EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES

FOR PREVENTION, SCREENING AND TREATMENT OF PERIPARTUM DEPRESSION

SHORT-VERSION

cost
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EVIDENCE-BASED PRACTICE GUIDELINES FOR PREVENTION, SCREENING AND TREATMENT OF PERIPARTUM DEPRESSION
is available at:
https://www.riseupppd18138.com/clinical-practice-guidelines.html

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These guidelines were developed to support healthcare decisions, by guiding professionals on the evidence-based interventions to support shared decision-making between them and their patients. These are evidence-based guidelines, informed by a systematic review of the evidence and an assessment of the benefits and harms of different treatment and care options. Therefore, recommendations should be considered within the intervention protocols available in the literature, and to some extent described in the literature synthesis sections. However, recommendations, even when strong, might not apply to all circumstances and all patients. Also, some recommendations might reflect that there are difficulties in the accessibility and availability of psychological treatments or resistance of women to pharmacological or psychological treatments. Of note, clinical practice guidelines do not supersede clinical judgment in diagnosis and personalised care considering the specific circumstances of each patient.

Table of Contents

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A. Development of the guidelines

A. // Development of the guidelines

Scope of the guidelines

These guidelines aim to synthesise the current evidence concerning interventions to prevent, screen, and treat peripartum unipolar depression (PPD). The guidelines are targeting at healthcare professionals who, in their clinical practice, care for women planning pregnancy, pregnant women or women within the first year postpartum, in relation to their risk for depression, or those that currently have depression. Throughout this work, the term "women" is used. We acknowledge that there could be individuals other than those identifying themselves as women planning pregnancy or being pregnant; however, because all the evidence that was extracted in this work concerns women, we opted for using women when referring to pregnant people. Additionally, there is increasing evidence that PPD also can affect fathers. However, the evidence is still too sparse to develop recommendations about treatment of paternal PPD.

Why were these guidelines developed?

In order to prevent PPD and offer timely screening followed by appropriate treatment, it is crucial to have clinical practice guidelines to instruct on all these steps, from prevention, to screening, and treatment with different options. A recent systematic review of the guidelines for PPD in European countries (Motrico et al., 2022) found 14 clinical practice recommendations in 11 countries (Belgium, Denmark, Finland, Germany, Italy, Malta, Netherlands, Norway, Serbia, Spain, and the United Kingdom). From these, only five recommendations were rated with adequate methodological quality, including recommendations from Finland, The Netherlands, and three from the United Kingdom and, in general, the information of prevention was scarce. In addition, only one of these recommendations (the one from Finland) was published within the last five years. Also, none of the existing guidelines, including the one published in 2023 by the American College of Obstetricians and Gynaecologists (ACOG)(«Screening and Diagnosis of Mental Health Conditions During Pregnancy and Postpartum», 2023; «Treatment and Management of Mental Health Conditions During Pregnancy and Postpartum», 2023), specifically focus on PPD. Considering that PPD is the most prevalent mental health disorder in the peripartum period, and given the large amount of new evidence in this field, up-to-

date evidence-based guidelines on preventing, screening and treatment of PPD are still needed.

The COST Action Research Innovation and Sustainable Pan-European Network in Peripartum Depression Disorder (Riseup-PPD) has pursued several lines of action (Fonseca et al., 2020) over the past four years. One of these lines was to identify clinical practice guidelines for the management of PPD and to tackle the remaining gaps in the field. The absence of specific guidelines for PPD management in European countries might lead to disparities in treating PPD across Europe and, consequently, to inequality for women with PPD. This is especially evident for recommendations on pharmacological treatment, given that recent synthesis of the European clinical practice guidelines (CPGs) for antidepressants and other psychotropic medication highlighted dissimilarities in the available recommendations and the need for evidence-based CPGs (Kittel-Schneider et al., 2022). As a result, we have developed this document by relying on the wealth of international evidence-based literature available. Additionally, we drew on the collective expertise of clinicians, researchers, ethicists, and women who have personally experienced PPD from various European countries.

Target users of the guidelines

These guidelines primarily target mental health professionals (MHP) (such as psychiatrists, psychologists, counsellors, psychosomatic medicine practitioners, and other MHPs), other healthcare professionals including midwives, obstetricians/gynaecologists, paediatricians, nurses, general practitioners, social workers, pharmacists, and others who play key roles in developing and implementing interventions for the prevention, screening, or treatment of PPD. Further targets for these guidelines also include politicians, economists, policy makers, and non-profit organisations, including patient organisations, who may be involved in decision-making about funding, developing and implementing interventions for preventing, screening, or treating PPD.

The interventions presented in these guidelines encompass a wide range of strategies, incorporating biological interventions such as pharmacotherapy and non-invasive brain stimulation, psychological and psychosocial interventions, and other non-conventional and complementary interventions in PPD.

Development of the recommendations

The development of the recommendations was based on the GRADE framework (Schünemann et al., 2013). This framework

offers a system for rating the quality of a body of evidence in systematic reviews and other evidence-synthesis documents, supporting the development of evidence-based recommendations. The evidence for each key question was synthesised and is presented in this document, in text and summary format.

To assess the quality of the evidence, the GRADE system's four levels (high, moderate, low and very low) were used. Two RU-GDG members for each study first rated the study up or down according to the factors that affect the quality of the evidence. According to the GRADE handbook, to rate the quality of the evidence downwards, five factors were considered: limitations in the study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision, and publication bias. Conversely, large magnitude of effects, adjustment for confounders, and presence of dose response gradient, were considered for increasing the quality of the evidence, if applicable.

Following the GRADE framework, two types of recommendations were used: strong recommendations and weak recommendations.

A strong recommendation is suggested when the RU-GDG finds strong evidence that desirable effects greatly overweight the undesirable ones. A weak recommendation is suggested when the RU-GDG is not absolutely certain of the balance between desirable and undesirable effects and the factors that support it, and therefore, increased caution is warranted.

Additionally, a Good Practice Point (GPP) may be added when there is a recommendation for best practice based on the experience of the RU-GDG.

