Long-Term Outcomes of Postpartum Psychosis:
A Systematic Review and Meta-Analysis

Janneke Gilden, MD[a,*]; Astrid M. Kamperman, PhD[a]; Trine Munk-Olsen, PhD[b]; Witte J. G. Hoogendijk, MD, PhD[a]; Steven A. Kushner, MD, PhD[a]; and Veerle Bergink, MD, PhD[a,c]

ABSTRACT

Objective: There is limited information on the longitudinal disease course after first-onset postpartum psychosis (PP). Some women will experience severe affective episodes outside the postpartum period, while for other women their vulnerability to mania and psychosis may be restricted to the postpartum period. This meta-analysis estimates the risk of recurrence after first-onset PP.

Data Sources: A computerized literature search was conducted using Embase, MEDLINE, Web of Science, PsycINFO, Cochrane Central, PubMed, and Google Scholar (first 100 hits) combining key terms regarding longitudinal studies of first-onset PP from inception through May 9, 2019. Two levels of screening were used on 2,807 citations.

Study Selection: A total of 6 English-language articles including patients with a first-onset PP within 1 year after childbirth and a minimum follow-up period of 18 months or more after the index episode were included in the quantitative analysis.

Data Extraction: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were used for data extraction, and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to independently assess the quality of the included studies. The primary outcome was recurrence, defined as any subsequent psychiatric episode after first-onset PP.

Results: Six studies and 645 patients could be included in the quantitative analyses; follow-up periods were 11–26 years. Of these patients, 279 did not experience subsequent severe episodes outside the postpartum period. Meta-analysis using random-effect estimation resulted in a weighted estimate of 43.5% (95% CI, 37.7% to 49.4%).

Conclusions: In this meta-analysis, more than 40% of women were classified as having "isolated postpartum psychosis," which could be considered a distinct diagnostic category with a more favorable prognosis. The remaining women had severe non-puerperal psychiatric episodes during longitudinal follow-up.

J Clin Psychiatry 2020;81(2):19r12906

To cite: Gilden J, Kamperman AM, Munk-Olsen T, et al. Long-term outcomes of postpartum psychosis: a systematic review and meta-analysis. *J Clin Psychiatry*. 2020;81(2):19r12906.

To share: https://doi.org/10.4088/JCP.19r12906

[a]Department of Psychiatry, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands

[b]National Center for Register-Based Research, University of Aarhus, Aarhus, Denmark

[c]Department of Psychiatry and Department of Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York City, New York

**Corresponding author:* Janneke Gilden, MD, Erasmus Medical Center Rotterdam, Department of Psychiatry, Postbus 2040, 3000 CA Rotterdam, The Netherlands (j.gilden@erasmusmc.nl).

Postpartum psychosis (*PP*) is an umbrella term for postpartum mania, psychosis, psychotic depression, or a mixed state that refers to an acute, severe, mainly affective episode shortly after childbirth.[1–3] The incidence of first-onset PP from population-based register studies of psychiatric admissions varies from 0.3 to 0.6 per 1,000 births.[4] Multiple studies[1,5,6] examining naturalistic cohorts of women with postpartum psychosis have documented the typical time of symptom onset as between 3 and 10 days after birth. The cardinal symptomatology is affective, and psychotic symptoms occur almost exclusively during periods of affective instability.[7] Given the high relative risk for suicide and infanticide, early recognition and adequate treatment are of great importance.[1,8] In many countries, inpatient mother-baby joint admission units are the preferred treatment settings due to associations with improved patient satisfaction and reduced time to recovery.[9–11] In the absence of a mother-baby unit, care is delivered in standard mental health treatment settings. With an adequate treatment regimen, nearly all women with PP achieve full remission,[12] and the majority of patients achieve good functional recovery.[13] However, after remission, women with a first-onset PP are known to be at high risk of subsequent postpartum and non-postpartum psychiatric episodes. For some women, first-onset PP is the incipient episode of a life-long affective disorder, mainly within the bipolar spectrum.[4] In contrast, other women will not be at risk of subsequent severe psychiatric episodes outside the postpartum period, and their vulnerability is entirely limited to the postpartum period, a pattern described as "isolated postpartum psychosis."[4,14] Unfortunately, the magnitude of this risk is currently unknown, and there is limited information on the longitudinal disease course after first-onset PP,[2,15–20] nor is much information available on prognostic markers for the disease course. An evidence-based overview of the occurrence of subsequent episodes after first-onset PP is therefore important, particularly with regard to risk-benefit analyses of maintenance pharmacotherapy. An overestimation of recurrence risk might lead to unfounded concerns for health care providers, patients, and their families, resulting in excessive medication use, unnecessary prevention strategies, or altered family planning. Conversely, underestimation of recurrence risk might lead to insufficient attention from health care professionals and insufficient maintenance treatment, potentially leading to impaired quality of life and increased

Clinical Points

- Meta-analysis estimated that 43.5% of women with postpartum psychosis did not have episodes outside the perinatal period during a mean follow-up period of 16 years.
- These women had "isolated postpartum psychosis," which could be considered as a distinct diagnostic category with a more favorable prognosis and no need for lifelong treatment.

risk for hospitalization or suicide. Therefore, we performed a systematic review and meta-analysis to improve the knowledge of the longitudinal course of women with first-onset PP. Our primary outcome was defined as recurrence of a psychiatric episode. We categorically specified the window of recurrence as either during the postpartum period or outside the postpartum period. Additionally, we collected data on subsequent pregnancies, functional recovery, and suicide.

METHOD

Literature Search

The computerized literature search was conducted from inception of database until May 9, 2019, in all large public medical electronic databases using search terms regarding first-onset postpartum psychosis. To identify as many relevant studies as possible, we used an exploratory search strategy and did not predefine the nature of the outcome. The full search strategies for all databases used are available in Supplementary Appendix 1. Details of the protocol for this systematic review were registered on PROSPERO (CRD42017057387).

Study Selection

Studies were eligible for inclusion in the qualitative and quantitative analysis when (1) they had a longitudinal study design (cohort studies, randomized controlled trials, and birth register studies), (2) patients had a first-onset psychotic or manic episode within 1 year after childbirth (according to *Diagnostic and Statistical Manual of Mental Disorders* [*DSM*] criteria, *International Classification of Diseases* [*ICD*] criteria, or the Research Diagnostic Criteria [RDC]), (3) the follow-up period was 18 months or more after the index episode, and (4) the whole article was written in the English language.

Publications were included if the study population consisted of patients diagnosed with first-onset PP (postpartum mania, psychosis, psychotic depression, or a mixed state). First onset was defined as the absence of psychiatric hospitalization or absence of prior psychiatric symptoms prior to the index episode. Mixed patient samples were included when more than 75% of the patients in the sample met our criteria or when outcomes were reported separately for patients with first-onset PP.

Articles published after March 1986 used *DSM*, *ICD*, or RDC criteria and were considered eligible. Studies reporting either incidence or prevalence rates of recurrence were considered eligible for inclusion. *Recurrence* was defined as any subsequent psychiatric episode after first-onset PP, assessed using criteria of the *DSM*/*ICD*/RDC or a clinical interview and/or psychiatric hospitalization.

We divided recurrence into 3 categories: (*a*) at least 1 subsequent postpartum episode but no episodes outside the postpartum period, (*b*) at least 1 subsequent episode outside the postpartum period, and (*c*) no subsequent episode of mania, psychosis, or severe depression (sustained remission).

