 95% CI 1.11--1.85); however, after controlling for treatment indication, these effects weakened or disappeared. The authors concluded that benzodiazepines should be used at the lowest effective doses, for the shortest possible time (the PRN principle—pro re nata, as needed), with preference for substances with a shorter half-life (lorazepam, oxazepam). Alprazolam, because of its very short half-life and strong addictive potential, is associated with the risk of a pronounced rebound effect and is particularly undesirable in the third trimester. [18]

It must not be forgotten that benzodiazepines constitute an important element of management in acute conditions such as epileptic seizure during pregnancy (intravenous diazepam as the drug of choice), severe manic agitation, or acute psychosis with aggression, where the benefit of rapidly controlling the clinical state clearly outweighs the risk of single neonatal exposure. In emergencies, benzodiazepines are acceptable, whereas their chronic use during pregnancy requires strict clinical justification and regular reassessment. [18]

3.5. Summary of Safety Data—Synthetic Table

Table 1 presents a synthetic summary of the safety profiles of the discussed psychiatric medications during pregnancy on the basis of the current literature.

Drug / class	**Safety profile**	**Main risks**	**Clinical recommendations**
Sertraline (SSRI)	Relatively favorable	PPHN (rare), NAS, no increase in overall MCM	Drug of choice among antidepressants [6]
Paroxetine (SSRI)	Unfavorable	Cardiac defects (consistent meta-analysis), NAS	Avoid; switch before pregnancy or in the first trimester [6]
Fluoxetine (SSRI)	Unfavorable—moderate	Cardiac defects, NAS, long T1/2	Avoid; sertraline as an alternative [6]
Escitalopram, citalopram	Moderately favorable	Possible cardiac defects (inconsistent data)	Acceptable if effective [6]
Venlafaxine (SNRI)	Moderate; limited data	More pronounced NAS, possible PPHN	Use cautiously; neonatal monitoring [6][7]
TCAs	Moderate; historical data	Anticholinergic symptoms in the newborn	Acceptable in the absence of alternatives [10]

Haloperidol (typical)	Relatively favorable	EPS symptoms in the newborn	First-line drug among antipsychotics [11]
Quetiapine (SGA)	Favorable; extensive literature	Gestational diabetes, NAS (rare)	Acceptable in bipolar disorder and psychosis [11][12]
Olanzapine (SGA)	Uncertain—a signal from the Finnish cohort	Possible congenital malformations; gestational diabetes	Use cautiously; prefer quetiapine [13]
Risperidone (SGA)	Potential teratogenic signal	Cardiac defects (inconsistent meta-analysis)	Avoid if possible [5]
Aripiprazole (SGA)	Moderate; encouraging data	No consistent MCM signal	Acceptable; concentration monitoring [12]
Clozapine (SGA)	Unfavorable	Neonatal agranulocytosis, floppy baby syndrome	Only when there is no alternative; hematological monitoring [13]
Lithium	Moderate; manageable risk	Ebstein's anomaly (rare), neonatal toxicity	Use with weekly concentration monitoring [3][14]
Lamotrigine	Favorable; first-line drug	Decline in concentrations during pregnancy; dose correction necessary	First-line drug in bipolar disorder; concentration monitoring [15]
Valproate	Absolutely unfavorable	Neural tube defects (14.3/1000), ASD (41.9/1000), reduced IQ	Absolutely contraindicated as a first-line drug [15]

Carbamazepine	Unfavorable; only in the absence of alternatives	Neural tube defects, cardiac defects	Avoid as first-line; prefer lamotrigine [15]
Lorazepam, oxazepam	Moderate; acceptable on an as-needed basis	NAS, neonatal hypotonia	PRN, lowest dose, avoid chronic use [18]
Diazepam, clonazepam	Unfavorable in the third trimester	Floppy baby syndrome, NAS, fetal accumulation	Avoid chronic use in the third trimester [18]

Table 1. Summary of the safety of psychiatric medications used during pregnancy based on the literature from 2020--2025. NAS—neonatal adaptation syndrome; PPHN—persistent pulmonary hypertension of the newborn; EPS—extrapyramidal symptoms; MCM—major congenital malformations; SGA—second-generation antipsychotics; ChAD—bipolar disorder. Sources: [3, 5, 6, 7, 11, 12, 13, 15, 18].

