Onderzoeksprogramma Postpartum Psychiatry Erasmus MC Rotterdam

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The overall aim of this study is to investigate the pathophysiology of PPMD, and identify predictors of longitudinal outcome.Primary Objective: The primary objective is to investigate the underlying neurobiology of first-onset PPMD using...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Psychiatric disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON53094

Source
ToetsingOnline

Brief title
OPPER

Condition

- Psychiatric disorders NEC

Synonym
postpartum mood disorder; postnatal psychiatric disorder

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Early child development, Magnetic Resonance Imaging, Postpartum mood disorders, Relapse

Outcome measures

Primary outcome

The primary objective is to investigate the underlying neurobiology of first-onset PPMD using longitudinal neuroimaging. Brain imaging will be performed during both the acute episode (median 4 weeks postpartum) and after full remission (12 months after onset). All MRI scans will be made by a trained researcher and trained research assistant. The scanning protocol contains a whole-brain structural MRI examination combined with Diffusion Tensor Imaging (DTI), functional MRI (fMRI) scans and Magnetic Resonance Spectroscopy (MRS). Because our previous research showed a possible auto-immune related cause of postpartum mood disorders, we expect changes in white matter. Therefore our primary measure will be white matter integrity, measured by the fractional anisotropy (FA). Fractional anisotropy is the most-widely used DTI-based index in brain research. Fractional anisotropy provides a gray-scale, 2D map, enhancing diffusion anisotropy difference with intensity limits between zero and one. In white matter, the anisotropy is high (approaching unity in most ordered areas), reflecting fast diffusivity along the fibers and slow diffusivity perpendicular to them. In gray matter and CSF, the anisotropy approaches zero as the diffusivity is similar in all directions. White matter abnormalities lead to a decrease in fractional anisotropy

Secondary outcome

Secondary endpoints include the longitudinal course of women with first-onset PPMD and predictive factors for the longitudinal disease course (and thus for the need for long-term maintenance therapy). Our main variable of interest is relapse.

Relapse will be defined as the occurrence of any affective or psychotic symptoms fulfilling DSM-IV-R criteria and severe enough to warrant treatment. We will make a clear distinction of relapse after a subsequent pregnancy versus a relapse outside the postpartum period, thereby enabling the distinction between women with episodes of affective psychosis entirely limited to the postpartum period (PPMD only) versus those with a lifelong mood disorder.

Our previous showed that overall relapse risk for women with only postpartum-onset psychoses is 31% (95% CI=22, 42) as derived from 13 studies, 595 deliveries, and 528 patients. The risk of a postpartum episode (affective psychosis, mania, mixed episode, or relapse requiring hospitalization) was significantly higher in patients with a history of postpartum psychosis (29%, 95% CI=20, 41) compared to women with more chronic forms of bipolar disorder. Further, in stark contrast to the high rates of relapse in women with bipolar disorder during pregnancy, women with a history of psychosis limited to the postpartum period are not at elevated risk of psychiatric episodes during pregnancy.

We hypothesize that predictive factors for the longitudinal course might include:

a. timing of onset

b. genetic vulnerability

c. immune related vulnerability

Timing of onset

The onset and severity of PPMD in the early postpartum period is not only of diagnostic importance, but it may also well predict the likelihood of subsequent conversion to a lifelong mood disorder. Several clinical experts in the field have discussed the perspective that very early PPMD is more likely to have a bipolar diathesis, especially if prominent manic symptoms are present. In contrast, from a neurobiological perspective, a very early onset could be suggestive for a favorable disease course (PPMD only), because the most prominent physiological changes occur within the first week postpartum (endocrine, immunological). Our Danish collaborators reported that primiparous women had an increased risk of incident hospital admission with any mental disorder through the first 3 months after childbirth, with the highest risk 10 to 19 days postpartum (relative risk [RR], 7.31; 95% confidence interval [CI], 5.44-9.81). This is consistent with our work; we found a median onset of postpartum psychosis 8 days following delivery, (interquartile range 5-14) in our clinical cohort. We will use the data of initial mental health contact as date of onset. We hypothesize that an earlier onset will correspond to a more favourable disease.