The EndNote X7 software package (Clarivate Analytics [formerly Thomson Reuter]; Philadelphia, Pennsylvania; 2013) was used for record management. Duplicate records and records without abstracts were removed. All remaining records were screened on the basis of title and abstract for eligibility. Next, full texts were screened. Screening was done by two researchers (J.G. and A.M.K.) independently. Disagreement between the two independent researchers was solved with the help from a third independent researcher (V.B.). Study selection was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[21] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE)[22] guidelines.

Data Extraction

Using a data extraction form, data were extracted by two researchers independently (J.G. and A.M.K.) who were not blind to authors, institutions, or journals. Differences in extracted data were discussed by all researchers (J.G., A.M.K., and V.B.). Patients experiencing recurrence events, including mania, psychosis, psychotic depression, a mixed state, and/or psychiatric hospitalization, were counted as the numerator. As the denominator, we used the total number of patients for whom information was available at the time of follow-up regarding our primary outcome.

Additionally, we extracted data on number of subsequent pregnancies, functional recovery, and suicide during the follow-up period as well as data on clinical and demographic predictors of recurrence, including primiparity, psychiatric family history, moment of illness onset, length and phenomenology of index admission, and medication at follow-up.

Quality Assessment

The reviewers independently used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[23] to assess the quality of the included studies. The full quality assessment for all included articles is available in Supplementary Table 1. Potential bias of these quality criteria was assessed.[24]

Procedure for Meta-Analyses

Primary outcomes were subjected to meta-analysis. To calculate the overall long-term risk of recurrence, we

used fixed- and random-effects estimation. We reported the pooled estimate and 95% CI. A *Q* test was used to examine whether heterogeneity over the pooled studies was greater than would have been expected by chance. If there is substantial heterogeneity, random-effects analysis produces a more reliable estimate than fixed-effects analysis does. Additionally, associations between outcome and (potential) predictor variables were explored. In case of categorical predictor variables, fixed-effects estimation was used to compare differences across categories. In case of continuous predictor variables, random-effects meta-regression analysis was performed. Cochrane *Q*, I^2 statistics, and significance levels are reported. Statistical analyses were performed using the metaprop and metan package in Stata 15 (StataCorp LLC; College Station, Texas). Metaprop is specifically suited to handle the underlying binomial distribution of the outcome.[25]

Publication Bias

Publication bias was assessed visually with a funnel plot depicting the risk estimates (on the log scale) against their standard error. Publication bias was also formally assessed by the regression-based test of Egger et al.[26] Both assessments were used to consider if recurrence risk decreased with increasing sample size. When publication bias is low or absent, plots with a funnel shape are considered to occur. Studies in the bottom left-hand corner are often omitted, since nonsignificant studies are less likely to be published.[27]

Heterogeneity and Sensitivity Analyses

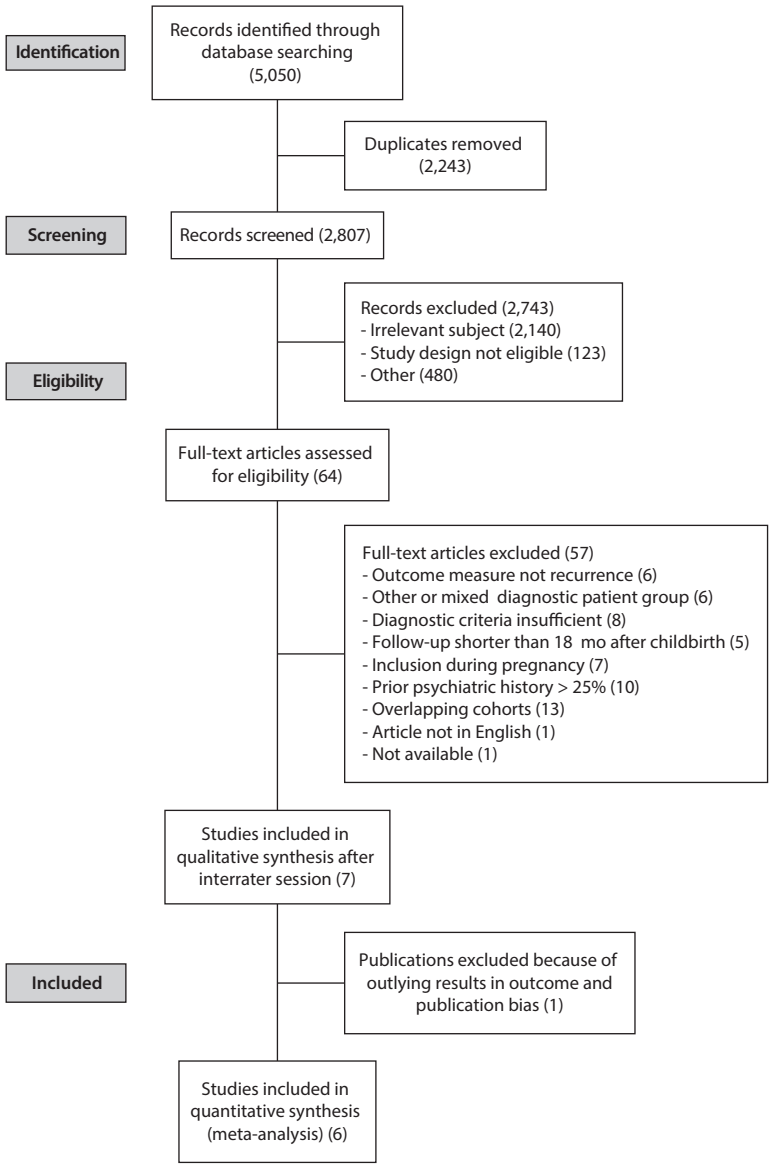
Heterogeneity of the recurrence risk between the studies was assessed using both the χ^2 test and the I^2 statistic.[28] We considered an I^2 value greater than 40% indicative of substantial heterogeneity. We conducted sensitivity analyses on the robustness of our results on the basis of study quality, design characteristics, and other relevant covariates as set forward in the preceding paragraphs.

RESULTS

Study Selection

The literature search produced 5,050 articles, a total that was narrowed to 2,807 articles, after deduplication. Two independent raters (A.M.K. and J.G.) screened the titles and abstracts of these articles for eligibility, resulting in an initial selection of 64 articles. After review of the full-text articles, 7 articles were included in this systematic review.[2,15–20] There was no overlap in the included cohorts. Publication dates of the articles included in the qualitative synthesis were between 1992 and 2014. The PRISMA flowchart of the selection process for this quantitative analysis is shown in Figure 1. Interrater reliability was high (raw interrater agreement: 98%; $\kappa = 0.90$; 95% CI, 0.80 to 0.99).