4. PRINCIPLES OF PSYCHIATRIC PHARMACOTHERAPY DURING PREGNANCY

4.1. Individualized Risk--Benefit Analysis

The fundamental principle of psychiatric pharmacotherapy during pregnancy is to perform an individualized, documented analysis of the risk--benefit ratio, taking into account: (1) the natural risk resulting from the course of untreated mental illness for the mother and fetus; (2) evidence for the efficacy of the given drug in the given indication; (3) teratological and neonatological data concerning the specific substance and its dosage; and (4) alternative non-pharmacological interventions (psychotherapy, cognitive-behavioral therapy, ECT). ACOG guidelines recommend that the decision to discontinue or continue medications should not be made solely because of pregnancy or breastfeeding, but should result from shared decision-making between the clinician and the patient, ideally with the participation of the partner or family. [11]

Particularly important is planning pharmacotherapy before conception. Hasser et al. (2024) recommend that a discussion on family planning, potential pregnancy, and the safety of

current medications be conducted with every psychiatric patient of reproductive age, regardless of her currently declared intention to become pregnant. Data from the Epilepsy Birth Control Registry indicate that more than 65% of pregnancies in women with mental disorders are unplanned, which means that the medication used outside pregnancy is often the same medication used at conception and throughout the critical first trimester of organogenesis. Prophylactic switching of medication—for example, from valproate to lamotrigine—before a planned pregnancy is decidedly safer than sudden discontinuation of medication after becoming aware of pregnancy or changing medication during an ongoing pregnancy. [3][15]

The decision to continue or discontinue pharmacotherapy should take into account disease severity, the number and frequency of previous episodes, the presence of suicidal ideation or severe psychotic symptoms, the availability of social support, and the possibility of outpatient monitoring. Women with mild symptoms, with access to effective psychotherapy (particularly cognitive-behavioral therapy [CBT]) and strong psychosocial support, may be candidates for gradual discontinuation of medications before a planned pregnancy or during pregnancy. In contrast, in women with severe illness—especially bipolar I disorder, schizophrenia, psychotic disorders, or a history of psychiatric hospitalization—continuation of pharmacotherapy is almost always clinically indicated. [5][11]

4.2. The Principle of the Lowest Effective Dose and Avoidance of Polytherapy

Polytherapy, defined as the concomitant use of two or more psychiatric medications, is associated with an increased risk of adverse pregnancy outcomes independently of the individual substances. In a population-based study conducted in a Swedish cohort of 874 women with bipolar disorder treated with mood stabilizers, polytherapy was found to be a significant risk factor for preterm birth (OR 2.7; 95% CI 1.4--5.4) after adjustment for disease type. The 2024 AAN guidelines consistently indicate a higher risk of congenital malformations for polytherapy compared with monotherapy for each of the mood stabilizers. Combining valproate with another teratogenic drug—for example, carbamazepine or topiramate—mutually increases the risk of neural tube defects and other structural malformations. [3][15]

The principle of using the lowest effective doses has particular justification in the light of data showing a dose--effect relationship for valproate (higher ASD risk at doses above 800 mg/day) and carbamazepine. In practice, this means that the clinician should aim for monotherapy with

optimal doses rather than use several drugs at suboptimal doses. In practically every pharmacological group, the use of a therapeutic dose rather than its empirical reduction below the therapeutic threshold is recommended, because ineffective pharmacotherapy does not reduce risk for the mother and may create a false sense of safety. [6][15]

