

Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <http://orca.cf.ac.uk/111157/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Meltzer-Brody, Samantha, Howard, Louise M., Bergink, Veerle, Vigod, Simone, Jones, Ian, Munk-Olsen, Trine, Honikman, Simone and Milgrom, Jeannette 2018. Postpartum psychiatric disorders. Nature Reviews Disease Primers 4 , 18022. 10.1038/nrdp.2018.22 file

Publishers page: <http://dx.doi.org/10.1038/nrdp.2018.22> <<http://dx.doi.org/10.1038/nrdp.2018.22>>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



1 **Postpartum Psychiatric Disorders**

2

3

4 **Samantha Meltzer-Brody¹, Louise M Howard², Veerle Bergink³, Simone Vigod⁴, Ian Jones⁵,**
5 **Trine Munk-Olsen⁶, Simone Honikman⁷, Jeannette Milgrom⁸**

6

7 ¹ The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

8 ² Kings College, London, United Kingdom

9 ³ Department of Psychiatry and Department of Obstetrics, Gynecology and Reproductive Medicine,
10 Icahn School of Medicine at Mount Sinai, New York

11 ⁴ University of Toronto, Toronto, Canada

12 ⁵ National Centre for Mental Health, MRC Centre for Neuropsychiatric Genetics and Genomics,
13 Division of Psychological Medicine, Cardiff University, Wales, United Kingdom

14 ⁶ Aarhus University, Aarhus, Denmark

15 ⁷ University of Cape Town, Cape Town, South Africa

16 ⁸ Parent-Infant Research Institute and University of Melbourne, Victoria, Australia

17

18 **Acknowledgements**

19 We would like to thank Dr. Alan Gemmill from Parent-Infant Research Institute and Holly Krohn
20 from the University of North Carolina at Chapel Hill for their contributions to the preparation of this
21 manuscript.

22

23

24 **Competing interests**

25 S.M-B. has received research grant support to The University of North Carolina at Chapel Hill from
26 Sage Therapeutics and Janssen. L.M.H. is funded through a National Institute for Health Research
27 (NIHR) Professorship in maternal mental health (NIHR-RP-R3-12-011). V.B. is supported by NWO
28 (VENI 91616036 and Clinical Fellowship 90715620) and the EMC fellowship. IJ is a trustee of
29 Action on Postpartum Psychosis and the Maternal Mental Health Alliance and is supported through
30 the National Centre for Mental Health grant from Health and Care Research Wales. All other
31 authors declare no competing interests.

32

33

34 **Author contributions**

35 Introduction (S.M-B. and all co-authors); Epidemiology (T.M-O.); Mechanisms/pathophysiology (I.J.
36 and S.M-B.); Diagnosis, screening and prevention (L.M.H., S.H. and J.M.); Management (S.V. and
37 V.B.); Quality of life (J.M.); Outlook (All); Overview of Primer (S.M-B.).

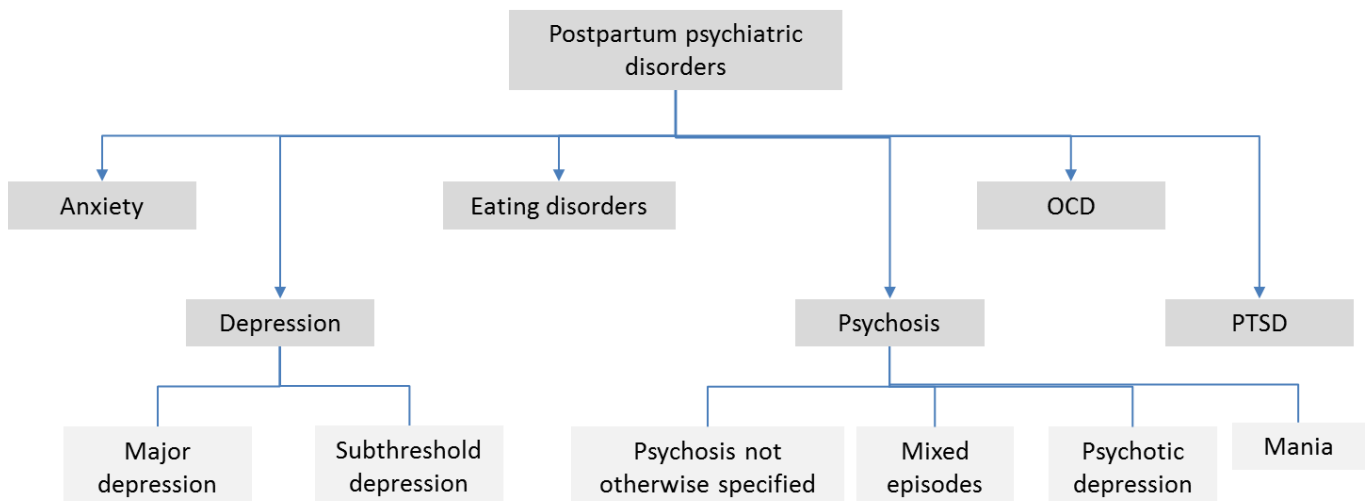
38 **Abstract**

39 Pregnancy is a complex and vulnerable period that presents a number of challenges to women,
40 including the development of postpartum psychiatric disorders (PPDs). These disorders can include
41 postpartum depression and anxiety, which are relatively common, and the rare but more severe
42 postpartum psychosis. In addition, other PPDs can include obsessive–compulsive disorder, post-
43 traumatic stress disorder and eating disorders. The aetiology of PPDs is a complex interaction of
44 psychological, social and biological factors, in addition to genetic and environmental factors. The
45 goals of treating postpartum mental illness are reducing maternal symptoms and supporting
46 maternal-child and family functioning. Women and their families should receive psychoeducation
47 about the illness, including evidence-based discussions on risks and benefits of each treatment
48 option. Developing effective strategies in global settings that allow the delivery of targeted therapies
49 to women with different clinical phenotypes and severities of PPD is essential.

50
51

52 **[H1] Introduction**

53 Pregnancy and the first year after childbirth (which collectively can be referred to as the perinatal
54 period) is arguably one of the most transformative times in a woman’s life. This timeframe is also a
55 complex and vulnerable period that presents a number of challenges for women. In particular, an
56 increased risk for onset or worsening of psychiatric illness including mood disorders, anxiety
57 disorders and psychosis exists during the first three months postpartum. All types of psychiatric
58 disorders can occur during the postpartum period, with many chronic disorders starting before
59 pregnancy and persisting throughout pregnancy into the postpartum period¹. In this Primer, we
60 focus specifically on the postpartum psychiatric disorders (PPDs). Collectively, the postpartum
61 psychiatric disorders (PPDs) can include postpartum depression, which is relatively common;
62 common anxiety disorders such as generalized anxiety disorder (GAD; which can include anxieties
63 about the health of the baby); post-traumatic stress disorder (PTSD; which can occur due to a
64 traumatic childbirth experience or can reflect pre-existing symptoms due to previous traumas
65 before conception or during pregnancy); and the rarer, but usually severe presentation of
66 postpartum psychosis. Other PPDs include eating disorders (which can worsen or recur
67 postpartum, particularly when the infant is undergoing weaning), and obsessive–compulsive
68 disorder (OCD)



69

70

71 In pregnancy, depressive and anxiety disorders are common with recent population estimates of
72 11% for depressive disorders and 15% for anxiety disorders.² Further, antenatal anxiety and
73 depression are one of the greatest risk factors for postpartum psychiatric disorders (PPD).³
74 Inadequate social support and a history of adverse life events increases the risk for PPDs in all
75 countries and levels of society^{4, 5}. However, this risk is increased in poorer socioeconomic
76 populations and lower income countries, due to poverty and limited access to health care.⁶

77 In recent years, awareness of the potentially serious adverse consequences in both the mother
78 and the baby associated with untreated perinatal psychiatric illness has increased. Maternal
79 suicide due to postpartum mood disorders (including unipolar and bipolar depressive disorders) is
80 a leading cause of maternal mortality.^{7, 8, 9} In addition, perinatal mood disorders are associated with
81 an increased risk for low birth weight and premature birth, impaired mother-infant attachment, and
82 infant malnutrition during the first year of life^{10, 11}.

83 In this Primer, we focus on maternal PPDs, as they are common, morbid, and have a growing
84 literature on the underlying pathophysiology. These disorders should not be confused with the so-
85 called 'baby blues', which are usually described as transient mild mood and anxiety symptoms that
86 often persist ≤ 2 weeks and usually resolve spontaneously with no sequelae.¹² If the symptoms of
87 the 'baby blues' worsen and/or persist, they are considered PPDs. Herein we discuss the
88 epidemiology of PPDs, and their underlying mechanisms and pathophysiology. We mainly focus on
89 maternal PPDs, although paternal disorders are mentioned in some instances (Box 1). Importantly,
90 we review the latest evidence on diagnosis, screening and prevention as well as management of
91 PPDs. Lastly, we hope to put in context the public health impact of these disorders on mothers,
92 their children and families to encourage wide scale adoption of strategies that make maternal
93 mental health a global priority¹³.

94

95 **[H1] Epidemiology**

96 Data on the incidence of postpartum depression are from studies conducted in countries across
97 the world, and variable incidence and prevalence are reported between countries¹⁴. By
98 comparison, studies estimating the incidence and prevalence of postpartum psychosis are
99 primarily carried out in Europe¹⁵, and demonstrate less variability in reported incidence and
100 prevalence^{16, 17}. Several methodological factors have influenced these differences. ¹⁸ For example,
101 particularly for postpartum depression, the definition of the postpartum period is variable between
102 studies, and has been defined as up to 4 weeks, 3 months, 6 months or 12 months postpartum¹⁹.
103 Differences in study designs, such as using different tools to define case-groups and phenotypes
104 can lead to variability in the reported number of cases. Data sources for postpartum depression
105 and postpartum psychosis include self-reports and interviews, in addition to some population-
106 based register data¹⁶. Moreover, the incomplete availability of longitudinal data that is needed to
107 distinguish between first-time and recurrent psychiatric episodes might impede calculations of the
108 true incidence and prevalence of PPDs. Consequently, a variation in reported incidence and
109 prevalence could be explained by differences in methodologies between studies, which make
110 direct comparisons difficult. In addition, the diverse symptoms of PPDs pose specific challenges to
111 the estimation of prevalence and incidence of these disorders²⁰.

112 As the literature surrounding the epidemiology of PPDs continues to grow with well-designed
113 studies, we will have a better understanding of if differences in the incidence and prevalence of
114 postpartum depression and postpartum psychosis are due to local/regional and national
115 differences, or if the differences are due to variable study designs and data sources. This
116 knowledge will assist hypothesis generating that might provide clues for the aetiology of these
117 disorders.

118

119 **[H2] Mood disorders and anxiety**

120 Postpartum depression, comprising major depressive disorder and subthreshold depression, has
121 an estimated point prevalence of 13% in high-income countries¹¹, and ~20% in low-income and
122 middle-income countries, 3 months postpartum (Box 2)²¹. In women with a history of any eating
123 disorder, the prevalence of postpartum depression has been estimated at 35%²². Studies of
124 postpartum depression often rely on self-reported questionnaires, including the commonly used
125 Edinburgh Postnatal Depression Scale (EPDS)^{14, 23}.

126 Although the prevalence estimates for postpartum mood disorders ranges between studies,
127 guidelines are available that state that these disorders pose substantial public health risks and
128 consequently, must be identified and treated^{24,25}. Moreover, there is consensus that childbirth is a
129 strong and potent risk factor for bipolar disorder. Indeed, the risk of underlying bipolarity in first-
130 onset depression that occurs in the postpartum period is higher than in first-onset depression that
131 occurs outside the perinatal period. In addition, women with bipolar disorder have a high risk of
132 postpartum episodes, including depression, anxiety, mania and psychosis^{26, 27}.

133 The estimated prevalence of postpartum anxiety disorders is ~10%, with a prevalence of 6% for
134 GAD²⁸. Anxiety disorders have substantial comorbidity with postpartum depression and other
135 disorders, including postpartum PTSD, eating disorders and the exacerbation of personality
136 disorders¹⁷.

137

138 [H2] Postpartum psychosis

139 The onset of a severe mental disorder requiring acute inpatient psychiatric treatment in the first
140 postpartum months is ~1 per 1,000 births²⁹⁻³², and are considered some of the most severe forms
141 of illness in psychiatry¹⁸. These severe psychiatric disorders that have an onset in the immediate
142 postpartum period are often called postpartum psychosis, which is an umbrella term for disorders
143 recorded as, for example, mania, mixed episodes, psychotic depression, or psychosis not
144 otherwise specified³³

145 http://journals.sagepub.com/doi/abs/10.1177/0004867414564698?url_ver=Z39.88-
146 [. Women with bipolar
147 disorder have the highest risk for postpartum psychosis than women with other psychiatric
148 diagnosis, as the risk for postpartum relapse in women with bipolar disorder is on average 37%¹⁸.
149 However, variations also occur within bipolar disorder, as the risk of a severe episode \(ie
150 postpartum psychosis\) is greater for women with bipolar I disorder than women with bipolar II
151 disorder³⁴. Additionally, the risk of symptom recurrence is particularly high for women with bipolar
152 disorder who are not receiving medication during pregnancy¹⁸ .](http://journals.sagepub.com/doi/abs/10.1177/0004867414564698?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&)

153 Relapse of psychosis can also occur in women with other psychiatric disorders, such as women
154 with schizophrenia, although this is less common³⁵ (~16% within the first 12 months postpartum)
155 Yes—it has been added now. <https://www.ncbi.nlm.nih.gov/pubmed/19188541> , and manifests
156 differently from what is observed in women with bipolar disorder¹⁶.

157 Despite the widespread use of the term postpartum psychosis, this diagnosis is not recognized in
158 current classification systems, including both ICD-10 and DSM-5³⁶. However, it is clear that
159 psychotic episodes are more prevalent during the postpartum period than in other periods in a
160 woman's life, and evidence clearly suggests a particular vulnerability in women with bipolar
161 disorder²⁹.

162
163 In women with severe postpartum psychiatric illness, maternal suicide is often a predominate
164 concern. Although maternal suicide is a leading cause of maternal mortality⁷, the rates of
165 completed suicide in postpartum women are lower than those in age-matched women without
166 children³⁷. Nonetheless, the prevention of maternal suicide is paramount and requires careful
167 monitoring during the postpartum period and possibly extending beyond the first year. For
168 example, one study demonstrated that most postpartum suicides occurred between 9 and 12

169 months postpartum and that the perinatal suicides were by highly lethal means (such as via
170 firearm), suggesting that limiting follow-up to 1, 3 or 6 months postpartum might be insufficient.³⁸

171

172 **[H1] Mechanisms/pathophysiology**

173 As previously mentioned, childbirth is one of the most potent triggers of psychiatric illness. Given
174 that postpartum mental health disorders are one of the few occurrences in psychiatry whereby a
175 biological trigger occurs at a known time point, elucidating the pathophysiology of these disorders
176 may shed light on the mechanisms of mood and psychiatric disorders more broadly, and is vital for
177 developing new treatment approaches.

178 The aetiology of all psychiatric disorders, including PPDs, is a complex interaction of psychological,
179 social and biological factors, including the effect of genetic and environmental influences on risk
180 (Figure 1)¹². The involvement of particular combinations of aetiological factors differs between
181 specific PPDs³⁴; for example, biological factors might have a greater role in the triggering of
182 postpartum psychosis, whereas psychosocial factors might have an important contribution in
183 postpartum depression.³⁴ These are areas of intense investigation and future research is needed to
184 extend our understanding of the many ways that psychological and biological processes interface.
185 Stopping or changing medications in women with a prior history of psychiatric disorders due to
186 concerns about the safety of medication during pregnancy could be considered a simple
187 explanation for the triggering of PPDs. However, continuing medication in pregnancy is protective
188 against mood disorders in a subset of patients³⁹. Similarly, discontinuation of medication does not
189 guarantee that a woman will relapse⁴⁰. However, there is much that is still not understood about
190 PPDs and the onset of PPDs reflects the outcome of many different pathways that manifest in
191 vulnerable women. Future research will need to disentangle the mechanisms of depression in
192 women before, during and after pregnancy to increase our understanding of the similarities and
193 differences between perinatal depression and depression occurring at other times in life. We will

194 next discuss current theories on psychosocial and biological contributions that increase risk for
195 PPDs.

196

197 ***[H2] Psychosocial factors and comorbidities***

223 Psychological and social stressors contribute to the development of maternal PPDs and are
224 associated with poorer outcomes in the infants or children^{41, 42}. In particular, adverse life events
225 and a history of trauma have a greater prevalence in women that develop postpartum mood
226 disorders, compared with mood disorders outside of the perinatal period^{4, 43, 44}. A history of
227 adverse early life experiences can substantially affect a mother's ability to have a strong
228 attachment with her infant⁴⁵, and adverse parent–infant interactions and worse attachment are
229 associated with development of PPDs⁴⁶⁻⁴⁸.

