REVIEW ARTICLE

CONTENTS

Contraceptive options for women with depression, bipolar disorder, schizophrenia, and premenstrual dysphoric disorder

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ABSTRACT

Aim: To select and analyse the scientific literature on the impact of contraception on women with depression, bipolar disorder, schizophrenia, and premenstrual dysphoric disorder.

Material and Methods: A detailed literature analysis was performed using PubMed, WebMD, ScienceDirect, and Google Scholar databases. The articles and books included were written in English and published between 2011 and 2024. A literature review was conducted in the PubMed, WebMD, ScienceDirect, and Google Scholar databases, analysing scientific articles in English from 2011 to 2024. Studies evaluating the relationship between contraceptive use and mental health conditions, including depression, bipolar disorder, schizophrenia, and premenstrual dysphoric disorder (PMDD), were selected. The search combined the following keywords using appropriate Boolean operators (i.e., AND, OR): "contraception", "depression", "bipolar disorder", "schizophrenia", "premenstrual dysphoric disorder", and "mental health".

Conclusions: The impact of hormonal contraception on mental health varies across conditions, making personalized contraceptive counselling essential. Further research is needed to fully understand these complex interactions and develop evidence-based guidelines.

KEY WORDS: bipolar disorder, schizophrenia, depression, contraception, premenstrual dysphoric disorder, mental health

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INTRODUCTION

Hormonal contraceptives are used worldwide by more than 100 million women [1]. An association between oral contraceptive use and the emergence of symptoms of mental disorders has been suggested. Despite their widespread use, the uptake of oral contraceptives has declined in recent years. This decrease is likely due to multiple factors, including more frequent choice of long-acting reversible contraception (LARC) methods, and growing awareness of potential side effects, particularly related to mental health issues [2]. For all reproductive-age women with psychiatric disorders, it is essential to address contraceptive needs and method selection as part of their care plan. Use of inappropriate methods, or non-use, may result in unintended pregnancy, and the sequelae of unplanned pregnancy can be significant, including high-risk pregnancy in the setting of poorly controlled disease or potential exposure to teratogenic medications [3]. Unintended pregnancy is also associated with new episodes of psychiatric disorders, including perinatal depression. Once an episode occurs, a recurrent cycle of risk evolves. The postpartum period is associated with an elevated risk of the emergence of mood disorders in women sensitive to rapid hormonal change. Psychiatric illness instability increases health risks for both the mother and the fetus. That is the reason why adequate information about the methods of contraception should be provided to all women with mental health disorders [4].

Patients and providers may also be concerned about the co-administration of hormonal contraceptives (HCs) with psychotropic medications, given the complex pharmacology of these drugs, so it is crucial to know if there are any interactions [5]. Women with psychiatric disorders often experience difficulties using contraceptive methods, leading to a higher risk of unintended pregnancies. This is partly due to factors such as forgetfulness, cognitive impairments, and the complexities of managing their health conditions alongside contraceptive practices [3]. The best contraceptive method for women with psychiatric disorders will depend on their specific needs and expectations; the goal of this article is to provide clinicians with guidance on choosing the appropriate form of contraception.

