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ARTICLE

Beyond the 'normal' worries: detection and treatment of perinatal anxiety and anxiety disorders

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SUMMARY

In clinical psychiatry, it is common to see pregnant and postpartum patients who express excessive anxiety and concerns about pregnancy or childbearing. This implies the need to distinguish between symptoms that could be considered to be an expected reaction to the situation, the diagnosis of an anxiety disorder or the presence of pregnancy-related (pregnancy-specific) anxiety. The last presents as a specific clinical phenomenon, identified in the literature as concerns exclusively linked to the situation of pregnancy or childbirth. In this article I review key points in the differential diagnosis of perinatal anxiety and its impact on both the pregnancy and the baby, as well as aspects of detection and diagnosis. I also give a brief summary of possible management approaches and treatments.

LEARNING OBJECTIVES

After reading this article you will be able to:

- differentiate between anxiety as an expected response and pathological anxiety
- understand the importance of detecting anxiety disorders in the perinatal period
- recommend evidence-based treatments in clinical practice.

KEYWORDS

Anxiety disorders; perinatal psychiatry; antidepressants; anti-anxiety drugs; screening tools.

The term perinatal is used to refer to both the pregnancy and the postpartum period. The concept of perinatal period used in this article includes the duration of the pregnancy up to 1 year following delivery, since this is the time frame most often used in anxiety prevalence studies (Vesga-López 2008; Fawcett 2019).

Background

Anxiety disorders are common in the general population, more so in women than in men. A meta-analysis of epidemiological studies carried out across different regions of the world found a 12-month prevalence of 8.7% in women and 4.3% in men. Although lower than in the case of anxiety disorders, the annual prevalence of mood disorders was also higher in women (7.3%) than in men (4.0%) (Steel 2014). In addition, anxiety and mood disorders have the highest magnitude of comorbidity according to a systematic review of surveys about comorbidity among different mental disorders conducted in the general population (Merikangas 2007).

When it comes to the perinatal population, the same picture appears: there is reported a higher frequency of anxiety disorders than depression, as well as higher rates of comorbidity. An epidemiological survey carried out in a community sample found that anxiety disorders presented themselves at a similar frequency among pregnant, non-pregnant, and postpartum women (13, 14.9 and 12.3% respectively), and these numbers surpassed the figures reported for depression in the same groups (8.1, 8.4 and 9.3% respectively). Furthermore, the same study showed that pregnant and postpartum women sought treatment for anxiety disorders less often than non-pregnant women (6.1, 7.5 and 11.6% respectively). These findings suggest that many women with perinatal anxiety are not likely to receive adequate treatment (Vesga-López 2008). The high comorbidity between depression and anxiety disorders appears again in the perinatal stage. For reference, research conducted among perinatal patients in tertiary care showed that in 38.5% of those sampled experienced depressive episodes in comorbidity with some form of anxiety disorder (Grigoriadis 2011).

In addition to anxiety disorders, self-reported anxiety symptoms in pregnancy and postpartum are also frequent. A systematic review and meta-analysis of studies found that the estimated prevalence of self-reported anxiety symptoms was 22.9% during pregnancy and 15.0% in the postnatal period (between 1 and 24 weeks) (Dennis 2017). This is a major health concern, as perinatal anxiety has effects on pregnancy outcomes.

Impact of perinatal anxiety

The importance of properly assessing and identifying perinatal anxiety is indicated by the association

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between this condition and the various problems that can occur during pregnancy. There is growing interest in how anxiety affects pregnancy outcomes. Although the literature is scarce regarding the distinction between general anxiety, pregnancy-specific (pregnancy-related) anxiety and perinatal anxiety disorders, information can be gleaned from various studies. A meta-analysis designed to appraise the effects that maternal anxiety can have on different pregnancy outcomes incorporated studies that evaluated the impact of both self-reported anxiety and clinically diagnosed anxiety disorders. Antenatal anxiety was significantly associated with an increased risk of preterm delivery and spontaneous preterm delivery, and of having an infant of low birth weight, small for gestational age and with smaller head circumference. In the case of low birth weight, the association was greater when there was a clinical diagnosis of anxiety disorder compared with self-reported anxiety. This information warns about the potentially harmful effects that anxiety can have during the pregnancy as well as the need to detect and treat it (Grigoriadis 2018). Additionally, anxiety during pregnancy is a risk factor for postpartum anxiety and depression (Sutter-Dallay 2004). However, the impact of anxiety is not just limited to the immediate results of childbirth. Recent evidence indicates that perinatal anxiety can negatively affect offspring's socio-emotional, cognitive and language development. This effect is reported to be greater for antenatal anxiety than for postnatal anxiety, and it increases further when there is comorbid depression (Rogers 2020). Thus, perinatal anxiety and depression both pose risks to maternal health, pregnancy outcomes and child development (Wand 2014). Therefore, the conditions should be adequately explored and treated.

Perinatal anxiety and perinatal anxiety disorders

Many women experience perinatal anxiety, which can function as an adaptive response. However, if the anxiety is high, persistent and disabling, it may be indicating of the presence of pregnancy-related anxiety or an anxiety disorder. What guidelines are to be followed in making the distinction between reasonable concerns that can be expected in pregnancy or postpartum and those that go beyond that limit, compromising the health of the patient and her baby? This will be reviewed in the following sections.

Anxiety as an adaptive response

Anxiety is an emotional response that can be considered adaptive in the face of situations of potential threat or stress. However, when it ceases to be that kind of response, it can become a problem that interferes with day-to-day functioning. Anxiety usually presents with physical symptoms due to autonomic activation (such as tachycardia and palpitations), emotional symptoms (restlessness, fear, experience of threat), cognitive manifestations (excessive worry, hypervigilance, apprehensive expectation) and motor signs (tremors, startles, muscle tension). As anxiety is an expected emotion, especially considering that pregnancy and childbirth are potentially stressful life situations, the first challenge will be to determine whether the woman is presenting with an adaptative reaction or a pathological condition that requires treatment. Another aspect to consider is that there are some manifestations of anxiety that can overlap with somatic symptoms of either pregnancy (palpitations, numbness, sweating in the hands) or the postpartum period (tiredness, difficulty sleeping), adding another problem to the differentiation process.