230 Social support has a vital role in either contributing to or mitigating the impact of postpartum mood
231 disorders on both the mother and child⁴⁹. Indeed, social support, or the degree of tangible support
232 provided from the social network of the mother and from the partner (such as financial support or
233 assisting with infant care), have the greatest effects on postpartum depression⁵⁰.

234

235 Other psychosocial risk factors include a past history of a mood disorder, which is consistently
236 associated with an increased risk of postpartum depression and postpartum psychosis³⁴. In
237 addition, although the strength of the association between risk factors and PPDs is variable
238 between high-income countries and low-income and middle-income countries, one of the strongest
239 psychosocial risk factors in both settings is domestic violence and previous abuse, including abuse
240 during childhood.^{4, 51} Other risk factors with a medium to strong association with PPDs include
241 marital difficulties, migration status and antenatal depression or anxiety^{17, 52}. In addition, poverty,
242 young age (between 14 and 21 years of age), substance misuse, increased parity, multiple births,
243 an unwanted pregnancy, neuroticism, pregnancy complications including obesity and comorbidities

244 (for example diabetes, hypertension and pre-eclampsia) and neonatal problems are associated with
245 PPDs¹⁷.

246

247 **[H2] Genetic factors**

248 Data from twin and adoption studies have implicated genetic factors in the aetiology of psychiatric
249 disorders outside of the perinatal period, including schizophrenia and mood disorders^{53, 54}.

250 However, only recently have genetic investigations, primarily of postpartum depression and
251 postpartum psychosis, been conducted.

252 Genetic epidemiological and linkage studies for postpartum depression have demonstrated the
253 involvement of genetic factors^{55, 56, 57} and two studies have demonstrated the increased heritability
254 of postpartum depression compared with depression outside of the perinatal period^{58, 59}. To date,
255 studies have suggested that episodes of postpartum psychosis are a marker for a more-familial
256 form of bipolar disorder and that the puerperal triggering of bipolar illness is familial.^{60, 61} However,
257 a genome-wide association study (GWAS) for either postpartum depression or postpartum
258 psychosis using modern genomics methods has not yet been carried out. Future genetic studies of
259 postpartum mood disorders using modern genomics methods will require international
260 collaborations and consortia to include large number of patients; these studies are currently
261 underway^{62, 63}.

262 Psychological stressors and early life adverse events have a lasting negative impact and can result
263 in pathophysiological changes and altered gene expression due to increased allostatic load (the
264 cumulative stress on the body that is a sum of lifetime exposure to stress)⁶⁴. Potential mechanisms
265 underlying how stressful life events change gene expression include epigenetic modification (such
266 as DNA methylation and histone modification that change DNA accessibility and chromatin
267 structure, subsequently regulating gene expression)⁶⁵, changes in transcriptional control of stress-
268 responsive pathways⁶⁶, and shortened telomere length^{67, 68}. Epigenetic alterations have been

269 reported in two genes, *HP1BP3* and *TTC9B*, which have different methylation patterns in women
270 with postpartum depression, depending on whether the mood symptoms begin during pregnancy
271 and continue into the postpartum period, compared with symptoms that develop postpartum only⁶⁹.
272⁷⁰. These data indicate that different gene patterns might arise based on the timing of symptom
273 onset. However, given the history of non-replication in many genetic studies, these findings require
274 replication and overall, the mechanism of action in postpartum depression remains to be
275 established.

276

277 **[H2] Sleep Disruption**

278 An almost universal feature of pregnancy and childbirth is disruption to sleep. In addition, sleep
279 and circadian rhythm disruption can trigger the onset of psychiatric disorders, particularly episodes
280 of mania in the postpartum period^{71, 72}. Thus, that circadian rhythm disruption has not received
281 more attention as a potential mechanism in PPDs is surprising.

282 Numerous studies have demonstrated profound changes in maternal sleep patterns during the
283 perinatal period. Pregnant women experience poorer subjective sleep quality, increased waking,
284 and more sleep-wake transitions than women who are not pregnant⁷³. In the postpartum period,
285 new mothers have frequent night waking, decreased night-time sleep, increased daytime napping,
286 and a more irregular sleep-wake schedule, which is speculated to increase the risk of PPDs⁷⁴. The
287 mechanisms underlying the reported disrupted maternal sleep patterns in the perinatal period have
288 been reported in two cross-sectional studies. The first study demonstrated a blunted melatonin
289 amplitude in postpartum women, compared with non-pregnant women,⁷⁵ and the second study
290 demonstrated differences in circadian rhythms between perinatal women with depression and
291 perinatal women without depression; indeed, in the second study, women with depression had
292 clinically-significant circadian rhythm phase shifts.⁷⁴ Further research is needed to better

293 understand the mechanisms of sleep disruption that might trigger PPDs and potential interventions
294 that target the circadian rhythm disruptions during the perinatal period⁷⁶.

295

296 ***[H2] Reproductive Hormones***

297 One important hypothesis for the aetiology of PPDs is based on the temporal onset of these
298 disorders immediately after childbirth, which is a time of major physiological change for women,
299 including alterations in hormonal systems. Multiple lines of evidence have demonstrated that
300 fluctuations in reproductive hormones (such as oestrogen and progesterone) during the perinatal
301 period are substantial contributors to the development of postpartum mood disorders in vulnerable
302 women. Gonadal steroid hormones (such as oestrogen and progesterone) are produced at very
303 high levels during pregnancy, but rapidly decrease to pre-pregnancy levels after childbirth. One
304 study simulated this pattern of hormone expression and demonstrated substantial mood symptoms
305 (such as sadness, anhedonia and anxiety) during the withdrawal period in five of eight women with
306 a history of postpartum depression, but in none of the eight women with no history of postpartum
307 depression⁷⁷. Thus, women who are vulnerable to postpartum psychiatric episodes might not have
308 gross abnormalities in endocrine physiology (such as no differences in the absolute levels of
309 hormones), but might have an abnormal response to the hormonal fluctuations of pregnancy and
310 childbirth.

311 Reproductive hormones have important functions in the central nervous system. Oestrogen and
312 progesterone receptors are expressed throughout the brain and can modulate neurotransmission
313 and neuroplasticity via both genomic and non-genomic mechanisms. For example, rodent studies
314 have shown that ovariectomy reduces and estradiol administration increases brain-derived
315 neurotrophic factor (BDNF) levels in the hippocampus and the forebrain⁷⁸; BDNF levels are
316 decreased by stress and depressive symptoms and are increased following treatment with
317 antidepressants⁷⁹. The rapid fall in oestrogen levels in the postpartum period might, therefore,

318 reduce BDNF levels and increase susceptibility to PPDs in women who are vulnerable. Similarly,
319 progesterone has an important role in regulating neurotransmitter synthesis, release and transport
320 ⁸⁰ and, has been shown to up-regulate BDNF expression in the hippocampus and cerebral cortex
321 in rodent models⁸¹.

322 The neurosteroid, allopregnanolone, which is a major metabolite of progesterone, might also have
323 an important role in the aetiology and, potentially, in the treatment of postpartum depression^{82, 83}.
324 Allopregnanolone is a positive allosteric modulator of synaptic and extrasynaptic GABA_A receptors⁸⁴,
325 ⁸⁵ and animal models have demonstrated that intravenous allopregnanolone administration
326 significantly reduces anxiety and depressive symptoms⁸⁶. Allopregnanolone concentrations reach
327 peak physiological levels during the third trimester of pregnancy and rapidly decrease following
328 childbirth^{87, 88}. The failure of GABA_A receptors to adapt to the rapid fluctuations in allopregnanolone
329 levels at childbirth is hypothesized to be a trigger for postpartum depression^{89, 90}. This line of inquiry
330 is being further explored by the development of brexanolone (a proprietary formulation of
331 allopregnanolone) as a treatment for postpartum depression^{91,92}.

332 Oxytocin is a neuroactive hormone that supports childbirth, lactation, maternal behavior, and social
333 bonding⁹³. Some studies have demonstrated an inverse association between circulating oxytocin
334 levels and postpartum depression⁹⁴ although other studies have not found this⁹⁵. The alterations in
335 the oxytocin system that occur during pregnancy and childbirth do not occur in isolation, and the
336 role of oxytocin in postpartum depression is likely to be complex and not accounted for by absolute
337 levels, similar to the roles of other neuroactive hormones ⁸³.

338 Further, recent neuroimaging data increases our understanding of the neurobiological basis
339 underlying perinatal mood disorders and the development of maternal behavior. Indeed, one study
340 demonstrated that the effects of a polymorphism in *BDNF* (*BDNF* Val⁶⁶Met) on hippocampal
341 function are selectively modulated by estradiol⁹⁶. This work lends further data to the importance of
342 the role of sex steroids on the regulation of behavioural functions associated with psychiatric

343 disorders, such as emotional processing, arousal, cognition, and motivation. Thus, it follows the
344 involvement of sex steroids of brain function could be revealed using neuroimaging. Indeed,
345 multiple cortical and subcortical brain regions have altered activity observed using functional MRI
346 or PET (such as, measurement of brain MAO-A⁹⁷) in mothers with depression, in response to infant
347 and non-infant emotional cues^{98, 99}. These alterations might impact important neuronal networks
348 that are associated with learned reward, reaction to stimuli, stress, motivation and executive
349 functioning. In addition, recent research from functional MRI studies shows distinct neurobiological
350 patterns that distinguish anxiety and depression occurring in the perinatal period, compared with
351 other times of a woman's life, and these patterns may have significant impact on the mother-infant
352 relationship¹⁰⁰.

353

354 **[H2] Other factors**

355 **[H3] Stress axis.** The postpartum period is a time of great flux for the HPA stress axis¹⁰¹. Indeed,
356 alterations in the hypothalamic–pituitary–adrenal (HPA) axis occur during pregnancy, such as
357 corticotropin-releasing hormone (CRH) production by the placenta, resulting in significantly
358 increased levels during pregnancy, which abruptly decline postpartum¹⁰², and rising levels of
359 gonadal steroids that contribute to puerperal hypertrophy of the pituitary and adrenal glands,
360 leading to increases in ACTH and cortisol levels¹⁰³. CRH fluctuations during the perinatal period
361 might trigger HPA axis dysregulation and contribute to the onset of depressive and anxiety
362 symptoms in a subset of vulnerable women¹⁰⁴; however, inconsistent findings have been
363 reported^{105, 106}.

364

365 **[H3] Thyroid hormones.** Thyroid hormones have been implicated in the development of
366 postpartum mood disorders. Thyroid binding globulin (TBG, which transports thyroid hormones in
367 the blood) concentrations increase during pregnancy and might be an index of sensitivity to

368 elevated oestrogen levels. Some data also suggest that decreased [Au:OK? YES] TBG levels are
369 a predictor of perinatal depression¹⁰⁷. In addition, first-onset postpartum autoimmune thyroid
370 disorders often co-occur with postpartum mood disorders¹⁰⁸. The occurrence of both disorders
371 coincides with the postpartum rebound phenomena of the maternal immune system, suggesting an
372 overlap in aetiology¹⁰⁹. Supporting this hypothesis, women with increased thyroid peroxidase
373 antibodies during pregnancy have an increased risk for postpartum psychiatric episodes^{109, 110}.
374 Accordingly, the assessment of thyroid function (such as measurement of thyroid-stimulating
375 hormone levels, tri-iodothyronine (T3) and tetraiodothyronine (T4)) is an essential part of diagnostic
376 evaluations in women with postpartum psychiatric episodes.

377

378 **[H3] Neuroimmune pathways.** Neuroimmune pathways might also have a role in the
379 pathophysiology of postpartum mood disorders^{101, 111-113}. The transition from pregnancy into the
380 postpartum period is characterized by an accelerated immune response (mediated through both
381 pro-inflammatory and anti-inflammatory mediators for healing and involution) during labor that
382 continues into the early postpartum period¹¹⁴. Consequently, immune changes at the end of
383 pregnancy might predict postpartum depression. IL-6 levels are increased in women with
384 postpartum depression compared with postpartum women who do not have depression in some,
385 but not all studies.^{112,115} However, leptin (a protein hormone made by adipose cells that regulates
386 energy and has inflammatory functions) might also be associated with postpartum depression.
387 Indeed, decreased maternal serum leptin levels during delivery are associated with a higher risk for
388 postpartum depression, and might potentially serve as a biomarker for postpartum depression¹¹⁵.
389 Lower levels of Clara cell protein (CC16, an endogenous anti-inflammatory compound) are
390 associated with PPD a few weeks later^{116, 117}. Furthermore, decreased levels of ω 3
391 polyunsaturated fatty acids (PUFAs) at the end of the third trimester are suggested to associate
392 with increased risk of PPD in the early postpartum period¹¹⁸. The underlying mechanism is
393 hypothesized to be increased peripheral inflammation¹¹⁸ owing to the anti-inflammatory effects of

394 ω 3 PUFAs. In summary, dysregulation of the crosstalk between the immune system and the HPA-
395 stress axis is hypothesized to be associated with the onset of postpartum depression^{101, 119}

396 Interestingly, first pregnancies are more often followed by psychiatric episodes than subsequent
397 pregnancies, which may illustrate the dysregulation of psychoneuroimmune systems. This effect is
398 hypothesized to be due to the biological differences between first and subsequent pregnancies,
399 and has raised the possibility of an aetiological link with other medical conditions that have a
400 similar increase in prevalence in first pregnancies such as pre-eclampsia¹²⁰. Intriguingly, pre-
401 eclampsia and postpartum psychosis are both associated with immune dysregulation, for example
402 the increased rates of postpartum autoimmune thyroiditis^{108, 109} and alterations in immune
403 biomarkers (such as, CNS autoantibodies) in women with postpartum psychosis¹²¹. In addition,
404 abnormalities in monocyte and T cell function and tryptophan breakdown has been demonstrated
405 in patients with postpartum psychosis or mania, compared with postpartum women without any
406 psychiatric symptoms.¹²² Patients with postpartum psychosis had monocytosis and failed to
407 demonstrate the physiological T- cell increase that is normally observed during the postpartum
408 period. These findings support the notion that immune system dysregulation contributes to
409 affective instability and severe postpartum episodes¹²².

410 Future studies are needed to extend our understanding of the ways in which psychological and
411 biological processes interact in PPDs. For example, social support might exert a stress-buffering
412 effect via the downregulation of stress responses, including inflammatory reactivity to stressors and
413 dampened sympathetic and hypothalamic-pituitary-adrenal (HPA) axis activity^{123, 124}.

414 **[H1] Diagnosis, Screening and Prevention**

415 As with all psychiatric disorders, the diagnosis of postpartum depression is reached by a
416 comprehensive clinical interview and diagnostic criteria that provide an operationalised definition of
417 the disorder, using classification systems such as the Diagnostic and Statistical Manual of Mental
418 Disorders, Fifth Edition (DSM-5)¹²⁵ or International Classification of Diseases, Tenth Edition

419 (ICD10)¹²⁶. Diagnostic criteria are similar across the DSM-5 and ICD-10, which are the two most
420 common classification systems; however, the DSM-5 uses the term 'depression with peripartum
421 onset' to refer to the onset of depression during pregnancy and into the first month postpartum,
422 whereas ICD10 does not use a primary code referring to the perinatal period, although a second
423 code denoting postpartum onset is available (which is not used in practice) . However, the
424 diagnosis of psychiatric disorders is more than a list of symptoms and the impact on symptoms of
425 functioning; diagnosis should also include an understanding of predisposing aetiological factors,
426 triggers and maintenance factors, which are elicited by a comprehensive biopsychosocial
427 assessment²⁴.

428 Postpartum depression is one of the most common postpartum psychiatric disorders, and can be
429 mild and relatively self-limiting lasting only a few weeks, or can be more severe, with severe
430 episodes potentially including psychotic symptoms¹⁷. Some symptoms of depression such as
431 fatigue, sleep disturbance and appetite disturbance need careful enquiry, as a woman with a baby
432 will be more tired than usual and have disrupted sleep (due to the baby needing a feed), although
433 appetite might not be affected as breastfeeding will stimulate appetite despite a low mood.

434 Checking whether the mother is able to sleep when the baby is asleep, whether the fatigue persists
435 after rest and the interest in food will help establish whether the symptoms are pathological and if
436 they are indicative of postpartum depression. Notably, anxiety might be a prominent symptom in
437 postpartum depression⁶³, or can be a symptom of a comorbid anxiety disorder¹²⁷. Diagnostic
438 assessment should evaluate a history of manic or hypomanic symptoms, as first-onset postpartum
439 depression can indicate underlying bipolar disorder²⁶. Diagnostic challenges include barriers to
440 disclosing symptoms due to stigma¹²⁸ and variations in the manifestation of symptoms, which might
441 reflect cultural or educational differences¹²⁹. In addition, it is important to ensure symptoms are not
442 due to an underlying medical condition such as thyroid disease or an early presentation of first
443 episode psychosis.