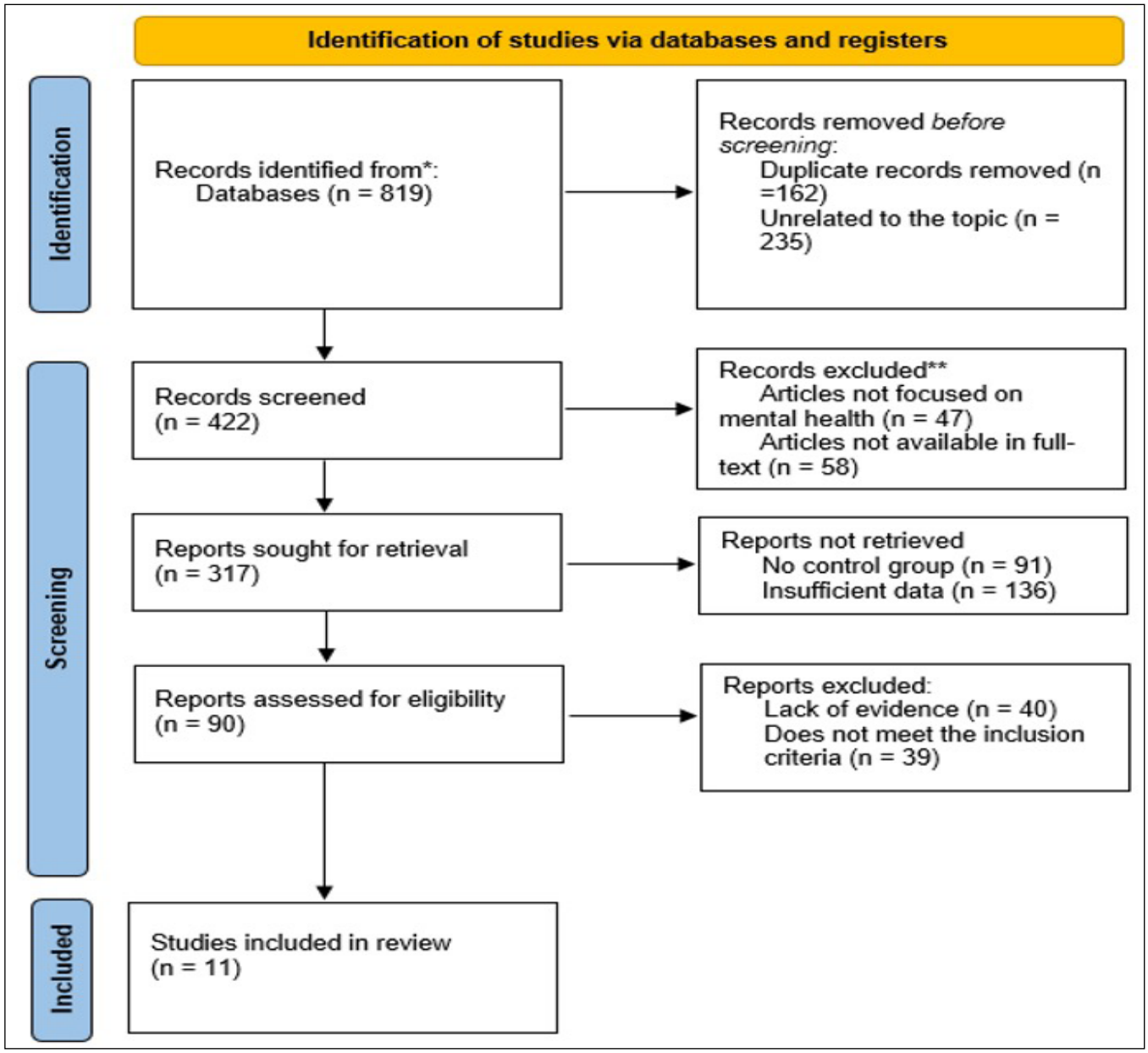

Fig. 1. PRISMA Flow Diagram of Study Selection Process. This figure illustrates the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart detailing the systematic review process, identifying and selecting studies examining contraceptive use, safety, and mental health outcomes in women with depression, bipolar disorder, schizophrenia, or premenstrual dysphoric disorder
Picture taken by the authors

AIM

To select and analyse the scientific literature on the impact of contraception on women with depression, bipolar disorder, schizophrenia, and premenstrual dysphoric disorder.