Moreover, worries are among the most frequent symptoms of anxiety. If these concerns are focused exclusively on issues related to pregnancy and childbirth, the patient, her family members and even her medical team may dismiss them as reasonable for the situation. In the perinatal period, it is common to observe excessive worries that appear, for example, before an ultrasound, in the obstetric consultation, near delivery or at the beginning of breastfeeding. If the symptoms are mild, they might not impede adequate functioning and might resolve after the situation has passed. However, sometimes these symptoms intensify and significantly interfere with performance, causing profound discomfort. Although it is not an established diagnosis in the current classification of mental disorders, it is important to highlight a clinical presentation of perinatal anxiety that has been identified in the literature as pregnancy-related anxiety or pregnancy-specific anxiety (see the next section). In this condition, concerns are directly tied to pregnancy, the maternal role and childbirth; they are highly disabling in day-to-day activities and can affect pregnancy outcomes.

Therefore, the first thing to consider in a patient with perinatal anxiety will be whether she already has a diagnosis of anxiety disorder with or without treatment. If this is ruled out, the main aspects to take into account will be the degree of severity and functional impact of the anxiety symptoms, whether they are mentioned by the patient or evidenced by clinical evaluation (e.g. if anxiety is reducing the patient's appetite so that she does not gain weight, or she has difficulties in initiating breastfeeding). Some guidelines for conducting this first evaluation are set out in Box 1.

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BOX 1 Establishing whether perinatal anxiety is an expected (normal) response

- Explore the personal and family history of diagnosed anxiety disorders, especially perinatal
- Determine the onset of anxiety symptoms; explore whether they are related to any current or past obstetric events (e.g. anxiety and fear of undergoing investigations after having had a miscarriage diagnosed by ultrasound)
- Evaluate the persistence of symptoms (e.g. if they disappear after the ultrasound scan)
- Evaluate the intensity of symptoms, interference with day-to-day functioning and the degree of performance impairment (e.g. feeding problems, difficulty in initiating breastfeeding)
- If the anxiety does not persist and does not interfere with functioning, it can be considered adaptive and managed with support and information to reassure the patient. If not, a thorough examination will be required to define it as an anxiety disorder

Pregnancy-related anxiety

Intense and disabling anxiety during pregnancy has been a concern regarding maternal and fetal health. That is why numerous studies have focused on evaluating the impact of anxiety symptoms and stress on the outcome of the pregnancy. Dunkel Schetter & Tanner (2012) warn that pregnancy-related anxiety is associated with shorter gestation and has adverse implications for fetal neurodevelopment, highlighting the concept of pregnancy-related anxiety as a powerful modulator of adverse outcomes.

The concept of pregnancy-related anxiety has been developed from the identification of a form of anxiety whose predominant clinical manifestations are excessive worries related exclusively to pregnancy, childbirth and maternal roles (Guardino 2014).

Although it is not currently a diagnostic entity in the ICD or DSM, there is research exploring the possibility that pregnancy-related anxiety is an independent construct, different from general anxiety, anxiety disorders and depression. To investigate this, Huizink et al (2004) administered anxiety and depression questionnaires to pregnant patients to define the construct that characterises pregnancy-related anxiety. Through factor analysis, a three-factor model was found: fear of giving birth, fear of having a child with disabilities and concern for one's physical appearance. Overall, measures of anxiety and depression explained only a small part of the variance in these fears. A subsequent analysis using a similar methodology confirmed these results, stating that pregnancy-related anxiety is a relatively different syndrome from the general indices of anxiety and depression. The recognition of pregnancy-related anxiety in the context of indices of general anxiety and depression could provide an opportunity for early intervention and improvement of pregnancy outcomes (Brunton 2019).

From a longitudinal perspective, two factors were identified in association with pregnancy-related anxiety: concerns about the health of the baby and concerns regarding delivery. These showed different patterns in the antenatal period and little association with scores for general anxiety and depression from other measures and clinical interviews. Likewise, pregnancy-related anxiety differed from conventional symptom measures in terms of associated characteristics and was a predictor of outcome variables such as birth weight (regardless of the presence of generalised anxiety disorder – GAD) and postnatal mood alterations (Blackmore 2016).

It is therefore important to detect the presence of pregnancy-related anxiety, as it has negative consequences for the pregnancy and postpartum outcomes but is at risk of being attributed to expected (normal) concerns about pregnancy and childbirth and not being treated. There are several screening questionnaires to detect pregnancy-related anxiety. For example, the Pregnancy-Related Anxiety Questionnaire (PRAQ) in its revised version adapted for parous and nulliparous women (PRAQ-R2) is an accessible and validated resource to use as a screening tool in both clinical consultations and research (Huizink 2016). The questionnaire itself can be found in the appendix to Huizink et al's article.

Perinatal anxiety disorders

As mentioned above, perinatal anxiety disorders (anxiety disorders in pregnant and postpartum women) have been reported to be common in community surveys (Vesga-López 2008). However, studies use different ways of recording anxiety (e.g. various self-administered questionnaires, clinical diagnoses through structured interviews) as well as different time points for evaluations. Furthermore, as anxiety disorders form a category that includes various disorders, other difficulties are added when reviewing the information, such as the limited number of studies per specific diagnosis, the grouping of different subsets of anxiety disorder, and difficulties in establishing comorbidities among these disorders.

To determine the frequency of anxiety disorders in pregnancy, a systematic review analysed studies in which the presence of one or more anxiety disorders was assessed using structured diagnostic interviews.