444 Although postpartum psychosis is not included as a primary diagnosis in the DSM-5 or ICD-10, this
445 disorder is still recognised clinically and is usually considered to be a severe mood disorder.¹⁶
446 Women with postpartum psychosis often have a history of bipolar disorder.¹⁶ Most women have
447 prodromal symptoms before the overt onset of postpartum psychosis; however, some women have
448 acute onset of severe symptoms^{130, 131}. Evaluation of women with postpartum psychosis includes
449 assessment of manic, depressed, anxious and psychotic symptoms, and the assessment of the
450 risk of causing harm to herself or her baby. Women with postpartum psychosis can present with
451 either low or high mood (both elation and irritability), or frequently can present with a mixed state,
452 including symptoms of both mania and ; a minority of women have an atypical symptom profile with
453 disorientation and/or disturbance of consciousness¹³². Symptoms can also manifest as delusions,
454 hallucinations, and particularly confusion and perplexity and patients can also have severe mood
455 swings, insomnia, agitation and rapid deterioration. Postpartum psychosis is usually a rapid onset
456 severe psychosis, typically starting within the first 2-4 weeks after birth, and is considered a
457 psychiatric emergency as a lack of self-care and an inability to care for the infant can lead to
458 suicide and/or, in rare cases, infanticide¹⁶. Accordingly, assessment should be carried out quickly
459 (for example, The National Institute for Health and Care Excellence (NICE) recommend
460 assessment within 4 hours of clinical presentation; in clinical practice this means within 24 hours of
461 the acute onset of severe psychiatric symptoms) to ensure the woman can be cared for safely and
462 appropriately. Excluding other medical disorders, such as cerebral space occupying lesions,
463 thyroid disorders or infections is important as part of the diagnostic work-up. In many cases the
464 mother's partner or family ask for psychiatric evaluation when the mother is irritated or agitated and
465 not aware that she is seriously ill.

466
467 Anxiety disorders (such as GAD and panic disorder), OCD and PTSD can all manifest in the
468 postpartum period. OCD is characterised obsessive thoughts. Obsessions are intrusive, repetitive
469 thoughts, images or impulses that are unacceptable and/or unwanted and give rise to subjective

470 resistance. By contrast, delusions that occur in psychotic disorders are fixed, false beliefs¹³³ that
471 need appropriate psychological intervention¹⁷. Postpartum OCD poses a particular diagnostic
472 challenge, as intrusive thoughts about harm befalling the infant (such as, what if I drop my infant or
473 I accidentally cut the infant with a knife when I'm cooking) might be perceived as delusional and
474 could lead to concerns about the safety of the infant. However, these thoughts are not associated
475 with actual direct harm and the obsessions remain very ego-dystonic and highly distressing to the
476 patient. Traumatic childbirth experiences can trigger PTSD, particularly in women with prior
477 histories of trauma¹³⁴. Differentiating the exacerbation of PTSD symptoms in women with past
478 trauma and new onset PTSD owing to traumatic childbirth is important¹³⁵. Past trauma history
479 should include assessment of prior childhood abuse, adult interpersonal or other violence, among
480 other forms of trauma. In addition, many women with PTSD or OCD present with symptoms of
481 anxiety and mood symptoms, making the diagnosis of any one particular disorder a challenge^{63, 136}.

482

483 Women with a previous history of psychiatric disorders will often experience a worsening of
484 symptoms during the postpartum period, although few studies have examined strategies to
485 mitigate this exacerbation of symptoms³⁹. For women without a prior history of psychiatric
486 disorders, the acute onset of psychiatric symptoms in the postpartum period is often highly
487 distressing. However, whether the first onset of psychiatric symptoms in the postpartum period
488 indicates the beginning of a more persistent and chronic mood disorder, or is a condition that will
489 be restricted only to the postpartum period is unclear. This is an important area for future study.

490

491 **[H2] Screening**

492 Screening for postpartum depression has attracted widespread interest from researchers, clinicians
493 and policy makers due to the high prevalence and associated sequelae in terms of maternal
494 morbidity and adverse child outcomes. In many countries, screening for postpartum depression

495 during routine obstetrical care, including care by health visitors, is inconsistent, and this strategy
496 has become an area of focus in many countries. In addition, up to 60% of perinatal women with
497 depression do not seek help¹³⁷. However, given the availability of screening instruments and
498 effective treatments¹³⁸, Clinical Practice Guidelines and recommendations are increasingly
499 supportive of routine screening^{139, 140}. More generally, international guidelines reflect a consensus
500 that improved identification of PPDs is vitally important^{141,142}. Accordingly, several national
501 campaign to increase awareness of PPDs are underway, such as the Maternal Mental Health
502 Alliance¹⁴³ in the UK. This alliance is a coalition of organizations that are dedicated to achieving
503 consistent, accessible and quality mental health care in the first year after giving birth. In addition,
504 state mandates for perinatal depression screening are increasing in the United States, including
505 the US Preventive Services Task Force recommendation¹⁴⁰. However, although this task force has
506 concluded that the evidence base that is sufficient to recommend screening for perinatal
507 depression when combined with adequate support systems^{25, 140} this conclusion has also been
508 criticised by others¹⁴⁴.

509 The most widely researched and used screening tool for postpartum depression is the brief 10-item
510 Edinburgh Postnatal Depression Scale (EPDS¹⁴⁵), which was designed to exclude symptoms that
511 can be normal features of the perinatal period, such as poor sleep, but that are often included in
512 other self-report measures. A cut-off score of 13 is most commonly used to recommend further
513 diagnostic assessment^{146, 147}. In addition, the EPDS includes question about thoughts of self-harm,
514 which can help to mobilise risk assessment and can predict suicidal intent¹⁴⁸. The EPDS has been
515 used prenatally and validated in a number of languages, its properties are relatively well-
516 understood¹⁴⁷ and it appears to be highly acceptable in the target population^{149,150}. High EPDS
517 scores can reflect several psychiatric diagnoses. For example, among the 826 screen-positive
518 women out of a sample of 10,000 women, the most common primary diagnosis was unipolar
519 depressive disorder (found in 68.5% of women), but almost two-thirds of women had co-morbid
520 anxiety disorder and 22.6% had a bipolar disorder¹⁵¹. These data highlight another potential

521 benefit of the EPDS: that most women with a false-negative result for unipolar depression have
522 another diagnosable, and potentially treatable, psychiatric condition.

523 Other generic or perinatal-specific depression measures have been used to identify perinatal
524 depression, but are not as well validated in perinatal women as the EPDS. Other measures include
525 the Postpartum Depression Screening Scale¹⁵², the Beck Depression Inventory-II¹⁵³ and the
526 Patient Health Questionnaire-9^{154,155}. Alternatively, two case finding questions (the so-called
527 Whooley questions ^{141, 156, 157}) can be asked to women to determine whether further mental health
528 assessment should be carried out, and the use of these questions is recommended by NICE
529 guidelines in the United Kingdom. The Whooley questions can also be used to detect any
530 psychiatric disorder, and are not limited to depression².

531 As previously mentioned, postpartum depression are frequently co-morbid with anxiety (in 4.3% of
532 women). As anxiety substantially impacts maternal functioning and fetal and infant development^{28,}
533 ^{158 159}, this has spurred efforts to screen for postpartum anxiety. Three sub-items of the EPDS (the
534 so-called EPDS-3A) can be used to identify perinatal anxiety disorders and sub-syndromal
535 anxiety¹⁶⁰. Other screening instruments for anxiety disorders include the Perinatal Anxiety
536 Screening Scale (PASS)¹⁶¹ and the generalized anxiety disorder scale (GAD-7)¹⁶². Screening tools
537 for perinatal OCD and PTSD are also available, such as the specific perinatal OCD screening scale
538 (The POCS),¹⁶³ and a short screening scale for PTSD (SPAN), respectively.¹⁶⁴.

539 The utility of routine screening for postpartum psychosis, hypomanic and manic symptoms and
540 bipolar disorder faces several barriers including a lack of evidence base of effectiveness and the
541 reduced predictive value of screening for a relatively rare condition. Despite steady progress in this
542 area^{165, 166} a consensus test with well-known precision and an agreed cut-off has not been
543 identified^{167,168}. However, the Mood Disorder Questionnaire (MDQ) has shown solid psychometric
544 properties for assessing bipolar disorder and is increasingly used ¹⁶⁹. Taking a full personal and
545 family history might help to identify vulnerability to bipolar disorders which could trigger further

546 diagnostic assessment, given the strong association between bipolar disorder and increased risk
547 for PPDs^{141, 142}.

548 In general, screening programs in the postpartum period should include a clear pathway from
549 screening, to diagnostic assessment and treatment¹⁷⁰. Best practice guidelines agree that all
550 women who have a positive screen need subsequent assessment, during which, co-morbidities
551 and the woman's wider psychosocial context can be explored. Currently, only such well-resourced,
552 integrated management programs have provided evidence that perinatal mental health is improved
553 by depression screening^{171, 172}. In this regard, e-screening and e-treatments to facilitate integrated,
554 cost-effective care might be useful¹⁷³. Few well-understood, validated screening approaches for
555 PPDs that can ultimately improve morbidity and mortality are available. Indeed, further building of
556 the evidence-base for screening, including the cost-effectiveness of perinatal depression screening
557 as a policy direction is required^{142, 174}.

558

559 **[H2] Prevention**

560 Interventions for the prevention of postpartum depression or postpartum anxiety are intended to
561 prevent the onset, duration, or recurrence of these disorders. Prevention can reduce the mental
562 health, physical health and socio-economic burden associated with postpartum depression for
563 mothers, their offspring and families, as well as for health systems. The effectiveness of prevention
564 of postpartum depression is facilitated by the fact that pregnant women are motivated to address
565 factors that will affect their baby¹⁷⁵. The assessment of risk factors for PPDs helps with diagnosis
566 and formulation, but is also important for identifying potentially modifiable targets for prevention
567 and treatment (**Box 3**)¹⁷⁶. Thus, it is a requirement for both symptom screening and risk
568 assessment that systems exist for adequate follow-up and support. Furthermore, women and
569 clinicians should be informed that the established risk factors might have limited predictive value

570 for individual patients and, therefore, do not guarantee which women will develop or not develop
571 postpartum depression.

572 Some psychosocial and psychological interventions have reduced the risk of women developing
573 postpartum depression, although no single intervention type or modality appears superior to
574 others. Data from trials included in a Cochrane review¹⁷⁶ as well as randomized controlled trials
575 included in a qualitative review,¹⁷⁵ point towards particularly positive impacts when interventions
576 target at-risk groups (such as women with a previous episode of depression or a recent life
577 stressor), or include interpersonal therapy (IPT). As relationship challenges and lack of social
578 support constitute strong risk factor for PPD, the interpersonal focus of the IPT intervention,
579 therefore aims to address this causative or aggravating factor. Interventions with the most promise
580 include interventions targeting at-risk groups (such as women with a previous episode of
581 depression or a recent life stressor).

582 Trials included in these reviews were conducted among high risk women, based on various factors,
583 as well as women enrolled from the general perinatal population. Trials assessing the use of
584 interpersonal therapy, cognitive behavioural therapy, peer support, parental preparedness, and
585 person-centred approaches for prevention of postpartum depression have demonstrated
586 significantly positive results, whereas trials assessing the use of cognitive behavioural therapy for
587 postpartum depression have demonstrated mixed results. These results, disaggregated for
588 universal, selective or indicated prevention strategies are summarized in a more recent systematic
589 review and meta-analysis¹⁷⁷. The interventions were delivered using several modalities, including
590 home visits and telephone support, provision by professional and lay practitioners, individual and
591 group-based sessions, through multiple contact sessions and at postpartum initiation¹⁷⁶.

592 There is conflicting evidence for the treatment of vulnerable women with antidepressants for the
593 prevention of depressive episodes or anxiety symptoms during the perinatal period as well as
594 anxiety symptoms has conflicting evidence¹⁷⁸. One of the earliest studies demonstrated a

595 reduction in recurrence of postpartum major depression with prophylactic antidepressant treatment
596 ¹⁷⁹. Small but emerging literature has suggested hormonal therapies, light therapy and other forms
597 of circadian manipulation might be promising therapies for prevention of depression¹⁸⁰. There is no
598 strong evidence for the use of hormonal therapies, acupuncture, supplementation with omega-3
599 polyunsaturated fatty acids, light therapy and other forms of circadian manipulation for prevention
600 of postpartum depression. ^{177,180}

601 Interventions for the prevention of postpartum psychosis include careful monitoring for symptom
602 development in women at high risk and adjustments of prophylactic medication, especially in
603 women with bipolar disorder^{18, 24}. Prophylactic treatment during pregnancy might reduce the rate of
604 postpartum relapse in women with bipolar disorder, although no evidence from randomized
605 controlled trials for this is available. For women with previous postpartum psychosis, prophylactic
606 treatment with lithium or antipsychotics immediately postpartum might reduce relapse¹⁸.

607

608 **[H1] Management**

609 The goals of treating mental illness in the postpartum period are to reduce maternal psychiatric
610 symptoms and to support maternal-child and family functioning. All women and their families
611 should receive education about the illness and the potential treatment options, including the
612 potential benefits and harms of each treatment option. Social support should be optimized and
613 physical and psychiatric comorbidities should be addressed. In addition, strategies to assist women
614 in obtaining sleep and a stable circadian rhythm are helpful, given that sleep deprivation is
615 common during the postpartum period. In many cases, the symptoms of PPDs influence maternal-
616 child interactions, which should be observed and discussed in a non-judgmental way.

617 Although specific recommended treatments depend on the underlying diagnosis, in general, a
618 stepped care approach is advocated, in which the intensity of the intervention matches the severity
619 and acuity of the clinical presentation. For example, women with mild symptoms of depressive,

620 anxiety, obsessive–compulsive and/or trauma or stressor-related disorders should first be offered
621 the lowest-intensity interventions such as peer support and guided self-help, whereas women who
622 do not respond to these treatments might require formal psychotherapeutic interventions, such as
623 psychological therapies. For women with severe symptoms, who do not respond to non-
624 pharmacological treatment, or who have bipolar disorder or psychosis, pharmacological
625 interventions are likely to be introduced as a first-line treatment, used alone or in combination with
626 a lower-intensity intervention. In such cases, the well-established benefits of breastfeeding on the
627 infant must be considered in the context of maternal mental wellbeing, the passage of psychotropic
628 medication into breast-milk and the infant, and the potential effects of medications on the neonate.
629 Indeed, when breast-feeding is challenging, and/or when frequent nighttime feedings leads to
630 sleep disruption, symptoms of depression or anxiety might be precipitated or exacerbated. In these
631 cases, the benefits of breastfeeding must be weighed against the risk of ongoing maternal mental
632 illness, and formula feeding is a viable and often recommended alternative. Other somatic
633 treatments, such as electroconvulsive therapy (ECT), can be considered in women with treatment-
634 refractory disorders. Throughout, monitoring progress to determine when or if to move to a higher-
635 intensity intervention, and to ensure safety for mother and child is important. In the initial
636 assessment and during treatment the patient and her family should be asked if thoughts of suicide
637 or infanticide have occurred. Safety concerns and/or evidence of active psychosis are medical
638 emergencies that require specialist consultation, emergency hospitalization and treatment.

639

640 **[H2] Mood disorders and anxiety**

641 Treatment of postpartum depression and other non-psychotic mental disorders (such as anxiety,
642 OCD and trauma and stressor-related disorders; **Box 4**) depends on the severity of the initial
643 presentation and the level of functional impairment, including the effect on the maternal–child
644 interaction.¹²⁸ For women with a past history of mental illness, the previous treatment response and
645 the time to response of previous episodes should be considered. The patient’s treatment

646 preference, in addition to as access to care and utilization of care should also be considered in all
647 women, as patients who receive their preferred treatment are most likely to benefit from this
648 treatment than other treatments.¹⁸¹ Most women with non-psychotic mental disorders often prefer
649 psychotherapy over pharmacological treatments, although the uptake and effectiveness of this
650 therapy can be limited due to barriers in attending appointments, such as unpredictable infant
651 schedules and competing childcare responsibilities.¹⁸² Similarly, fathers also prefer psychological
652 treatments to pharmacological therapy.¹⁸³ However, some women prefer pharmacological
653 treatment alone, so individualizing treatments based on patient preferences is important. Treating
654 maternal postpartum depression might not always improve the maternal–infant relationship, and
655 additional interventions aimed at the mother–infant dyad or the family as a whole might be
656 required.¹⁸⁴

657

658 **[H3] Psychological Interventions.** Most trials for postpartum depression have focused on non-
659 pharmacological treatments. For women with mild postpartum depression, psychosocial treatments
660 including peer support, guided self-help, and supportive counseling by trained professions such as
661 public health nurses (at home, or in support groups) can improve symptoms. For example, one
662 systematic review of 5 trials demonstrated a 1 year remission rate of 68% in women with
663 postpartum depression who received psychosocial treatments compared with a remission rate of
664 54% in women treated with standard primary care.¹⁸⁵ For women with moderate symptoms of
665 depression, or women who do not responded to psychosocial strategies, psychotherapies such as
666 cognitive-behaviour therapy (CBT) and interpersonal therapy (IPT) that specifically address the
667 psychological and related challenges of transitioning to parenthood are effective when delivered in
668 individual, group, and partner-assisted formats, and either in-person, by telephone, or online.¹⁸⁶ A
669 systematic review of 4 CBT and 1 IPT trials demonstrated a pooled remission rate of 60.3% for
670 these interventions, compared with a rate of 48.1% for usual care.¹⁸⁵

671

672 In addition, a CBT-based program was demonstrated to reduce worry and depressive symptoms in
673 women with postpartum anxiety disorders, including GAD, social phobia and OCD, compared with
674 symptoms at baseline.¹⁸⁷ The effectiveness of CBT for postnatal OCD symptoms was confirmed in
675 a small RCT.¹⁸⁸ Although additional research is required, CBT-based interventions for postpartum
676 anxiety disorders, and specifically interventions such as eye movement desensitization and
677 reprocessing (EMDR) and trauma-focused CBT for trauma and stressor related disorders, can be
678 used, although the latter two interventions have not been specifically evaluated in postpartum
679 women [189].