Figure 1. PRISMA Flowchart of the Article Selection Process in a Meta-Analysis of Risk of Recurrence After First Onset of Postpartum Psychosis



Study Characteristics

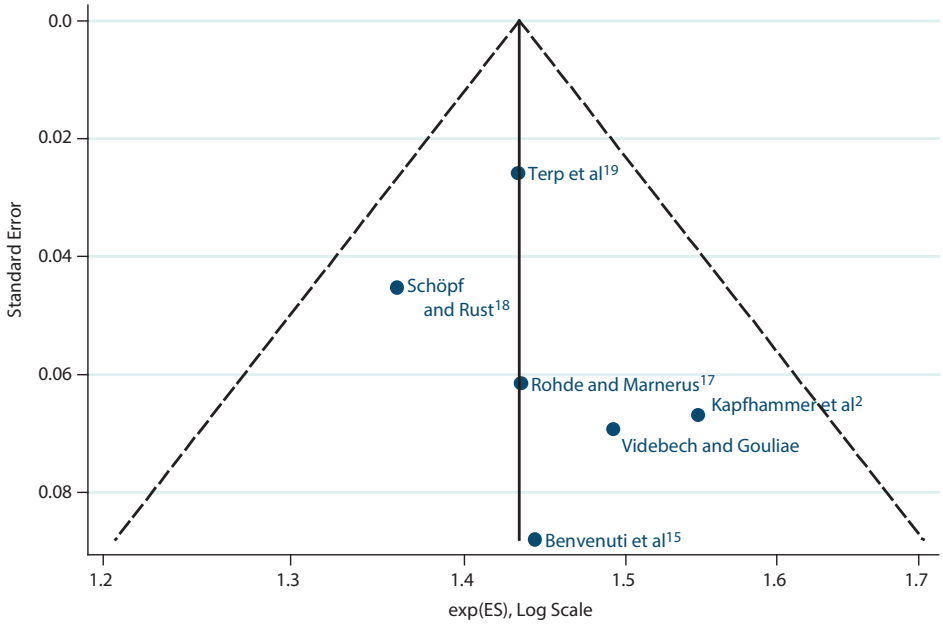
Detailed characteristics and results of the studies included in the qualitative and quantitative analyses are summarized in Table 1. In the 7 studies included in the qualitative analyses, the longitudinal disease course (mean follow-up = 16 years; range, 11–26 years) of 1,018 patients was described.

Table 1. Overview of Characteristics of Studies Included in the Qualitative Synthesis

Study	Cohort/ Location	Study Design	Time Frame	Homogeneity Of Patient Sample	Patients Included With First-Onset Postpartum Psychosis	Patients Included in Qualitative and Quantitative Analysis[a]	Moment of Illness Onset	Sustained Remission (no Recurrence), % (n/Total n)	≥1 Subsequent Episode Limited to the Postpartum Period, % (n/Total n)	≥1 Subsequent Episode Outside the Postpartum Period, % (n/Total n)	Subsequent Pregnancy, % (n/Total n)	Recurrence Rate After Subsequent Pregnancy, % (n/Total n)	Functional Recovery, % (n/Total n)[b]	Suicide
Benvenuti et al (1992)[15]	Florence, Italy	Retrospective cohort	1973–1987	100% First onset	30	30	<8 wk	37% (11/30)	13% (4/30)	50% (15/30)	23% (7/30)	57% (4/7)	NA	NA
Kapfhammer et al (2014)[2]	Munich, Germany	Retrospective cohort	1975–1995	61% First onset, 39% with prior psychotic episode	60	55	<4 wk	44% (24/55)	13% (7/55)	44% (24/55)	38% (23/60)	52% (12/23)	67% (37/55)	8% (5/60)
Kirpinar et al (1999)[16]	Erzurum, Turkey	Retrospective cohort	1973–1994	100% First onset	64	64	<3 mo	19% (12/64)	39% (25/64)	42% (27/64)	NA	NA	NA	NA
Rohde and Marneros (1993)[17]	Cologne and Bonn, Germany	Prospective cohort	1950–1979	100% First onset	86	61	<6 wk	36% (22/61)	5% (3/61)	59% (36/61)	36% (31/86)	26% (8/31)	NA	NA
Schöpf and Rust (1994)[18]	Lausanne and Zurich, Switzerland	Retrospective cohort	1949–1990	87% First onset, 13% with prior psychotic symptoms not leading to hospitalization	119	104	<3 mo	31% (32/104)	3% (3/104)	66% (69/104)	35% (42/119)	40% (17/42)	NA	11% (13/119)
Terp et al (1999)[19]	Birth register (Denmark)	Birth register	NA	100% First onset	609	345	<91 d	36% (124/345)	8% (27/345)	56% (194/345)	36% (217/609)	22% (47/217)	NA	NA
Videbech and Gouliaev (1995)[20]	Birth register (Denmark)	Birth register	NA	100% First onset	50	50	<12 mo	40% (20/50)	4% (2/50)	56% (28/50)	32% (16/50)	25% (4/16)	66% (31/47)	4% (2/50)

[a]Number is based on patients for whom information regarding the current study's primary outcome was available at time of follow-up.
[b]Number is based on patients alive and for whom information was available at time of follow-up.
Abbreviation: NA = not available.

Figure 2. Funnel Plot With Pseudo–95% Confidence Limits for Studies Included in Meta-Analysis (k = 6)



Abbreviation: exp(ES) = the exponential of the effect size (effect size used for this analysis is sustained remission).

Quantitative Analysis

Supplementary Figure 1 shows a forest plot of the outcomes of the 7 studies included in this review.[2,15–20] Supplementary Figure 2 shows the accompanying funnel plot. Kirpinar et al[16] reported outlying results, both in terms of outcomes and based on the funnel plot (Supplementary Figure 2), resulting in high levels of heterogeneity. Specifically, the sample of Kirpinar et al included 27 cases (42% of the total sample) with a final diagnosis of schizophrenia, which is known to be rare for first-onset affective psychosis. After removal of the study by Kirpinar et al, the funnel plot was symmetrical (Figure 2). We therefore present results from this meta-analysis both with and without the study by Kirpinar et al.[16] The remaining 6 studies involved a total of 954 patients, of whom 645 patients could be included in our longitudinal analysis.

Recurrence Risk

As shown in Figure 3, 412 of 645 women with first-onset PP experienced a recurrence during the follow-up period (64.0%; 95% CI, 60.3 to 67.7, according to both fixed- and random-effects estimation) in absence of heterogeneity ($I^2 = 0\%$, $P = .70$). Of these, 46 of 645 women experienced subsequent episodes exclusively limited to the postpartum period. Meta-analysis using random-effects estimation resulted in a weighted estimate of 6.1% (95% CI, 3.3% to 8.9%) with substantial heterogeneity ($I^2 = 47\%$, $P = .10$). More than half of the women (366/645) experienced ≥1 subsequent episode outside the postpartum period (weighted estimate: 56.5%; 95% CI, 50.6 to 62.3, using random-effects estimation). Women with subsequent episodes both inside and outside the postpartum period were also included in this category. Heterogeneity was substantial ($I^2 = 44\%$, $P = .10$). The remaining 233 women did not experience a subsequent severe episode during the follow-up period. Meta-analysis using fixed- and random-effects estimation resulted in identical results (36.0%, 95% CI, 32.3% to 39.7%) in the absence of heterogeneity ($I^2 = 0\%$, $P = .70$) (see Figure 4). Thus, these articles showed that 279 of 645 women with first-onset PP did not experience subsequent episodes outside the postpartum period. Meta-analysis using random-effects estimation resulted in a weighted estimate of 43.5% (95% CI, 37.7% to 49.4%) in presence of substantial heterogeneity ($I^2 = 44\%$, $P = .12$) (due to substantial heterogeneity in a subset of the analysis, the weighted estimates do not necessarily add up).