The prevalence range for any anxiety disorder in pregnancy was between 4.4 and 39%, a range that related to the heterogeneity of the included studies (Goodman 2014).

The abovementioned meta-analysis by Dennis et al (2017) reported the overall prevalence of a diagnosis of any anxiety disorder was 15.2% in the antenatal period and 9.9% in the postpartum (between 1 and 24 weeks after birth). This indicates a high presence of these disorders in the perinatal period. Of the various anxiety disorders, they reported data only on GAD, which had an overall prevalence of 4.1% in the antenatal period and 5.7% in the postnatal.

One of the difficulties that arise when conducting meta-analyses is that studies that include different numbers of diagnoses and different subsets are combined. This suggests that estimating the prevalence of a diagnostic category by combining studies that differ in terms of the disorders included might underestimate the true prevalence. Fawcett et al (2019) propose a model that uses individual data from study participants to estimate the prevalence of each anxiety disorder and comorbidity between disorders. They used this model to perform a meta-analysis of the prevalence rates of perinatal anxiety disorders. They included 26 articles reporting the prevalence of one or more anxiety disorders in women during pregnancy or up to 12 months after delivery, diagnosed according to DSM-IV (American Psychiatric Association 1994) or ICD-10 (World Health Organization 1992) criteria through structured interviews. The diagnoses included were panic disorder, agoraphobia, obsessive–compulsive disorder, GAD, social phobias, specific phobia, post-traumatic stress disorder and anxiety not otherwise specified. Bayesian multivariate modelling estimated the prevalence of at least one anxiety disorder in pregnancy or postpartum at 20.7%, i.e. 1 in 5 women were diagnosed with a perinatal anxiety disorder. Regarding comorbidity, 1 in 20 women (5.5% of the total sample) presented criteria for at least two anxiety diagnoses. The most frequent anxiety disorders in this study were specific phobia, GAD and social phobia. Of note, substantial between-study heterogeneity was observed, suggesting that the 'true' prevalence varies broadly across samples (Fawcett 2019).

This information reinforces the idea that the prevalence of perinatal anxiety disorders is high, although it is still difficult to estimate the frequency of individual disorders. The available evidence suggests that GAD would be one of the most frequent ones, but the presence of excessive worries that is characteristic of GAD poses a difficulty when differentiating the disorder from expected worries about pregnancy and the postpartum period. Although the diagnostic criteria for GAD in DSM-5 (American Psychiatric Association 2013) include symptoms of at least 6 months duration, it has been suggested that presence of symptoms for at least 1 month be used in cases of perinatal onset (Misri 2015). This could allow for earlier diagnosis and prompt treatment, reducing the impact of untreated disorder. In addition to assessing the history of illness and conducting the appropriate diagnostic interview, it may be useful to apply the PRAQ-R2 questionnaire to detect pregnancy-related anxiety (see above) and differentiate it from general anxiety.

The clinical situation and issues that the diagnosis presents

In this section I examine the clinical situation in which a pregnant or postpartum woman presents with anxiety symptoms that affect her day-to-day functioning. Perinatal anxiety is common, perhaps more so than perinatal depression, and severe anxiety during pregnancy can affect outcomes and is a risk factor for postpartum pathology. In addition, there is a specific form of pregnancy-related anxiety (with excessive worry that could be confused with GAD) that, although it is not a DSM or ICD diagnosis, is sufficient to be detected and affects pregnancy outcomes. The recommendations for this clinical scenario include the possibility of using an initial screening tool such as a self-administered questionnaire and subsequently conducting a diagnostic clinical interview that allows the clinician to pinpoint the problem and determine proper treatment.

Self-report questionnaires for perinatal anxiety

There are many questionnaires that attempt to capture the presence of anxiety symptoms, but their validity in the perinatal population is not as widespread. A systematic review of anxiety self-report scales in pregnancy explored their psychometric properties and observed some symptoms and domains that could be useful in detecting antenatal anxiety and pregnancy-related anxiety (elevated levels of worry, symptoms of panic, fear of childbirth and excessive worries about the baby's health). This study also highlights the scarcity of quality studies evaluating the psychometric properties of these questionnaires in pregnant women (Sinesi 2019).

Among the self-report tools, the above-mentioned PRAQ-R2, the Edinburgh Postnatal Depression Scale anxiety subscale (EPDS-3A) and the Perinatal Anxiety Screening Scale (PASS) are proposed here, since they are freely accessible, widely used and validated in perinatal samples.

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The three-item Edinburgh Postnatal Depression Scale

The EPDS (Cox 1987) is one of the most widely used screening tools both in clinical practice and in research, and is validated in pregnancy and postpartum. Its three-item anxiety subscale (EPDS-3A) has been postulated as possibly useful in determining the presence of pathological perinatal anxiety. On this subscale, the items are 'I have blamed myself unnecessarily when things went wrong', 'I have been anxious or worried for no good reason' and 'I have felt scared or panicky for no very good reason' (maximum score 9). It has been shown to be adequate and practical in the detection of both probable antenatal and postnatal anxiety, with a cut-off score of ≥6 in the postnatal population (Matthey 2008) and ≥5 in the antenatal and postnatal population (Smith-Nielsen 2021).

The Perinatal Anxiety Screening Scale

The PASS was designed to detect a wide range of anxiety symptoms in the perinatal period, so it would be useful as a complement to the diagnostic interview. It consists of 31 items that explore 4 categories of anxiety symptoms evaluated in the past month: acute anxiety and adjustment; general worry and specific fears; perfectionism, control and trauma; and social anxiety. The total score is obtained by adding all item scores. It has demonstrated adequate sensitivity and specificity with a cut-off score of 26 points, and this score is recommended to differentiate between high and low risk of presenting an anxiety disorder (Somerville 2014).

