Pre-eclampsia and first-onset postpartum psychiatric episodes: a Danish population-based cohort study

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Background. Recent evidence suggests that postpartum psychiatric episodes may share similar etiological mechanisms with immune-related disorders. Pre-eclampsia is one of the most prevalent immune-related disorders of pregnancy. Multiple clinical features are shared between pre-eclampsia and postpartum psychiatric disorders, most prominently a strong link to first pregnancies. Therefore, we aimed to study if pre-eclampsia is a risk factor for first-onset postpartum psychiatric episodes.

Method. We conducted a cohort study using the Danish population registry, with a total of 400 717 primiparous women with a singleton delivery between 1995 and 2011. First-lifetime childbirth was the main exposure variable and the outcome of interest was first-onset postpartum psychiatric episodes. The main outcome measures were monthly incidence rate ratios (IRRs), with the period 11–12 months after birth as the reference category. Adjustments were made for age, calendar period, reproductive history, and perinatal maternal health including somatic and obstetric co-morbidity.

Results. Primiparous women were at particularly high risk of first-onset psychiatric episodes during the first month postpartum [IRR 2.93, 95% confidence interval (CI) 2.53–3.40] and pre-eclampsia added to that risk (IRR 4.21, 95% CI 2.89–6.13). Having both pre-eclampsia and a somatic co-morbidity resulted in the highest risk of psychiatric episodes during the 3-month period after childbirth (IRR 4.81, 95% CI 2.72–8.50).

Conclusions. We confirmed an association between pre-eclampsia and postpartum psychiatric episodes. The possible explanations for this association, which are not mutually exclusive, include the psychological impact of a serious medical condition such as pre-eclampsia and the neurobiological impact of pre-eclampsia-related vascular pathology and inflammation.

Introduction

Childbirth has the highest relative risk of any vulnerability factor for the onset of serious psychiatric episodes such as depression, mania and psychosis (Jones *et al.* 2014). Furthermore, childbirth has also been associated with the substantial risk of additional psychiatric morbidity including personality, anxiety, adjustment and post-traumatic stress disorders (Howard *et al.* 2014). Several studies have demonstrated an increased risk during the first months after delivery for the onset of these episodes, compared with the risk of occurrence outside the postpartum period (Kendell *et al.* 1987; Munk-Olsen *et al.* 2006, 2009). The acute onset of postpartum psychiatric episodes is a serious event for which both the mother and the child are at risk of infanticide and/or maternal suicide, as well as long-term effects on social, emotional and cognitive outcomes (Grace *et al.* 2003; Stein *et al.* 2014). Therefore, a deeper understanding of the underlying etiologies would greatly facilitate both the prevention and treatment of postpartum psychiatric episodes.

The pathogenesis of postpartum psychiatric disorders is considered complex and heterogeneous. Childbirth is a major life event with profound and often stressful changes in every aspect of daily life, which could make women vulnerable for psychiatric episodes. In addition, several neurobiological pathways are highly sensitized in the immediate

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postpartum period and could function as potential triggers (Bloch *et al.* 2003). Major alterations occur in steroid and stress hormones following delivery. However, evidence of a causual influence of steroid hormones on the onset of postpartum psychiatric episodes remains limited (Klier *et al.* 2007) and findings in the stress hormone axis in postpartum mood disorders have been inconclusive, as both increased and decreased activity have been reported (Harris *et al.* 1996; Parry *et al.* 2003; Groer & Morgan, 2007). Alternatively, the risk of postpartum psychiatric episodes might be more sensitive to the rapid change of hormone levels, rather than simply to the absolute levels of the hormones themselves (Bloch *et al.* 2003). In addition, it is likely that genetic factors influence the maternal response to these peripartum triggers. Accordingly, there is evidence for the familiarity of postpartum episodes but specific genes have not yet been identified (Jones *et al.* 2007; Byrne *et al.* 2014).