Additional Outcomes

Subsequent pregnancies and postpartum recurrence. For all studies, information on subsequent pregnancies was available.[2,15,17–20] In these studies, 954 women were included, of whom 336 (35%) had a subsequent pregnancy. Of these 336 women with a subsequent pregnancy, 92 (27%) experienced a subsequent postpartum episode.

Functional recovery. Kapfhammer et al[2] and Videbech and Gouliaev[20] provided information about functioning at follow-up. In the study by Kapfhammer et al,[2] functioning was measured with the Disability Assessment Scale

Figure 3. Disease Course After First-Onset Postpartum Psychosis (Absolute Numbers)

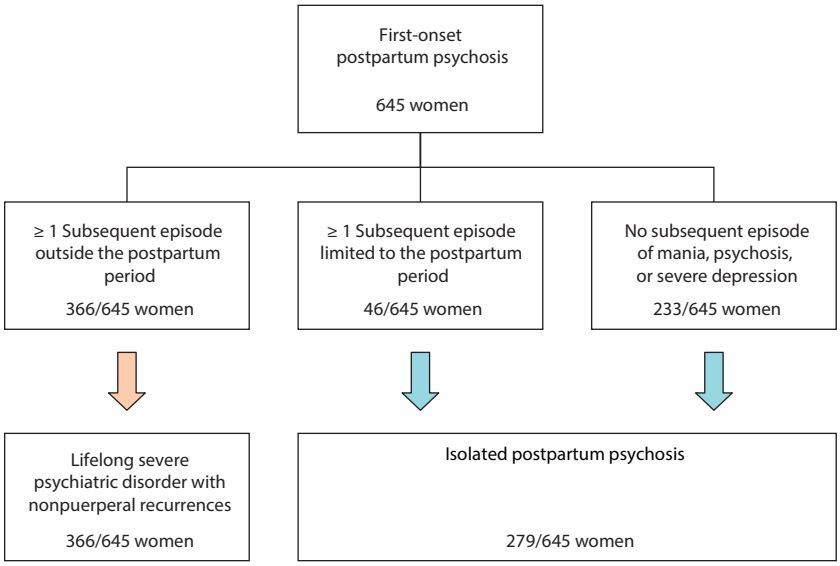
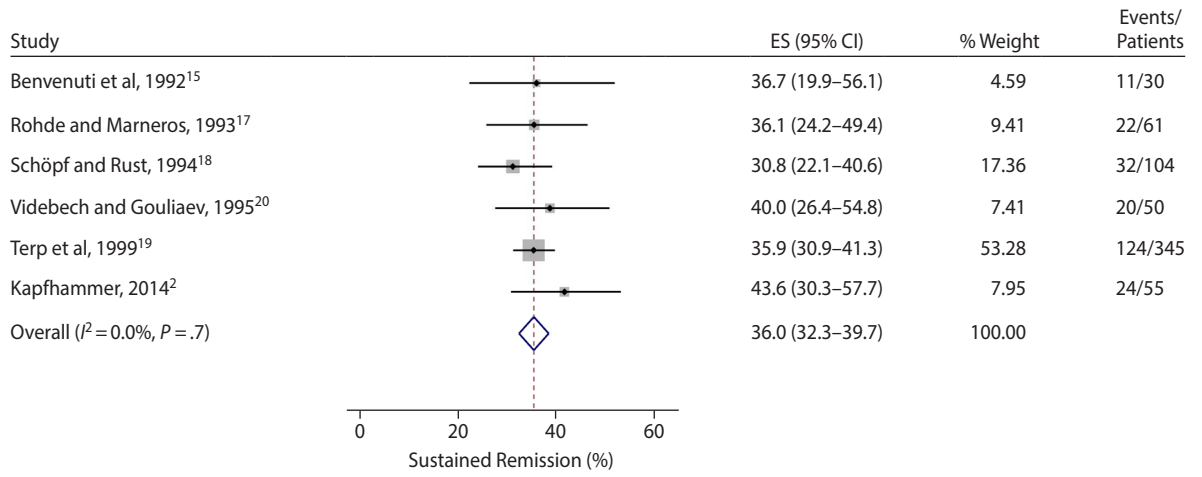


Figure 4. Sustained Remission in Women With First-Onset Postpartum Psychosis



Abbreviation: ES = effect size (effect size used for this analysis is sustained remission).

(DAS-M)[29] and 67% of women had no disturbance in psychosocial functioning after a mean of 12 years after the index episode. In the study by Videbech and Gouliaev,[20] functioning was measured as working capacity during the follow-up assessment. In that study, 66% of women with first-onset PP regained full working capacity after a median of 11 years after the index episode. Both studies[2,20] found an association between impaired functioning and psychiatric episodes during follow-up.

Suicide. Four studies[2,17,18,20] provided information about suicide. The study by Rohde and Marneros[17] was excluded from this analysis because they described suicide risk in a heterogeneous sample including women with a previous history of severe psychiatric illness and therefore the specific suicide risk for women with first-onset PP could not be determined. The remaining 3 studies reported 20 suicides in 229 patients. Kapfhammer et al[2] described suicide in 5 women (5/60), all within just a few weeks after discharge from the psychiatric hospital. As far as could be reconstructed from reports of the family, these women were in a state of depression at the time of their suicide. Similarly, Schöpf and Rust[18] described that 12 of the 13 suicides (13/119) within their study cohort occurred "during an episode of illness." They did not provide information on the type of episode. Videbech and Gouliaev[20] did not provide additional information of the 2 women (2/50) who committed suicide, although they reported a clinical picture of depression during the index episode for both patients.

Additionally, the available data from these 4 studies were insufficient to allow for a distinction in relative suicide risk between women with isolated postpartum psychosis and those with recurrences outside the postpartum period.

Only Kapfhammer et al[2] mentioned infanticide in their study sample. Three patients committed an extended suicide attempt that resulted in 2 infanticides. They described this infanticide risk in a heterogeneous sample including women with a previous history of severe psychiatric illness and therefore the specific infanticide risk for women with first-onset PP could not be determined.

Predictors

We analyzed the impact of parity and very early onset of symptoms (within the first week postpartum), but neither seemed to have an effect on subsequent episodes during follow-up ($\beta = 0.25$; 95% CI, −0.40 to 0.90; $P = .35$ and $\beta = -0.06$; 95% CI, −0.79 to 0.68; $P = .78$, respectively). Owing to insufficient data, we were not able to calculate the impact of other potential predictors, such as length and phenomenology of index admission, psychiatric family history, life events, or medication use, on the longitudinal disease course.

Sensitivity Analyses

To estimate the robustness of our findings, we performed a series of sensitivity analyses based on the design and characteristics of the studies: year of publication, country of study (Germany vs Denmark), study design (cohort vs register), outcome measure (prevalence vs incidence), length of follow-up, definition of inclusion (*ICD-8* vs *DSM*), and definition of recurrence (clinical interview vs *DSM* vs hospitalization).