Interviews for diagnosing anxiety disorders

Clearly, there are difficulties in diagnosing anxiety and perinatal anxiety disorders. The best way to screen for perinatal anxiety and detect the presence of anxiety levels that require a thorough diagnostic examination has not yet been established, although the trend is to consider a clinical diagnostic interview after any of the abovementioned screening tools (Ayers 2015).

In psychiatric practice, the gold standard is the clinical diagnostic interview conducted by a trained professional, such as the Mini-International Neuropsychiatric Interview (MINI) (Sheehan 1998). However, there are questions about the application of these criteria to the perinatal population, owing either to the overlap of symptoms with changes related to pregnancy or to the fact that the construct established for each anxiety diagnosis does not capture the problem in the perinatal period. Additionally, those criteria may not be met by all individuals with clinically significant anxiety (Ayers 2015). In this sense, for example, it has been suggested that adding to the diagnostic interview a question about the attribution of symptoms to the gestational state or the emotional state could provide greater consistency in the diagnosis of anxiety disorders, especially when screening for GAD (Matthey 2011).

Summary

If the clinical situation portrays a patient in the perinatal period with symptoms of anxiety and excessive worry related to this stage that interfere with her day-to-day functioning, the differentiation between pregnancy-related anxiety and perinatal anxiety disorders will present a challenge. If the patient has already been diagnosed with an anxiety disorder (past or current), the first orientation will be to consider a relapse of that disorder. If there is no previous diagnosis, anxiety as an adaptive response should be considered. If that can be ruled out and the symptoms are severe and persistent, the examination will have to be deepened. A search for pregnancy-related anxiety or the presence of anxiety disorders should be carried out, implementing any of the proposed screening tools and a diagnostic interview (Fig. 1).

Treatment of pregnancy-related anxiety and perinatal anxiety disorders

The complexity of these situations requires a careful evaluation that takes into account the clinical, social, ethical and legal context. An exploration of these aspects can be found in Wand (2014).

If the presence of expected adaptive anxiety has been ruled out, treatment options should be considered for pregnancy-related anxiety and anxiety disorders, as they can have an adverse effect on the mother and baby if they are not treated.

Pregnancy-related anxiety

Given that pregnancy-related anxiety has not yet been included as a DSM or ICD diagnosis, treatment recommendations are oriented towards a symptomatic approach. Guardino & Dunkel Schetter (2014) suggest emphasising education about childbirth and providing support before and after diagnostic procedures. They also propose a resilience-based approach in communicating with the patient and helping them to understand information about risks, which sometimes can be excessive and overwhelming for anxious pregnant women. To avoid generating additional anxiety, the clinician should try to give the patient a sense of control over outcomes and foster her ability to care for herself and her family.

There is currently no evidence on the use of benzodiazepines or antidepressants as a treatment for pregnancy-related anxiety. However, if anxiety