Genetic vulnerability

Information on the family history of both bipolar and postpartum episodes will allow a unique look at the extent to which the genetic vulnerability for PPMD and bipolar disorder are distinct or shared. It is well known that the heritability for bipolar disorder is estimated to be up to 80%. In addition, there is increasing evidence of a high heritability for postpartum episodes of affective psychosis. Our Danish collaborators found that bipolar family psychopathology represents a significant risk factor for the first onset of psychiatric episodes in the postpartum period. It is very interesting to investigate what the risk of a further bipolar disease course will be after this first onset episode, if a family member suffers from bipolar affective disorder. Moreover, within a larger consortium we will investigate genetic loci that are associated with vulnerability to severe postpartum onset. Our hypothesis is that bipolar family history is an important risk factor for a bipolar disease course.

Immune related vulnerability

Interestingly, the pathophysiology of every non-psychiatric medical condition known to have a postpartum flare pattern has been established to arise from immune dysfunction, including rheumatoid arthritis, multiple sclerosis, autoimmune thyroid dysfunction, autoimmune hepatitis, and myasthenia gravis. Common characteristics of these pregnancy-related autoimmune diseases include familial occurrence, progression from subclinical to clinical disease, a cyclical exacerbation- remission pattern, and a high recurrence risk with subsequent pregnancies. Remarkably, PPMD has shown to possess all of these

clinical features and we postulate that postpartum activation of the immune system is central to the pathogenesis of these postpartum mood disorders. Our previous work showed that patients with postpartum psychosis have significantly elevated rates of autoimmune thyroiditis and pre-eclampsia, both of which have established autoimmune etiologies. Recently, we showed that a very small subgroup of patients suffered from undiagnosed autoimmune encephalitis. Lastly, we observed abnormalities in monocyte activation, T cell function and tryptophan breakdown in patients with postpartum psychosis during the acute phase compared to postpartum controls,all suggestive for immune system dysfunction. We intend to investigate if immune abnormalities are predictive for the disease course.

Another secondary study parameter will be early child development.

Study description

Background summary

Childbirth has the highest relative risk of any vulnerability factor associated with the onset of severe psychiatric illness. The three main conditions that are associated with childbirth are the maternity blues, postnatal depression and post-partum psychosis. Postpartum blues are mild mood changes that commonly occur during the early postpartum period and these are not the focus on this current protocol. In contrast, postpartum depression and psychosis are serious clinical disorders, here called postpartum mood disorders (PPMD). Postpartum depression is a clinical syndrome of moderate to severe depressive symptoms that lasts longer than postpartum blues and has a greater impact on the family. The prevalence of postpartum depression is about 10% and occurs within 4 weeks of childbirth, according to the DSM-IV. However most researchers suggests that it can occur within the first year postpartum. The signs and symptoms of postpartum depression are generally indistinguishable from those associated with major depression occurring at other times and

include depressed mood, anhedonia, low energy and guilty ruminations. There are, however subtle differences, including: (a) difficulty sleeping when the baby sleeps, (b) lack of enjoyment in the maternal role, (c) feelings of guilt related to parenting ability.
Postpartum psychosis is the most severe form of pregnancy-related psychiatric illness, with a prevalence in the general population of 0.1%. Postpartum psychosis occurs most frequently in primiparous women without a psychiatric history and generally manifests acutely within 4 weeks after delivery. The relative risk for the first onset of affective psychosis such as mania or psychotic depression is 23 times higher within 4 weeks after delivery, compared to any other period during a woman*s life. The cardinal symptomatology is affective and severe, including acute mania, depression, or a mixed state. Psychotic symptoms almost exclusively occur within the setting of affective instability. The initial clinical evaluation for postpartum psychosis requires a thorough physical and neurological evaluation.
From a research perspective, PPMD is among the few psychiatric disorders in which the etiological event is known. Childbirth is the responsible trigger for PPMD, but there are many important unanswered questions regarding pathophysiology and prognosis.