Despite extensive efforts, a definitive pathophysiology for postpartum psychiatric disorders has remained elusive. Recently, based on a convergence of both immunological and epidemiological studies, there has been increasing support for the hypothesis that first-onset postpartum disorders may share similar etiological mechanisms with immune-related disorders (Gleicher, 2007; Bergink *et al.* 2013; Osborne & Monk, 2013). In our recent work, we showed that patients with severe first-onset postpartum episodes had abnormalities in monocyte activation and T cell function during the acute phase (Bergink *et al.* 2013) and a small subgroup of patients suffered from undiagnosed autoimmune encephalitis (Bergink *et al.* 2015*a*). In support of this hypothesis is the consistent finding that medical conditions with a postpartum flare pattern – including postpartum thyroiditis, multiple sclerosis and rheumatoid arthritis – have an etiology originating from immune system dysfunction (Buyon, 1998; Confavreux *et al.* 1998; Gleicher, 2007; Haupl *et al.* 2008; Weetman, 2010).

Pre-eclampsia is a severe immune-related disorder of pregnancy. Interestingly, multiple clinical features are shared between pre-eclampsia and first-onset postpartum psychiatric disorders (Di Florio *et al.* 2014). The initial onset of both disorders is strongly associated with first pregnancy, compared with subsequent pregnancies. Furthermore, a history of a prior episode is the strongest known risk factor for each disorder in subsequent pregnancies (Steegers *et al.* 2010; Robillard *et al.* 2011; Munk-Olsen *et al.* 2014). Finally, several pre-eclampsia studies have demonstrated increasing risk with longer intervals between subsequent pregnancies, a relationship that has recently been confirmed for first-onset postpartum psychiatric episodes (Munk-Olsen *et al.* 2014). Together, the shared pattern of risk between pre-eclampsia and postpartum psychiatric

disorders may be evidence of a more fundamental relationship in their underlying pathophysiology (Steegers *et al.* 2010; Robillard *et al.* 2011; Di Florio *et al.* 2014; Munk-Olsen *et al.* 2014).

To date, the association between pre-eclampsia and severe postpartum psychiatric disorders has been examined only within disease-specific clinical cohorts (Brockington, 1996; Bergink *et al.* 2011). There is evidence linking pre-eclampsia and general psychiatric symptomatology such as anxiety and depressive symptoms (Delahaije *et al.* 2013), but conclusions were limited by difficulty in controlling for prepregnancy mental health. Therefore, the present study was designed to investigate the risk of a first-onset psychiatric episode after pre-eclampsia in primiparous women without psychiatric history. This large population-based Danish cohort study is the first epidemiological study in a general population on this topic.

Method

Study design and study population

We conducted an epidemiological population-based cohort study to investigate the association between pre-eclampsia (exposure) and the risk of a first-onset postpartum psychiatric episode (outcome). We identified all singleton births to primiparous women between 1 January 1995 and 31 December 2011. Each woman was followed within the cohort from the date of delivery until a postpartum psychiatric episode, migration, death or 31 December 2012, whichever occurred first. As an additional restriction for uniformity, we considered only women born in Denmark from 1 January 1960 to 31 December 1995. In total, we identified 400 717 women who contributed 372 067 person-years, of which 2723 mothers were recorded as having received either in-patient or out-patient treatment at a psychiatric facility within the initial 360 days postpartum.

Data resources and study variables

Information from three nationwide registers was linked for the present study. Registers were combined based on the unique Danish identification number assigned to each person at birth. We included information from the Civil Registration System on date of birth, parents' personal identification numbers, and daily updated information on vital status and migration (Pedersen, 2011).

Our main exposure variable was pre-eclampsia during primiparous pregnancies, identified using The Danish National Patient/Hospital Register (Andersen *et al.* 1999; Lynge *et al.* 2011). This register contains

information on all in-patient and out-patient treatment administered at medical hospitals in Denmark since 1995. Pre-eclampsia was defined by International Classification of Diseases, tenth version (ICD-10) code O14 (including moderate and severe pre-eclampsia). Importantly, pregnancy-induced hypertension (ICD-10 code O13) and eclampsia (ICD-10 code O15) were not considered as exposure variables for the present study.