680 The increasing use of internet-based CBT and the development of mobile apps that use this
681 treatment modality demonstrates the power of digital health, which is often more accessible than
682 traditional psychotherapy, and extends to individuals who can't participate in psychotherapy. A
683 good example of this is MumMoodBooster, which was developed in Australia¹⁷³.

684

685 **[H3] Drug therapies.** Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and
686 serotonin norepinephrine reuptake inhibitors (SNRIs) are the mainstay of pharmacological
687 treatment for postpartum anxiety and depressive disorders. These therapies can be used alone or
688 in combination with psychosocial or psychological treatments. In a systematic review, the pooled
689 remission rate was significantly higher in patients receiving SSRIs (46.0%) compared with those
690 receiving placebo (25.7%).¹⁹⁰ Although pharmacological therapies can be used alone or in
691 combination with psychosocial or psychological treatments, whether combinatorial therapy is
692 superior to either one alone has not been evaluated in postpartum women. However, combinatorial
693 treatment does not lead to further improvements in functional outcomes compared with medication
694 alone, in non-perinatal populations.^{191, 192} To our knowledge, there are no drug treatment trials in
695 maternal anxiety disorders, or in paternal postpartum depression or anxiety. However, SSRI and
696 SNRI medications are first line pharmacological treatments for anxiety and depression outside the
697 postpartum period. The duration of antidepressant therapy required for new-onset postpartum

698 depression, anxiety or a related disorder has not been studied, but clinicians are recommended to
699 follow guidelines for these disorders in the general population. For depression, the initial treatment
700 should be continued for 6 months to 1 year after remission; longer durations are required for
701 severe and/or recurrent illness.¹⁹³

702

703 Many women and their partners are concerned about the safety of using antidepressant drugs
704 during breastfeeding. However, the use of antidepressants during the postpartum period is not a
705 contraindication to breastfeeding, and indeed, the avoidance of medication when needed for
706 severe illness is associated with maternal suicides¹⁹⁴. The passage of SSRIs and SNRIs into
707 breast-milk is variable between drugs, but most pass into the breast-milk at <10% of the maternal
708 dose, which is compatible with breast-feeding.¹⁹⁵ As such, changing the antidepressant drug or the
709 dose during the perinatal period to switch to a drug with lower breast-milk passage is generally not
710 recommended. For new-onset postpartum depression, sertraline is often recommended as a first-
711 line pharmacological treatment due to very minimal passage into breast-milk (Figure 2). However,
712 in patients with a prior history of psychiatric disorders, therapies that have previously demonstrated
713 efficacy should be considered, even those that have less data regarding safety during
714 breastfeeding. Other SSRIs, SNRIs or mirtazapine (an atypical antidepressant) also have minimal
715 passage into breast-milk, so these drugs are unlikely to be a cause for concern. Bupropion is
716 generally not given to lactating women due to case reports of infant seizures associated with
717 exposure to this drug.¹⁹⁶ In cases of severe depression and/or anxiety (with or without psychotic
718 features), older antidepressants, other therapies such as benzodiazepines or antipsychotics might
719 be indicated.

720

721 **[H3] Other treatments.** Given the likely role of hormonal fluctuations in the aetiology of postpartum
722 depression, hormonal treatments have been evaluated. Transdermal oestrogen therapy reduced
723 the symptoms of postpartum depression in one small study, but further trial are required. Progestin

724 therapy worsens postpartum depressive symptoms.¹⁹⁷ One trial of demonstrated the superiority of
725 allopregnenalone to placebo in improving depressive symptoms in 21 women with severe
726 postpartum depression,⁹² although this requires further investigation. Complementary and
727 alternative medicine treatments (for example, folate, s-adenosylmethionine, massage and
728 acupuncture) are not well-supported by evidence.¹⁹⁸ However, using aerobic exercise for
729 postpartum depression was recently examined in a systematic review and has good supporting
730 evidence for mild symptomatology ¹⁹⁹. ECT can be considered in severe or treatment-refractory
731 cases of depression.

732

733 **[H2] Postpartum psychosis**

734 Fluctuations in symptoms are common in women with postpartum psychosis, and thoughts of
735 infanticide or suicide are often well hidden. Thus, outpatient treatment is not safe and psychiatric
736 hospitalization is recommended for diagnostic evaluation and treatment ¹⁵. The preferred treatment
737 setting is a mother–baby joint admission unit, but these units are not available worldwide ^{200, 201}.
738 Alternatives are the admission of the mother only to a hospital with expertise in perinatal
739 psychiatric care or women’s mental health, or, if these facilities are unavailable, admission to a
740 standard mental health inpatient setting, or based on a careful assessment of the safety of both the
741 mother and the infant, intensive home treatment where available and with appropriate
742 supervision¹⁶. The effect of these approaches on long term outcomes of the mother and baby are
743 being investigated¹⁵.

744 The management of postpartum psychosis is dependent on psychiatric history. For women with
745 known severe psychiatric illness with non-perinatal episodes, reviewing the nature and
746 effectiveness of past treatments and restarting previous effective treatment is important.
747 Management of women without a history of bipolar disorder or other severe psychiatric disorder are
748 summarized in Figure 2. The main treatment goals for women without a prior history of bipolar

749 disorder, psychosis or other severe psychiatric disorder include the limitation of the current episode
750 and the prevention of a bipolar disease course with multiple episodes. Accordingly, management in
751 the first year postpartum should focus on full recovery (that is, complete symptom remission and
752 social and vocational functioning). In the absence of guidelines and controlled trials, treatment
753 recommendations are based on results from naturalistic cohort studies and expert consensus
754 groups^{24, 202}. The largest study (consisting of 68 patients) demonstrated the efficacy of a stepwise
755 sequence of short-term benzodiazepines, antipsychotics and lithium, and showed high remission
756 rates (remission in 98.4% of women) in the acute phase²⁰³. Moreover, this study demonstrated
757 that lithium monotherapy is protective against relapse of psychosis, depression and mania within
758 one year. The second largest study described successful ECT treatment in 34 patients with
759 postpartum psychosis of whom many had symptoms of catatonia²⁰⁴. The effectiveness of lithium
760 and ECT is supported by case reports²⁰⁵. Successful treatment with antipsychotics has been
761 described in case reports^{206, 207}, but antipsychotic monotherapy did not show efficacy in a cohort
762 study²⁰³. Together, lithium monotherapy might be the preferred initial intervention for postpartum
763 psychosis but adjunctive treatment with benzodiazepines or antipsychotics is useful for the acute
764 treatment of agitation, mania and psychotic symptoms, given the well documented effectiveness in
765 non-perinatal populations. Several antipsychotics are used for the treatment of severe PPDs
766 including risperidone, quetiapine and olanzapine²⁰⁸. ECT is the primary treatment for patients with
767 severe catatonic or depressed psychotic features, or if patient's prefer this therapy¹⁵.

768 Anticonvulsants (that is, antiepileptic medications) are also used less frequently as mood
769 stabilizers in the treatment of bipolar disorder because of concerns of teratogenicity. However,
770 valproate use during pregnancy and lactation is associated with neural tube defects and
771 neurocognitive developmental delays in the offspring^{24, 209}. Thus, valproate use is not advised
772 during the perinatal period, unless the risk/benefit assessment determines a prior efficacy in
773 particular women. By contrast, lamotrigine is used for the treatment of bipolar–depression (not
774 bipolar–mania) and is not associated with an increased risk of congenital malformations in

775 offspring.²¹⁰ A review of recent studies demonstrated that lamotrigine had no adverse outcomes
776 on infant IQ or neurodevelopment.²¹¹

777 The management of a breastfeeding woman with a severe psychiatric episode is challenging
778 due to concerns about the exposure of breastmilk to pharmacological therapies and the need
779 for sleep preservation in the mother¹⁵. The use of lactation inhibitors should be avoided. In some
780 countries, the mother is recommended to breastfeed only if extensive psychiatric support and
781 access to a pediatric professional that can monitor the infant are available. Moreover, the mother
782 and her partner should be educated about the risks of breastfeeding with pharmacotherapy. In
783 other countries, a more individualized approach (for example, NICE guidelines) based on previous
784 responses to medication, preferences regarding breastfeeding and psychopathology²⁴, other than
785 avoidance of breastfeeding if lithium (rather than an antipsychotic) is used. Small case series have
786 provided information regarding the safety of lithium in lactation^{212, 213}. When possible, level of
787 lithium in the infants serum should be closely monitored; on average, the serum level of lithium is
788 25% of the maternal levels, but the range can vary and dehydration can lead to toxic levels^{15, 213}.
789 No adverse effects were reported in ten infants of breastfeeding mothers who received ECT²⁰⁴.

790

791 **[H1] Quality of life**

792 The symptoms and morbidity of postpartum depression are often reported in the academic
793 literature, but this offers only a rather constricted view of the quality of life (QOL) of women with
794 PPDs.^{125, 214 215} Nevertheless, the classic core symptoms of a depressive disorder would be
795 expected to decrease the subjective quality of both an individual's inner life experience (anhedonia,
796 sadness, hopelessness, thoughts of death), and their functioning (psychomotor retardation or
797 agitation, disturbed sleep). Anxiety is frequently co-morbid and this further influences quality of life
798 with persistent worry symptoms.

799 Definitions vary, but QoL is a broader multidimensional construct which commonly incorporates
800 two central aspects: emotional well-being (including, frequency and intensity of joy, sadness,
801 affection) and life evaluation (how satisfied one is with one's life, for example, housing,
802 employment). Health, and the ability to function, as an essential component of QoL is referred to as
803 health-related quality of life (HRQoL). Maternal QoL during the postpartum period also affects her
804 infant's current and future quality of life. Many mothers with postpartum depression have difficulty
805 interacting with their infants in a positive way²¹⁶, such as making less eye contact, showing less
806 synchronous responsiveness, being uninvolved and showing restricted affect during mother-infant
807 interactions.²¹⁷⁻²¹⁹ Infant attachment security is a key predictor of child outcomes, including
808 neurological, psychological and social outcomes over the course of development²²⁰. In addition,
809 children of mothers with perinatal depression might have poorer psychological outcomes when
810 they reach 18 years of age²²¹. Some women have an intrusive engagement style that might lead to
811 long-term difficulties in child social, cognitive and behavioural domains²²². Women with postpartum
812 psychosis face even more many parenting challenges often including disrupted attachment, which
813 impact on the quality of life for mother and child.²²³

814 One of the most widely used generic measures of QOL is the 36 item short-form (SF-36)^{224, 225},
815 which has eight health domains that measure limitations in physical or usual role activities due to
816 health issues, limitations in usual role or social activities due to emotional issues, pain, mental
817 health, vitality, and general health perceptions. The SF-36 has been used in over 1,000
818 publications and for over 130 disorders including those that occur during the postpartum period,
819 and both the full and short versions of this scale have been validated by numerous studies^{225, 226}.
820 However, few measures of QOL have been developed specifically for use in the postpartum
821 period²²⁷. Only ²²⁸ three instruments for use during the postpartum period were reported in one
822 systematic review: The Mother-Generated Index (MGI)²²⁹, the Maternal Postpartum Quality of Life
823 Questionnaire (MAPP-QOL)²³⁰ and the Rural Postpartum QOL scale (RPQoL)²³¹. The MGI requires
824 women to specify domains of their life that have been affected by the birth of their baby, either

825 positive or negative, and to then score these out of 10.²³² The most common changes reported
826 were tiredness, less personal time, less time with partner or other family members, a worse
827 relationship with partner or other family members, physical complaints, low self-esteem, financial
828 worries, negative feelings towards the baby, more housework, poor sex life, decreased pleasure
829 from baby, less sense of happiness or fulfilment²²⁹.

830 Not surprisingly, people with depressive illness in general report lower scores on generic QoL and
831 HRQoL measures, as do women experiencing postpartum depressed mood.^{233 234} Small studies in
832 postpartum women also suggest QoL is amenable to intervention. Improvements in QoL are not
833 fully explained by improvements in the severity of depressive symptom suggesting that
834 interventions should go beyond the mere reduction of symptom severity and consider other factors
835 that contribute to QoL as targets for intervention. . Maternal-specific measures of QoL could be
836 integrated into postpartum depression screening programs or routine postnatal care^{235, 236}. Indeed,
837 QoL measures that allow a women to identify which areas of her life are most important to her,
838 could be used to allow women to indicate where she would like to see improvements.²²⁹ Emerging
839 studies have highlighted the beneficial effect of social support on QOL²³⁷, in addition to risk factors
840 for reduced QOL such as younger age and lower socio-economic status in women with postpartum
841 depression²³⁸.

842 PPDs have economic considerations and can affect quality-adjusted life years (QALY)¹⁴². QALY
843 takes into account how treatment affects quality and quantity of life, and accordingly, QoL
844 measurement is necessary for studies of cost-effectiveness of treatments. Compelling data from
845 the London School of Economics²³⁹ demonstrated the high economic costs of PPDs and the need
846 to address the loss of QALYs of women and their children, by treatment and prevention of these
847 disorders. This finding is particularly pertinent given the short and long-term effects of postpartum
848 depression. Indeed, as most women recover from postpartum mood disorders, these disorders can
849 become chronic in a subgroup of women²⁴⁰. One study demonstrated that, for each one-year

850 cohort of births, perinatal depression, anxiety and psychosis cost the UK around £8.1 billion in the
851 long-term.²³⁹

852

853 **[H1] Outlook**

854 The postpartum period is a vulnerable time for onset of psychiatric illness. Indeed, postpartum mood
855 and anxiety are heterogeneous and might be triggered by biopsychosocial factors including a
856 vulnerability to the robust endocrine and immune-related changes that occur at childbirth. The
857 heterogeneity of these disorders requires a thoughtful approach to assessment and treatment
858 planning that includes the clinical presentation, family and personal psychiatric history, other
859 psychosocial risk factors (including history of trauma), and awareness of potential biological or
860 genetic contributions that might influence risk and vulnerability.

861 The precise vulnerability that leads to some women developing PPDs is currently unknown and novel
862 research approaches are needed to identify the underlying pathophysiology of both prepartum and
863 postpartum anxiety, depression and psychosis. This will require a multi-faceted approach in
864 preclinical, clinical and translational research, to determine the mechanisms behind the neurobiology
865 and physiological correlates of PPDs, and the observed peripartum mood and mothering behaviors.
866 Additionally, these strategies must address the differences in the timing of symptom onset and the
867 diverse types of symptoms.

868 Given the morbidity and mortality of postpartum psychosis, episodes of psychosis might be best
869 considered to represent women with a bipolar disorder diathesis with a puerperal trigger.

870 Understanding this trigger will be beneficial and should allow the development of new treatments
871 and, ultimately, enable the prevention of psychosis or prevent unfavourable outcomes in women at
872 high risk. Effective evidence based treatment approaches are available for psychosis and
873 depression, including psychopharmacology, psychotherapy and ECT and circadian manipulation.

874 However, postpartum depression and postpartum psychosis require different and targeted

875 treatment approaches and therefore, bipolarity must be considered in the evaluation and
876 management of all women with postpartum mood and anxiety disorders. In addition, primary
877 treatment goals should include the limitation of the current episode and the prevention of future
878 episodes (including unipolar or bipolar disease with multiple episodes, and chronic anxiety).
879 Whether there a continuum of severity between postpartum depression and postpartum psychosis,
880 or whether these disorders represent different conditions with different aetiological factors requires
881 further study.

882 A potential barrier to the engagement and retention of women in the treatment of postpartum mood
883 disorders is stigma. Understand this stigma and the fear that women have regarding postpartum
884 mood disorders is essential. The voices of women with postpartum mood disorders must be
885 incorporated into the development of services to ensure the needs of women, their infants and
886 families are met^{241, 242}.