MATERIALS AND METHODS

SEARCH STRATEGY

A literature review was conducted in the PubMed, WebMD, ScienceDirect, and Google Scholar databases, analysing scientific articles in English from 2011 to 2024. Studies evaluating the relationship between contraceptive use and mental health conditions, including depression, bipolar disorder, schizophrenia, and premenstrual dysphoric disorder (PMDD), were selected. The search combined the following keywords using appropriate Boolean operators (i.e., AND, OR): "contraception", "depression", "bipolar disorder", "schizophrenia", "premenstrual dysphoric disorder", and "mental health".

INCLUSION AND EXCLUSION CRITERIA

Studies meeting the following criteria were included in the review:

1. Analysis of contraceptive methods in women diagnosed with mental health conditions, specifically depression, bipolar disorder, schizophrenia, or PMDD, with a focus on method selection, safety, and impact on mental health.
2. Study populations included reproductive-age women diagnosed with one or more of the listed psychiatric disorders, as well as healthy control groups without psychiatric diagnoses.

Studies were excluded if they met any of the following criteria:

1. Conference papers or editorials;
2. Duplicated studies.

DATA ANALYSIS

The studies' results were evaluated using Microsoft Excel (Microsoft Corp., Redmond, WA, USA).

STUDY SELECTION

A total of 819 articles were identified. After removing duplicates and those not meeting the inclusion criteria, a portion was selected for full-text review. 11 studies were determined to meet the inclusion criteria. The results are outlined in the PRISMA diagram (Fig. 1).

REVIEW AND DISCUSSION

CONTRACEPTION AND DEPRESSION

Hormonal contraceptive use, a prevalent method of birth control globally, has been linked to the onset of depressive symptoms in some women, sparking ongoing debates in the scientific community. Several studies have found that hormonal contraception, especially among adolescents, is associated with an increased risk of antidepressant use and depression diagnosis, indicating a potential adverse effect on mental health [1,6]. In particular, younger women are considered the most vulnerable to these risks, with adolescent use of oral contraceptives possibly elevating the likelihood of depression later in life [7]. Furthermore, hormonal contraception has been correlated with a higher risk of suicide attempts, with adolescents showing the highest relative risk [8].

The levonorgestrel-releasing intrauterine system (LNG-IUS) is linked to the onset of depression in a dose-dependent way, with low-, medium-, and high-dose levonorgestrel in the IUS all demonstrating this association. While the observational nature of the study prevents any definitive conclusions about causality, the dose-response pattern adds to the evidence suggesting a connection between levonorgestrel exposure and the risk of developing depression [9].

On the other hand, other research has suggested that hormonal contraceptives do not directly cause depressive disorders, and some studies have found no significant association between contraceptive use and depression [10,11].

Since women in different contraceptive use categories often differ in age, parity, education, exercise habits, health behaviors, smoking status, and various other factors, it can sometimes be challenging to determine whether contraceptives are the direct cause of depression [12]. While oral contraceptive use was not linked to depressive symptoms across all age groups combined, 16-year-old girls reported higher scores for depressive symptoms when using oral contraceptives [13]. Young women appear to be the most vulnerable to the effects of hormonal contraception. Teens should be informed about the potential risks of hormonal contraceptives, including the possibility of a link to depression [14].

A theory suggests that hormonal changes can trigger depressive symptoms, although the exact mechanisms by which this occurs in some women are still unclear. There is also evidence pointing to a genetic predisposition for hormone-induced depression. For example, a twin study identified a genetic basis for depressive symptoms associated with contraceptive use [15]. Additionally, women with depression are more likely to experience unintentional pregnancies, often due to contraceptive errors, which can negatively impact both the parents and the unborn child [16].