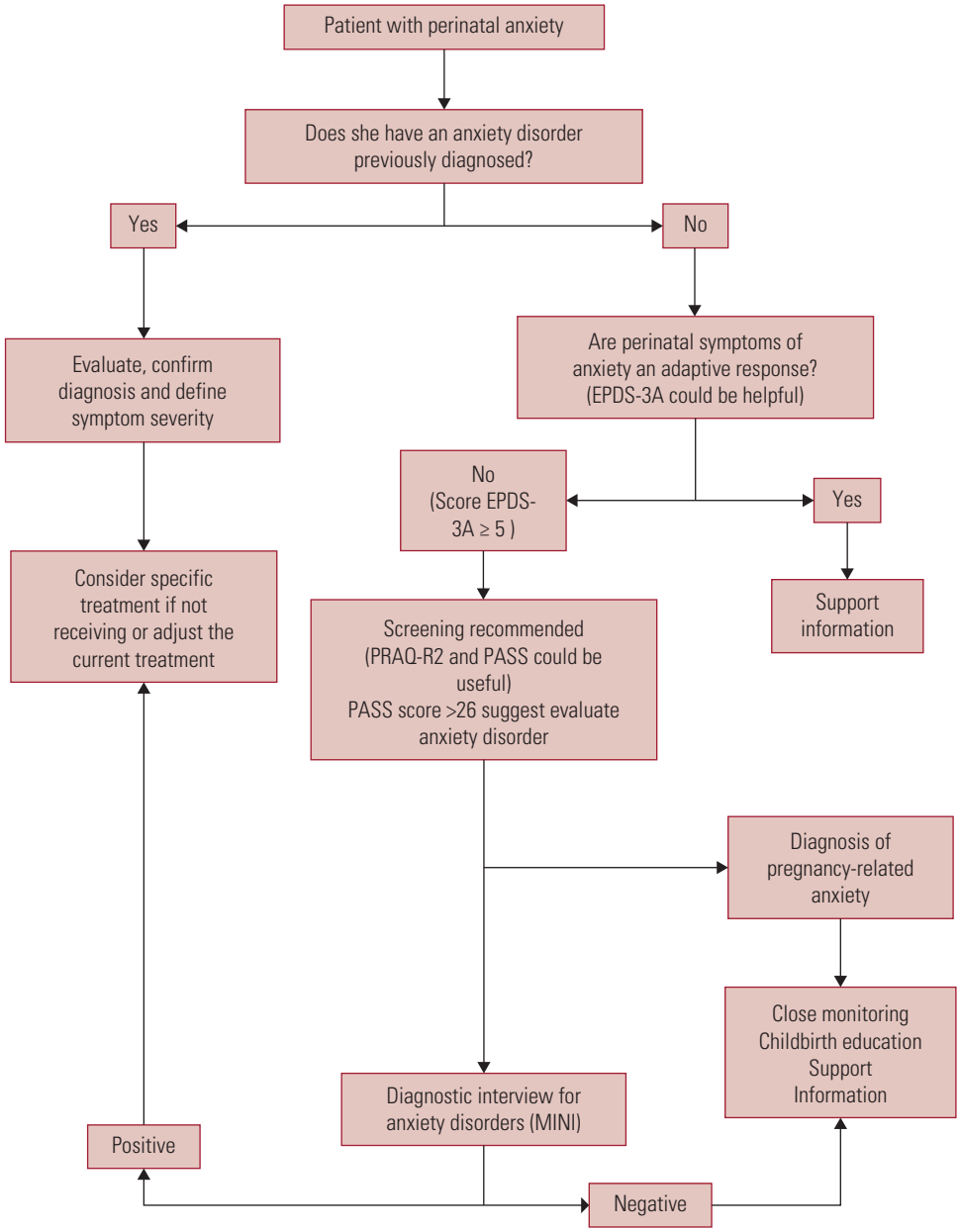

FIG 1 Suggested diagnostic sequence for differentiating between pregnancy-related anxiety and perinatal anxiety disorders. EPDS-3A, Edinburgh Postnatal Depression Scale three-item anxiety subscale; PRAQ-R2, Pregnancy-Related Anxiety Questionnaire revision 2; PASS, Perinatal Anxiety Screening Scale; MINI, Mini-International Neuropsychiatric Interview.

levels are disabling, the use of these psychotropic drugs (see below) could be considered symptomatically and in a limited way.

Perinatal anxiety disorders

The recommended first-line treatment for anxiety disorder diagnosed in pregnancy or postpartum is psychotherapy and especially cognitive–behavioural therapy (CBT) (Katzman 2014; Marchesi 2016), although there is not as much evidence in this population.

Regarding psychopharmacological treatment of diagnosed anxiety disorder, the drugs of choice for the general population are antidepressants and benzodiazepines (Katzman 2014). Here I will review selected data on their use in the perinatal period. It should be taken into account that these data come from observational studies, in which it is difficult to fully control the confounding effect of the underlying disease.

Antidepressants in pregnancy

The use of antidepressants during pregnancy has been extensively studied. The main evaluated risks are summarised in Box 2 and are reviewed in this section.

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BOX 2 Risks to the fetus of antidepressants in pregnancy

- Some data show a small increased risk of cardiovascular malformations, but the absolute number is low
- Preterm birth: inconsistent associations
- Poor neonatal adaptation syndrome (PNAS): difficult to define, but could be an event to take into account at the time of delivery in mothers exposed to antidepressants
- Persistent pulmonary hypertension of the newborn (PPHN): association possible in low absolute number
- Neurodevelopment: based on the evidence, it cannot be established that prenatal exposure to antidepressants is associated with a higher risk for developing autism spectrum disorders or attention-deficit hyperactivity disorder

One comprehensive review encompassed 29 cohort studies that included 9 085 954 births (Gao 2018). Overall, selective serotonin reuptake inhibitors (SSRIs) were associated with an increased risk of general congenital anomalies and congenital heart defects, but these associations lost statistical significance when observation was restricted to women with a psychiatric diagnosis (RR = 1.04, 95% CI 0.95–1.13 compared with RR = 1.06, 95% CI 0.90–1.26).

A recent meta-analysis investigated the increased risk of cardiac malformations associated with the use of antidepressants (De Vries 2021). The 20 included studies showed that the use of SSRIs in the first trimester increased the risk by 1.3 times and the use of serotonin noradrenaline reuptake inhibitors (SNRIs) increased it by 1.7 times, but it found no association with the use of tricyclic antidepressants. Analyses for individual SSRIs showed that paroxetine increased likelihood of congenital heart defects by approximately 1.6 times, followed by fluoxetine (1.4 times) and sertraline (1.3 times). In light of this finding and considering the available prescribing information, paroxetine should be avoided if possible during pregnancy (US Food and Drug Administration 2019). In contrast, a Danish register-based study that evaluated the same risk using data from both prenatal and postnatal diagnoses of cardiac malformations (pregnancies that had ended in abortion, neonatal death or babies who had received surgery in the first year of life) did not find a significant association with the use of SSRIs but with the use of the SNRI venlafaxine, although in a low absolute number (Kolding 2021).

Poor neonatal adaptation syndrome (PNAS) (also known as neonatal abstinence syndrome or postnatal adaptation syndrome, among other terms) is a variously defined condition that refers to the presentation of respiratory, digestive and neurological symptoms in newborns of mothers exposed to antidepressants during pregnancy. In general, it is self-limiting and requires no more than observation. It might be due to withdrawal or toxicity, and the frequency ranges between 0 and 30% (Betcher 2020). In defining and specifying symptoms, the problem arises with the diversity of outcomes and the numerous ways of measuring them. In a recent systematic review, it was found that babies exposed to SSRIs were at higher risk of having lower Apgar scores, feeding problems, breathing problems, tremors, hypoglycaemia and thermal dysregulation (which could be considered symptoms within PNAS) (Kautzky 2022). However, this exposure was also associated with a higher risk of preterm delivery, being small for gestational age and being admitted to an intensive care unit. The authors warn about the low quality of the included studies and the difficulty in combining the results because there is no agreement on how to define PNAS.

In a broader view, an umbrella review examined 22 meta-analyses including 1 175 720 women who used antidepressants in pregnancy and investigated 25 outcomes (Biffi 2020). The associations between exposure to antidepressants and outcomes were graded as 'convincing', 'highly suggestive', 'suggestive' or 'weak', depending on the strength and validity of the evidence. No association was graded as convincing, and only highly suggestive evidence was obtained for the association between antidepressant or SSRI exposure with the risk of preterm birth (<37 weeks), between SSRI use and the risk of respiratory distress, and between SSRI exposure in the first trimester of pregnancy and the risk of cardiovascular malformations. These findings suggest that these associations would not be supported by high-quality evidence, and that more prospective studies and comprehensive analyses of the evidence are needed.