4.3. Dose Modification in Individual Trimesters

Pregnancy induces significant pharmacokinetic changes that alter serum concentrations of psychiatric medications in a manner that differs depending on the substance and trimester. The volume of distribution increases by 30--50% as a result of water retention and increased blood volume, lowering the concentrations of drugs that require higher doses to achieve therapeutic levels. Renal clearance increases by 50--70% (especially in the second and third trimesters), which particularly affects lithium and lamotrigine. CYP3A4 activity increases during pregnancy, affecting the metabolism of quetiapine, haloperidol, and clozapine, whereas CYP1A2 activity—crucial for clozapine metabolism—decreases significantly in the second half of pregnancy, which may lead to increased concentrations of this drug and an increased risk of toxicity. [14]

For lamotrigine, clearance may increase two- to threefold during pregnancy, especially in the third trimester, requiring active dose increases to maintain therapeutic concentrations. Hasser et al. (2024) recommend measuring lamotrigine concentrations every 1--2 weeks from the beginning of the second trimester until delivery, with dose adjustment according to the results. After delivery, lamotrigine clearance decreases rapidly—usually within 1--2 weeks—which without dose reduction may provoke toxicity symptoms: dizziness, diplopia, ataxia, and nausea. In the case of lithium, the increase in renal clearance requires gradual dose increases in the second and third trimesters and rapid reduction after delivery, ideally planned in advance. [3][14]

For SSRIs and atypical antipsychotics, pharmacokinetic changes are less dramatic; however, clinical monitoring and—where available—serum concentration measurements in the second and third trimesters are recommended by the guidelines. Venlafaxine and duloxetine may require dose increases in the third trimester because of intensified metabolism. Reducing the dose of SSRIs below the effective level without a clear indication is not recommended, because it promotes relapse of perinatal depression and the resulting complications for the mother and fetus. [6][11]

4.4. Preparation for Delivery and the Obstetric Care Plan

A comprehensive perinatal care plan in a woman receiving psychiatric treatment should be developed in a multidisciplinary manner by a psychiatrist, obstetrician, and neonatologist, ideally before pregnancy or at its beginning. The plan includes: (1) information for delivery-room staff about the medications used; (2) a neonatal management plan—indications for observation in the neonatal ward, duration of observation (48--72 hours in the case of exposure to SSRIs/SGAs in the third trimester, 1--2 weeks in the case of exposure to benzodiazepines or lithium), criteria for substitution therapy; and (3) a pharmacological postpartum plan—the decision on continuation or dose modification during the first 24--72 hours after delivery, when pharmacokinetics undergo the most dynamic changes. [11][14]

For lithium, dose reduction by 20--30% in the week preceding the planned due date and intensive concentration monitoring during the first 2 weeks postpartum are recommended because of the rapid normalization of renal clearance. Regarding breastfeeding: for sertraline, lamotrigine in low doses, and quetiapine, available data generally do not constitute an absolute contraindication, but continued observation of the newborn for excessive sedation, hypotonia, and sucking disturbances is necessary. For valproate and clozapine, breastfeeding is considered unacceptable because of the concentrations of these medications in breast milk and the associated risk to the newborn—respectively hepatotoxicity and agranulocytosis. [5][11][14]

5. ELECTROCONVULSIVE THERAPY (ECT) AS AN ALTERNATIVE THERAPEUTIC OPTION DURING PREGNANCY

Electroconvulsive therapy is an established non-pharmacological method for the treatment of severe affective episodes, catatonia, treatment-resistant psychosis, and life-threatening conditions—severe depression with suicidal risk, refusal of food and fluids, and mania unresponsive to pharmacotherapy—both outside pregnancy and during pregnancy. ECT is a particularly valuable therapeutic alternative in situations in which pharmacotherapy is absolutely contraindicated (e.g., the need to avoid valproate in a woman with bipolar disorder resistant to other treatment), ineffective, or when the mother’s condition requires rapid intervention measured in days rather than weeks. [19][21]