Patients with depression may require special consideration due to the potential interactions between psychotropic medications used for depression and hormonal contraception. Some drugs, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are safe and can be used together with any contraceptive method. However, medications used for refractory depression, such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antipsychotics, may interact with hormonal contraception. TCAs and MAOIs can affect steroid metabolism in the liver, potentially decreasing the effectiveness of contraceptive methods like implants, combined oral contraceptive pills, patches, rings, injectables, and progesterone-only pills. In such cases, locally acting IUDs are the preferred choice. Atypical antipsychotics such as risperidone, aripiprazole, and ziprasidone may cause hyperprolactinemia, leading to abnormal menstrual cycles, fertility problems, and galactorrhea. These side effects can be managed with COCPs [17]. Additionally, the herbal remedy St. John's Wort, used to treat mild depression,

induces cytochrome P450 enzymes, particularly CYP3A4, which may speed up the metabolism of both the ethinyl estradiol and progestin components in hormonal contraceptives, lowering their effectiveness and increasing the risk of unintended pregnancy. As a result, locally acting IUDs are considered the preferred alternative [18].

CONTRACEPTION AND BIPOLAR DISORDER

Bipolar disorder is a chronic, recurrent condition characterized by fluctuations in mood and energy, impacting more than 1% of the global population [19]. One of the symptoms of bipolar disorder is impulsivity, which is characterized by a tendency to act fast, without considering the consequences for oneself or others [20] there is mixed evidence as to whether impulsivity is a trait feature of the disorder, present in the euthymic state in the absence of mania. The aim of this systematic review and meta-analysis was to examine whether impulsivity is elevated in euthymic BD in comparison to controls. Electronic databases were searched for papers published until April 2022 reporting data on a self-report or behavioural measure of impulsivity in a euthymic BD group and a healthy control group. In total, 46 studies were identified. Euthymic BD showed significantly higher levels of self-reported impulsivity compared to controls (large effect size. As a result, women with bipolar disorder are more likely to engage in risky sexual behaviors, increasing the likelihood of unwanted pregnancies, which often lead to abortions [20,21]there is mixed evidence as to whether impulsivity is a trait feature of the disorder, present in the euthymic state in the absence of mania. The aim of this systematic review and meta-analysis was to examine whether impulsivity is elevated in euthymic BD in comparison to controls. Electronic databases were searched for papers published until April 2022 reporting data on a self-report or behavioural measure of impulsivity in a euthymic BD group and a healthy control group. In total, 46 studies were identified. Euthymic BD showed significantly higher levels of self-reported impulsivity compared to controls (large effect size. This is linked to challenges in planning their actions, a lack of proper sex education, and insufficient counseling from healthcare providers, which can result in negative obstetric outcomes and an inadequate ability to care for their children [21].

According to a study conducted by Meliha Zengin Eroglu et al. [22], the rate of unplanned pregnancies in women with bipolar disorder was significantly higher compared to women without the disorder, with rates of 49.52% and 15.04%, respectively. Although most of the women with bipolar disorder used contraception, they were more likely to choose less reliable methods (e.g., withdrawal, calendar method). Therefore, it is recommended that all clinicians provide information about effective contraception to women with bipolar disorder to prevent sexually transmitted infections and unplanned pregnancies, thus protecting the health of both the mother and fetus.

Women with bipolar disorder may benefit from the use of COCPs, as they may experience a milder disease course compared to those using nonhormonal methods or no contraception. This may be linked to a pattern where mood swings in women with bipolar disorder align with their menstrual cycle. However, it remains uncertain whether these mood changes are specifically related to bipolar disorder or are also influenced by the presence of co-occurring premenstrual dysphoric disorder, which could also improve with hormonal contraceptives [12].

CONTRACEPTION AND SCHIZOPHRENIA

Hormonal contraceptive use, a prevalent method of birth control globally, has been linked to the onset of depressive symptoms in some women, sparking ongoing debates in the scientific community. Several studies have found that hormonal contraception, especially among adolescents, is associated with an increased risk of antidepressant use and depression diagnosis, indicating a potential adverse effect on mental health [1,6]. In particular, younger women are considered the most vulnerable to these risks, with adolescent use of oral contraceptives possibly elevating the likelihood of depression later in life [7]. Furthermore, hormonal contraception has been correlated with a higher risk of suicide attempts, with adolescents showing the highest relative risk [8].