Table 2. Types of recommendations that can be suggested

Strong recommendation for the intervention	Benefits clearly outweigh harms/risks. The great majority of patients will benefit from this intervention and therefore should receive it.
Weak recommendation for the intervention	There is some uncertainty regarding the balance between the benefits and harms/risks, although it is expected that some patients will benefit from this intervention. The benefit may be uncertain and will vary depending on patient characteristics and their values, preferences and personal circumstances. Additionally, contextual resources that determine the unavailability/ inaccessibility of higher quality interventions are considered. When an intervention is weakly recommended, special attention is recommended and should be dedicated in assuring tailored and shared decision-making between the healthcare professional and the patient to best support the healthcare decision that is most suitable to each patient
No recommendation	There is not enough evidence to make a recommendation.
Strong recommendation against the intervention	Harms/risks and burdens clearly outweigh the benefits. Most patients will not benefit from this intervention and therefore should not receive it.
Weak recommendation against the intervention	There is some uncertainty regarding the balance between t he benefits and harms/risks, and it is expected that only a few patients will benefit from this intervention. The benefit may be uncertain and will vary depending on patient characteristics and their values, preferences and personal circumstances. When an intervention is weakly recommended, special attention is recommended and should be dedicated in assuring tailored and shared decision-making between the healthcare professional and the patient to best support the healthcare decision that is most suitable to each patient.
Recommended in research setting	There is insufficient evidence to recommend the use (or no use) of the intervention, but there is great potential of research to reducing the uncertainty about the effects of the intervention at a reasonable cost
GPP	Recommendation for best practice based on the experience of the RU-GDG members

The recommendations will be presented with the following display and symbols:

Table 3. Example of the table of recommendations.

Overall recommendation	Strength of ecommendation	Quality of evidence	Comment
Text of the recommendation.	Strong or Weak	High ⊕⊕⊕⊕ Moderate ⊕⊕⊕◯ Low ⊕⊕◯◯ Very Low ⊕◯◯◯	A comment providing additional information regarding the recommendation.

B. Introduction

B. // Introduction

Definition, prevalence, impact and cost of peripartum depression

Definition of peripartum depression

Peripartum depression (PPD) is formally defined as an episode of unipolar major depressive disorder (MDD) with onset during pregnancy or within four weeks after childbirth (American Psychiatric Association (APA)., 2013). However, several studies in this field show that it can occur up to one year postpartum (Gavin et al., 2005; Gelaye et al., 2016) so, for the purpose of this document, the RU- GDG adopted the broad definition of PPD including pregnancy and postpartum up to one year after childbirth. The symptoms of PPD are supposed to be similar to those in depression outside the peripartum period. As described in the DSM-5 classification system, these include the core symptoms of "depressed mood" and "loss of interest or pleasure in nearly all activities", and at least three other symptoms of the following: changes in weight, sleep, loss of energy, psychomotor changes (agitation or retardation), feelings of worthlessness or inappropriate guilt, impaired concentration, thought of death, or suicidal ideation. These symptoms should last at least two weeks and should give significant distress or impairment in important areas of functioning (American Psychiatric Association (APA)., 2013).

Although PPD is not yet considered as an entity separate from MDD, increasing evidence makes a strong case for symptoms that are typical for PPD when compared to MDD. These symptoms include increased anxiety, psychomotor symptoms, obsessive thoughts, impaired concentration /decision-making, fatigue and loss of energy, and specific guilt about not being a good mother, but less sad mood and suicidal ideation, compared to MDD (Beck & Indman, 2005; Hoertel et al., 2015; Kettunen et al., 2014). Whether depression during pregnancy is distinct from postpartum depression is still understudied, but there is some evidence that they present with different symptoms (Batt et al., 2020; Di Florio & Meltzer-Brody, 2015). In addition, the literature suggests that the manifestation of PPD symptoms may differ across different cultures (Di Florio et al., 2017).

It is noteworthy to differentiate PPD from baby blues, which occurs in up to 50% of postpartum women during the first ten days postpartum (Chechko et al., 2023). Baby blues is not considered

a mental disorder due to its transient state, a non-debilitating condition, which therefore does not need additional professional interventions.

Prevalence and incidence

The prevalence of postpartum depression varies across countries and regions, and there are several factors that influence its occurrence. According to a comprehensive meta-analysis of postpartum depression conducted by Wang et al. (Z. Wang et al., 2021), including 565 studies from 80 different countries, the overall global prevalence rate is approximately 17.4%. In Europe the prevalence of moderate-to-severe depressive symptoms by region is diverse. During pregnancy, this rate ranges from 3.5% in Northern Europe, to 4.9% in Western Europe, and 5.9% in Eastern Europe. During postpartum, it ranges from 3.3% in Northern Europe to 5.8% in Eastern and 6.1% in Western Europe.

The use of different assessment instruments might have influenced the prevalence rates of postpartum depression found. The Postpartum Depression Screening Scale (PDSS) resulted in the highest prevalence rate of 37.2%, while the Structured Clinical Interview for DSM Disorders (SCID) had the lowest prevalence rate of 10.1%. The Edinburgh Postnatal Depression Scale (EPDS) was the most used diagnostic tool, with a prevalence rate of 16.9%.

Sample size of the pooled studies may also influence the reported prevalence rates of postpartum depression. Overall, studies with more than 1,000 participants had lower prevalence rates (13.0%) compared to studies with fewer than 1,000 participants (19.4%).

The global prevalence of postpartum depression also varied across different time periods after childbirth, being higher in the first 1-3 months (17.7%), followed by 3-6 months (15.3%), 6-12 months (18.2%), and greater than 12 months (18.0%).

Another influential predictor found by Z. Wang et al. (2021), was country development level. Interestingly, developed countries or high-income areas displayed lower rates of postpartum depression. Furthermore, the prevalence of postpartum depression was influenced by cultural variations, diverse reporting practices, different viewpoints on mental health issues, the stigma surrounding mental health, socioeconomic class, poverty, limited access to social services, deficient nutrition, elevated stress levels, and biological factors.