The outcome of interest was first-onset psychiatric episodes during the postpartum period. These data were derived from The Danish Psychiatric Central Research Register (Mors *et al.* 2011), which holds information on all contacts with a psychiatric treatment facility in Denmark as in-patient and out-patient treatment during the entire study period. The diagnostic classification system used in Denmark is the ICD-10 (World Health Organization, 1994), from which we specifically used all diagnoses of mental and behavioral disorders in chapter V (F00–F99). A postpartum psychiatric episode was defined as any recorded contact with a psychiatric in-patient or out-patient treatment facility within the first 360 days postpartum, divided into monthly intervals (0–12 months). In addition, we conducted subanalyses for a more narrowly defined postpartum period within the first 90 days following delivery (0–3 months) compared with 4–12 months postpartum, as the first 3 months following childbirth have been associated with the highest lifetime risk of first-onset psychiatric episodes (Munk-Olsen *et al.* 2006). More detailed analyses were conducted on three diagnostic postpartum groups: unipolar depression (ICD-10 codes: F32, F33, F34, F38, F39), adjustment disorders (ICD-10 code: F43), and remaining diagnoses (remaining chapter V ICD-10 codes). Note that the subdivision into unipolar depression and adjustment disorders was made to provide additional clarification, since these episodes are the most frequently recorded diagnoses during the postpartum period. Further diagnostic subdivisions (e.g. bipolar disorder or a distinct diagnosis of postpartum psychosis (Bergink *et al.* 2015*b*) were not possible due to the reduction in statistical power that would result from the limited number of cases in many of the diagnostic subtypes. The analyses were restricted to include only first-onset episodes of mental disorders and not chronic disorders. Therefore, women with a registered diagnosis of any mental disorder occurring prior to the date of delivery were excluded from this study.

A range of potential confounders were considered as covariates: gestational diabetes (ICD-10 codes O24.4 and O24.9) and birth complications (an overall measure of number of recorded birth-related complications divided into three groups: 0–8 recorded complications, 9–14 recorded complications and 15+ complications).

We furthermore adjusted for reproductive histories, defined as records of induced abortions (ICD-10 codes O04, O05, O06), spontaneous abortions (ICD-10 codes O021, O03) and stillbirths (ICD-10 codes Z371, Z374, Z377, P95). Additionally, we adjusted the analyses for family history of psychiatric disorders (grandparents of index child having records of any treatment at a psychiatric facility) and somatic co-morbidities using the Charlson co-morbidity index (Charlson *et al.* 1987). The Charlson co-morbidity index is an indicator of medical disease burden and consists of 19 severe chronic diseases. Each disease is assigned a weight from one to six corresponding to the severity of the disease, and the score is subsequently calculated as the sum of all weights. All of the mentioned covariates were handled as time-dependent variables.

Statistical analysis

For the present study, analyses included calculation of incidence rates of psychiatric hospital contacts per 1000 person-years under risk. Furthermore, we conducted a survival analysis (Poisson regression) and calculated incidence rate ratios (IRRs). We calculated the IRRs of psychiatric contacts at monthly intervals for the first year postpartum, while the incidence rate 11–12 months after the birth was defined as the reference category. In the interaction analysis of pre-eclampsia with the Charlson co-morbidity index and gestational diabetes, we examined the risks of overall psychiatric episodes from 0–3 months (0–90 days) and 4–12 months (91–360 days) postpartum, due to the limited number of cases. We adjusted the IRRs for age, calendar period, reproductive history, gestational diabetes, maternal well-being around childbirth (number of diagnoses related to the specific childbirth), somatic co-morbidity (Charlson co-morbidity index) and family history of psychiatric disorders.