Women with schizophrenia are more likely to experience unplanned pregnancies compared to the general population. These pregnancies may stem from factors such as social vulnerability, a higher risk of sexual assault, and a greater prevalence of concurrent substance use disorders among women with schizophrenia. Schizophrenia is also associated with impaired cognitive processing, social difficulties, and distorted perception of reality. These challenges can make it hard to plan and consistently use contraception during intimate relationships, even in planned and consensual sexual encounters [26]. These women have complex health needs that require specific reproductive counseling. Women who have multiple sexual partners should receive advice on barrier contraception methods. For women who don't want to have children soon,

long-acting reversible contraception (LARC) methods such as intrauterine devices (IUDs), progesterone depot injections, or implants are reasonable options [27]. Targeted reproductive counseling and support are essential to address the unique health needs of women with schizophrenia, helping them make informed choices about their reproductive health.

THE INTERACTION OF HORMONAL CONTRACEPTION WITH MEDICATIONS USED FOR BIPOLAR DISORDER OR SCHIZOPHRENIA TREATMENT

Bipolar disorder and schizophrenia are distinct, but the overlap in symptoms leads to similarities in treatment approaches. As a result, medications prescribed for both conditions often belong to the same classes, including mood stabilizers (lithium and anticonvulsants), atypical and typical antipsychotics [28]and psychotropic drugs represent cornerstones in the treatment. The primary aim of the review was to summarize the latest evidence with regards to the efficacy and effectiveness of drug treatment of schizophrenia and the manic phases of bipolar disorder. Schizophrenia systematic reviews conclude that antipsychotic drugs are effective in treating overall symptoms of psychosis and in preventing relapse. Some of the newer agents, the second-generation antipsychotics (SGAs.

Hormonal contraceptives may interact with anticonvulsants such as lamotrigine, valproate, carbamazepine, oxcarbazepine, and topiramate. Serum concentrations of lamotrigine and valproate are decreased when ethinyl estradiol is co-administered, probably due to accelerated glucuronidation. Serum concentrations of lamotrigine may be reduced by more than 50%, whereas the effect on valproate concentrations was small and of unclear clinical significance [29]. To prevent the risk of decreased lamotrigine concentrations, women taking lamotrigine should be advised to avoid combined hormonal contraceptives containing ethinyl estradiol, such as combined oral contraceptive pills, patches, or rings. Recommended alternatives include IUDs, implants, injectables, or progesterone-only pills [17].

Carbamazepine, oxcarbazepine, and topiramate induce the cytochrome (CYP) 450 3A4 enzyme. This induction enhances the metabolism of estrogen and progesterone, potentially reducing the contraceptive efficacy of oral contraceptive pills; therefore, an alternative contraceptive option should be chosen [27].

Antipsychotic drugs like risperidone, aripiprazole, and ziprasidone can lead to hyperprolactinemia. In such cases, COCPs are the first choice of treatment [17].

Antipsychotic medications clozapine and chlorpromazine are metabolized by (CYP)3A4, 1A2, and 2C19. These liver enzymes are inhibited by estrogen and progesterone; therefore, if clozapine or chlorpromazine are taken together with COCP, the concentration of antipsychotics increases. For patients using these antipsychotic drugs, alternatives to hormonal contraception should be explored, and patients should be informed about possible interactions. If oral contraceptives are selected, levels of clozapine and chlorpromazine must be regularly checked [27,30]. The antipsychotic ziprasidone, despite being metabolized by the CYP 3A4 enzyme, does not significantly inhibit it at clinically relevant doses [27].

Additionally, it is essential to acknowledge that certain mood stabilizers, particularly valproic acid and lithium, are teratogenic and should be avoided in women of reproductive age. If switching to safer alternatives, such as lamotrigine or certain atypical antipsychotics, is not possible, it is crucial to ensure effective contraception to prevent unplanned pregnancies and potential adverse outcomes [31].