Prevalence of depression during pregnancy has been also extensively studied. According to recent systematic review and meta-analysis (Yin et al., 2021), the pooled prevalence of any type of depression during

pregnancy across 173 studies was found to be 20.7%, with a pooled prevalence of major depression being 15.0%. Globally, high-income countries showed a prevalence rate of depression during pregnancy of 8.1%, and in the European region it was 17.9%. When analysing different stages of pregnancy, the prevalence of depression was found to be 21.2% during the first trimester, 15.8% during the second trimester, and 18.9% during the third trimester.

Risk factors for PPD

The risk factors for PPD are often considered from the biological, psychosocial, and environmental domains («Screening and Diagnosis of Mental Health Conditions During Pregnancy and Postpartum», 2023). The major risk factors for antenatal depression are low socioeconomic status, unplanned pregnancy, history of mental disorders, and experience of violence (Míguez & Vázquez, 2021; Yin et al., 2021). Some of the above factors, but also history of premenstrual syndrome, variations of the 5-HTTLPR polymorphism, gestational diabetes, anaemia during pregnancy, preterm birth and operative delivery mode constitute risk factors for postpartum depression (Gastaldon et al., 2022; Hutchens & Kearney, 2020) While, on the other hand, a very sharp drop in hormones after birth is held partly responsible for postpartum depression, the hormonal changes during pregnancy are more gradual. An inverse relationship between oestradiol levels and monoamine oxidase A gene expression has been demonstrated in animal models, as well as MAO-A activity in a human PET study in the immediate postpartum period. These are the first indications of how the sharp drop in hormone levels after birth could contribute to the development of depression via increased degradation of monoamine neurotransmitters such as serotonin. There are still far fewer findings on pregnancy, as human studies during this period are even more challenging from an ethical perspective than in the postpartum period. The progesterone level, which rises 20-fold during pregnancy, also drops back to the level of the menstrual cycle a few days after birth (for an overview see Sacher et al., 2020). This too could possibly trigger fluctuations in the neurotransmitter balance and thus contribute to depressive symptoms, but there is no evidence on this yet.

The first studies that looked at structural changes in the brain during and after pregnancy focused on the pituitary gland as a control organ of the stress axis and performed regional analyses that

showed an increase in volume during late pregnancy and the first days after birth compared to early pregnancy and the later postpartum period. Whole-brain analyses demonstrated plasticity of grey matter volume after pregnancy. Comparison of structural data before delivery and before conception showed a significant decrease in brain size and an increase in ventricular size, while comparison of pre-birth images with those six months postpartum indicated an increase in brain and ventricular size. These dynamic and initially physiological changes could also contribute to the triggering of depressive symptoms in vulnerable women, but there are no data on this yet regarding pregnancy depression. There are several more potential biological risk mechanisms that have been shown to be associated with maternal postpartum depression, lower BDNF levels in the blood (Y. Lee et al., 2021), higher sensitivity to periportal progesterone/ allopregnanolone fluctuations (Rathi et al., 2022), history of premenstrual syndrome (PMS) (Hahn et al., 2021) and (hair) cortisol alterations (Stickel et al., 2021). Recent studies show a large genetic overlap with unipolar depression in general, but also differentially associated genes in PPD such as genes expressed in ovarian tissue. Identification of the neurobiological mechanisms of PPD would contribute to developing predictive biomarkers and revealing new prevention and treatment targets in the future (Kiewa et al., 2022).

Impact of PPD

Impact on mothers, children and the family

The literature has documented the negative impact of PPD on mothers and families (Rodriguez- Muñoz, et al. 2023). PPD affects the mother and her well-being with symptoms such as guilt, loss of interest in doing things, shame, irritability, or even suicidal ideation (Fonseca et al., 2020; Legazpi et al., 2022). In addition, the literature has identified how PPD is associated with adverse peripartum outcomes among which are smoking, substance abuse, and increased poor adherence to medical care routines (Marcos-Nájera et al., 2020; Slomian et al., 2019).

The literature has specified that children of mothers with symptoms of depression were more likely to have shorter gestation, a lower birth weight, lower Apgar score, or more time at the nursery (Aoyagi & Tsuchiya, 2019; Dowse et al., 2020; Slomian et al., 2019). Additionally, problems in mother-child interactions, including difficulties in bonding or breastfeeding, or problems

associated with the maternal role, seem to be more frequent in women presenting depressive symptoms (Höflich et al., 2022; Nakić Radoš et al., 2023; Slomian et al., 2019). In studies of older children, the consequences of maternal PPD to the offspring are emotional., behavioural, cognitive and language problems or special educational needs (Bauer et al., 2015; Slomian et al., 2019). Fathers also suffer from the effects of maternal postpartum depression. The impacts of maternal PPD on fathers have been linked especially to a higher risk of relational problems including low marital satisfaction, difficulties in coping with maternal emotions (D. Wang et al., 2021), and paternal depression (Thiel et al., 2020). In summary, there is a bulk of evidence showing the detrimental effects of maternal PPD for the mother, the infant, the partner, and the family as a whole.

Impact on the wider context/society

In addition to the consequences of PPD for the mother, the children and their family, it is important to note that PPD has significant economic costs to the society. In an economic report about the lifetime costs of PPD and anxiety, Bauer et al. (2016) examined the consequences and costs of anxiety and depression in women during pregnancy and 12 months after giving birth. The authors used a decision-modelling approach and adopted a lifetime perspective, meaning that the costs included expenses related to the mother and the child across life. Results highlight the elevated cost of the peripartum depression, with an estimated total cost of more than £75,000 (about €88,000 in 2023) per woman diagnosed. The authors identified that the majority of the costs were related not to the mother but to the adverse impacts on the child. Costs related to the mother are linked with health and social care expenses (which are especially borne by the public sector), loss of productivity, and health-related quality of life losses. Costs related to the child are linked with healthcare, developmental difficulties, and mental health and educational issues. This study highlighted the high cost of peripartum mental illness, and it is suggested that the actions undertaken to prevent depression during the peripartum are likely to be cost effective, especially for the public sector (Bauer et al., 2015).