Results

A total of 400 717 women were included in our cohort study, of whom 17 149 had a diagnosis of pre-eclampsia (4.28%). A total of 2723 women received psychiatric treatment for any type of psychiatric diagnosis within the first 360 days postpartum, including 435 women via in-patient treatment and 2297 receiving treatment at out-patient mental health services. Out of the 2723 women with psychiatric episodes during the first 360 days postpartum, 162 had pre-eclampsia during pregnancy (5.93%). Among the 39.8% (*n* = 1087) of women who received their psychiatric diagnosis during the first 3 months postpartum, 71 had pre-eclampsia during pregnancy (6.53%).
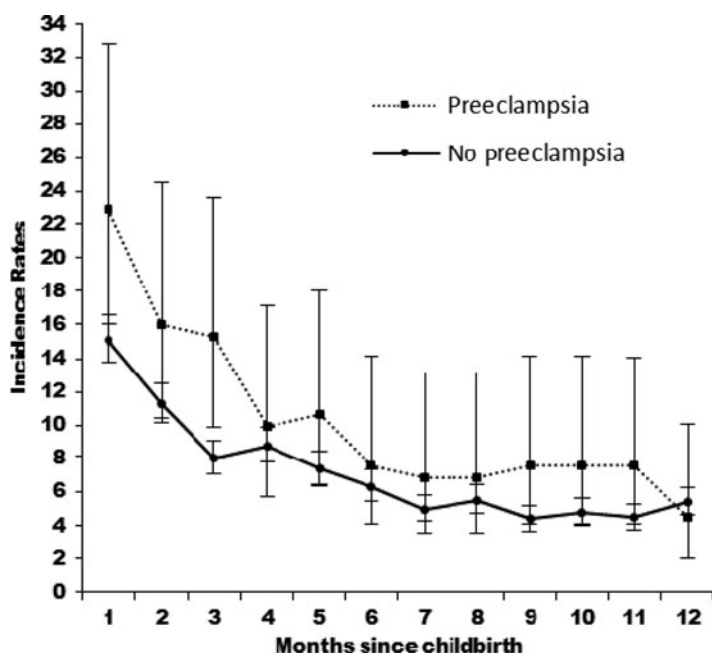
Fig. 1. Incidence rates per 1000 person-years for psychiatric contacts in primiparous mothers with and without pre-eclampsia 0–12 months postpartum. Values are incidence rates, with 95% confidence intervals represented by vertical bars.

Incidence rates of psychiatric contacts during the postpartum period are shown in Fig. 1, with the highest incidence of first-onset psychiatric episodes within the first month postpartum observed in women with or without pre-eclampsia. The corresponding IRRs are shown in Fig. 2. The first month postpartum was associated with the highest risk of psychiatric episodes for mothers with pre-eclampsia [IRR 4.21, 95% confidence interval (CI) 2.89–6.13] and without pre-eclampsia (IRR 2.93, 95% CI 2.53–3.40), compared with the reference category of women who gave birth 11–12 months prior with no pre-eclampsia (Fig. 2). The overall effect of pre-eclampsia on the risk of psychiatric episodes from 0 to 12 months after birth was IRR 1.43 (95% CI 1.22–1.68; results not shown).

For subanalyses, we defined three diagnostic groups [unipolar depression (ICD-10 codes: F32, F33, F34, F38, F39), adjustment disorder (F43) and other psychiatric diagnoses (any other chapter V code)] to identify possible changes in the risk of occurrence of an episode (Table 1). For all three groups, the highest risks were observed 0–3 months postpartum in women with pre-eclampsia [unipolar depression (IRR 2.85, 95% CI 1.84–4.42), adjustment disorder (IRR 4.04, 95% CI 2.85–5.72), other disorders (IRR 1.90, 95% CI 1.17–3.07)]. As CIs were overlapping for the above-mentioned results, there was no statistical difference in risk of the studied diagnostic subgroups. For this reason the results presented below focus on the single overall diagnostic group containing all psychiatric disorders as the outcome variable.