Rationale primary objective
This will be the first neuroimaging study conducted in women with severe postpartum psychiatric episodes. The primary aim is to investigate the underlying neural mechanisms of PPMD, with a particular focus on white matter integrity. Our previous research provided novel evidence for a central role of the immune system in the pathogenesis of postpartum disorder. The postpartum period is well established as a high-risk period for demyelinating autoimmune central nerve system diseases, such as multiple sclerosis , neuromyelitis optica, and radiologically isolated syndrome- the precursor of multiple sclerose. In these demyelinating diseases, and highly similar to PPMD, the postpartum period confers a dramatically increased risk of both first-onset and relapse episodes. Interestingly, psychotic symptoms are not infrequently observed in patients with multiple sclerose. Furthermore, clinical features of demyelination are observed in a substantial proportion of patients with anti-NMDA receptor encephalitis, for which psychosis is frequently observed, including postpartum psychosis. White matter abnormalities are widely demonstrated to be the central pathophysiological cause in multiple sclerose, even in areas that appear normal on standard Magnetic Resonance Imaging (MRI). A more subtle form of white matter pathology has previously been shown in bipolar patients using both brain imaging and postmortem immunohistochemistry. This has also been shown in patients with a unipolar major depression . Both grey and white matter abnormalities have been shown to be present during the early stages of bipolar disorder. They are of potential pathophysiological significance in bipolar disorder as they are associated with a poor clinical and functional outcome with cognitive decline, suicide attempts and treatment resistance.
The development of modern neuroimaging techniques, such as diffusion tensor

imaging, has allowed white matter abnormalities and the resulting abnormal functional connectivity to be investigated in greater detail. Therefore, to identify the underlying neurobiology of first-onset PPMD, we will use a longitudinal prospective design, with neuroimaging both during the first-onset acute phase, as well as after complete remission. Specifically, we will examine white matter volume (structural imaging), whole-brain and tract-based white matter microstructure (diffusion weighted imaging), and functional connectivity (resting state and passive viewing fMRI). Besides we will examine lithium concentration in the brain with magnetic resonance spectroscopy (MRS). Our overall hypothesis is that white matter integrity will be impaired in women with PPMD, and potentially distinguishable between women with a lifelong mood disorder versus those with a vulnerability limited to the postpartum period.

Rationale secondary objectives
In current clinical practice, most women with first-onset severe postpartum episodes are given a diagnosis of a lifelong mood disorder, mostly bipolar disorder, mainly because of these severe affective symptoms. With an adequate treatment regime, nearly all women with PPMD achieve a full remission. After complete remission of this first episode, women get the recommendation to use long-term maintenance pharmacotherapy. The traditional rationale underlying the recommendation for chronic pharmacotherapy is the prevention of subsequent psychotic and affective episodes. Importantly however, retrospective studies have documented that a substantial proportion of women with PPMD appear not to be at increased risk for subsequent episodes outside the postpartum period. These women do not develop a lifelong bipolar disorder, with the most significant implication being that these women might be unnecessarily exposed to the potentially severe side effects of medication. They have vulnerability to a mood disorder that is limited to the postpartum period (PPMD only). Together, women with PPMD have one of two disease courses:
- Lifelong mood disorder with episodes outside the postpartum,
- PPMD only

The distinction is of profound clinical relevance given that the current practice of diagnosing all women with classical bipolar disorder following postpartum psychosis of postpartum depression has likely led to a substantial proportion of women receiving long-term pharmacotherapy without any potential benefit.
Therefore, a secondary objective of our research is to describe the longitudinal course of women with a first-onset PPMD. Based on previous research, we hypothesize that 60% of women have classical bipolar disorder, while 40% of women will exhibit a vulnerability to affective psychosis or depression that is limited to the postpartum period (PPMD only). Our main variable of interest is relapse.
Relapse will be defined as the occurrence of any affective or psychotic symptoms fulfilling DSM-IV-R criteria and severe enough to warrant treatment. We will make a clear distinction of relapse after a subsequent pregnancy versus a relapse outside the postpartum period, thereby enabling the distinction

between women with episodes of affective psychosis entirely limited to the postpartum period (PPMD only) versus those with a lifelong mood disorder. Another secondary objective is to find predictive factors for the longitudinal disease course (and thus for the need for long-term maintenance therapy) of PPMD. Postpartum psychosis is a psychiatric condition with an intrinsically defined onset wi

Study objective

The overall aim of this study is to investigate the pathophysiology of PPMD, and identify predictors of longitudinal outcome.