887 To date, the amount of research provides an important road map for PPDs in general, and
888 guidelines for screening or identification and treatment for perinatal depression in many countries
889 gives a strong mandate to improve mental health care for all women in the perinatal period. Thus,
890 developing effective strategies in low, middle and high income countries that allow the delivery of
891 targeted therapies to women with different clinical phenotypes and severity of PPDs is imperative.
892 In addition, whether the current ICD-10 and DSM-5 classification systems are adequate for
893 detecting specific phenotypes or diagnostic groups of patients should be evaluated. We should
894 also consider that PPDs might be phenotypically different than psychiatric disorders that begin
895 during pregnancy. Indeed, disorders that occur postpartum might have unique characteristics in
896 epidemiology, pathophysiology, psychosocial contributions, prevention and management than
897 disorders that occur during pregnancy.

898 In summary, PPDs are morbid and costly disorders. Advocating for early identification and
899 screening that begins in pregnancy to identify women at risk, in addition to timely and effective

900 treatments of PPDs is essential. Given the recent advances in knowledge, this an incredibly
901 exciting time for research in perinatal mood disorders. New approaches might allow the
902 identification of the underlying causes of postpartum mood disorders, which could lead efforts to
903 identify women at risk and personalize treatment. Although genetic, biological and hormonal
904 signals likely have an important role in risk of these disorders, psychosocial contributions including
905 the current impact of lifetime stressors must be part of comprehensive work-up and treatment plan.
906 The social determinants of postpartum mood disorders, such as poverty, domestic violence, poor
907 housing, and insecure migrant status, should also be assessed as part of routine practice of
908 maternal health care for all women. Finally, we must recognize that maternal mental health is
909 necessary for the physical and mental health of mothers, infants and families¹⁷ and advocating and
910 protecting this population is our obligation.

911

912

913 **Display items**

914

915 **Box 1. Paternal postpartum depression.**

916 Fathers can also experience depression after the birth of a child. Indeed, in men, the prevalence of
917 depression after the birth of a child is greater than at other times during life²⁴³. Although the
918 literature of paternal depression is much smaller than that for maternal depression, the available
919 literature demonstrates that paternal depression increases the risk for long-term adverse outcomes
920 in the child due to potential impairments in parenting^{244, 245}. In addition, a strong link between
921 maternal depression and paternal depression has been reported. Pregnant women who had
922 partners with depression during their pregnancy had worse depression symptom severity during
923 the first six months postpartum²⁴⁶. Thus, including fathers in health assessments during the
924 postpartum period and screening fathers for postpartum psychiatric disorders at similar time
925 intervals as maternal screening is important. Efforts aiming to improve the overall health and
926 functioning of the family unit will lead to best outcomes for the child^{243, 245}.

927

928

929

930 **Box 2. Postpartum mental illness in low-income and middle-income countries**

931 In resource-poor settings, women of reproductive age typically have socio-economic and health
932 challenges that interplay in mutually reinforcing ways.^{247, 248} For example, low levels of education,
933 low gender status, food insecurity, domestic abuse and lack of access to social and health services
934 leave women and girls vulnerable to maternal mortality and chronic morbidities, including common
935 mental health disorders.^{249, 250} Indeed, the prevalence of common perinatal mental disorders in low-
936 and lower-middle-income countries is higher than in high-income countries. One systematic review
937 and meta-analysis²¹ demonstrated a weighted mean prevalence of 15.6% in pregnant women and
938 19.8% in women after childbirth. The most strongly associated factors for perinatal mental
939 disorders are socio-economic disadvantage, unintended pregnancy, younger age, unmarried
940 status, lacking intimate partner empathy and support, hostile inlaws, partner violence, insufficient
941 emotional and practical support, a history of mental health problems and in certain settings, a
942 female infant.²¹

943

944 **[H1] Considerations for management**

945 Mental health prevention and treatment investments in high-income countries is more than US\$50
946 per year per person, compared with less than US\$2 in most LMIC,²⁵¹ resulting in a profound
947 paucity of mental health providers in these settings. The intervention coverage for common mental
948 disorders (including those that occur during the perinatal period) ranges from 7% to 28% in
949 LMICs.²⁵² The low monetary allocation represents, in part, poor appreciation by decision makers of
950 the effect of mental illness on population disability and socio-economic development, low levels of
951 political will and capacity, and competing health and development priorities.²⁵³ Interventions that
952 are most likely to succeed in LMICs would, therefore, need to adopt a systems strengthening,
953 integrated and low-cost approach. Examples showing promise have integrated mental health into
954 primary care, maternal and child health services or into the routine community based delivery of

955 health services (carried out by trained lay workers, or primary care healthworkers, using a task-
956 sharing approach)²⁵⁴. Emerging evidence supports the benefit of including poverty alleviation
957 strategies in to mental health interventions.²⁵⁵

958

959 **[H1] Types of interventions**

960 A systematic review and meta-analysis of evidence of common perinatal mental disorder trials from
961 LMIC, reported similar relative risk outcomes in studies carried out in high-income countries²⁵⁶. For
962 the 13 trials selected, the pooled effect size for maternal depression was -0.38 . In this review,
963 trials that demonstrated positive results used several culturally adapted treatment paradigms,
964 either singly or in combination. The Thinking Health Program in Pakistan was a cognitive behaviour
965 therapy (CBT) intervention delivered in homes in a semi-rural setting by Lady Health Workers.²⁵⁷
966 Uptake of the intervention leveraged the belief, within multi-generational households, that the
967 intervention with the mother would improve the infant's well-being . In an urban, deprived setting in
968 Chile, midwives and nurses were trained to deliver eight weekly structured psychoeducational
969 group sessions. These sessions included information about symptoms and treatments, some
970 problem solving strategies, behavioural activation strategies (such as scheduling pleasurable
971 activities) and some cognitive techniques using postnatal examples ²⁵⁸ .

972 Subsequently, a trial in Zimbabwe ²⁵⁹ used peer counsellors to deliver six weeks of group problem
973 solving therapy adapted for the local setting to postnatal women with depression. In this study,
974 family members were co-opted to support the mothers through strategies identified in the problem
975 solving and a specific treatment element that explored community resources and support systems
976 was included. Six weeks after the intervention, the drop in mean EPDS score was greater in the
977 PST group than the control group who received antidepressant therapy. No difference in outcomes
978 between women with or without HIV was reported.

979

980 **Box 3. Targeting risk factors for postpartum depression.**

981 Assessing the common psychosocial risk factors for postpartum depression might have the
982 following functions:

- 983 • Assisting in the initiation of targeted interventions or determining rational management
984 decisions to mitigate the risks across several global settings through
 - 985 ○ risk reduction interventions (for example, referring women for social grants, to
986 domestic violence support groups or to a women’s shelter and provision of
987 integrated interventions for the mood disorder, which also addresses domestic
988 violence ²⁶⁰
 - 989 ○ activation of protective factors, (such as interpersonal therapy for relationship
990 difficulties or activating social support networks) ^{175, 260}.
- 991 • Assisting in screening of women who have an increased risk of postpartum depression but
992 do not currently have the disorder.
- 993 • Assisting in timely referral for support in women with suspected postpartum depression and
994 complicated psychosocial risk factors who are reluctant to endorse symptoms during
995 screening due to stigma and poor contextual validity of the screening tool in some global
996 settings, among other reasons²⁶¹. This approach acknowledges that there may be several
997 contextual factors contributing to false negative mental health screening results.

998

999

1000 **Box 4. General management guidelines for non-psychotic psychiatric disorders**

- 1001 1. Identify somatic comorbidities and optimize their management.
- 1002 2. Check the mode of delivery, if complications were present and if delivery was experienced
1003 as traumatic. In the case of post-traumatic stress symptoms, consider specific treatments.
- 1004 3. Assess for suicidal thoughts and intrusive thoughts of harm toward the baby. Consider the
1005 safety of the baby and whether the mother can provide care for the baby if she is alone or if
1006 other adult supervision is required.
- 1007 4. Ask the mother of her attitude towards her baby and observe maternal-child interactions.
1008 Consider specific treatments with signs of problematic interactions or bonding.
- 1009 5. Review the feeding pattern of the baby. Address problems with breast or bottle-feeding.
- 1010 6. Provide strategies to preserve sleep, such as finding another person to feed the infant at
1011 night.
- 1012 7. Assess psychiatric history before delivery. Review the nature and effectiveness of past
1013 treatments, and restart previous effective treatment when appropriate.

1014

1015

1016

1017 **Figure 1, Mechanisms of postpartum psychiatric disorders.**

1018 Several factors have been implicated in the aetiology of postpartum psychiatric disorders, including
1019 both postpartum depression and postpartum psychosis. These factors include psycho-social
1020 factors and biological factors that are specific to pregnancy and the postpartum period, such as
1021 drastic alterations in gonadal sex steroids and impaired mother-infant interactions. Whether the
1022 aetiology of psychiatric disorders occurring in prenatally, during pregnancy or during the
1023 postpartum period is different requires future study.

1024

1025 **Figure 2. Management of first onset postpartum psychiatric disorders.**

1026 Management of postpartum psychiatric disorders should take into account the diagnosis (such as
1027 psychosis, anxiety or depression), symptom severity and, with regards to mood and anxiety
1028 disorders, whether the mother is breastfeeding.

1029

1030 **Bibliography: [Au: There are 5 pairs of duplicated references, can you please fix these using**
1031 **your reference manager:-- YES, this has been fixed. Thanks for letting me know!**

- 1032 • **27 and 147-- corrected**
- 1033 • **16 and 19-- corrected**
- 1034 • **30 and 162-- corrected**
- 1035 • **11 and 22—corrected.**
- 1036 • **20 and 56] --corrected**

- 1037 1. Munk-Olsen, T., Laursen, T.M., Pedersen, C.B., Mors, O. & Mortensen, P.B. New parents and
1038 mental disorders: a population-based register study. *The journal of the American Medical*
1039 *Association* **296**, 2582-2589 (2006).
- 1040 2. Howard LM, R.E., Trevillion K, Anderson F, Bick D, Bye A, Byford S, O'Connor S, sands P,
1041 Demilew J, Milgrom J, Pickles P. . The accuracy of the Whooley questions and the Edinburgh
1042 Postnatal Depression Scale in identifying mental disorders in early pregnancy. *British Journal*
1043 *of Psychiatry* (in press).
- 1044 3. Heron, J., O'Connor, T.G., Evans, J., Golding, J. & Glover, V. The course of anxiety and depression
1045 through pregnancy and the postpartum in a community sample. *Journal of affective disorders*
1046 **80**, 65-73 (2004).
- 1047 4. Guintivano, J. et al. Adverse life events, psychiatric history, and biological predictors of
1048 postpartum depression in an ethnically diverse sample of postpartum women. *Psychol Med*, 1-
1049 14 (2017).
- 1050 5. Perry, A. et al. Adverse childhood life events and postpartum psychosis in bipolar disorder. *J*
1051 *Affect Disord* **205**, 69-72 (2016).
- 1052 6. Sawyer, A., Ayers, S. & Smith, H. Pre- and postnatal psychological wellbeing in Africa: a
1053 systematic review. *J Affect Disord* **123**, 17-29 (2010).
- 1054 7. Johannsen, B.M. et al. All-Cause Mortality in Women With Severe Postpartum Psychiatric
1055 Disorders. *Am J Psychiatry* **173**, 635-42 (2016).
- 1056 8. Gaynes, B.N. et al. Perinatal depression: prevalence, screening accuracy, and screening
1057 outcomes. *Evid Rep Technol Assess (Summ)*, 1-8 (2005).
- 1058 9. Chesney, E., Goodwin, G.M. & Fazel, S. Risks of all-cause and suicide mortality in mental
1059 disorders: a meta-review. *World Psychiatry* **13**, 153-60 (2014).
- 1060 10. Parsons, C.E., Young, K.S., Rochat, T.J., Kringelbach, M.L. & Stein, A. Postnatal depression and its
1061 effects on child development: a review of evidence from low- and middle-income countries. *Br*
1062 *Med Bull* **101**, 57-79 (2012).
- 1063 11. Gavin, N.I. et al. Perinatal depression: a systematic review of prevalence and incidence. *Obstet*
1064 *Gynecol* **106**, 1071-83 (2005).
- 1065 12. Meltzer-Brody, S. New insights into perinatal depression: pathogenesis and treatment during
1066 pregnancy and postpartum. *Dialogues Clin Neurosci* **13**, 89-100 (2011).
- 1067 13. Meltzer-Brody, S. & Stringer, E.M. Global maternal, newborn, and child health. *N Engl J Med*
1068 **370**, 1072 (2014).
- 1069 14. Norhayati, M.N., Hazlina, N.H., Asrenee, A.R. & Emilin, W.M. Magnitude and risk factors for
1070 postpartum symptoms: a literature review. *J Affect Disord* **175**, 34-52 (2015).
- 1071 15. Bergink, V., Rasgon, N. & Wisner, K.L. Postpartum Psychosis: Madness, Mania, and Melancholia
1072 in Motherhood. *Am J Psychiatry* **173**, 1179-1188 (2016).
- 1073 16. Jones, I., Chandra, P.S., Dazzan, P. & Howard, L.M. Bipolar disorder, affective psychosis, and
1074 schizophrenia in pregnancy and the post-partum period. *Lancet* **384**, 1789-99 (2014).
- 1075 17. Howard, L.M. et al. Non-psychotic mental disorders in the perinatal period. *Lancet* **384**, 1775-
1076 88 (2014).

- 1077 18. Wesseloo, R. et al. Risk of Postpartum Relapse in Bipolar Disorder and Postpartum Psychosis: A
1078 Systematic Review and Meta-Analysis. *Am J Psychiatry* **173**, 117-27 (2016).
- 1079 19. Stewart, D.E. & Vigod, S. Postpartum Depression. *N Engl J Med* **375**, 2177-2186 (2016).
- 1080 20. Munk-Olsen, T. et al. Perinatal psychiatric episodes: a population-based study on treatment
1081 incidence and prevalence. *Transl Psychiatry* **6**, e919 (2016).
- 1082 21. Fisher, J. et al. Prevalence and determinants of common perinatal mental disorders in women
1083 in low- and lower-middle-income countries: a systematic review. *Bull World Health Organ* **90**,
1084 139G-149G (2012).
- 1085 22. Franko, D.L. et al. Pregnancy complications and neonatal outcomes in women with eating
1086 disorders. *Am J Psychiatry* **158**, 1461-6 (2001).
- 1087 23. Cox, J.L., Holden, J.M. & Sagovsky, R. Detection of postnatal depression. Development of the 10-
1088 item Edinburgh Postnatal Depression Scale. *Br.J.Psychiatry* **150**, 782-786 (1987).
- 1089 24. Excellence, N.N.I.f.H.a.C. in The British Psychological Society and the Royal College of
1090 Psychiatrists (London, United Kingdom, 2014).
- 1091 25. O'Connor, E., Rossom, R.C., Henninger, M., Groom, H.C. & Burda, B.U. Primary Care Screening for
1092 and Treatment of Depression in Pregnant and Postpartum Women: Evidence Report and
1093 Systematic Review for the US Preventive Services Task Force. *JAMA* **315**, 388-406 (2016).
- 1094 26. Liu, X. et al. Depression and Anxiety in the Postpartum Period and Risk of Bipolar Disorder: A
1095 Danish Nationwide Register-Based Cohort Study. *J Clin Psychiatry* **78**, e469-e476 (2017).
- 1096 27. Sharma, V., Doobay, M. & Baczynski, C. Bipolar postpartum depression: An update and
1097 recommendations. *J Affect Disord* **219**, 105-111 (2017).
- 1098 28. Dennis, C.L., Falah-Hassani, K. & Shiri, R. Prevalence of antenatal and postnatal anxiety:
1099 systematic review and meta-analysis. *Br J Psychiatry* **210**, 315-323 (2017).
- 1100 29. Munk-Olsen, T., Laursen, T.M., Pedersen, C.B., Mors, O. & Mortensen, P.B. New Parents and
1101 Mental Disorders. A Population-Based Register Study. *JAMA* **296**, 2582-2589 (2006).
- 1102 30. Harlow, B.L. et al. Incidence of hospitalization for postpartum psychotic and bipolar episodes in
1103 women with and without prior pregnancy or prenatal psychiatric hospitalizations.
1104 *Arch.Gen.Psychiatry* **64**, 42-48 (2007).
- 1105 31. Kendell, R.E., Chalmers, J.C. & Platz, C. Epidemiology of puerperal psychoses. *Br.J.Psychiatry*
1106 **150**, 662-673 (1987).
- 1107 32. Valdimarsdottir, U., Hultman, C.M., Harlow, B., Cnattingius, S. & Sparen, P. Psychotic illness in
1108 first-time mothers with no previous psychiatric hospitalizations: a population-based study.
1109 *PLoS.Med.* **6**, e13 (2009).
- 1110 33. Bergink, V., Boyce, P. & Munk-Olsen, T. Postpartum psychosis: a valuable misnomer. *Aust N Z J*
1111 *Psychiatry* **49**, 102-3 (2015).
- 1112 34. Di Florio, A. et al. Perinatal episodes across the mood disorder spectrum. *Journal of the*
1113 *American Medical Association: Psychiatry* **70**, 168-75 (2013).
- 1114 35. Munk-Olsen, T. et al. Risks and predictors of readmission for a mental disorder during the
1115 postpartum period. *Archives of general psychiatry* **66**, 189-95 (2009).
- 1116 36. Florio, A.D., Munk-Olsen, T. & Bergink, V. The birth of a psychiatric orphan disorder:
1117 postpartum psychosis. *Lancet Psychiatry* **3**, 502 (2016).
- 1118 37. Lysell, H. et al. Maternal suicide - Register based study of all suicides occurring after delivery in
1119 Sweden 1974-2009. *PLoS One* **13**, e0190133 (2018).
- 1120 38. Grigoriadis, S. et al. Perinatal suicide in Ontario, Canada: a 15-year population-based study.
1121 *CMAJ* **189**, E1085-E1092 (2017).
- 1122 39. Kimmel, M. et al. Family history, not lack of medication use, is associated with the development
1123 of postpartum depression in a high-risk sample. *Arch Womens Ment Health* (2014).
- 1124 40. Viguera, A.C. et al. Risk of recurrence in women with bipolar disorder during pregnancy:
1125 prospective study of mood stabilizer discontinuation. *Am J Psychiatry* **164**, 1817-24; quiz 1923
1126 (2007).