Stratified analyses were performed for somatic co-morbidity and gestational diabetes to investigate potentially moderating influences in the relationship between postpartum psychiatric episodes and pre-eclampsia. Having both pre-eclampsia and a somatic co-morbidity defined by the Charlson co-morbidity index yielded the highest risk of first-onset psychiatric episodes during the interval of 0–3 months postpartum, compared with women without somatic co-morbidities in the reference category (IRR 4.81, 95% CI 2.72–8.50) (Table 2). In particular, women with both gestational diabetes and pre-eclampsia had a significantly elevated risk of psychiatric episodes 0–3 months postpartum compared with mothers without these two disorders (IRR 3.86, 95% CI 1.24–12.00) (Table 3).

Discussion

This population-based cohort study demonstrates that all primiparous women are at risk of first-onset psychiatric episodes during the early postpartum period, but that pre-eclampsia adds considerably to that risk. This is observed broadly across psychiatric diagnoses in general, as well as independent for each of the following diagnostic groups: unipolar depression, adjustment disorders, and other psychiatric disorders. Further, our study confirms the well-described association between somatic co-morbidities and psychiatric episodes, as an increasing burden of somatic diseases or pregnancy complications such as gestational
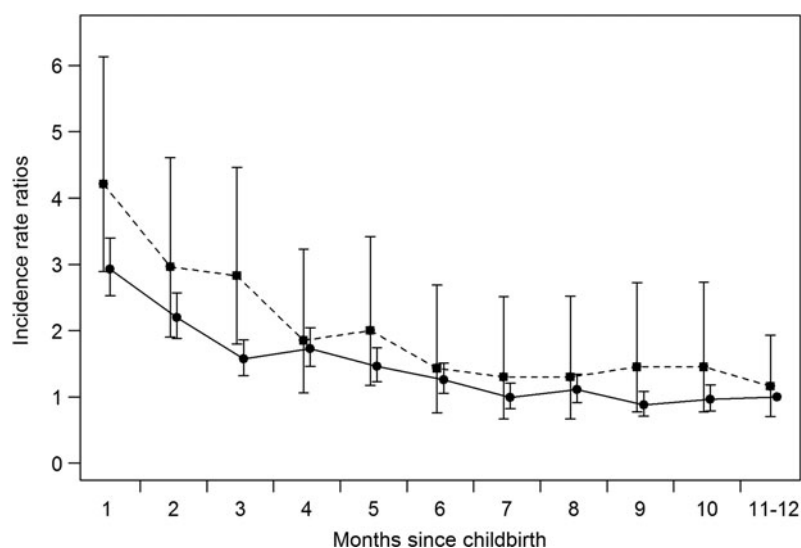
Fig. 2. Incidence rate ratios for psychiatric contacts in primiparous mothers with (--■--) and without (–●–) pre-eclampsia 0–12 months postpartum. Adjusted for age, calendar period, birth complications (number of diagnoses related to childbirth), reproductive history, gestational diabetes, somatic co-morbidities and family history of psychiatric disorders. Values are incidence rate ratios, with 95% confidence intervals represented by vertical bars.

Table 1. *Incidence rate ratios of first-onset depression, adjustment and remaining diagnoses 0–3 months and 4–12 months postpartum in primiparous mothers*[a]

Postpartum diagnostic groups	Pre-eclampsia		No pre-eclampsia	
	0–3 months postpartum	4–12 months postpartum	0–3 months postpartum	4–12 months postpartum
Unipolar depression	2.85 (1.84–4.42)	1.25 (0.84–1.84)	2.11 (1.83–2.43)	1 (reference category)
n	21	27	325	456
Adjustment disorder	4.04 (2.85–5.72)	1.54 (1.10–2.14)	2.29 (2.02–2.61)	1 (reference category)
n	34	38	420	537
Other disorders	1.90 (1.17–3.07)	0.99 (0.67–1.47)	1.49 (1.29–1.72)	1 (reference category)
n	17	26	289	570

Data are given as incidence rate ratio (95% confidence interval).