A systematic review by Leiknes et al., including 339 documented ECT procedures in pregnant women, showed that this method is generally safe for the fetus when appropriate precautions are used: continuous cardiotocographic monitoring during the procedure and for at least 30 minutes afterward, maternal prehydration to minimize the risk of decreased placental perfusion, and appropriate optimization of general anesthesia parameters (selection of anesthetics with a documented safety profile in pregnancy, avoidance of hyperventilation). The most common complications were uterine contractions and transient fetal heart rate deceleration, without long-term clinical consequences. [19][21]

A review of reports concerning ECT in the third trimester (n = 45 cases) found that properly performed ECT with cardiotocographic monitoring was not associated with a significantly higher rate of obstetric complications—preterm births, placental abruption, intrauterine growth restriction—than standard general anesthesia used in non-obstetric procedures. ECT is one of the few psychiatric treatment methods for which there are no data indicating any direct teratogenic effect. Its mechanism of action—transcranial electrical discharge inducing a generalized seizure—is not associated with fetal exposure to pharmacological substances. A condition of safety is performance of the procedures in centers with the possibility of immediate obstetric intervention. [19][21]

The efficacy of ECT in severe depression and mania is high and at least comparable to pharmacotherapy—meta-analyses show a treatment response rate of 60--80% in severe depression resistant to pharmacotherapy. The rapid onset of action of ECT (improvement after only 3--5 procedures) constitutes an important advantage in clinical situations in which waiting 2--4 weeks for the effect of pharmacotherapy is unacceptable because of the severity of the patient's condition. The decision to use ECT should be made in a multidisciplinary manner with the participation of a psychiatrist, anesthesiologist, obstetrician, and—where possible—the patient herself and her caregivers. [19][21]

6. DISCUSSION

The results of this review indicate that psychiatric pharmacotherapy during pregnancy is not a monolithic concept—the risk of individual substances differs dramatically, from drugs with an acceptable safety profile (sertraline, haloperidol, lamotrigine, quetiapine), through substances requiring particular caution and intensive monitoring (lithium, carbamazepine), to drugs absolutely not recommended as first-line drugs in pregnant women (valproate, paroxetine, clozapine except in exceptional circumstances). The fundamental clinical message

remains unchanged and is consistent across all systematic reviews and guidelines from 2020--2025: the benefits of adequate treatment of severe mental illness during pregnancy generally outweigh the risks associated with the use of safer psychiatric medications, and untreated mental illness constitutes as real—or greater—a threat to the mother and fetus as the potential effects of pharmacotherapy. [5][11]

One of the key issues under discussion is the methodological difficulty of studies on the teratogenicity of psychiatric medications—the problem of indication bias. Women using psychiatric medications are by definition burdened with illnesses that themselves may negatively affect pregnancy outcomes through biological mechanisms (hypercortisolemia, altered neurotransmitter concentrations, disturbances of the HPA axis) and behavioral mechanisms (neglect of prenatal care, smoking, substance abuse). Higher-quality meta-analyses, especially those including control groups with psychiatric disorders treated non-pharmacologically or with unchanged treatment indication, consistently demonstrated a reduced or abolished effect of SSRIs on congenital malformations and ASD risk after adjustment for indication. This underscores the fundamental difficulty in interpreting the results of observational studies in this field. [6][9]

A particularly controversial area remains the issue of ASD and ADHD risk after prenatal exposure to psychiatric medications. Historical concerns related to SSRI use and ASD risk have not been confirmed in meta-analyses taking treatment indication into account as a confounding variable. In contrast, for valproate, ASD risk is one of the best documented effects of prenatal exposure—the odds ratio of 2.9 (95% CI 2.0--4.2) in the meta-analysis by Veroniki et al. from 2021, confirmed in multiple independent cohorts, constitutes clear evidence of the need to avoid valproate in pregnant women and in women of reproductive age planning pregnancy. The mechanism underlying this association—epigenetic regulation of neurodevelopmental genes through HDAC inhibition—distinguishes valproate from all the other substances discussed and partly explains why folic acid supplementation cannot provide protection. [9][16][17]