CONTRACEPTION AND PREMENSTRUAL DYSPHORIC DISORDER

Premenstrual symptoms, including both psychological and physical effects, occur cyclically before menstruation and fade after it. While most women experience at least mild discomfort, around 5% of women meet the diagnostic criteria for PMDD. The first-line treatment of PMDD is the use of serotonin reuptake inhibitors; however, it can also be treated with combined oral contraceptive pills (COCP) [32].

A study in the Japanese population conducted by Takashi Takeda et al. [33] investigated the effects of COCPs containing drospirenone 3 mg plus ethinyl estradiol 20 μg taken in a 24/4 regimen on PMDD symptoms. 48 women received the treatment, and by the third and sixth treatment cycles, most premenstrual symptoms had significantly improved.

Meanwhile, progesterone-only contraceptives, such as the mini-pill or the LNG-IUS, may worsen mood symptoms in some women, suggesting that progesterone could have a negative impact on mood for women with PMDD [34]affecting 2-5% of women. Combined oral contraceptive pills (COCPs. Therefore, women with PMDD seeking contraception should be offered combined hormonal contraceptive pills.

The relationship between hormonal contraception and psychiatric conditions, such as depression, bipolar disorder, schizophrenia, and premenstrual dysphoric disorder, presents a multifaceted area of research.

In the case of depression, findings are ambivalent.

Table 1. Contraceptive recommendations for depression, bipolar disorder, schizophrenia, and premenstrual dysphoric disorder

Psychiatric Disorder	Medications	Recommendations
Depression	- TCA/MAOI/St. John's Wort can decrease contraceptive hormone levels, increasing the risk of unintended pregnancy. - SSRIs and SNRIs are safe to use with all types of contraception	-LARCs are recommended for high efficacy and low maintenance when adherence is compromised. - CHCs may worsen mood symptoms, especially in adolescents. Alternative contraception methods are preferred - LNG-IUD may worsen mood symptoms in a dose-dependent manner, individualize based on patient response.
Bipolar Disorder Schizophrenia	- Antiepileptics (carbamazepine, oxcarbazepine, topiramate) decrease contraceptive hormone levels, increasing pregnancy risk. - Antipsychotic medication (clozapine and chlorpromazine) serum levels may increase when using COCPs - Atypical antipsychotics may increase prolactin levels, causing irregular periods, fertility problems, and galactorrhea. Estradiol can help to manage these side effects. - Lamotrigine levels are reduced when combined with CHCs, so mood stability should be monitored.	- LARCs are recommended for high efficacy and low maintenance when adherence is compromised. - Barrier methods advised for STI risk, especially with multiple partners - COCPs may improve mood symptoms related to the menstrual cycle. - Ensure effective contraception for women of reproductive age taking valproate or lithium.
Premenstrual Dysphoric Disorder	-	- COCPs with ethinyl estradiol and drospirenone are effective for both contraception and treating PMDD. - Monitor mood with progesterone-only methods, as they may worsen symptoms.

Source: compiled by the authors based on [7,9,12,17,18,22,27,29-32]

While some studies suggest that there is an association between hormonal contraceptives and the worsening of depressive symptoms, other studies show no significant relationship, especially with the use of progestin-only contraception [1,6,10,11]. The users who seem particularly susceptible to these mood-related side effects are adolescents [7]. That highlights the need for age-specific guidelines and mental health support for young women starting to use or already using hormonal contraceptives. However, given the wide range of studies, the lack of clear causality suggests the possible involvement of other factors, such as genetics and pre-existing mental health conditions, in mediating these effects [12]. Women with depression on SSRIs or SNRIs can use any contraceptive method since they do not interact with hormonal contraception. However, those taking TCAs, MAOIs, and St. John's Wort may benefit more from locally acting IUDs due to potential interactions affecting the efficacy of other hormonal contraceptives [17,18].