- 1127 41. Fonagy, P., Sleded, M. & Baradon, T. Randomized Controlled Trial of Parent-Infant
1128 Psychotherapy for Parents with Mental Health Problems and Young Infants. *Infant Ment Health*
1129 *J* **37**, 97-114 (2016).
- 1130 42. Stein, A. et al. Effects of perinatal mental disorders on the fetus and child. *Lancet* **384**, 1800-19
1131 (2014).
- 1132 43. Faisal-Cury, A., Menezes, P.R., d'Oliveira, A.F., Schraiber, L.B. & Lopes, C.S. Temporal
1133 relationship between intimate partner violence and postpartum depression in a sample of low
1134 income women. *Matern Child Health J* **17**, 1297-303 (2013).
- 1135 44. Onoye, J.M., Goebert, D., Morland, L., Matsu, C. & Wright, T. PTSD and postpartum mental health
1136 in a sample of Caucasian, Asian, and Pacific Islander women. *Arch Womens Ment Health* **12**,
1137 393-400 (2009).
- 1138 45. Gonzalez, A., Jenkins, J.M., Steiner, M. & Fleming, A.S. Maternal early life experiences and
1139 parenting: the mediating role of cortisol and executive function. *J Am Acad Child Adolesc*
1140 *Psychiatry* **51**, 673-82 (2012).
- 1141 46. Hipwell, A.E., Goossens, F.A., Melhuish, E.C. & Kumar, R. Severe maternal psychopathology and
1142 infant-mother attachment. *Development and psychopathology* **12**, 157-75 (2000).
- 1143 47. Goodman, S.H. et al. Maternal depression and child psychopathology: a meta-analytic review.
1144 *Clin Child Fam Psychol Rev* **14**, 1-27 (2011).
- 1145 48. Muzik, M. et al. Psychopathology and parenting: An examination of perceived and observed
1146 parenting in mothers with depression and PTSD. *J Affect Disord* **207**, 242-250 (2017).
- 1147 49. Yim, I.S., Tanner Stapleton, L.R., Guardino, C.M., Hahn-Holbrook, J. & Dunkel Schetter, C.
1148 Biological and psychosocial predictors of postpartum depression: systematic review and call
1149 for integration. *Annu Rev Clin Psychol* **11**, 99-137 (2015).
- 1150 50. Xie, R.H. et al. Prenatal family support, postnatal family support and postpartum depression.
1151 *Aust N Z J Obstet Gynaecol* **50**, 340-5 (2010).
- 1152 51. Rogathi, J.J. et al. Postpartum depression among women who have experienced intimate
1153 partner violence: A prospective cohort study at Moshi, Tanzania. *J Affect Disord* **218**, 238-245
1154 (2017).
- 1155 52. Fiala, A., Svancara, J., Klanova, J. & Kasperek, T. Sociodemographic and delivery risk factors for
1156 developing postpartum depression in a sample of 3233 mothers from the Czech ELSPAC study.
1157 *BMC Psychiatry* **17**, 104 (2017).
- 1158 53. Craddock, N. & Forty, L. Genetics of affective (mood) disorders. *Eur J Hum Genet* **14**, 660-8
1159 (2006).
- 1160 54. Lichtenstein, P. et al. Common genetic determinants of schizophrenia and bipolar disorder in
1161 Swedish families: a population-based study. *Lancet* **373**, 234-9 (2009).
- 1162 55. Byrne, E.M. et al. Applying polygenic risk scores to postpartum depression. *Arch Womens Ment*
1163 *Health* (2014).
- 1164 56. Forty, L. et al. Familiality of postpartum depression in unipolar disorder: results of a family
1165 study. *The American Journal of Psychiatry* **163**, 1549-1553 (2006).
- 1166 57. Mahon, P.B. et al. Genome-wide linkage and follow-up association study of postpartum mood
1167 symptoms. *The American journal of psychiatry* **166**, 1229-37 (2009).
- 1168 58. Treloar, S.A., Martin, N.G., Bucholz, K.K., Madden, P.A. & Heath, A.C. Genetic influences on post-
1169 natal depressive symptoms: findings from an Australian twin sample. *Psychol Med* **29**, 645-54
1170 (1999).
- 1171 59. Viktorin, A. et al. Heritability of Perinatal Depression and Genetic Overlap With Nonperinatal
1172 Depression. *Am J Psychiatry*, appiajp201515010085 (2015).
- 1173 60. Jones, I. et al. Bipolar affective puerperal psychosis: genome-wide significant evidence for
1174 linkage to chromosome 16. *The American Journal of Psychiatry* **164**, 1099-1104 (2007).
- 1175 61. Jones, I., Craddock, N., Jones, I. & Craddock, N. Searching for the puerperal trigger: molecular
1176 genetic studies of bipolar affective puerperal psychosis. *Psychopharmacology Bulletin* **40**, 115-
1177 28 (2007).

- 1178 62. Consortium, P.D.A.T.C.a.T.P. Heterogeneity of postpartum depression: a latent class analysis.
1179 *Lancet Psychiatry* **2**, 59-67 (2015).
- 1180 63. Putnam, K.T. et al. Clinical phenotypes of perinatal depression and time of symptom onset:
1181 analysis of data from an international consortium. *Lancet Psychiatry* **4**, 477-485 (2017).
- 1182 64. Geronimus, A.T., Hicken, M., Keene, D. & Bound, J. "Weathering" and age patterns of allostatic
1183 load scores among blacks and whites in the United States. *Am J Public Health* **96**, 826-33
1184 (2006).
- 1185 65. Perroud, N. et al. Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with
1186 a history of childhood maltreatment: a link with the severity and type of trauma. *Transl*
1187 *Psychiatry* **1**, e59 (2011).
- 1188 66. Schwaiger, M. et al. Altered Stress-Induced Regulation of Genes in Monocytes in Adults with a
1189 History of Childhood Adversity. *Neuropsychopharmacology* **41**, 2530-40 (2016).
- 1190 67. Vincent, J. et al. Assessing the contributions of childhood maltreatment subtypes and
1191 depression case-control status on telomere length reveals a specific role of physical neglect. *J*
1192 *Affect Disord* **213**, 16-22 (2017).
- 1193 68. Mitchell, A.M., Kowalsky, J.M., Epel, E.S., Lin, J. & Christian, L.M. Childhood adversity, social
1194 support, and telomere length among perinatal women. *Psychoneuroendocrinology* **87**, 43-52
1195 (2017).
- 1196 69. Osborne, L. et al. Replication of Epigenetic Postpartum Depression Biomarkers and Variation
1197 with Hormone Levels. *Neuropsychopharmacology* **41**, 1648-58 (2016).
- 1198 70. Guintivano, J., Arad, M., Gould, T.D., Payne, J.L. & Kaminsky, Z.A. Antenatal prediction of
1199 postpartum depression with blood DNA methylation biomarkers. *Mol Psychiatry* **19**, 560-7
1200 (2014).
- 1201 71. Murray, G. & Harvey, A. Circadian rhythms and sleep in bipolar disorder. *Bipolar Disord* **12**,
1202 459-72 (2010).
- 1203 72. Lewis, K.J., Foster, R.G. & Jones, I.R. Is sleep disruption a trigger for postpartum psychosis? *Br J*
1204 *Psychiatry* **208**, 409-11 (2016).
- 1205 73. Marques, M. et al. Is insomnia in late pregnancy a risk factor for postpartum
1206 depression/depressive symptomatology? *Psychiatry Res* **186**, 272-80 (2011).
- 1207 74. Parry, B.L. et al. Plasma melatonin circadian rhythm disturbances during pregnancy and
1208 postpartum in depressed women and women with personal or family histories of depression.
1209 *Am J Psychiatry* **165**, 1551-8 (2008).
- 1210 75. Thomas, K.A. & Burr, R.L. Melatonin level and pattern in postpartum versus nonpregnant
1211 nulliparous women. *J Obstet Gynecol Neonatal Nurs* **35**, 608-15 (2006).
- 1212 76. Sharkey, K.M., Pearlstein, T.B. & Carskadon, M.A. Circadian phase shifts and mood across the
1213 perinatal period in women with a history of major depressive disorder: A preliminary
1214 communication. *Journal of Affective Disorders* **150**, 1103-1108 (2013).
- 1215 77. Bloch, M. et al. Effects of gonadal steroids in women with a history of postpartum depression.
1216 *The American Journal of Psychiatry* **157**, 924-30 (2000).
- 1217 78. Sohrabji, F., Miranda, R.C. & Toran-Allerand, C.D. Estrogen differentially regulates estrogen and
1218 nerve growth factor receptor mRNAs in adult sensory neurons. *J Neurosci* **14**, 459-71 (1994).
- 1219 79. Shimizu, E. et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in
1220 depressed patients with or without antidepressants. *Biol Psychiatry* **54**, 70-5 (2003).
- 1221 80. Finocchi, C. & Ferrari, M. Female reproductive steroids and neuronal excitability. *Neurol Sci* **32**
1222 **Suppl 1**, S31-5 (2011).
- 1223 81. Pluchino, N. et al. Steroid hormones and BDNF. *Neuroscience* **239**, 271-9 (2013).
- 1224 82. Epperson, C.N. et al. Preliminary evidence of reduced occipital GABA concentrations in
1225 puerperal women: a 1H-MRS study. *Psychopharmacology (Berl)* **186**, 425-33 (2006).
- 1226 83. Schiller, C.E., Meltzer-Brody, S. & Rubinow, D.R. The role of reproductive hormones in
1227 postpartum depression. *CNS Spectr* **20**, 48-59 (2015).
- 1228 84. Paul, S.M. & Purdy, R.H. Neuroactive steroids. *FASEB J* **6**, 2311-22 (1992).

- 1229 85. Majewska, M.D., Harrison, N.L., Schwartz, R.D., Barker, J.L. & Paul, S.M. Steroid hormone
1230 metabolites are barbiturate-like modulators of the GABA receptor. *Science* **232**, 1004-7 (1986).
- 1231 86. Deligiannidis, K.M. et al. Peripartum neuroactive steroid and gamma-aminobutyric acid profiles
1232 in women at-risk for postpartum depression. *Psychoneuroendocrinology* **70**, 98-107 (2016).
- 1233 87. Luisi, S. et al. Serum allopregnanolone levels in pregnant women: changes during pregnancy, at
1234 delivery, and in hypertensive patients. *J Clin Endocrinol Metab* **85**, 2429-33 (2000).
- 1235 88. Nappi, R.E. et al. Serum allopregnanolone in women with postpartum "blues". *Obstet Gynecol*
1236 **97**, 77-80 (2001).
- 1237 89. Maguire, J., Mody, I., Maguire, J. & Mody, I. GABA(A)R plasticity during pregnancy: relevance to
1238 postpartum depression. *Neuron* **59**, 207-13 (2008).
- 1239 90. Paoletti, A.M. et al. Observational study on the stability of the psychological status during
1240 normal pregnancy and increased blood levels of neuroactive steroids with GABA-A receptor
1241 agonist activity. *Psychoneuroendocrinology* **31**, 485-92 (2006).
- 1242 91. Kanes, S.J. et al. Open-label, proof-of-concept study of brexanolone in the treatment of severe
1243 postpartum depression. *Hum Psychopharmacol* **32** (2017).
- 1244 92. Kanes, S. et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised
1245 controlled trial. *Lancet* **390**, 480-489 (2017).
- 1246 93. Algie, S.B. & Way, B.M. Evidence for a role of the oxytocin system, indexed by genetic variation
1247 in CD38, in the social bonding effects of expressed gratitude. *Soc Cogn Affect Neurosci* **9**, 1855-
1248 61 (2014).
- 1249 94. Cox, E.Q. et al. Oxytocin and HPA stress axis reactivity in postpartum women.
1250 *Psychoneuroendocrinology* **55**, 164-72 (2015).
- 1251 95. Zelkowitz, P. et al. Psychosocial stress moderates the relationships between oxytocin, perinatal
1252 depression, and maternal behavior. *Horm Behav* **66**, 351-60 (2014).
- 1253 96. Wei, S.M. et al. Brain-derived neurotrophic factor Val66Met genotype and ovarian steroids
1254 interactively modulate working memory-related hippocampal function in women: a
1255 multimodal neuroimaging study. *Mol Psychiatry* (2017).
- 1256 97. Sacher, J. et al. Relationship of monoamine oxidase-A distribution volume to postpartum
1257 depression and postpartum crying. *Neuropsychopharmacology* **40**, 429-35 (2015).
- 1258 98. Wonch, K.E. et al. Postpartum depression and brain response to infants: Differential amygdala
1259 response and connectivity. *Soc Neurosci* **11**, 600-17 (2016).
- 1260 99. Musser, E.D., Kaiser-Laurent, H. & Ablow, J.C. The neural correlates of maternal sensitivity: an
1261 fMRI study. *Dev Cogn Neurosci* **2**, 428-36 (2012).
- 1262 100. Pawluski, J.L., Lonstein, J.S. & Fleming, A.S. The Neurobiology of Postpartum Anxiety and
1263 Depression. *Trends Neurosci* **40**, 106-120 (2017).
- 1264 101. Roomruangwong, C. et al. A neuro-immune, neuro-oxidative and neuro-nitrosative model of
1265 prenatal and postpartum depression. *Prog Neuropsychopharmacol Biol Psychiatry* (2017).
- 1266 102. Glynn, L.M., Davis, E.P. & Sandman, C.A. New insights into the role of perinatal HPA-axis
1267 dysregulation in postpartum depression. *Neuropeptides* **47**, 363-70 (2013).
- 1268 103. Ferguson, E.H. et al. HPA axis reactivity to pharmacologic and psychological stressors in
1269 euthymic women with histories of postpartum versus major depression. *Arch Womens Ment*
1270 *Health* **20**, 411-420 (2017).
- 1271 104. Iliadis, S.I. et al. Associations between a polymorphism in the hydroxysteroid (11-beta)
1272 dehydrogenase 1 gene, neuroticism and postpartum depression. *Journal of Affective Disorders*
1273 **207**, 141-147 (2017).
- 1274 105. Zaconeta, A.M. et al. Cerebrospinal Fluid CRH Levels in Late Pregnancy Are Not Associated With
1275 New-Onset Postpartum Depressive Symptoms. *J Clin Endocrinol Metab* **100**, 3159-64 (2015).
- 1276 106. Hahn-Holbrook, J., Fox, M. & Glynn, L.M. Letter to the Editor: Demonstration of Elevated
1277 Cerebrospinal Fluid CRH Levels During Pregnancy Provides Support for (Not Against) the Link
1278 Between CRH and Postpartum Depression. *J Clin Endocrinol Metab* **101**, L5-6 (2016).