C. Clinical practice recommendations: Summary list of recommendations

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#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Prevention of PPD				
Psychological and psychosocial preventive interventions				
1	Psychological and psychosocial interventions are strongly recommended for preventing PPD among pregnant and postpartum women at-risk for developing PPD, as well as among pregnant and postpartum women with no symptoms and no known risk factors.	Strong	Moderate ⊕⊕⊕◯	While there is moderate evidence on psychological and psychosocial interventions, there is no information about cost-effectiveness of these interventions, so this should be taken into account when deciding on preventive implementations.
2	Psychological interventions are weakly recommended to prevent PPD among women with sub-clinical depressive symptoms.	Weak	Low ⊕⊕◯◯	The recommendation is weak, based on the lack of evidence on the effectiveness of preventive interventions in women with subclinical symptoms. Although offering preventive interventions may have positive effects, it is uncertain whether it is efficient in preventing PPD in women with subclinical symptoms. Only one systematic review and meta-analysis examined the effectiveness of PPD preventive interventions for women with sub-clinical depressive symptoms and their findings were inconclusive.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Psychopharmacological preventive interventions				
3	It is not recommended to use antidepressant medication for prevention of postpartum depression in women with previous depression.	Strong	Low ⊕⊕◯◯	There is limited evidence available to support initiating antidepressants after delivery for prevention of postpartum depression.
4	It is not recommended to use antidepressants for prevention of depression during pregnancy.	Strong	Very Low ⊕◯◯◯	There is no evidence available to support the efficacy of antidepressants for prevention of antenatal depression.
Dietary supplements preventive interventions				
5	We have no recommendation on use of dietary supplements to prevent PPD.	No recommendation		There is no evidence supporting the effect of dietary supplements in preventing PPD.
Physical activity based preventive interventions				
6	Physical activity is weakly recommended to prevent PPD among pregnant and postpartum women from the general population.	Weak	Moderate ⊕⊕⊕◯	The participants in the literature that was examined were not assessed for risk factors. There are populations that may have medical conditions to which physical activity may be harmful
Interventions for screening for PPD				
Screening programmes for the general population				
7	Screening programmes for depression during pregnancy and in the postpartum period are strongly recommended.	Strong	Moderate ⊕⊕⊕◯	Due to ethical considerations, screening should be implemented as long as appropriate diagnosis, treatment and follow-up can be ensured.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Screening programmes for high-risk women				
8	Screening programmes for the presence of risk factors for vulnerability to PPD are weakly recommended.	Weak	Very low ⊕◯◯◯	Screening women is important after receiving information on how to interpret the screening results and which preventive interventions can be offered.
Interventions for treating PPD				
Psychological treatment				
9	Cognitive-behavioural therapy (CBT) is strongly recommended for the treatment of depressive symptoms during pregnancy and postpartum.	Strong	High ⊕⊕⊕⊕	Most women find psychological treatment acceptable and were satisfied. The major advantage is that for most women, any undesirable effects will probably be trivial, and no adverse effects for pregnant women, mothers and foetus/ infants are expected.
10	Third wave CBT therapies, including behavioural activation and mindfulness techniques, are weakly recommended for the treatment of depressive symptoms during pregnancy and postpartum.	Weak	Low ⊕⊕◯◯	There is a lack of information about acceptability and satisfaction with third-wave CBT therapies. However, undesirable and adverse effects for pregnant women, mothers and foetus/ infants are not expected.
11	Interpersonal therapy (IPT) is weakly recommended for the treatment of depressive symptoms during pregnancy and postpartum.	Weak	Low ⊕⊕◯◯	There is a lack of information about acceptability and satisfaction with IPT However, undesirable and adverse effects for pregnant women, mothers and foetus/ infants are not expected.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Pharmacological treatment				
Pregnancy				
12	Antidepressant medication in pregnancy is strongly recommended, after careful consideration of individual risk-benefit ratio for each woman and her unborn child. The decision-making about antidepressant intervention should consider the history of depression recurrence and severity of symptoms, previous response to the intervention, and individual preference.	Strong	Low ⊕⊕◯◯	There is no evidence available from systematic reviews and meta-analyses on the efficacy of antidepressant intervention in pregnancy. There is moderate evidence on the reproductive safety of antidepressants in pregnancy on maternal and offspring outcomes. Individual risk-benefit assessment of the intervention is needed for each woman, but antidepressant medication should be considered in women with moderate to severe depressive symptoms or after non-response to non-pharmacological interventions.
13	Women with severe and/or recurrent depression are strongly recommended not to discontinue the antidepressant medication during pregnancy due to the increased risk of relapse.	Strong	Low ⊕⊕◯◯	Evidence supports the elevated risk of relapse of the depression with discontinuation of the intervention, particularly in cases of severe or recurrent depression.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
18	It is strongly recommended that clinicians provide information to women about the possible risks of antidepressant exposure in pregnancy on maternal-child health versus the potential risks posed by maternal depression.	Strong	Moderate ⊕⊕⊕◯	Both maternal depression and the antidepressant intervention in pregnancy can increase the risk of multiple negative health outcomes in mother-child pairs. Women must be informed about both sets of risks in order to make informed clinical decisions about their antidepressant treatment. However, there are no data about interventions informing or not informing women about potential risks and benefits of medication vs untreated PPD.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
19	It is strongly recommended that all women under antidepressant interventions and their offspring should be closely monitored during pregnancy, as well as delivery being in a specialised obstetric centre with neonatal intensive care unit.	Strong	Moderate ⊕⊕⊕◯	There is an elevated risk of poor neonatal adaptation at birth in infants prenatally exposed to antidepressant intervention as well as in mothers with depressive disorders in general, which supports the recommendation to deliver in a specialised obstetric centre.
Postpartum				
20	It is strongly recommended to treat depression during the postpartum period with antidepressant medication, after careful consideration of individual risk-benefit ratio for each woman and her child if breastfed. The decision-making about antidepressant intervention should consider the history of depression recurrence and severity in the woman, previous response to the intervention, and individual preference as well as the health condition of the breastfed child.	Strong	Low ⊕⊕◯◯	Few data are available about the efficacy of antidepressant intervention in postpartum. However, as opposed to reproductive safety data about antidepressants in pregnancy, there is substantially less data about the short- and long-term safety of children exposed to antidepressant while breastfed. However, the risk of untreated depression and the benefits of breastfeeding on those negative outcomes needs to be weighed in each woman and child individually. In case a woman does not breastfeed, there is weak evidence of the effectiveness of antidepressant treatment for postpartum depression, however, there is also no risk to the child to be considered.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
21	It is strongly recommended to use brexanolone for moderate to severe postpartum depression treatment if available and if accepted as a treatment option by the woman.	Strong	Moderate ⊕⊕⊕◯	The strong recommendation is based on the clinical effectiveness of this intervention. However, it must be considered that few aspects may affect its use : (i) need of inpatient care, which may be less acceptable for women, due to the possibility of separation of the newborn; (ii) breastfeeding cessation for 3 days, which also may affect women's acceptability of the intervention; (iii) the very high cost, making the intervention less accessible than others; (iv) there is scarcity of evidence on the safety of brexanolone exposure via breast milk on the infant. Brexanolone is currently not licensed In Europe. Therefore, although brexanolone is strongly recommended for moderate to severe cases of depression, its use requires careful discussion between the woman and her HCP.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Non-invasive Brain Stimulation interventions				
Repetitive transcranial magnetic stimulation (rTMS)				
Pregnancy				
22	rTMS is weakly recommended for the treatment of mild to moderate depressive symptoms.	Weak	Very Low ⊕◯◯◯	rTMS might be beneficial and risks of adverse effects for the woman or the foetus are unlikely. The evidence on its effectiveness is very low. Our recommendation considers that in clinical settings where it might be difficult to access psychological treatments or there is resistance of women to pharmacological or psychological interventions, rTMS could be an alternative treatment, if accessible and available, for women with mild to moderate depressive symptoms.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Postpartum				