Although the proportion of sustained remission increased across the period of study inclusion, with highest proportions of patients in sustained remission in the most recent studies, the year of publication did not show a significant impact on recurrence risk ($\beta = .005$; 95% CI, −0.005 to 0.014; $P = .25$). Further, we found no significant differences regarding the country where the study was conducted ($Q_1 = 0.36$, $P = .55$), whether the data involved cohort studies or register-based studies ($Q_1 = 0.08$, $P = .77$), whether studies reported incidence or prevalence rates ($Q_1 = 0.39$, $P = .53$), or whether dropout was explicitly reported ($Q_1 = 1.20$, $P = .27$). Also, no differences were found regarding the criteria used for inclusion (*ICD-8* vs *DSM-II* or *DSM-IV*) ($Q_1 = 0.08$, $P = .77$) or recurrence (*DSM* vs clinical interview vs hospitalization) ($Q_2 = 1.80$, $P = .41$). Finally, there was no impact of the duration of longitudinal follow-up ($\beta = -0.005$; 95% CI, −0.017 to 0.007; $P = .30$).

Together, although power was limited, these sensitivity analyses supported the overall validity of our findings.

Publication Bias

A visual inspection of the funnel plot revealed that the study by Kirpinar et al[16] was an outlier (Supplementary Figure 2). After the removal of this study, the funnel plot was symmetrical (Figure 2). The Egger test did not suggest the presence of a small study bias (intercept = 0.18; 95% CI, −3.94 to 4.29, $P = .92$ [including the study by Kirpinar et al[16]] or intercept = 0.59; 95% CI, −1.59 to 2.76; $P = .49$ [excluding the study by Kirpinar et al[16]]).

DISCUSSION

This systematic review and meta-analysis shows that 36.0% (95% CI, 32.3% to 39.7%) of the patients with first-onset PP (weighted estimate) had no recurrences. These patients had a single episode and remained in remission during longitudinal follow-up (mean follow-up of 16 years). An additional 6.1% (95% CI, 3.3% to 8.9%) of women with a first-onset PP had a recurrence after a subsequent pregnancy but not outside the perinatal period. Together, 43.5% (95% CI, 37.7% to 49.4%) of women had an "isolated postpartum psychosis": they had episodes of mania, psychosis, or severe psychotic depression limited to the postpartum period. The remaining women had at least 1 subsequent episode outside the postpartum period. For these women, delivery was the incipient episode of a psychiatric disorder with a more disabling disease course and broader window of recurrence vulnerability.

Currently, the *DSM-5* is widely used as a classification system for psychiatric disorders.[30,31] Within the *DSM-5*, postpartum psychosis (including psychotic, manic, psychotic depressed, or mixed episodes) is not a distinct disease category.[31] Given that the majority of women with PP have prominent manic or mixed episode features,[31] by the current *DSM-5* criteria these women should therefore be diagnosed with bipolar disorder at the time of their first-onset postpartum psychosis. However, our findings raise doubt about the validity of this approach. It appears inaccurate to assign a diagnosis of bipolar disorder at the time of a first-onset postpartum psychosis, given the finding that 43.5% of women have no manic or psychotic recurrence outside the postpartum period. Therefore, and also because these episodes might have a different etiology,[4,32,33] a distinct diagnostic category might be more appropriate. To distinguish between isolated postpartum psychosis and lifelong psychiatric disorders, information about time to recurrence after first-onset PP is needed. Unfortunately, the information in the included studies was not detailed enough to investigate this highly relevant clinical outcome. A recent meta-analysis[34] reported recurrence rates of 59% after 2 years in women with first-onset manic or mixed episodes outside the perinatal period, with most recurrences occurring within the first year. This finding might guide diagnostic decision-making as well as conclusions on length of maintenance treatment after first-onset PP.

Subsequent Pregnancy and the Risk of Recurrence

In our study, only 35% of women had a subsequent pregnancy. Women might have been anxious about

experiencing another postpartum episode. In addition, some health care providers might have advised against further pregnancies.[35] More women might have had a relapse if they had another child, which would have lowered the number (n = 233) of women in sustained remission. In those women who had a subsequent pregnancy, 27% experienced a severe postpartum recurrence. This percentage is similar to that found in a previous meta-analysis,[14] in which the risk of recurrence of a PP episode in women with a history of postpartum psychosis after a subsequent pregnancy was found to be 29%. Given the high risk specifically in the postpartum period, we previously recommended[4] that women develop an individualized postpartum prevention plan in collaboration with their health care providers for implementation during a subsequent pregnancy to agree on specific preventive strategies for the postpartum period. One of the most effective interventions thus far identified is the initiation of prophylactic pharmacotherapy, preferably with lithium on the day of delivery.[36]

Suicide

In our systematic review, only 3 studies[2,18,20] reported suicide rates for women with first-onset PP, and in these studies the suicide rates were very high (4%–11%). In contrast, a recent Danish register study,[37] designed to investigate mortality after postpartum episodes, reported death by suicide in 29 (0.01%) of 2,699 women with a first psychiatric contact within 3 months after giving birth. The mean follow-up time for the women in that cohort was 26.26 years. One explanation for the lower suicide rates in that study is the severity of the episode, because both women with inpatient contact and those with outpatient contact were included. Another explanation could be the timing; the Danish register study collected data at the end of the 20th and beginning of the 21st century (1970–2011). In contrast, the 3 studies mentioned in the present review included data from the 20th century (1949–1995). An older Danish register study (data collection between 1973 and 1993)[38] reported a suicide rate of 3.3%. That study followed 1,567 women after postpartum admission to a psychiatric hospital. Our findings highlight the need to be very alert to the increased risk of suicidality in women with postpartum psychosis, especially during acute episodes, in the period following hospital discharge, and when depressive symptoms are present.[39,40]

Limitations

This systematic review is the first to describe the longitudinal course after first-onset PP. Although only a few studies could be included, sensitivity analyses confirmed the homogeneity and validity of our findings.

A limitation of this study is that we could not investigate other important clinical outcomes such as minor episodes, roughening, or treatment response, because these were not always sufficiently described in the included studies. In addition, even though the mean follow-up in the included studies was 16 years, we cannot draw definitive conclusions about long-term outcomes or lifetime prognosis. Follow-up in these studies also was not long enough to comment on recurrence risk during menopause, which is generally considered a period of high risk for mood episodes. Overall, given the mean length of the follow-up, we consider the risk of underestimating recurrence to be limited, which is supported by our sensitivity analysis.

All included studies were executed in Western Europe, and therefore our results may not be applicable to other contexts. Moreover, all studies were performed in the 1970s and 1980s, which hampered the generalizability of our results. More recent studies have shown a lower recurrence rate of psychiatric episodes,[41] possibly because of prevention programs and prophylactic pharmacotherapy. It could be that recurrence risk is lower today.

Finally, it is not possible to study a true recurrence risk in a naturalistic setting, since many of the women included in these follow-up studies might have received targeted treatment to prevent recurrence.

CONCLUSIONS

This review describes the longitudinal course after first-onset PP and therefore provides novel prognostic insight. For a majority of women, postpartum psychosis was the incipient episode of a psychiatric disorder with subsequent severe non-postpartum recurrence. For the remaining sizeable proportion of women, their risk of recurrence appears limited to the period following delivery. Accordingly, a distinct diagnostic category might be more appropriate for this group.[42] We found a high suicide risk, particularly after hospital discharge. This finding is alarming, given that PP is a condition with a generally optimistic prognosis following remission of the initial acute episode.

Submitted: May 6, 2019; accepted October 17, 2019.
Published online: March 10, 2020.