- 1279 107. Pedersen, C. et al. Late pregnancy thyroid-binding globulin predicts perinatal depression.
1280 *Psychoneuroendocrinology* **65**, 84-93 (2016).
- 1281 108. Bergink, V. et al. Comorbidity of autoimmune thyroid disorders and psychiatric disorders
1282 during the postpartum period: a Danish nationwide register-based cohort study. *Psychol Med*,
1283 1-9 (2017).
- 1284 109. Wesseloo, R., Kamperman, A.M., Bergink, V. & Pop, V.J.M. Thyroid peroxidase antibodies during
1285 early gestation and the subsequent risk of first-onset postpartum depression: A prospective
1286 cohort study. *J Affect Disord* **225**, 399-403 (2018).
- 1287 110. Groer, M.W. & Vaughan, J.H. Positive thyroid peroxidase antibody titer is associated with
1288 dysphoric moods during pregnancy and postpartum. *J Obstet Gynecol Neonatal Nurs* **42**, E26-32
1289 (2013).
- 1290 111. Anderson, G. & Maes, M. Postpartum depression: Psychoneuroimmunological underpinnings
1291 and treatment. *Neuropsychiatric Disease and Treatment* **9**, 277-287 (2013).
- 1292 112. Osborne, L.M. & Monk, C. Perinatal depression--the fourth inflammatory morbidity of
1293 pregnancy?: Theory and literature review. *Psychoneuroendocrinology* **38**, 1929-52 (2013).
- 1294 113. Haim, A. et al. A survey of neuroimmune changes in pregnant and postpartum female rats.
1295 *Brain Behav Immun* **59**, 67-78 (2017).
- 1296 114. Nilsen-Hamilton, M. et al. Tissue involution and the acute phase response. *Ann N Y Acad Sci*
1297 **995**, 94-108 (2003).
- 1298 115. Skalkidou, A. et al. Risk of postpartum depression in association with serum leptin and
1299 interleukin-6 levels at delivery: a nested case-control study within the UPPSAT cohort.
1300 *Psychoneuroendocrinology* **34**, 1329-37 (2009).
- 1301 116. Maes, M. et al. Immune activation in the early puerperium is related to postpartum anxiety and
1302 depressive symptoms. *Psychoneuroendocrinology* **25**, 121-37 (2000).
- 1303 117. Maes, M. et al. Effects of pregnancy and delivery on serum concentrations of Clara Cell Protein
1304 (CC16), an endogenous anticytokine: lower serum CC16 is related to postpartum depression.
1305 *Psychiatry Res* **87**, 117-27 (1999).
- 1306 118. De Vriese, S.R., Christophe, A.B. & Maes, M. Lowered serum n-3 polyunsaturated fatty acid
1307 (PUFA) levels predict the occurrence of postpartum depression: further evidence that lowered
1308 n-PUFAs are related to major depression. *Life Sci* **73**, 3181-7 (2003).
- 1309 119. Corwin, E.J. et al. Bidirectional psychoneuroimmune interactions in the early postpartum
1310 period influence risk of postpartum depression. *Brain Behav Immun* **49**, 86-93 (2015).
- 1311 120. Bergink, V. et al. Pre-eclampsia and first-onset postpartum psychiatric episodes: a Danish
1312 population-based cohort study. *Psychol Med* **45**, 3481-9 (2015).
- 1313 121. Bergink, V. et al. Autoimmune Encephalitis in Postpartum Psychosis. *Am J Psychiatry* **172**, 901-
1314 8 (2015).
- 1315 122. Bergink, V. et al. Immune system dysregulation in first-onset postpartum psychosis. *Biol*
1316 *Psychiatry* **73**, 1000-7 (2013).
- 1317 123. Uchino, B.N., Cacioppo, J.T. & Kiecolt-Glaser, J.K. The relationship between social support and
1318 physiological processes: a review with emphasis on underlying mechanisms and implications
1319 for health. *Psychol Bull* **119**, 488-531 (1996).
- 1320 124. Dickerson, S.S., Zoccola, P.M. & Hooker, E. in *The Oxford handbook of positive psychology*
1321 (2009).
- 1322 125. Association, A.P. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* (American
1323 Psychiatric Publishing, Arlington, VA, 2013).
- 1324 126. WHO, W.H.O. (World Health Organization, Geneva, 1992).
- 1325 127. Falah-Hassani, K., Shiri, R. & Dennis, C.L. The prevalence of antenatal and postnatal co-morbid
1326 anxiety and depression: a meta-analysis. *Psychological Medicine* **47**, 2041-2053 (2017).
- 1327 128. Howard, L.M., Megnin-Viggars, O., Symington, I., Pilling, S. & Guideline Development, G.
1328 Antenatal and postnatal mental health: summary of updated NICE guidance. *BMJ* **349**, g7394
1329 (2014).

- 1330 129. Di Florio, A. et al. The impact of education, country, race and ethnicity on the self-report of
1331 postpartum depression using the Edinburgh Postnatal Depression Scale. *Psychol Med*, 1-13
1332 (2016).
- 1333 130. Heron, J., McGuinness, M., Blackmore, E.R., Craddock, N. & Jones, I. Early postpartum symptoms
1334 in puerperal psychosis. *BJOG* **115**, 348-53 (2008).
- 1335 131. Bergink, V., Lambregtse-van den Berg, M.P., Koorengevel, K.M., Kupka, R. & Kushner, S.A. First-
1336 onset psychosis occurring in the postpartum period: a prospective cohort study. *J Clin*
1337 *Psychiatry* **72**, 1531-7 (2011).
- 1338 132. Kamperman, A.M., Veldman-Hoek, M.J., Wesseloo, R., Robertson Blackmore, E. & Bergink, V.
1339 Phenotypical characteristics of postpartum psychosis: A clinical cohort study. *Bipolar Disord*
1340 (2017).
- 1341 133. Feeney, E.J., Groman, S.M., Taylor, J.R. & Corlett, P.R. Explaining Delusions: Reducing
1342 Uncertainty Through Basic and Computational Neuroscience. *Schizophr Bull* **43**, 263-272
1343 (2017).
- 1344 134. Muzik, M. et al. Ptsd Symptoms across Pregnancy and Early Postpartum among Women with
1345 Lifetime Ptsd Diagnosis. *Depress Anxiety* **33**, 584-91 (2016).
- 1346 135. Kendall-Tackett, K.A. Violence against women and the perinatal period: the impact of lifetime
1347 violence and abuse on pregnancy, postpartum, and breastfeeding. *Trauma Violence Abuse* **8**,
1348 344-53 (2007).
- 1349 136. Schofield, C.A., Battle, C.L., Howard, M. & Ortiz-Hernandez, S. Symptoms of the anxiety
1350 disorders in a perinatal psychiatric sample: a chart review. *J Nerv Ment Dis* **202**, 154-60 (2014).
- 1351 137. McGarry, J., Kim, H., Sheng, X., Egger, M. & Baksh, L. Postpartum depression and help-seeking
1352 behaviour. *Journal of Midwifery and Women's Health* **54**, 50-56 (2009).
- 1353 138. Dennis, C.L. & Hodnett, E. Psychosocial and psychological interventions for treating postpartum
1354 depression. *Cochrane Database of Systematic Reviews* **Issue 4** (2007).
- 1355 139. Guidelines, B.B.C.P. (ed. Blue, B.) (2011).
- 1356 140. Siu, A.L. et al. Screening for Depression in Adults: US Preventive Services Task Force
1357 Recommendation Statement. *JAMA* **315**, 380-7 (2016).
- 1358 141. NICE. Antenatal and postnatal mental health: Clinical management and service guidance. The
1359 British Psychological Society & The Royal College of Psychiatrists. (National Institute for Health
1360 and Care Excellence (NICE). <http://guidance.nice.org.uk/cg192.www.nice.org.uk/CG45>, 2014).
- 1361 142. Milgrom, J. & Gemmill, A.W. (eds.) Identifying Perinatal Depression and Anxiety: Evidence-
1362 based Practice in Screening, Psychosocial Assessment and Management (Wiley-Blackwell,
1363 Chichester, 2015).
- 1364 143. Alliance, M.M.H.
- 1365 144. Screening for perinatal depression: a missed opportunity (Lancet. 2016 Feb 6;387(10018):505.
1366 doi: 10.1016/S0140-6736(16)00265-8).
- 1367 145. Cox, J. & Holden, J. Perinatal Mental Health. A Guide to the Edinburgh Postnatal Depression
1368 Scale (EPDS) (Gaskell, London, 2003).
- 1369 146. Myers, E. et al. (Agency for Healthcare Research and Quality, Rockville, MD, 2013).
- 1370 147. Hewitt, C. et al. Methods to identify postnatal depression in primary care: an integrated
1371 evidence synthesis and value of information analysis. *Health Technology Assessment* **13**, 1-145,
1372 147-230 (2009).
- 1373 148. Howard, L.M., Flach, C., Mehay, A., Sharp, D. & Tylee, A. The prevalence of suicidal ideation
1374 identified by the Edinburgh Postnatal Depression Scale in postpartum women in primary care:
1375 findings from the RESPOND trial. *BMC pregnancy and childbirth* **11**, 57 (2011).
- 1376 149. Brealey, S.D., Hewitt, C., Green, J.M., Morrell, J. & Gilbody, S. Screening for postnatal
1377 depression—Is it acceptable to women and healthcare professionals? A systematic review and
1378 meta-synthesis. *Journal of Reproductive and Infant Psychology* **28**, 328-344 (2010).

- 1379 150. Gemmill, A.W., Leigh, B., Ericksen, J. & Milgrom, J. A survey of the clinical acceptability of
1380 screening for postnatal depression in depressed and non-depressed women. *BMC Public Health*
1381 **6**, 211 (2006).
- 1382 151. Wisner, K. et al. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with
1383 screen-positive depression findings. *JAMA Psychiatry* **70**, 490-498 (2013).
- 1384 152. Beck, C.T. & Gable, R.K. Postpartum Depression Screening Scale: development and
1385 psychometric testing. *Nursing research* **49**, 272-82 (2000).
- 1386 153. Beck, A.T., Steer, R.A. & Brown, G.K. Manual for the BDI-II (The Psychological Corporation, San
1387 Antonio, TX, 1996).
- 1388 154. Kroenke, K., Spitzer, R.L. & Williams, J.B. The PHQ-9: validity of a brief depression severity
1389 measure. *Journal of General Internal Medicine* **16**, 606-13 (2001).
- 1390 155. Yawn, B.P. et al. TRIPPD: A practice-based network effectiveness study of postpartum
1391 depression screening and management. *The Annals of Family Medicine* **10**, 320-329 (2012).
- 1392 156. Whooley, M., Avins, A. & Miranda, J. Case-finding instruments for depression: two questions are
1393 as good as many. *J Gen Intern Med* **12**, 439-445 (1997).
- 1394 157. Arroll, B., Smith, F.G., Kerse, N., Fishman, T. & Gunn, J. Effect of the addition of a "help" question
1395 to two screening questions on specificity for diagnosis of depression in general practice:
1396 diagnostic validity study. *BMJ* **331**, 884 (2005).
- 1397 158. Falah-Hassani, K., Shiri, R. & Dennis, C.L. The prevalence of antenatal and postnatal co-morbid
1398 anxiety and depression: a meta-analysis. *Psychol Med* **47**, 2041-2053 (2017).
- 1399 159. Milgrom, J. et al. Feasibility study and pilot randomised trial of an antenatal depression
1400 treatment with infant follow-up. *Archives of Women's Mental Health* **18**, 717-30 (2015).
- 1401 160. Matthey, S., Fisher, J. & Rowe, H. Using the Edinburgh postnatal depression scale to screen for
1402 anxiety disorders: Conceptual and methodological considerations. *Journal of Affective Disorders*
1403 **146**, 224-230 (2013).
- 1404 161. Somerville, S. et al. Detecting the severity of perinatal anxiety with the Perinatal Anxiety
1405 Screening Scale (PASS). *Journal of Affective Disorders* **186**, 18-25 (2015).
- 1406 162. Spitzer, R.L., Kroenke, K., Williams, J.B. & Lowe, B. A brief measure for assessing generalized
1407 anxiety disorder: the GAD-7. *Arch Intern Med* **166**, 1092-7 (2006).
- 1408 163. Lord, C., Rieder, A., Hall, G.B., Soares, C.N. & Steiner, M. Piloting the perinatal obsessive-
1409 compulsive scale (POCS): development and validation. *J Anxiety Disord* **25**, 1079-84 (2011).
- 1410 164. Meltzer-Brody, S., Churchill, E. & Davidson, J.R. Derivation of the SPAN, a brief diagnostic
1411 screening test for post-traumatic stress disorder. *Psychiatry Res* **88**, 63-70 (1999).
- 1412 165. Frey, B.N., Simpson, W., Wright, L. & Steiner, M. Sensitivity and specificity of the Mood Disorder
1413 Questionnaire as a screening tool for bipolar disorder during pregnancy and the postpartum
1414 period. *Journal of Clinical Psychiatry* **73**, 1456-1461 (2012).
- 1415 166. Clark, C.T. et al. Does Screening with the MDQ and EPDS Improve Identification of Bipolar
1416 Disorder in an Obstetrical Sample? *Depression and Anxiety* **32**, 518-26 (2015).
- 1417 167. Chessick, C.A. & Dimidjian, S. Screening for bipolar disorder during pregnancy and the
1418 postpartum period. *Arch Women Ment Health* **13**, 233-248 (2010).
- 1419 168. Kelly, E. & Sharma, V. Diagnosis and treatment of postpartum bipolar depression. *Expert review*
1420 *of neurotherapeutics* **10**, 1045-1051 (2010).
- 1421 169. Stanton, K. & Watson, D. Explicating the structure and relations of the Mood Disorder
1422 Questionnaire: Implications for screening for bipolar and related disorders. *J Affect Disord* **220**,
1423 72-78 (2017).
- 1424 170. Yawn, B.P., LaRusso, E.M., Bertram, S.L. & Bobo, W.V. in *Identifying Perinatal Depression and*
1425 *Anxiety* 32-50 (John Wiley & Sons, Ltd, 2015).
- 1426 171. Milgrom, J. & Gemmill, A.W. in *Applied Topics in Health Psychology* (eds. Caltabiano, M. &
1427 Ricciardelli, L.) 212-227 (Wiley, Chichester, 2013).
- 1428 172. O'Connor, E., Rossom, R.C., Henninger, M., Groom, H.C. & Burda, B.U. Primary care screening for
1429 and treatment of depression in pregnant and postpartum women evidence report and

- 1430 systematic review for the US preventive services task force. *JAMA - Journal of the American*
 1431 *Medical Association* **315**, 388-406 (2016).
- 1432 173. Milgrom, J. et al. Internet Cognitive Behavioral Therapy for Women With Postnatal Depression:
 1433 A Randomized Controlled Trial of MumMoodBooster. *J Med Internet Res* **18**, e54 (2016).
- 1434 174. Wilkinson, A., Anderson, S. & Wheeler, S.B. Screening for and Treating Postpartum Depression
 1435 and Psychosis: A Cost-Effectiveness Analysis. *Maternal and Child Health Journal* **21**, 903-914
 1436 (2017).
- 1437 175. Werner, E., Miller, M., Osborne, L.M., Kuzava, S. & Monk, C. Preventing postpartum depression:
 1438 review and recommendations. *Archives of Women's Mental Health* **18**, 41-60 (2015).
- 1439 176. Dennis, C.L. & Dowswell, T. Psychosocial and psychological interventions for preventing
 1440 postpartum depression. *Cochrane Database Syst Rev*, CD001134 (2013).
- 1441 177. Morrell, C.J. et al. A systematic review, evidence synthesis and meta-analysis of quantitative
 1442 and qualitative studies evaluating the clinical effectiveness, the cost-effectiveness, safety and
 1443 acceptability of interventions to prevent postnatal depression. *Health Technology Assessment*
 1444 **20**, 1-414 (2016).
- 1445 178. Payne, J.L. Recent Advances and Controversies in Peripartum Depression. *Curr Obstet Gynecol*
 1446 *Rep* **5**, 250-256 (2016).
- 1447 179. Wisner, K.L. & Wheeler, S.B. Prevention of recurrent postpartum major depression. *Hosp*
 1448 *Community Psychiatry* **45**, 1191-6 (1994).
- 1449 180. Dennis, C.L. & Dowswell, T. Interventions (other than pharmacological, psychosocial or
 1450 psychological) for treating antenatal depression. *Cochrane Database Syst Rev*, CD006795
 1451 (2013).
- 1452 181. Kwan, B.M., Dimidjian, S. & Rizvi, S.L. Treatment preference, engagement, and clinical
 1453 improvement in pharmacotherapy versus psychotherapy for depression. *Behav Res Ther* **48**,
 1454 799-804 (2010).
- 1455 182. Dennis, C.L. & Chung-Lee, L. Postpartum depression help-seeking barriers and maternal
 1456 treatment preferences: a qualitative systematic review. *Birth* **33**, 323-31 (2006).
- 1457 183. Cameron, E.E., Hunter, D., Sedov, I.D. & Tomfohr-Madsen, L.M. What do dads want? Treatment
 1458 preferences for paternal postpartum depression. *J Affect Disord* **215**, 62-70 (2017).
- 1459 184. de Camps Meschino, D., Philipp, D., Israel, A. & Vigod, S. Maternal-infant mental health:
 1460 postpartum group intervention. *Arch Womens Ment Health* **19**, 243-51 (2016).
- 1461 185. Dennis, C.L. & Hodnett, E. Psychosocial and psychological interventions for treating postpartum
 1462 depression. *Cochrane Database Syst Rev*, CD006116 (2007).
- 1463 186. Ashford, M.T., Olander, E.K. & Ayers, S. Computer- or web-based interventions for perinatal
 1464 mental health: A systematic review. *J Affect Disord* **197**, 134-46 (2016).
- 1465 187. Goodman, J.H., Watson, G.R. & Stubbs, B. Anxiety disorders in postpartum women: A systematic
 1466 review and meta-analysis. *J Affect Disord* **203**, 292-331 (2016).
- 1467 188. Challacombe, F.L. et al. A pilot randomized controlled trial of time-intensive cognitive-
 1468 behaviour therapy for postpartum obsessive-compulsive disorder: effects on maternal
 1469 symptoms, mother-infant interactions and attachment. *Psychol Med* **47**, 1478-1488 (2017).
- 1470 189. Bisson, J.I., Roberts, N.P., Andrew, M., Cooper, R. & Lewis, C. Psychological therapies for chronic
 1471 post-traumatic stress disorder (PTSD) in adults. *Cochrane Database Syst Rev*, CD003388
 1472 (2013).
- 1473 190. Molyneaux, E., Howard, L.M., McGeown, H.R., Karia, A.M. & Trevillion, K. Antidepressant
 1474 treatment for postnatal depression. *Cochrane Database Syst Rev*, CD002018 (2014).
- 1475 191. Milgrom, J. et al. Treatment of postnatal depression with cognitive behavioural therapy,
 1476 sertraline and combination therapy: a randomised controlled trial. *Aust N Z J Psychiatry* **49**,
 1477 236-45 (2015).
- 1478 192. Lam, R.W. et al. Effects of combined pharmacotherapy and psychotherapy for improving work
 1479 functioning in major depressive disorder. *Br J Psychiatry* **203**, 358-65 (2013).