Another reported association of antidepressant use in the perinatal period is an increased risk of persistent pulmonary hypertension of the newborn (PPHN), defined as a failure of normal relaxation in the fetal pulmonary vascular bed during fetal-to-neonatal circulatory transition. PPHN occurs shortly after birth, with varying degrees of severity, in approximately 0.6–1 infants per 1000 live births. Although the association is significant (OR = 2.5, 95% CI 1.32–4.73), the absolute risk is low (2.9–3.5 per 1000 live births) (Grigoriadis 2014). A recent meta-analysis found a similar association (OR = 1.82, 95% CI 1.31–2.54), being able to identify sertraline as the antidepressant with the lowest

risk of association with PPHN through a network meta-analysis (Masarwa 2019).

Regarding the possible effects of antidepressants on neurodevelopment, a recent meta-analysis of 18 studies explored the use of antidepressants (SSRIs or SNRIs) during pregnancy and the risk of autism spectrum disorders (ASD) and attention-deficit hyperactivity disorder (ADHD) in the offspring (Leshem 2021). It found an association between prenatal antidepressant exposure and the risk of ASD (OR = 1.42, 95% CI 1.23–1.65) and ADHD (OR = 1.26, 95% CI 1.07–1.49) in the offspring. However, similar associations with ASD (OR = 1.39, 95% CI 1.24–1.56) and ADHD (OR = 1.63, 95% CI 1.50–1.78) in the offspring were obtained in women exposed to antidepressants before pregnancy, suggesting confounding by indication. This study shows that the associations were not statistically significant even in mothers who were exposed to SSRIs or SNRIs before pregnancy and their babies were not exposed to those medications *in utero*. Thus far, based on the evidence, it cannot be established that prenatal exposure to antidepressants represents a higher risk for developing ASD or ADHD in offspring.

Benzodiazepines in pregnancy

The use of benzodiazepines is generally proposed as a symptomatic approach to anxiety. Currently available evidence does not show an association with an increased risk of congenital malformations. Some evidence has associated them with neonatal adaptation difficulties, such as respiratory distress and neurobehavioral changes (Betcher 2020). However, as it is a symptomatic approach, this type of medication may be useful during pregnancy, especially on an as-needed basis.

Antidepressants and benzodiazepines in breastfeeding

In general, antidepressants commonly used in the treatment of anxiety disorders (SSRI and SNRIs) are considered compatible with breastfeeding, as they have low passage into breast milk. However, there are some factors to be taken into consideration. If the mother has previously taken an antidepressant and had a good response to it, this would be the first choice, as it increases the chances of a good response to the first treatment attempt. If she was already receiving an antidepressant during pregnancy and it was effective, the idea would be to continue with it so as not to expose the baby to a new drug. If it is the beginning of treatment in the postpartum, among the SSRIs, sertraline and paroxetine are recommended, followed by citalopram and escitalopram, owing to their lower passage into breast milk. Venlafaxine and desvenlafaxine could also be used with caution (Anderson 2021).

If benzodiazepines have been used in pregnancy or previously, the same concepts apply as those mentioned for the use of antidepressants: the one that has shown efficacy or to which the baby has already been exposed is preferred. Benzodiazepines are excreted only in small amounts in breast milk, so their use could be compatible with breastfeeding. If treatment is beginning postpartum, lorazepam, alprazolam or clonazepam are suggested (Nishimura 2021).

Management guidelines for perinatal anxiety disorders

Case vignette: perinatal anxiety with a history of GAD

A 35-year-old woman in week 12 of her desired first pregnancy attends a psychiatric consultation. After her last obstetric check-up, she started to suffer from a sensation of tightness in the chest and shortness of breath when being home alone. She appears to be excessively worried about whether her pregnancy is going well, whether she will have a healthy baby and even if she will be a good mother. Moreover, she has feelings of tension and difficulty falling asleep. She cannot understand why she feels so bad if, according to the obstetric evaluation, everything is fine. Besides, she is concerned about the possibility of having symptoms of GAD, a condition that was diagnosed at the age of 25 and for which she was in treatment with sertraline for 3 years until complete remission. Although many of her concerns related to pregnancy could be considered as pregnancy-related anxiety, the presence of other symptoms and history allows establishing the diagnosis of GAD. The suggested treatment is to employ the same antidepressant that helped her before. She agrees to start treatment with sertraline 50 mg daily, and after 6 weeks she shows notable improvement with functional recovery.

The patient returns 15 days after giving birth to a healthy, full-term baby. In the 36th week of pregnancy, she decided to stop taking sertraline as she was feeling well. Now, she has difficulty breastfeeding since her baby cries constantly; she cannot calm him for more than a couple of hours after feeding. In the pediatric consultation, she is advised to breastfeed on demand. She does so day and night, but she feels exhausted, anxious and she fears she is doing things wrong. Her partner suggests asking the paediatrician about feeding options and the doctor recommends a combination of breastfeeding and bottle-feeding to ensure her some sleep time. The diagnosis is the relapse of her underlying disorder (GAD) related to postpartum and discontinuation of psychopharmacological treatment. The psychiatrist proposes that she recommences with sertraline as it is compatible with breastfeeding. The patient agrees and shows improvement after a few weeks of treatment.

In the above vignette the psychiatrist applied the following guidelines, which are applicable to anxiety disorders both in pregnancy and postpartum.