Author contributions: J. Gilden, MD; A. M. Kamperman, PhD; and V. Bergink, MD, PhD, performed the literature search and selected relevant articles. J. Gilden, MD, produced the tables. A. M. Kamperman, PhD, performed the data analysis and produced the figures. All authors contributed to interpretation of the data, writing, editing, and approval of the final manuscript.

Potential conflicts of interest: The authors report no financial or other relationship relevant to the subject of this article.

Funding/support: None.

Acknowledgments: The authors thank Wichor M. Bramer, BSc, biomedical information specialist at the Erasmus University Medical Center, Rotterdam, the Netherlands, for his assistance with the systematic literature retrieval. Mr Bramer has no conflict of interest to declare.

Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. Bergink V, Lambregtse-van den Berg MP, Koorengevel KM, et al. First-onset psychosis occurring in the postpartum period: a prospective cohort study. *J Clin Psychiatry*. 2011;72(11):1531–1537.
2. Kapfhammer HP, Reininghaus EZ, Fitz W, et al. Clinical course of illness in women with early onset puerperal psychosis: a 12-year follow-up study. *J Clin Psychiatry*. 2014;75(10):1096–1104.
3. Osborne LM. Recognizing and managing postpartum psychosis: a clinical guide for obstetric providers. *Obstet Gynecol Clin North Am*. 2018;45(3):455–468.
4. Bergink V, Rasgon N, Wisner KL. Postpartum psychosis: madness, mania, and melancholia in motherhood. *Am J Psychiatry*. 2016;173(12):1179–1188.
5. Klompenhouwer JL, van Hulst AM. Classification of postpartum psychosis: a study

of 250 mother and baby admissions in The Netherlands. *Acta Psychiatr Scand*. 1991;84(3):255–261.
6. Kendell RE, Chalmers JC, Platz C. Epidemiology of puerperal psychoses. *Br J Psychiatry*. 1987;150(5):662–673.
7. Bergink V, Armangue T, Titulaer MJ, et al. Autoimmune encephalitis in postpartum psychosis. *Am J Psychiatry*. 2015;172(9):901–908.
8. Wisner KL, Peindl K, Hanusa BH. Symptomatology of affective and psychotic illnesses related to childbearing. *J Affect Disord*. 1994;30(2):77–87.
9. Glangeaud-Freudenthal NM, Sutter AL, Thieulin AC, et al. Inpatient mother-and-child postpartum psychiatric care: factors associated with improvement in maternal mental health. *Eur Psychiatry*. 2011;26(4):215–223.
10. Kimmel MC, Lara-Cinisomo S, Melvin K, et al. Treatment of severe perinatal mood disorders on a specialized perinatal psychiatry inpatient unit. *Arch Women Ment Health*. 2016;19(4):645–653.
11. Chandra PS, Desai G, Reddy D, et al. The establishment of a mother-baby inpatient psychiatry unit in India: adaptation of a Western model to meet local cultural and resource needs. *Indian J Psychiatry*. 2015;57(3):290–294.
12. Bergink V, Burgerhout KM, Koorengevel KM, et al. Treatment of psychosis and mania in the postpartum period. *Am J Psychiatry*. 2015;172(2):115–123.
13. Burgerhout KM, Kamperman AM, Roza SJ, et al. Functional recovery after postpartum psychosis: a prospective longitudinal study. *J Clin Psychiatry*. 2017;78(1):122–128.
14. Wesseloo R, Kamperman AM, Munk-Olsen T, et al. Risk of postpartum relapse in bipolar disorder and postpartum psychosis: a systematic review and meta-analysis. *Am J Psychiatry*. 2016;173(2):117–127.
15. Benvenuti P, Cabras PL, Servi P, et al. Puerperal psychoses: a clinical case study with follow-up. *J Affect Disord*. 1992;26(1):25–30.
16. Kirpinar I, Coşkun I, Cayköylü A, et al. First-case postpartum psychoses in Eastern Turkey: a clinical case and follow-up study. *Acta Psychiatr Scand*. 1999;100(3):199–204.
17. Rohde A, Marneros A. Postpartum psychoses: onset and long-term course. *Psychopathology*. 1993;26(3-4):203–209.
18. Schöpf J, Rust B. Follow-up and family study of postpartum psychoses, part I: overview. *Eur Arch Psychiatry Clin Neurosci*. 1994;244(2):101–111.
19. Terp IM, Engholm G, Møller H, et al. A follow-up study of postpartum psychoses: prognosis and risk factors for readmission. *Acta Psychiatr Scand*. 1999;100(1):40–46.
20. Videbech P, Gouliaev G. First admission with puerperal psychosis: 7–14 years of follow-up. *Acta Psychiatr Scand*. 1995;91(3):167–173.
21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
22. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008–2012.
23. von Elm E, Altman DG, Egger M, et al; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453–1457.
24. Tooth L, Ware R, Bain C, et al. Quality of reporting of observational longitudinal research. *Am J Epidemiol*. 2005;161(3):280–288.
25. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health*. 2014;72(1):39.
26. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634.
27. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol*. 2001;54(10):1046–1055.
28. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560.
29. Jung E, Krumm B, Biehl H, et al. *Mannheimer Skala zur Einschätzung sozialer Behinderung, DAS-M*. Weinheim, Germany: Beltz; 1989.
30. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
31. Kamperman AM, Veldman-Hoek MJ, Wesseloo R, et al. Phenotypical characteristics of postpartum psychosis: a clinical cohort study. *Bipolar Disord*. 2017;19(6):450–457.
32. Kumar MM, Venkataswamy MM, Sathyanarayanan G, et al. Immune system aberrations in postpartum psychosis: an immunophenotyping study from a tertiary care neuropsychiatric hospital in India. *J Neuroimmunol*. 2017;310:8–13.
33. Dazzan P, Fusté M, Davies W. Do defective immune system-mediated myelination processes increase postpartum psychosis risk? *Trends Mol Med*. 2018;24(11):942–949.
34. Kessing LV, Andersen PK, Vinberg M. Risk of recurrence after a single manic or mixed episode—a systematic review and meta-analysis. *Bipolar Disord*. 2018;20(1):9–17.
35. Viguera AC, Cohen LS, Bouffard S, et al. Reproductive decisions by women with bipolar disorder after prepregnancy psychiatric consultation. *Am J Psychiatry*. 2002;159(12):2102–2104.
36. Bergink V, Bouvy PF, Vervoort JS, et al. Prevention of postpartum psychosis and mania in women at high risk. *Am J Psychiatry*. 2012;169(6):609–615.
37. Johannsen BM, Larsen JT, Laursen TM, et al. All-cause mortality in women with severe postpartum psychiatric disorders. *Am J Psychiatry*. 2016;173(6):635–642.
38. Appleby L, Mortensen PB, Faragher EB. Suicide and other causes of mortality after post-partum psychiatric admission. *Br J Psychiatry*. 1998;173(3):209–211.
39. Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1999;56(7):617–626.
40. Qin P, Nordentoft M. Suicide risk in relation to psychiatric hospitalization: evidence based on longitudinal registers. *Arch Gen Psychiatry*. 2005;62(4):427–432.
41. Polachek IS, Fung K, Vigod SN. First lifetime psychiatric admission in the postpartum period: a population-based comparison to women with prior psychiatric admission. *Gen Hosp Psychiatry*. 2016;40:25–32.
42. Florio AD, Munk-Olsen T, Bergink V. The birth of a psychiatric orphan disorder: postpartum psychosis. *Lancet Psychiatry*. 2016;3(6):502.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Long-Term Outcomes of Postpartum Psychosis: A Systematic Review and Meta-Analysis