23	rTMS is weakly recommended for the treatment of mild to moderate depressive symptoms in the postpartum period.	Weak	Low ⊕⊕◯◯	rTMS might be beneficial and risks of adverse effects for the mother or the breastfed child are unlikely. The evidence on its effectiveness is low. Our recommendation considers that in clinical settings where it might be difficult to access psychological treatments or there is resistance of women to pharmacological or psychological interventions, rTMS could be an alternative treatment, if accessible and available, for women with mild to moderate depressive symptoms in postpartum.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Transcranial direct current stimulation (tDCS)				
Pregnancy				
24	Transcranial direct current stimulation (tDCS) is weakly recommended for the treatment of mild to moderate depressive symptoms in pregnant women.	Weak	Low ⊕⊕◯◯	tDCS might be beneficial and risks of adverse effects for the mother or the foetus are unlikely. The evidence on its effectiveness is low. Our recommendation considers that in clinical settings where it might be difficult to access psychological treatments or there is resistance of women to pharmacological or psychological interventions, tDCS could be an alternative treatment, if accessible and available, for women with mild to moderate depressive symptoms during pregnancy.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Postpartum				
25	There is not enough evidence to make a recommendation regarding the use of tDCS in the treatment of depression for women in the postpartum.	No recommendation		There is one single case study reported in a systematic review showing the efficacy of tDCS in reducing depressive symptoms in a postpartum woman. For this reason, although no harmful effects are expected to occur in the postpartum, the RU-GDG considered that there is not enough evidence on the efficacy of tDCS in women in the postpartum. Therefore, we cannot yet make a recommendation.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Q3.3.3 Electroconvulsive therapy (ECT)				
Pregnancy				
26	ECT is strongly recommended for the treatment of therapy-resistant or life-threatening severe depression in pregnant women. The treatment should take place under strict obstetrical monitoring.	Strong	Very Low ⊕◯◯◯	ECT is a relatively fast-acting option in severe cases of depression during pregnancy and despite the moderate risks of adverse effects (for the mother and the foetus) and pregnancy/ delivery complications, the benefits seem to outweigh the adverse effects if women did not respond to previous regular treatment or in need of urgent treatment due to life-threatening situations. Therefore, ECT is strongly recommended and should be offered within specialised hospitals to women presenting severe depression (with or without psychotic features) which did not respond to previous regular treatment or in need of urgent treatment due to life-threatening situations.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Postpartum				
27	ECT is strongly recommended for the treatment of therapy resistant or life-threatening severe depression in the postpartum period.	Strong	Very Low ⊕◯◯◯	ECT is a relatively fast-acting treatment that seems to be beneficial in severe cases of postpartum depression. Risks of adverse effects (prolonged seizures due to co-administered medication and transient memory loss particularly after the first ECT sessions) are small. ECT should be offered within specialised hospitals to women presenting severe depression (with or without psychotic features) which did not respond to previous regular treatment or in need of urgent treatment due to life-threatening situations.
Bright light therapy (BLT)				
Pregnancy				
28	There is no evidence on the efficacy of BLT in pregnancy, therefore we cannot make a recommendation.	No recommendation		There are no systematic reviews and meta-analyses available supporting the efficacy of BLT in reducing depressive symptoms in pregnant women.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Postpartum				
29	There is no evidence on the efficacy of BLT in postpartum, therefore we cannot make a recommendation.	No recommendation		There are no systematic reviews and meta-analysis available supporting the efficacy of BLT in reducing depressive symptoms in postpartum women.
Complementary and alternative treatment interventions				
Physical activity				
Pregnancy				
30	Physical activity is weakly recommended for the treatment of mild to moderate depressive symptoms in otherwise healthy pregnant women.	Weak	Very Low ⊕◯◯◯	Physical activity might be beneficial for otherwise healthy women and risk for the foetus is unlikely. Our recommendations are based on very low quality of evidence available for women with uncertain severity of depressive symptoms and assuming good physical health.
Postpartum				
31	Low-to-moderate intensity physical activity is weakly recommended for the treatment of mild to moderate depressive symptoms in postpartum as it might be beneficial, and no risks of adverse effects are reported.	Weak	Low ⊕⊕◯◯	Physical activity might be beneficial for otherwise healthy women and risks for newborn is unlikely. Our recommendations are based on low to moderate quality of the evidence available for women with uncertain severity of depressive symptoms. In these conditions, supervised and specialised physical activity could be an accessible alternative treatment for women with mild to moderate depressive symptoms during the postpartum.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Yoga				
Pregnancy				
32	Yoga is weakly recommended for the treatment of mild to moderate depressive symptoms as it might be beneficial, and no risks of adverse effects are reported.	Weak	Low ⊕⊕◯◯	Yoga might be beneficial for otherwise healthy women and risk for the foetus is unlikely. Our recommendations are based on low quality of the evidence available for women with uncertain severity of depressive symptoms.
Postpartum				
33	There is no evidence on the efficacy of yoga in postpartum, therefore we cannot make a recommendation.	No recommendation		There are no systematic reviews available supporting the efficacy of yoga in reducing depressive symptoms in postpartum women.
Massage				
Pregnancy				
34	Massage is weakly recommended for the treatment of mild to moderate depressive symptoms during pregnancy.	Weak	Low ⊕⊕◯◯	This recommendation is based on low quality evidence that showed positive effects in the reduction of depressive symptoms in pregnant women. Effects found were of moderate size and risk for the foetus is unlikely.
Postpartum				
35	There is no evidence on the efficacy of massage in postpartum, therefore we cannot make a recommendation.	No recommendation		There are no systematic reviews and meta-analysis supporting the efficacy of massage in reducing depressive symptoms in postpartum women.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Music therapy				
Pregnancy				
36	There is no evidence on the efficacy of music therapy during pregnancy, therefore we cannot make a recommendation.	No recommendation		There are no studies supporting the efficacy of music therapy in reducing depressive symptoms in pregnant women.
Postpartum				
37	There is no information on the effectiveness of music therapy as a stand-alone treatment. Music therapy is weakly recommended as an additive intervention when combined with other interventions (such as psychological treatment, Chinese medicine or pharmacotherapy) for the treatment of mild to moderate depressive symptoms as it might be beneficial, and no risks of adverse effects are reported.	Weak	Low ⊕⊕◯◯	Music therapy might be beneficial in addition to other treatments. Our recommendations are based on low quality of the evidence available for women with uncertain severity of depressive symptoms.
Peer support				
Pregnancy				
38	There is no evidence on the efficacy of peer support in pregnancy, therefore we cannot make a recommendation.	No recommendation		There is only one single study supporting the efficacy of peer support in reducing depressive symptoms in pregnant women.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Postpartum				
39	There is no evidence to support a recommendation regarding traditional face-to-face peer support. Technology-based peer support is weakly recommended for the treatment of mild to moderate depressive symptoms in the postpartum period.	Weak	Very Low ⊕◯◯◯	Peer support that was assessed in the literature refers to peers which are women with lived experience of PPD. Technology-based peer support might be beneficial and risks of adverse effects are unlikely.
Chinese herbs				
Pregnancy				
40	There is no evidence on the efficacy of the use of Chinese herbs in pregnancy, therefore we cannot make a recommendation.	No recommendation		There are no studies available supporting the efficacy and reproductive risks of Chinese herbs in reducing depressive symptoms in pregnant women.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Postpartum				
41	Chinese herbs alone and in combination are weakly recommended for the treatment of mild to moderate depressive symptoms in the postpartum period.	Weak	Low ⊕⊕◯◯	There is evidence that specific Chinese herbs might be beneficial as a stand-alone treatment and also in combination treatment (with antidepressants) and have low risks of acute adverse effects, in women who are not breastfeeding. A special caution is made for the specific Chinese herbs that also contain of St John's wort, because in combination with other antidepressants, it might cause serotonine syndrome.
Acupuncture				
Pregnancy				
42	There is no evidence on the efficacy of the use of acupuncture in pregnancy, therefore we cannot make a recommendation	No recommendation		Evidence about the efficacy of acupuncture during pregnancy is inconsistent.
Postpartum				
43	There is no evidence on the efficacy of the use of acupuncture in the postpartum, therefore we cannot make a recommendation	No recommendation		Evidence about the efficacy of acupuncture in the postpartum is inconsistent.