For both bipolar disorder and schizophrenia, unplanned pregnancies are a common concern due to a combination of impulsivity, cognitive challenges, and difficulties with consistent contraceptive use [20,21,26] there is mixed evidence as to whether impulsivity is a trait feature of the disorder, present in the euthymic state in the absence of mania. The aim of this systematic review and meta-analysis was to examine whether impulsivity is elevated in euthymic BD in comparison to controls. Electronic databases were searched for papers published until April 2022 reporting data on a self-report or behavioural measure of impulsivity in a euthymic BD group and a healthy control group. In total, 46 studies were identified. Euthymic BD showed significantly higher levels of self-reported impulsivity compared to controls (large effect size. Therefore, LARCs are reliable options that require less frequent adherence, making them particularly suitable for these populations [27]. Additionally, targeted counselling is essential to ensure women with bipolar disorder and schizophrenia understand the most effective contraceptive options and how these choices may intersect with their mental health needs. Medications commonly used to manage these disorders can interact with hormonal contraceptives. The anticonvulsant lamotrigine may have reduced efficacy when combined with hormonal contraceptives containing ethinyl estradiol, necessitating alternative options like non-hormonal IUDs or progesterone-only methods [17,29]. Carbamazepine, oxcarbazepine, and topiramate can reduce the effectiveness of oral contraceptives by accelerating the metabolism of estrogen and progesterone, increasing the risk of unintended pregnancies; therefore, alternative contraceptive methods should

be considered [27]. Clozapine and chlorpromazine can have pharmacodynamic interactions with hormonal contraceptives, which may increase the plasma concentration of antipsychotic medications, requiring careful monitoring or the use of non-hormonal contraception [27,30]. For women taking atypical antipsychotics, such as risperidone, aripiprazole, and ziprasidone, combined oral contraceptive pills may help manage symptoms of hyperprolactinemia [17].

For premenstrual dysphoric disorder, combined oral contraceptives containing drospirenone and ethinyl estradiol have demonstrated promising effects in reducing severe premenstrual symptoms, offering advantages of symptom relief and contraception. This is particularly important, as PMDD greatly affects quality of life, and COCs may provide both effective contraception and symptom management [33].

While hormonal contraception is important for reproductive control, its possible effects on mental health call for personalized, closely monitored approaches. More comprehensive research is needed to explore the long-term mental health impacts of different contraceptive formulations and their interactions with psychotropic medications. Personalized counseling and education on the benefits and risks of hormonal contraception are crucial, especially for adolescents and women with mental health conditions (Table 1).

CONCLUSIONS

The impact of hormonal contraception on mental health is complicated, with differences across different conditions and individuals. Hormonal contraceptives are widely used, but studies suggest they may pose mental health risks, particularly for adolescents, who appear more prone to depression and suicide attempts. COCPs can be an effective option for managing premenstrual dysphoric disorder and may serve as a second-line treatment. These pills might also offer benefits to women with bipolar disorder by alleviating mood fluctuations tied to the menstrual cycle.

There are potential interactions with some of the medications used for depression, bipolar disorder, and schizophrenia. The efficacy of contraception may be reduced when it is taken together with St. John's Wort, TCAs, MAOIs, carbamazepine, oxcarbazepine, and

topiramate, which can potentially lead to unintended pregnancies. Additionally, hormonal contraception can lower the efficacy of lamotrigine, thus reducing its effectiveness, and may increase plasma levels of clozapine and chlorpromazine, which can lead to severe side effects. On the other hand, COCPs may help manage symptoms of hyperprolactinemia for those taking atypical antipsychotics.

Patients with bipolar disorder and schizophrenia are at a higher risk of unplanned pregnancies, so it is important for healthcare professionals to provide essential information on effective methods of contraception and STI prevention, helping them choose the option best suited to their needs.

Given these complexities, individualized contraceptive counseling is essential to ensure safe and effective choices for women with mental health disorders. Further research is needed to confirm the credibility of existing evidence.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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