Author(s): Janneke Gilden, MD; Astrid M. Kamperman, PhD; Trine Munk-Olsen, PhD; Witte J. G. Hoogendijk, MD, PhD; Steven A. Kushner, MD, PhD; and Veerle Bergink, MD, PhD

DOI Number: https://doi.org/10.4088/JCP.19r12906

List of Supplementary Material for the article

1. Appendix 1 — A systematic electronic literature search was performed…
2. Table 1 — Quality assessment according to STROBE guidelines
3. Figure 1 — Sustained remission in women with first onset postpartum psychosis including Kirpinar
4. Figure 2 — Funnel plot with pseudo 95% confidence limits for studies included in the systematic review including Kirpinar (n=7)

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Appendix 1

A systematic electronic literature search was performed by a medical information specialist on longitudinal studies of postpartum psychosis. The following public medical electronic databases were systematically searched: Embase (via embase.com), Medline (via Ovid), Web-of-Science, PsycINFO (via OvidSP), Cochrane Central (via Wiley), PubMed, and Google Scholar (first 100 hits). Additionally, reference lists of key papers and review articles were screened for missing publications. The search was conducted from inception of database until May 9, 2019. Our search strategy combined terms regarding first-onset postpartum psychosis. To identify as many relevant studies as possible, we used an exploratory search strategy and did not predefine the nature of the outcome. The full search strategies for all databases used are available in this supplement. Details of the protocol for this systematic review were registered on PROSPERO (CRD42017057387).

Embase.com 2074

('puerperal psychosis'/de OR (('puerperium'/de OR 'puerperal disorder'/de OR childbirth/de OR 'puerperal depression'/de OR delivery/exp) AND 'psychosis'/exp) OR (((puerper* OR postpart* OR post-part* OR after-pregnan* OR childbirth* OR child-birth* OR new-mother* OR labor OR labour OR Caesarean OR delivery OR deliveries OR postnatal* OR post-natal* OR Parturition*) NEAR/6 (psychosis* OR psychotic* OR psychoses* OR bipolar* OR mania*))):ab,ti) AND [english]/lim NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim)

Medline Ovid 163

((("Postpartum Period"/ OR "Puerperal Disorders"/ OR Parturition/ OR "Depression, Postpartum"/ OR exp "Delivery, Obstetric"/) AND "Psychotic Disorders"/) OR (((puerper* OR postpart* OR post-part* OR after-pregnan* OR childbirth* OR child-birth* OR new-mother* OR labor OR labour OR Caesarean OR delivery OR deliveries OR postnatal* OR post-natal* OR Parturition*) ADJ6 (psychosis* OR psychotic* OR psychoses* OR bipolar* OR mania*))).ab,ti.) AND english.la. NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.

PsycINFO Ovid 134

("Postpartum Psychosis"/ OR (("Postpartum Depression"/ OR exp "Labor (Childbirth)"/) AND " Psychosis "/) OR (((puerper* OR postpart* OR post-part* OR after-pregnan* OR childbirth* OR child-birth* OR new-mother* OR labor OR labour OR Caesarean OR delivery OR deliveries OR postnatal* OR post-natal* OR Parturition*) ADJ6 (psychosis* OR psychotic* OR psychoses* OR bipolar* OR mania*))).ab,ti.) AND english.la. NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.

Cochrane 18

((((puerper* OR postpart* OR post-part* OR after-pregnan* OR childbirth* OR child-birth* OR new-mother* OR labor OR labour OR Caesarean OR delivery OR deliveries OR postnatal* OR post-natal* OR Parturition*) NEAR/6 (psychosis* OR psychotic* OR psychoses* OR bipolar* OR mania*))):ab,ti)

Web of science 365

TS=(((((puerper* OR postpart* OR "post-part*" OR "after-pregnan*" OR childbirth* OR "child-birth*" OR "new-mother*" OR labor OR labour OR Caesarean OR delivery OR deliveries OR postnatal* OR "post-natal*" OR Parturition*) NEAR/5 (psychosis* OR psychotic* OR psychoses* OR bipolar* OR mania*))))) AND DT=(article)

Google scholar 53

First 100:
"puerperal|postpartum psychosis|psychotic|psychoses"
First 100:
"puerperal|postpartum psychosis|psychotic|psychoses" "first onset"

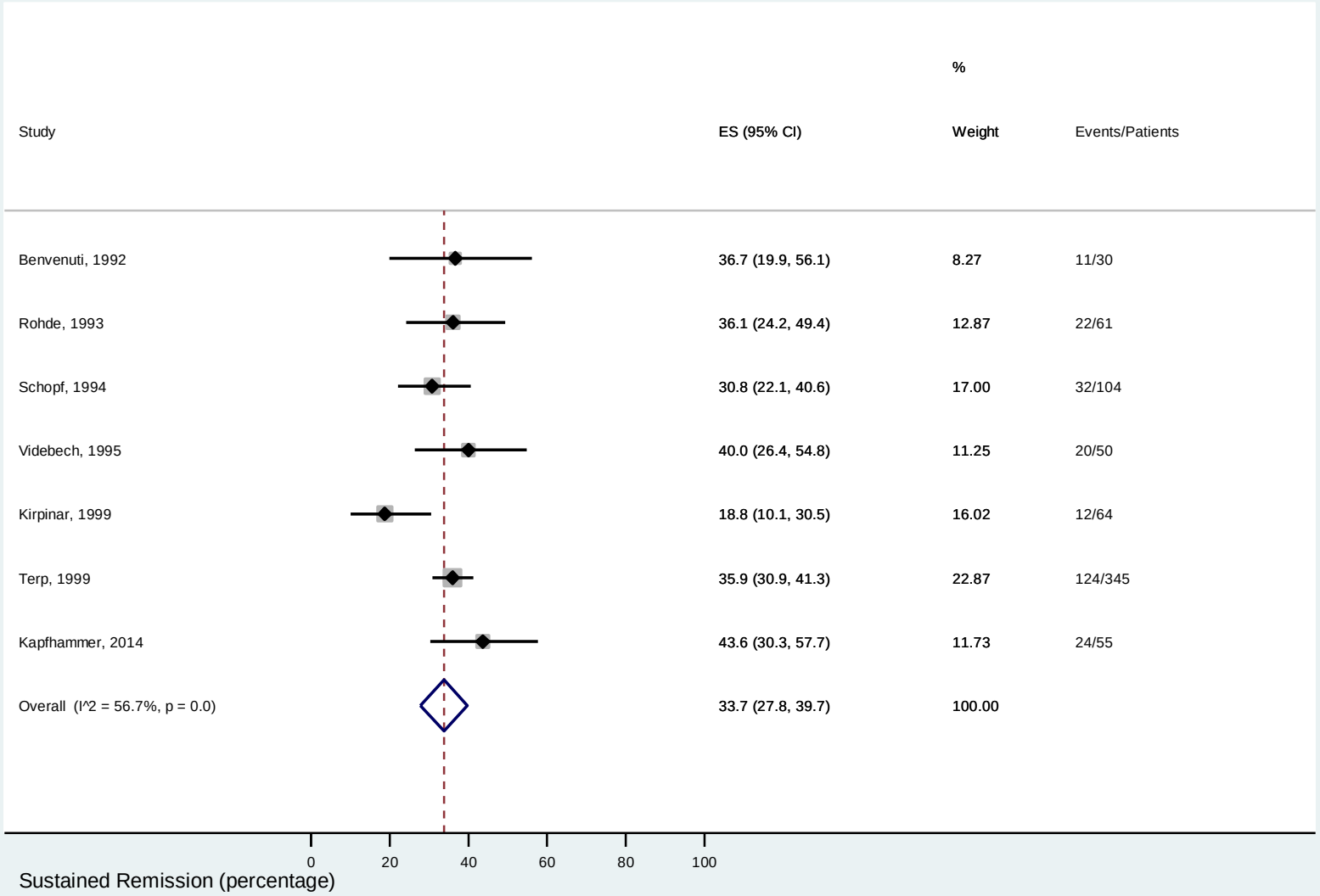
Supplementary Table 1. Quality assessment according to STROBE guidelines