(1) Establish the diagnosis of anxiety disorder (Box 1 and Fig. 1).
(2) Assess the risk related to the disorder (course, clinical characteristics), considering its history

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BOX 3 Managing perinatal psychopharmacological treatment for anxiety disorders

If the patient is being treated with an antidepressant and gets pregnant:

- be aware that stopping antidepressants can increase risk of relapse
- minimise exposure to the fetus (e.g. changing the antidepressant or relapsing duplicates exposure).
- it is preferable to maintain the dose if she is in remission
- if possible, do not add another psychotropic (e.g. a benzodiazepine)

If a pregnant patient with a history of anxiety disorder is not on antidepressant treatment but has a relapse:

- try to use the same antidepressant that showed efficacy before (pregnancy is not the time for trying out alternatives, unless essential)

If a postpartum patient who wants to breastfeed:

- has a new-onset anxiety disorder, choose an antidepressant with the lowest passage into breast milk
- has a relapse of pre-pregnancy anxiety disorder, choose an antidepressant known to be effective before (if compatible with breastfeeding)
- has been using an antidepressant during pregnancy, it is recommended to keep it the same, since the baby has already been exposed to that drug
- if possible, avoid adding another psychotropic (e.g. a benzodiazepine)

and current state (severity of the illness, and risk of relapse in the postpartum).

(3) Define the need for treatment. If it is a first episode and there has been no previous diagnosis and pharmacological treatment, consider non-pharmacological treatment as the first option.

(4) If pharmacological treatment is indicated, evaluate the safety data of the antidepressant in pregnancy and breastfeeding.

For a quick reference on perinatal psychopharmacological management see Box 3. Online US information resources on the effects of medication on pregnancy and lactation include MotherToBaby (www.mothertobaby.org) and the LactMed® database (https://www.ncbi.nlm.nih.gov/books/NBK501922/).

Conclusions

Perinatal anxiety disorders are common, difficult to diagnose and have an impact on pregnancy outcomes. The possibility of ruling out adaptive anxiety responses and identifying pregnancy-related anxiety and anxiety disorders allows an approach to achieving optimum treatment for both the mother and baby. No exposure is risk-free, so the aim is to find the intervention with the lowest risk.

MCQ answers
1 e 2 c 3 b 4 e 5 b

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Declaration of interest

None.

References

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM-IV). American Psychiatric Publishing.

American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental* Disorders (5th edn) (DSM-5). American Psychiatric Publishing.

Anderson PO (2021) Antidepressants and breastfeeding. *Breastfeeding Medicine*, **16**: 5–7.

Ayers S, Coates R, Matthey S (2015) Identifying perinatal anxiety in women. In *Identifying Perinatal Depression and Anxiety: Evidence-Based Practice in Screening, Psychosocial Assessment, and Management* (eds J Milgrom, A Gemmill): 93–107. John Wiley & Sons.

Betcher HK, Wisner KL (2020) Psychotropic treatment during pregnancy: research synthesis and clinical care principles. *Journal of Women's Health*, **29**: 310–8.

Biffi A, Cantarutti A, Rea F, et al (2020) Use of antidepressants during pregnancy and neonatal outcomes: an umbrella review of meta-analyses of observational studies. *Journal of Psychiatric Research*, **124**: 99–108.

Blackmore ER, Gustafsson H, Gilchrist M, et al (2016) Pregnancy-related anxiety: evidence of distinct clinical significance from a prospective longitudinal study. *Journal of Affective Disorders*, **197**: 251–8.

Brunton R, Dryer R, Saliba A, et al (2019) Re-examining pregnancy-related anxiety: a replication study. *Women and Birth*, **32**(1): e131–7.

Cox JL, Holden JM, Sagovsky R (1987) Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry*, **150**: 782–6.

Dennis CL, Falah-Hassani K, Shiri R (2017) Prevalence of antenatal and postnatal anxiety: systematic review and meta-analysis. *British Journal of Psychiatry*, **210**: 315–23.

De Vries C, Gadzhanova S, Sykes MJ, et al (2021) A systematic review and meta-analysis considering the risk for congenital heart defects of antidepressant classes and individual antidepressants. *Drug Safety*, **44**: 291–312.

Dunkel Schetter C, Tanner L (2012) Anxiety, depression and stress in pregnancy: implications for mothers, children, research, and practice. *Current Opinion in Psychiatry*, **25**: 141–8.

Fawcett EJ, Fairbrother N, Cox ML, et al (2019) The prevalence of anxiety disorders during pregnancy and the postpartum period: a multivariate Bayesian meta-analysis. *Journal of Clinical Psychiatry*, **80**(4): 18r12527.

Gao SY, Wu QJ, Sun C, et al (2018) Selective serotonin reuptake inhibitor use during early pregnancy and congenital malformations: a systematic review and meta-analysis of cohort studies of more than 9 million births. *BMC Medicine*, **16**(1): 205.

Goodman JH, Chenausky KL, Freeman MP (2014) Anxiety disorders during pregnancy: a systematic review. *Journal of Clinical Psychiatry*, **75**: e1153–84.

Grigoriadis S, de Camps Meschino D, Barrons E, et al (2011) Mood and anxiety disorders in a sample of Canadian perinatal women referred for psychiatric care. *Archives of Women's Mental Health*, **14**: 325–33.

Grigoriadis S, Vonderporten EH, Mamisashvili L, et al (2014) Prenatal exposure to antidepressants and persistent pulmonary hypertension

of the newborn: systematic review and meta-analysis. *BMJ*, **348**: f6932.

Grigoriadis S, Graves L, Peer M, et al (2018) Maternal anxiety during pregnancy and the association with adverse perinatal outcomes: systematic review and meta-analysis. *Journal of Clinical Psychiatry*, **79** (5): 17r12011.

Guardino CM, Dunkel Schetter C (2014) Understanding pregnancy anxiety: concepts, correlates, and consequences. *Zero to Three*, **34**: 12–21.

Huizink AC, Mulder EJ, Robles de Medina PG, et al (2004) Is pregnancy anxiety a distinctive syndrome? *Early Human Development*, **79**: 81–91.

Huizink AC, Delforterie MJ, Scheinin NM, et al (2016) Adaption of pregnancy anxiety questionnaire-revised for all pregnant women regardless of parity: PRAQ-R2. *Archives of Women's Mental Health*, **19**: 125–32.

Katzman MA, Bleau P, Blier P, et al (2014) Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*, **14**(suppl 1): S1.