- 1480 193. Lam, R.W. et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical
1481 Guidelines for the Management of Adults with Major Depressive Disorder: Section 1. Disease
1482 Burden and Principles of Care. *Can J Psychiatry* **61**, 510-23 (2016).
- 1483 194. Khalifeh, H., Hunt, I.M., Appleby, L. & Howard, L.M. Suicide in perinatal and non-perinatal
1484 women in contact with psychiatric services: 15 year findings from a UK national inquiry.
1485 *Lancet Psychiatry* **3**, 233-42 (2016).
- 1486 195. Orsolini, L. & Bellantuono, C. Serotonin reuptake inhibitors and breastfeeding: a systematic
1487 review. *Hum Psychopharmacol* **30**, 4-20 (2015).
- 1488 196. Sriraman, N.K., Melvin, K. & Meltzer-Brody, S. ABM Clinical Protocol #18: Use of
1489 Antidepressants in Breastfeeding Mothers. *Breastfeed Med* **10**, 290-9 (2015).
- 1490 197. Dennis, C.L., Ross, L.E. & Herxheimer, A. Oestrogens and progestins for preventing and treating
1491 postpartum depression. *Cochrane Database Syst Rev*, CD001690 (2008).
- 1492 198. Deligiannidis, K.M. & Freeman, M.P. Complementary and alternative medicine therapies for
1493 perinatal depression. *Best Pract Res Clin Obstet Gynaecol* **28**, 85-95 (2014).
- 1494 199. Pritchett, R.V., Daley, A.J. & Jolly, K. Does aerobic exercise reduce postpartum depressive
1495 symptoms? a systematic review and meta-analysis. *Br J Gen Pract* **67**, e684-e691 (2017).
- 1496 200. Meltzer-Brody, S. et al. Evaluating the clinical effectiveness of a specialized perinatal psychiatry
1497 inpatient unit. *Arch Womens Ment Health* (2013).
- 1498 201. Glangeaud-Freudenthal, N.M., Howard, L.M. & Sutter-Dallay, A.L. Treatment - mother-infant
1499 inpatient units. *Best Pract Res Clin Obstet Gynaecol* **28**, 147-57 (2014).
- 1500 202. Health, A.G.D.o. (Commonwealth of Australia, 2013).
- 1501 203. Bergink, V. et al. Treatment of psychosis and mania in the postpartum period. *Am J Psychiatry*
1502 **172**, 115-23 (2015).
- 1503 204. Babu, G.N., Thippeswamy, H. & Chandra, P.S. Use of electroconvulsive therapy (ECT) in
1504 postpartum psychosis-a naturalistic prospective study. *Arch Womens Ment Health* **16**, 247-51
1505 (2013).
- 1506 205. Lichtenberg, P., Navon, R., Wertman, E., Dasberg, H. & Lerer, B. Post-partum psychosis in adult
1507 GM2 gangliosidosis. A case report. *Br J Psychiatry* **153**, 387-9 (1988).
- 1508 206. Doucet, S., Jones, I., Letourneau, N., Dennis, C.L. & Blackmore, E.R. Interventions for the
1509 prevention and treatment of postpartum psychosis: a systematic review. *Arch Womens Ment*
1510 *Health* (2010).
- 1511 207. Gobbi, G. Quetiapine in postpartum psychosis. *J Clin Psychopharmacol* **34**, 744-5 (2014).
- 1512 208. Smith, B. & Dubovsky, S.L. Pharmacotherapy of mood disorders and psychosis in pre- and post-
1513 natal women. *Expert Opin Pharmacother* **18**, 1703-1719 (2017).
- 1514 209. Meador, K.J. et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years
1515 (NEAD study): a prospective observational study. *Lancet Neurol* **12**, 244-52 (2013).
- 1516 210. Bromley, R.L., Weston, J. & Marson, A.G. Maternal Use of Antiepileptic Agents During Pregnancy
1517 and Major Congenital Malformations in Children. *JAMA* **318**, 1700-1701 (2017).
- 1518 211. Ornoy, A., Weinstein-Fudim, L. & Ergaz, Z. Antidepressants, Antipsychotics, and Mood
1519 Stabilizers in Pregnancy: What Do We Know and How Should We Treat Pregnant Women with
1520 Depression. *Birth Defects Res* **109**, 933-956 (2017).
- 1521 212. Bogen, D.L., Sit, D., Genovese, A. & Wisner, K.L. Three cases of lithium exposure and exclusive
1522 breastfeeding. *Arch Womens Ment Health* **15**, 69-72 (2012).
- 1523 213. Viguera, A.C. et al. Lithium in breast milk and nursing infants: clinical implications. *Am J*
1524 *Psychiatry* **164**, 342-5 (2007).
- 1525 214. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders
1526 (American Psychiatric Press, Arlington, VA, 2013).
- 1527 215. Kahneman, D. & Deaton, A. High income improves evaluation of life but not emotional well-
1528 being. *Proceedings of the National Academy of Sciences of the United States of America* **107**,
1529 16489-93 (2010).

- 1530 216. Diego, M.A. & al., e. Withdrawn and intrusive maternal interaction style and infant frontal EEG
1531 asymmetry shifts in infants. *Infant Behavior & Development* **29**, 220-229 (2006).
- 1532 217. Reck, C. et al. Interactive regulation of affect in postpartum depressed mothers and their
1533 infants: an overview. *Psychopathology* **37**, 272-80 (2004).
- 1534 218. Murray, L. et al. Controlled trial of the short- and long-term effect of psychological treatment of
1535 post-partum depression: 2. Impact on the mother-child relationship and child outcome. *British*
1536 *Journal of Psychiatry* **182**, 420-7 (2003).
- 1537 219. Field, T.M. Early interactions between infants and their postpartum depressed mothers. *Infant*
1538 *Behavior & Development* (2002).
- 1539 220. Lyons-Ruth, K. Contributions of the Mother-Infant Relationship to Dissociative, Borderline, and
1540 Conduct Symptoms in Young Adulthood. *Infant Ment Health J* **29**, 203-218 (2008).
- 1541 221. Pearson, R.M. et al. Maternal depression during pregnancy and the postnatal period: risks and
1542 possible mechanisms for offspring depression at age 18 years. *JAMA Psychiatry* **70**, 1312-9
1543 (2013).
- 1544 222. Cooper, P.J., De Pascalis, L., Woolgar, M., Romaniuk, H. & Murray, L. Attempting to prevent
1545 postnatal depression by targeting the mother-infant relationship: a randomised controlled
1546 trial. *Prim Health Care Res Dev* **16**, 383-97 (2015).
- 1547 223. Abel, K.M., Webb, R.T., Salmon, M.P., Wan, M.W. & Appleby, L. Prevalence and predictors of
1548 parenting outcomes in a cohort of mothers with schizophrenia admitted for joint mother and
1549 baby psychiatric care in England. *J Clin Psychiatry* **66**, 781-9; quiz 808-9 (2005).
- 1550 224. Ware, J.E., Jr. & Sherbourne, C.D. The MOS 36-item short-form health survey (SF-36). I.
1551 Conceptual framework and item selection. *Medical Care* **30**, 473-83 (1992).
- 1552 225. Kalyoncu, U., Dougados, M., Daures, J.P. & Gossec, L. Reporting of patient-reported outcomes in
1553 recent trials in rheumatoid arthritis: a systematic literature review. *Annals of the Rheumatic*
1554 *Diseases* **68**, 183-90 (2009).
- 1555 226. Ware, J., Jr., Kosinski, M. & Keller, S.D. A 12-Item Short-Form Health Survey: construction of
1556 scales and preliminary tests of reliability and validity. *Medical Care* **34**, 220-33 (1996).
- 1557 227. Zubaran, C. & Foresti, K. Investigating quality of life and depressive symptoms in the
1558 postpartum period. *Women and birth : journal of the Australian College of Midwives* **24**, 10-6
1559 (2011).
- 1560 228. Mogos, M.F., August, E.M., Salinas-Miranda, A.A., Sultan, D.H. & Salihu, H.M. A Systematic Review
1561 of Quality of Life Measures in Pregnant and Postpartum Mothers. *Appl Res Qual Life* **8**, 219-250
1562 (2013).
- 1563 229. Symon, A., MacDonald, A. & Ruta, D. Postnatal quality of life assessment: Introducing the
1564 Mother-Generated Index. *Birth: Issues in Perinatal Care* **29**, 40-46 (2002).
- 1565 230. Hill, P.D., Aldag, J.C., Hekel, B., Riner, G. & Bloomfield, P. Maternal Postpartum Quality of Life
1566 Questionnaire. *Journal of Nursing Measurement* **14**, 205-20 (2006).
- 1567 231. Huang, K., Tao, F., Liu, L. & Wu, X. Does delivery mode affect women's postpartum quality of life
1568 in rural China? *Journal of Clinical Nursing* **21**, 1534-43 (2012).
- 1569 232. Ruta, D.A., Garratt, A.M., Leng, M., Russell, I.T. & MacDonald, L.M. A new approach to the
1570 measurement of quality of life. The Patient-Generated Index. *Medical Care* **32**, 1109-26 (1994).
- 1571 233. Brenes, G.A. Anxiety, depression, and quality of life in primary care patients. *Prim Care*
1572 *Companion J Clin Psychiatry* **9**, 437-43 (2007).
- 1573 234. Roberts, J., Lenton, P., Keetharuth, A.D. & Brazier, J. Quality of life impact of mental health
1574 conditions in England: results from the adult psychiatric morbidity surveys. *Health Qual Life*
1575 *Outcomes* **12**, 1477-7525 (2014).
- 1576 235. Barkin, J.L., Wisner, K.L., Bromberger, J.T., Beach, S.R. & Wisniewski, S.R. Assessment of
1577 functioning in new mothers. *Journal of Womens Health* **19**, 1493-9 (2010).
- 1578 236. Sadat, Z., Abedzadeh-Kalahroudi, M., Kafaei Atrian, M., Karimian, Z. & Sooki, Z. The Impact of
1579 Postpartum Depression on Quality of Life in Women After Child's Birth. *Iran Red Crescent Med J*
1580 **16**, 5 (2014).

- 1581 237. Webster, J., Nicholas, C., Velacott, C., Cridland, N. & Fawcett, L. Quality of life and depression
1582 following childbirth: impact of social support. *Midwifery* **27**, 745-9 (2011).
- 1583 238. Bodhare, T.N., Sethi, P., Bele, S.D., Gayatri, D. & Vivekanand, A. Postnatal quality of life,
1584 depressive symptoms, and social support among women in southern India. *Women and Health*
1585 **55**, 353-65 (2015).
- 1586 239. Bauer, A., Parsonage, M., Knapp, M., Iemmi, V. & Adelaja, B. (London School of Economics and
1587 the Centre for Mental Health, London, 2014).
- 1588 240. Vliegen, N., Casalin, S. & Luyten, P. The course of postpartum depression: a review of
1589 longitudinal studies. *Harvard Review of Psychiatry* **22**, 1-22 (2014).
- 1590 241. Dolman, C., Jones, I.R. & Howard, L.M. Women with bipolar disorder and pregnancy: factors
1591 influencing their decision-making. *BJPsych Open* **2**, 294-300 (2016).
- 1592 242. Dolman, C., Jones, I. & Howard, L.M. Pre-conception to parenting: a systematic review and
1593 meta-synthesis of the qualitative literature on motherhood for women with severe mental
1594 illness. *Arch Womens Ment Health* **16**, 173-96 (2013).
- 1595 243. Paulson, J.F. & Bazemore, S.D. Prenatal and postpartum depression in fathers and its
1596 association with maternal depression: a meta-analysis. *JAMA* **303**, 1961-9 (2010).
- 1597 244. Davis, R.N., Davis, M.M., Freed, G.L. & Clark, S.J. Fathers' depression related to positive and
1598 negative parenting behaviors with 1-year-old children. *Pediatrics* **127**, 612-8 (2011).
- 1599 245. Hoffman, C., Dunn, D.M. & Njoroge, W.F.M. Impact of Postpartum Mental Illness Upon Infant
1600 Development. *Curr Psychiatry Rep* **19**, 100 (2017).
- 1601 246. Paulson, J.F., Bazemore, S.D., Goodman, J.H. & Leiferman, J.A. The course and interrelationship
1602 of maternal and paternal perinatal depression. *Archives of Women's Mental Health* **19**, 655-663
1603 (2016).
- 1604 247. Lund, C. et al. Poverty and mental disorders: breaking the cycle in low-income and middle-
1605 income countries. *Lancet* **378**, 1502-14 (2011).
- 1606 248. Allen, J., Balfour, R., Bell, R. & Marmot, M. Social determinants of mental health. *Int Rev*
1607 *Psychiatry* **26**, 392-407 (2014).
- 1608 249. Naila, K. Gender, poverty, and inequality: a brief history of feminist contributions in the field of
1609 international development. *Gender and Development* **23** (2015).
- 1610 250. Burns, P.A., Zunt, J.R., Hernandez, B. Intimate Partner Violence, Poverty, and Maternal Health
1611 Care-Seeking Among Young Women in Kenya: a Cross-Sectional Analysis Informing the New
1612 Sustainable Development Goals. *Global and Social Welfare* (2018).
- 1613 251. WHO, H.W. (World Health Organization, Geneva, 2014).
- 1614 252. Chisholm, D. et al. Scaling-up treatment of depression and anxiety: a global return on
1615 investment analysis. *Lancet Psychiatry* **3**, 415-24 (2016).
- 1616 253. Chisholm, D., Lund, C. & Saxena, S. Cost of scaling up mental healthcare in low- and middle-
1617 income countries. *Br J Psychiatry* **191**, 528-35 (2007).
- 1618 254. Rahman, A., Surkan, P.J., Cayetano, C.E., Rwagatare, P. & Dickson, K.E. Grand challenges:
1619 integrating maternal mental health into maternal and child health programmes. *PLoS Med* **10**,
1620 e1001442 (2013).
- 1621 255. Patel, V. et al. Addressing the burden of mental, neurological, and substance use disorders: key
1622 messages from Disease Control Priorities, 3rd edition. *Lancet* **387**, 1672-85 (2016).
- 1623 256. Organization, B.o.W.H. (ed. [PDF], d.h.d.o.B.) (2013).
- 1624 257. Rahman, A., Malik, A., Sikander, S., Roberts, C. & Creed, F. Cognitive behaviour therapy-based
1625 intervention by community health workers for mothers with depression and their infants in
1626 rural Pakistan: a cluster-randomised controlled trial. *Lancet* **372**, 902-9 (2008).
- 1627 258. Rojas, G. et al. Treatment of postnatal depression in low-income mothers in primary-care
1628 clinics in Santiago, Chile: a randomised controlled trial. *Lancet* **370**, 1629-37 (2007).
- 1629 259. Chibanda, D. et al. Group problem-solving therapy for postnatal depression among HIV-positive
1630 and HIV-negative mothers in Zimbabwe. *J Int Assoc Provid AIDS Care* **13**, 335-41 (2014).

- 1631 260. Jahanfar, S., Howard, L.M. & Medley, N. Interventions for preventing or reducing domestic
1632 violence against pregnant women. *Cochrane Database Syst Rev*, CD009414 (2014).
- 1633 261. Shrestha, S.D., Pradhan, R., Tran, T.D., Gualano, R.C. & Fisher, J.R. Reliability and validity of the
1634 Edinburgh Postnatal Depression Scale (EPDS) for detecting perinatal common mental
1635 disorders (PCMDs) among women in low-and lower-middle-income countries: a systematic
1636 review. *BMC Pregnancy Childbirth* **16**, 72 (2016).
- 1637
- 1638