A significant limitation of the available data is the lack of randomized clinical trials—impossible for ethical reasons. The overwhelming majority of evidence comes from observational studies burdened by non-random participant selection, varying definitions of exposure (drug in the first trimester vs. any trimester vs. throughout pregnancy), variable quality of adjustment for confounding variables (treatment indication, comorbidities, other

medications), and heterogeneous definitions of endpoints. Selective reporting, in which cases of adverse outcomes may be reported more often than uncomplicated pregnancies, is an additional limitation. Some effects—such as the risk of Ebstein's anomaly after lithium—were overestimated for years precisely as a result of selective reporting of cases. [6]

Insufficient representation of women with severe mental disorders in pregnancy registries constitutes another important limitation. Women with schizophrenia or bipolar I disorder, treated with high doses of medications or polytherapy, are underrepresented both in prospective registries and in retrospective database analyses because they are less likely to present to specialized centers or are lost to follow-up. The results of the meta-analysis by Etchecopar-Etchart et al. (2024) confirmed that women with bipolar disorder are exposed to a range of complications independently of pharmacotherapy—which emphasizes the need for multidisciplinary perinatal care involving psychiatry, obstetrics, neonatology, and clinical psychology. [1]

A clinically urgent problem remains the shortage of data concerning newer psychiatric medications—lurasidone, cariprazine, amisulpride, agomelatine, brexpiprazole, lumateperone, and newer mood stabilizers. For these substances, no pregnancy registries including more than a dozen cases exist, and the number of described exposed pregnancies is too small for a reliable assessment of teratogenic risk. In such a situation, the principle of caution and preference for substances with a longer history of use during pregnancy—while preserving clinical efficacy—are fully justified. However, changing a well-tolerated and effective medication to an older analogue solely because of pregnancy should be avoided if it entails a risk of psychiatric destabilization. [11]

The role of folic acid deserves separate emphasis in the context of psychiatric pharmacotherapy during pregnancy. Standard folic acid supplementation (0.4 mg/day) is recommended for all women planning pregnancy and throughout the first trimester in order to prevent idiopathic neural tube defects. The 2024 AAN guidelines indicate, however, that this dose does not protect against dysraphism caused by valproate or carbamazepine. For women taking these medications, a higher dose of folic acid (5 mg/day) was historically recommended, but there is no reliable evidence that higher supplementation reduces the teratogenic risk of valproate—the mechanism of HDAC inhibition is independent of folate status. Therefore, changing the medication to a safer alternative, rather than merely increasing folic acid supplementation, is the appropriate preventive strategy. [15][16]

The clinical perspective in Poland requires taking into account the specificity of the healthcare system: limited availability of perinatal mental health clinics, fragmentation of care between psychiatric and obstetric-gynecological clinics, and still low awareness among clinicians of current safety data on psychiatric medications during pregnancy. European data indicate that only 15--30% of women with mental disorders during pregnancy receive comprehensive psychiatric--obstetric care, which increases the risk of inadequate therapeutic decisions—both unnecessary discontinuation of effective medications and unjustified continuation of substances with an unfavorable safety profile. [5]

7. CONCLUSIONS

On the basis of the review of the current literature concerning the safety of psychiatric medications used during pregnancy, the following conclusions can be formulated:

1. The decision regarding psychiatric pharmacotherapy during pregnancy should result from an individualized risk--benefit analysis. Discontinuation of medications without such an analysis is not an optimal strategy because untreated mental disorders themselves significantly increase the risk of adverse pregnancy outcomes—both for the mother (relapse of illness, suicidal risk, bonding disturbances) and for the fetus (low birth weight, prematurity, impaired neurogenesis). [1][3][5]

2. Among antidepressants, sertraline demonstrates the most favorable safety profile and is the drug of choice in the pharmacotherapy of depression in pregnant women. Paroxetine and fluoxetine should be avoided because of the consistent, repeatedly confirmed signal of increased risk of cardiac defects in many independent meta-analyses. Escitalopram and citalopram constitute acceptable alternatives. [6]