Kautzky A, Slamanig R, Unger A, et al (2022) Neonatal outcome and adaption after in utero exposure to antidepressants: a systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, **145**: 6–28.

Kolding L, Ehrenstein V, Pedersen L, et al (2021) Antidepressant use in pregnancy and severe cardiac malformations: Danish register-based study. *BJOG*, **128**: 1949–57.

Leshem R, Bar-Oz B, Diav-Citrin O, et al (2021) Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) during pregnancy and the risk for autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) in the offspring: a true effect or a bias? A systematic review & meta-analysis. *Current Neuropharmacology*, **19**: 896–906.

Marchesi C, Ossola P, Amerio A, et al (2016) Clinical management of perinatal anxiety disorders: a systematic review. *Journal of Affective Disorders*, **190**: 543–550.

Masarwa R, Bar-Oz B, Gorelik E, et al (2019) Prenatal exposure to selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors and risk for persistent pulmonary hypertension of the newborn: a systematic review, meta-analysis, and network meta-analysis. *American Journal of Obstetrics and Gynecology*, **220**: 57.e1–13.

Matthey S (2008) Using the edinburgh posnatal depression scale to screen for anxiety disorders. *Depression and Anxiety*, **25**(11): 926–31.

Matthey S, Ross-Hamid C (2011) The validity of DSM symptoms for depression and anxiety disorders during pregnancy. *Journal of Affective Disorders*, **133**: 546–52.

Merikangas KR, Kalaydjian A (2007) Magnitude and impact of comorbidity of mental disorders from epidemiologic surveys. *Current Opinion in Psychiatry*, **20**: 353–8.

Misri S, Abizadeh J, Sanders S, et al (2015) Perinatal generalized anxiety disorder: assessment and treatment. *Journal of Women's Health*, **24**: 762–70.

Nishimura A, Furugen A, Umazume T, et al (2021) Benzodiazepine concentrations in the breast milk and plasma of nursing mothers: estimation of relative infant dose. *Breastfeeding Medicine*, **16**: 424–31.

Rogers A, Obst S, Teague SJ, et al (2020) Association between maternal perinatal depression and anxiety and child and adolescent development: a meta-analysis. *JAMA Pediatrics*, **174**: 1082–92.

Sheehan DV, Lecrubier Y, Sheehan KH, et al (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, **59**(suppl 20): 22–57.

Sinesi A, Maxwell M, O'Carroll R, et al (2019) Anxiety scales used in pregnancy: systematic review. *BJPsych Open*, **5**(1): e5.

Smith-Nielsen J, Egmose I, Wendelboe KI, et al (2021) Can the Edinburgh Postnatal Depression Scale-3A be used to screen for anxiety? *BMC Psychology*, **9**(1): 118.

Somerville S, Dedman K, Hagan R, et al (2014) The Perinatal Anxiety Screening Scale: development and preliminary validation. *Archives of Women's Mental Health*, **17**: 443–54.

Steel Z, Marnane C, Iranpour C, et al (2014) The global prevalence of common mental disorders: a systematic review and meta-analysis 1980–2013. *International Journal of Epidemiology*, **43**: 476–93.

Sutter-Dallay AL, Giaconne-Marcesche V, Glatigny-Dallay E, et al (2004) Women with anxiety disorders during pregnancy are at increased risk of intense postnatal depressive symptoms: a prospective survey of the MATQUID cohort. *European Psychiatry*, **19**: 459–63.

US Food and Drug Administration (2019) *Prescribing Information: Paxil CR (Paroxetine) Extended-Release Tablets, for Oral Use*. FDA (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020936s047lbl.pdf).

Vesga-López O, Blanco C, Keyes K, et al (2008) Psychiatric disorders in pregnant and postpartum women in the United States. *Archives of General Psychiatry*, **65**: 805–15.

Wand APF (2014) Making decisions in the management of perinatal depression and anxiety. *Advances in Psychiatric Treatment*, **20**(3): 175–83.

World Health Organization (1992) *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. WHO.

MCQs

Select the single best option for each question stem

1 Clinicians should suspect that perinatal anxiety may be more than an expected reaction:
a if it persists over time
b if it interferes with everyday life
c if there is a history of diagnosed anxiety disorder
d if it coincides with a particular situation (e.g. initiation of breastfeeding, an ultrasound examination) and does not improve when the situation has passed
e all of the above.

2 Pregnancy-related anxiety (pregnancy-specific anxiety) is:
a a diagnosis included in the category of anxiety disorders in DSM-5
b the name given to the presence of generalised anxiety disorder during pregnancy
c a form of anxiety in pregnancy characterised by excessive worries about the baby's health and delivery, distinct from general anxiety and depression
d a normal reaction to pregnancy
e a form of perinatal anxiety that has no negative impact on the pregnancy or postpartum.

3 According to current research, the estimated prevalence of at least one perinatal anxiety disorder is:
a 2%
b 20.7%
c 34.3%
d 15%
e 51.8%.

4 Antenatal anxiety and anxiety disorders:
a are significantly associated with an increased risk of preterm delivery, low birth weight and being small for gestational age
b are a risk factor for postpartum anxiety
c are a risk factor for postpartum depression
d can negatively affect offspring's socio-emotional, cognitive and language development
e all of the above

5 A 30-year-old female patient currently on maintenance treatment with escitalopram 10 mg for GAD wants to get pregnant and asks about the risks posed by the medication she is taking. According to the available evidence, her clinician should inform her that:
a all antidepressants increase the risk of congenital malformations by 5 times
b the use of SSRIs during pregnancy is associated with an increased risk of poor neonatal adaptation syndrome (PNAS)
c the use of antenatal escitalopram is associated with an increased risk of ADHD in offspring
d antenatal use of SSRIs is not associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN)
e escitalopram cannot be used in postpartum, since it has a high passage into breast milk so she will not be able to breastfeed.