Study	Study design	Homogeneity of patient sample	Definition of inclusion	Moment of onset of first-onset postpartum psychosis	Definition of recurrence	Follow up range	Mean Follow-up	Confounders reported	Missing data reported
Benvenuti et al (1992)[1]	Retrospective Cohort	100% first-onset	DSM III R	< 8 weeks pp	DSM III	4-18 years	13.4 years	None	Yes
Kapfhammer et al (2014)[2]	Retrospective Cohort	61% first-onset 39% former psychotic episode	DSM IV	< 4 weeks pp	DSM IV	7-24 years	12 years	None	Yes
Kirpinar et al (1999)[3]	Retrospective Cohort	100% first-onset	DSM IV	< 3 months pp	Clinical interview	2-23 years	11.2 years	None	Yes
Rohde and Marneros (1993)[4]	Prospective Cohort	100% first-onset	DSM III, DSM III R	< 6 weeks pp	Clinical interview	12-41 years	25.6 years	None	Yes
Schöpf and Rust (1994)[5]	Retrospective Cohort	87% first-onset 13% former psychotic symptoms not leading to hospitalization	DSM III R	< 3 months pp	Clinical interview	3-35 years	21.2 years	None	No
Terp et al (1999)[6]	Birth register	100% first-onset	ICD 8	< 91 days pp	Hospitalization	10-20 years	15 years	None	No
Videbech and Gouliaev (1995)[7]	Birth register	100% first-onset	ICD 8	< 12 months pp	Hospitalization	7-14 years	11 years	Age Parity	Yes

Abbreviation: pp = postpartum.

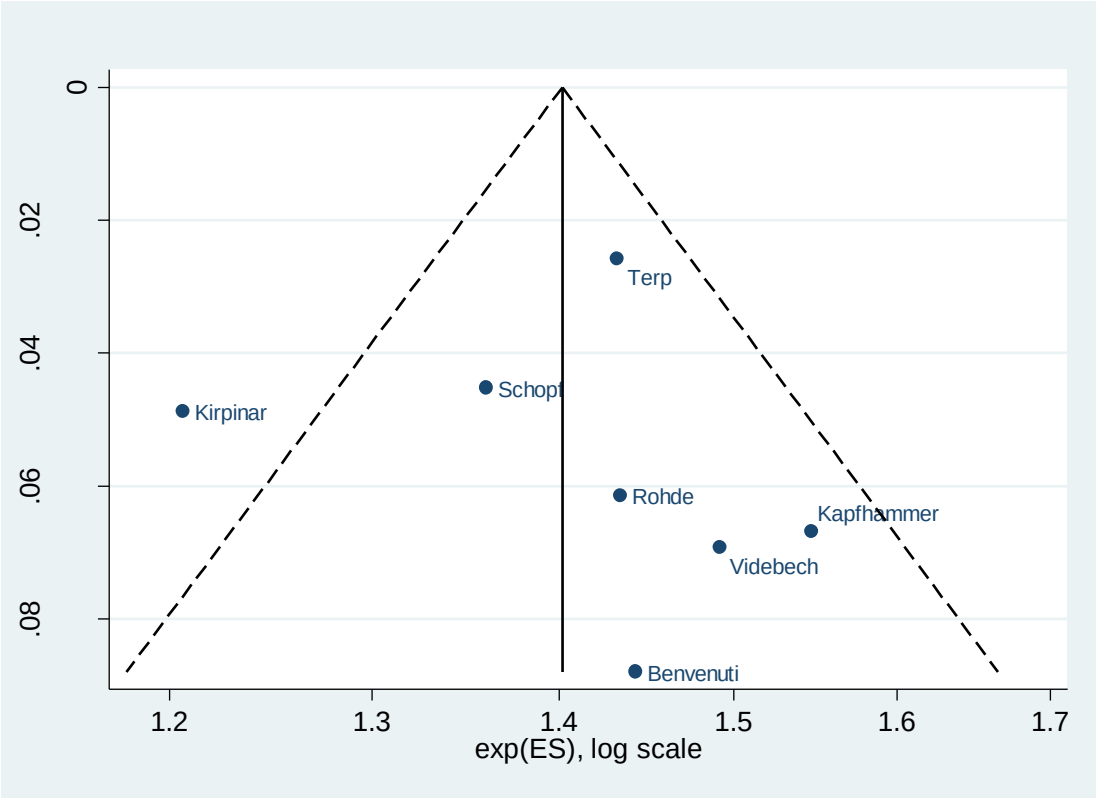
1. Benvenuti P, Cabras PL, Servi P, Rosseti S, Marchetti G, Pazzagli A. Puerperal psychoses: a clinical case study with follow-up. *J Affect Disord.* 1992;26(1):25-30.
2. Kapfhammer HP, Reininghaus EZ, Fitz W, Lange P. Clinical course of illness in women with early onset puerperal psychosis: a 12-year follow-up study. *J Clin Psychiatry.* 2014;75(10):1096-1104.
3. Kirpinar I, Coskun I, Caykoylu A, Anac S, Ozer H. First-case postpartum psychoses in Eastern Turkey: a clinical case and follow-up study. *Acta Psychiatr Scand.* 1999;100(3):199-204.
4. Rohde A, Marneros A. Postpartum psychoses: onset and long-term course. *Psychopathology.* 1993;26(3-4):203-209.
5. Schöpf J, Rust B. Follow-up and family study of postpartum psychoses. Part I: Overview. *Eur Arch Psychiatry Clin Neurosci.* 1994;244(2):101-111.
6. Terp IM, Engholm G, Moller H, Mortensen PB. A follow-up study of postpartum psychoses: prognosis and risk factors for readmission. *Acta Psychiatr Scand.* 1999;100(1):40-46.
7. Videbech P, Gouliaev G. First admission with puerperal psychosis: 7-14 years of follow-up. *Acta Psychiatr Scand.* 1995;91(3):167-173.

Supplementary Figure 1. Sustained remission in women with first onset postpartum psychosis including Kirpinar



Abbreviation: ES = effect size. Effect size used for this analysis is sustained remission.

Supplementary Figure 2. Funnel plot with pseudo 95% confidence limits for studies included in the systematic review including Kirpinar (n=7)



Abbreviation: exp(ES) = the exponential of the effect size. Effect size used for this analysis is sustained remission.