#	Recommendation	Strength of the recommendation	Quality of the evidence	Comments
Fatty acids				
44	Fatty acids are weakly recommended for the treatment of mild to moderate depressive symptoms in pregnancy and in the postpartum period.	Weak	Low ⊕⊕◯◯	Fatty acids might be beneficial and low risks of adverse effects are reported.

D. Overview of the clinical recommendations

D. // Overview of the clinical recommendations

Below, we present three figures offering a schematic overview of the clinical recommendations for preventing, screening and treating PPD during pregnancy (Figure 1) and in the postpartum period (Figure 2).

Figure 1. Overview of the clinical recommendations for interventions during pregnancy

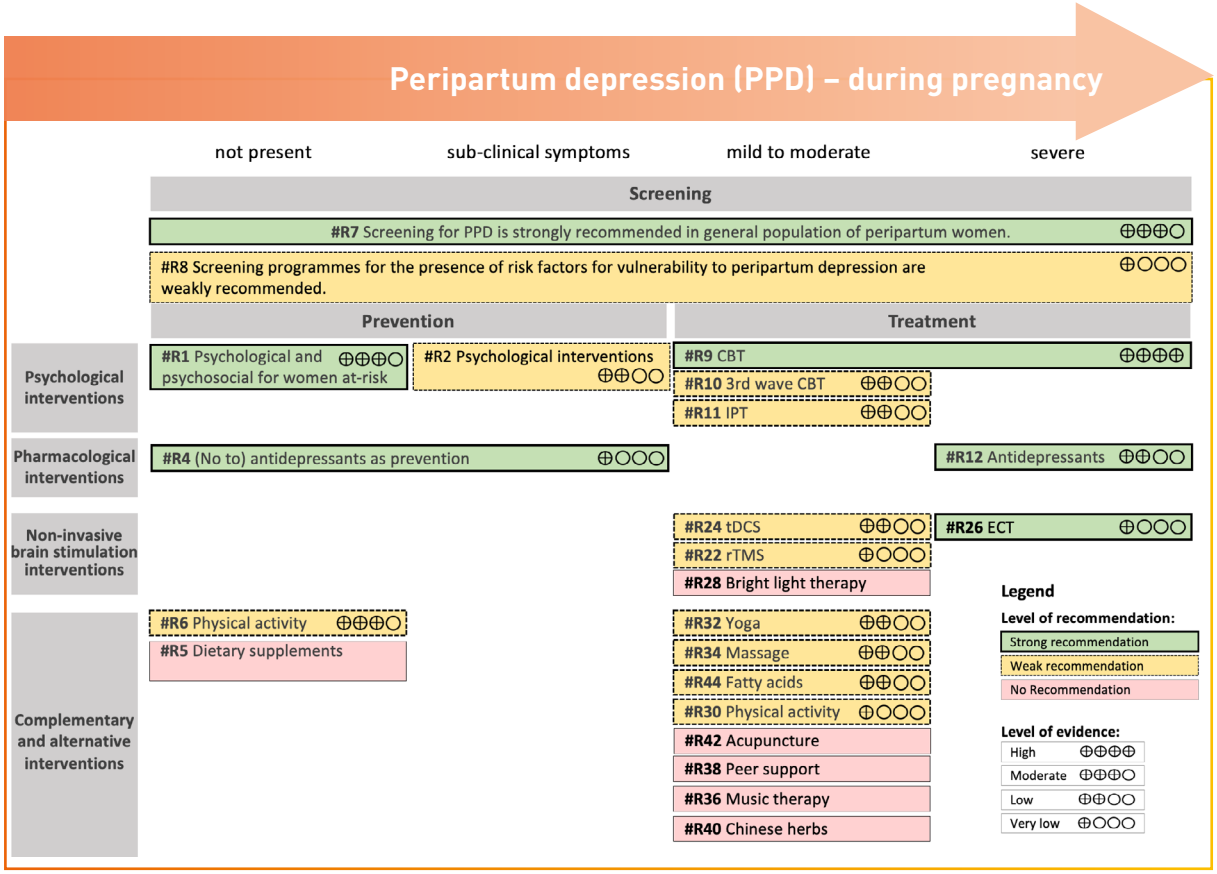
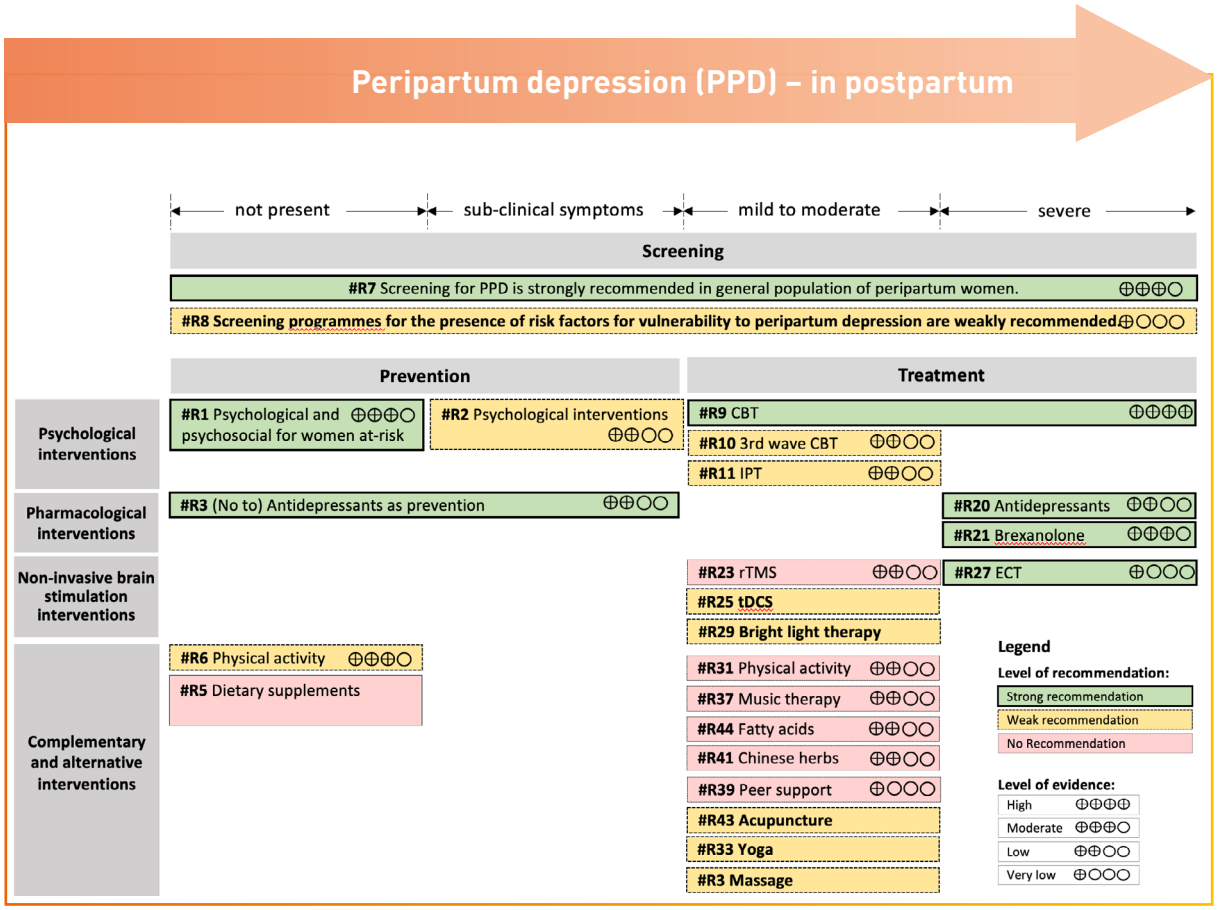
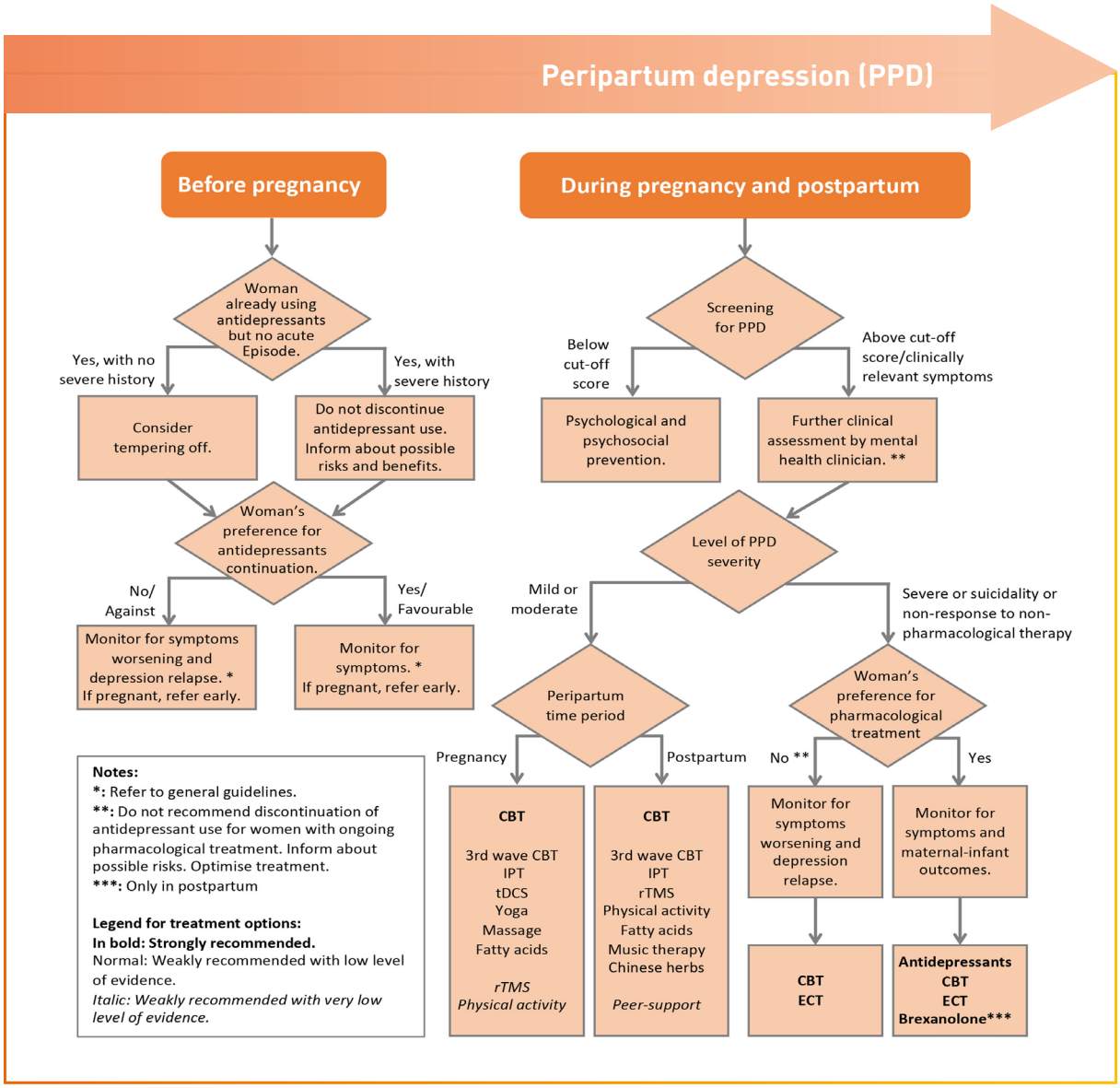