3. Atypical antipsychotics—particularly quetiapine and aripiprazole—demonstrate an acceptable safety profile in current studies and are first-line drugs among SGAs during pregnancy. Olanzapine requires particular caution because of the signal from the Finnish cohort study; clozapine should be used only when no safer alternative exists and only with hematological monitoring of both mother and newborn. [11][12][13]

4. Haloperidol remains the antipsychotic with the longest documented history of use during pregnancy and is considered the drug of choice among typical antipsychotics in situations requiring rapid pharmacological intervention, including acute agitation. [5][11]

5. Lamotrigine is the preferred mood stabilizer during pregnancy because of its relatively low risk of congenital malformations and favorable neurodevelopmental profile (IQ 105.8 in the MONEAD study). It requires strict monitoring of serum concentrations and active dose correction throughout pregnancy because of estrogen-induced UGT1A4 induction, with dose reduction required after delivery. [3][15]

6. Sodium valproate is absolutely contraindicated as a first-line drug in pregnant women and in women of reproductive age planning pregnancy. Its use is associated with the highest risk of congenital malformations (96.7/1000), ASD (41.9/1000), and reduced IQ in offspring among all analyzed substances. Switching from valproate to a safer alternative should be carried out before a planned pregnancy, with appropriate advance timing and clinical monitoring. [15][17]

7. Carbamazepine has a considerably more favorable safety profile than valproate, but remains a substance associated with an increased risk of neural tube defects (5.6/1000) and is preferred only in the absence of a safer alternative. [15]

8. Benzodiazepines should be used during pregnancy at the lowest doses and for the shortest possible time (the PRN principle). In the third trimester, the use of long-acting benzodiazepines (diazepam, clonazepam) is associated with significant neonatal risk—floppy baby syndrome and neonatal withdrawal syndrome. Short-acting substances are preferred: lorazepam and oxazepam. [18]

9. Electroconvulsive therapy (ECT) constitutes a safe and effective alternative to pharmacotherapy in severe psychiatric conditions during pregnancy, particularly when medications are contraindicated or ineffective, or when rapid clinical improvement is required. There are no data indicating teratogenicity of ECT. [19][21]

10. Pregnancy induces significant pharmacokinetic changes requiring active monitoring of medication concentrations and dose adjustment—particularly for lithium (increased renal clearance) and lamotrigine (UGT1A4 induction). A comprehensive perinatal care plan should be developed in a multidisciplinary manner, ideally before conception. [3][14]

11. Future studies should focus on substances with limited data during pregnancy (lurasidone, cariprazine, agomelatine, brexpiprazole), on the epigenetic mechanisms of valproate teratogenicity and possibilities for their modification, and on long-term neurodevelopmental outcomes in children exposed to psychiatric medications in utero, taking into account the effects of maternal illness as a confounding variable.

DISCLOSURE

AUTHORS'S CONTRIBUTION

Conceptualization: KI, MK, AG, DG, PK
Methodology: KI, GP, WG, MKU, AU
Software: KI, TK, MKO, HB, MK
Check: KI, AG, DG, PK, GP
Formal Analysis: KI, WG, MKU, AU, TK
Investigation: KI, MKO, HB, MK, AG
Resources: KI, DG, PK, GP, WG
Data Curation: KI, MKU, AU, TK, MKO
Writing-Rough Preparation: KI, HB, MK, AG, DG
Writing-Review and Editing: KI, PK, GP, WG, MKU
Visualization: KI, AU, TK, MKO, HB
Supervision: KI, MK, AG, DG, PK
Project Administration: KI, GP, WG, MKU, AU

All authors have read and agreed with the published version of the manuscript.

Funding statement:
This review was not externally funded.

Statement of the institutional review board:
Not applicable.

Statement of informed consent:
Not applicable.

Statement of data availability:
Not applicable.

Conflict of interest:
The authors report no conflicts of interest

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