Primary Objective:
The primary objective is to investigate the underlying neurobiology of first-onset PPMD using longitudinal neuroimaging.

Our overall hypothesis is that white matter integrity will be impaired in women with PPMD, and potentially distinguishable between women with classical bipolar disorder versus those with a vulnerability limited to the postpartum period.

Secondary Objective(s):
Secondary objectives are to describe the longitudinal course of women with first-onset PPMD and to find predictive factors for the longitudinal disease course (and thus for the need for long-term maintenance therapy).

We hypothesize, based on previous studies, that women with PPMD will emerge into two primary subgroups; women for whom post-partum psychosis or depression represents the onset of a lifelong course of bipolar disorder (60%) and women in which episodes of affective psychosis or depression are entire limited to the postpartum period (40%) (1-6). Our main variable of interest is relapse, which will be defined as the occurrence of any affective or psychotic symptoms fulfilling DSM-IV-R criteria and severe enough to warrant treatment. We will make a clear distinction of relapse after a subsequent pregnancy versus a relapse outside the postpartum period, thereby enabling the distinction between women with episodes of affective psychosis entirely limited to the postpartum period (PPMD only) versus those with a lifelong mood disorder.

Also we hypothesize that predictive factors for the longitudinal course might include:
(a) timing of onset
(b) genetic vulnerability
(c) immune related vulnerability

Another secondary objective will be the assessment of early child development.

Study design

Design: Longitudinal naturalistic prospective cohort study
Duration: This is an ongoing prospective cohort study
Follow-up: 4 years
Setting: This is a multicenter prospective cohort study in the Netherlands in which three mental health institutions collaborate: Erasmus Medical Center Rotterdam, St. Antonius Ziekenhuis, Utrecht and Leiden University Medical Center

This study will be a longitudinal clinical cohort study examining white matter integrity through MRI to identify the underlying neurobiology of PPMD (primary objective). Subjects will be enrolled through the Onderzoeksprogramma Postpartum Psychiatry Erasmus MC Rotterdam (OPPER) study. Additionally a healthy control group of women from the normal population matched on demographics and postpartum interval at the time of neuroimaging will be included. The longitudinal design of this study with matched postpartum controls is the ideal approach for both within-subject and between-group comparisons.
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Study burden and risks

The design of the study is non-therapeutic. The risks of participation are minimal. No side effects of MRI are known. In addition, no contrast agents, sedation, or X-rays are needed. The burden for participants will be the time of scanning. The burden for the healthy control group will mainly be the actual visits to the Erasmus MC and the time of the research. Benefit of participation is an assessment of the early development of their child and appropriate care if necessary. The information letter for participants discusses the possible advantages and disadvantages of the study.
Important benefit of the proposed study is that it has the potential to both advance our understanding of PPMD, as well as to identify risk and protective factors guiding clinical decision-making.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in the OPPER study, a subject must meet all of the following criteria (inclusion criteria OPPER study):, Inclusion criteria patients:
• Age: 18-45
• Postpartum onset psychosis, mania or severe depression
• Written informed consent, Also, parents will be asked for consent to include their children in our study (between the age of 2 and 5 years). , Inclusion criteria healthy control:
• Age: 18-45
• No history or current DSM-V diagnosis
• Written informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in the OPPER study (exclusion criteria OPPER study):
• Patients whom are incapable to understand the information and to give informed consent. And patients whom are unable to read or write.
• Drug/ alcohol dependence last 3 months
• Mental retardation (IQ < 80)
• Serious medical illness, Additional exclusion criteria for MRI scanning phase
Women will be excluded from the scanning phase of the study if they have any contraindications for MRI scanning such as metal-containing implants. Before the MRI scan all participants need to fill out a questionnaire to screen for

contraindications (see Annex F1a).

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-01-2017
Enrollment:	150
Type:	Actual

Ethics review

Approved WMO Date:	13-12-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2019
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Not approved Date:	24-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL58913.078.16