Figure 2. Overview of the clinical recommendations for interventions in the postpartum period



Below, we provide a decision flowchart for the management of PPD for women with or without previous depression who either plan pregnancy or are pregnant or in the postpartum period. Proposed interventions are based on the previously outlined recommendations. This flowchart provides a rationale for the management of PPD, but requires careful consideration of the specific country, context and setting where the interventions will take place.

Figure 3. Clinical pathway for managing PPD in clinical settings



E. Final remarks

E. // Final remarks

Our Evidence-based Clinical Practice Guidelines for the Prevention, Screening, and Treatment of PPD represent a subs—tantial advancement toward improved and high-quality peripartum mental health care. Nevertheless, their effectiveness per se is limited due to three overarching factors:

1) disparities in existing knowledge and available data across countries and regions;

2) disparities in the availability of local resources for peripartum mental health care;

3) disparities of women contextual/social conditions.

Disparities in existing knowledge and available data are not restricted to global variations but also manifest within regions and individual countries, even inside Europe. These disparities add to the complex nature of addressing peripartum depression comprehensively. Despite our best efforts during the development of these Evidence-based Guidelines, we acknowledge that the landscape of peripartum mental health research and data availability is biased toward the accessible data, falling short to depict those not easily represented across studies (e.g., minorities, immigrants, people living in conflict areas). Recognising such intra-regional and intra-national disparities is essential for understanding the limitations of the current work and being sensitive to fully accommodating the unique features, circumstances and needs of specific populations, into improved effective strategies for prevention, screening, and treatment of peripartum depression.

Additionally, disparities in the availability of local resources for peripartum mental health care further add to the challenge of addressing peripartum depression. Access to adequate healthcare services, trained and updated mental health professionals, and strong support networks can vary significantly from one community to another. These resource disparities create uneven opportunities in what concerns prevention, early detection, and adequate intervention and care for individuals experiencing peripartum depression. To ensure that every woman receives the care and support she needs during this critical period, policy-makers and health managers need to work toward minimising these resource gaps, aiming for equitable access to mental health services for all, regardless geographic location or socioeconomic status.

Furthermore, it is essential to acknowledge the disparities in contextual and social conditions experienced by women, which significantly influence their vulnerability to peripartum depression. Women's experiences and challenges during pregnancy and the postpartum period can vary greatly based on factors such as socioeconomic status, access to education, employment opportunities, and social support networks. Additionally, cultural norms and societal expectations exert considerable pressure, affecting women's mental well-being. Such contextual and social disparities underscore the need for a comprehensive approach to mental health in pregnancy and postpartum that not only addresses clinical aspects but also takes into account these societal and cultural factors that contribute to the increased risk of peripartum depression.

Recognising and addressing these three overarching factors and the disparities each entail, is fundamental to ensure that all women receive the comprehensive care and support they need during this critical phase of their lives, ultimately impacting at least two generations at once.

Appendix 1. The Guidelines Development Group

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EUROPEAN COOPERATION
IN SCIENCE & TECHNOLOGY

Funded by
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RISEUP-PPD
Research Network
in PeriPartum
Depression Disorder