[a] Adjusted for age, calendar period, birth complications (number of diagnoses related to childbirth), reproductive history, somatic co-morbidities (Charlson co-morbidity index) and family history of psychiatric disorders. If a woman had records of more than one of the diagnoses of interest (dual diagnoses), she contributed with information in more than one category.

diabetes significantly increases the risk for postpartum psychiatric episodes, especially in women with pre-eclampsia. Explanations for the association between pre-eclampsia and first-onset psychiatric episodes could be sought in both psychological and neurobiological models, which are not mutually exclusive.

Effects of maternal and neonatal adverse events

Pre-eclampsia is associated with perinatal complications such as preterm delivery, poor neonatal outcome and death. It is plausible that these adverse events lead to feelings of stress and grief, making women vulnerable for psychiatric episodes after delivery. Indeed, unfavorable outcomes after pre-eclampsia have been described as a risk factor for postpartum depression (Hoedjes *et al.* 2011). In the present studies, cases of eclampsia or neonatal death were excluded and therefore by adjusting the results for gestational age and birth complications, we aimed to overcome this potential bias. Nevertheless, the psychological impact of a serious medical condition such as pre-eclampsia might have contributed to the vulnerability for psychiatric episodes postpartum.

Table 2. *Somatic co-morbidity, pre-eclampsia and incidence rate ratios of first-onset psychiatric episodes 0–3 months and 4–12 months postpartum in primiparous mothers*[a]

Charlson co-morbidity index	Pre-eclampsia		No pre-eclampsia	
	0–3 months postpartum	4–12 months postpartum	0–3 months postpartum	4–12 months postpartum
Yes (1+ score)	4.81 (2.72–8.50)	1.22 (0.63–2.35)	2.18 (1.73–2.76)	1.43 (1.20–1.69)
n	12	9	75	143
No (0 score)	2.78 (2.14–3.61)	1.32 (1.06–1.65)	1.97 (1.81–2.14)	1 (reference category)
n	59	82	941	1402

Data are given as incidence rate ratio (95% confidence interval).

[a] Adjusted for age, calendar period, birth complications (number of diagnoses related to childbirth), reproductive history, gestational diabetes and family history of psychiatric disorders.

Table 3. *Gestational diabetes, pre-eclampsia and incidence rate ratios of first-onset psychiatric episodes 0–3 and 4–12 months postpartum in primiparous mothers*[a]

Gestational diabetes	Pre-eclampsia		No pre-eclampsia	
	0–3 months postpartum	4–12 months postpartum	0–3 months postpartum	4–12 months postpartum
Yes	3.86 (1.24–12.00)	1.32 (0.43–4.12)	2.35 (1.49–3.70)	1.60 (1.15–2.23)
n	3	3	19	37
No	2.89 (2.27–3.69)	1.28 (1.03–1.59)	1.94 (1.79–2.10)	1 (reference category)
n	68	88	997	1508

Data are given as incidence rate ratio (95% confidence interval).

[a] Adjusted for age, calendar period, birth complications (number of diagnoses related to childbirth), reproductive history, somatic co-morbidities (Charlson co-morbidity index) and family history of psychiatric disorders.

Maternal–fetal incompatibility

There are three clinical characteristics of serious postpartum psychiatric episodes that show a remarkable overlap with pre-eclampsia: primiparity, a high recurrence risk after a subsequent pregnancy, and increased risk with prolonged birth interval. Accordingly, these associations raise the possibility of a shared biological mechanism. Pre-eclampsia is considered to be a disease of immunological maternal–fetal incompatibility. An immunological maternal–fetal conflict is thought to result in pathophysiological changes in the placenta early in pregnancy, preceding the clinical symptoms of pre-eclampsia (Sargent *et al.* 2006; Steegers *et al.* 2010; Roberts & Bell, 2013). During a first pregnancy, paternally inherited antigens expressed by the fetus are viewed by the maternal immune system as foreign. In contrast, during subsequent pregnancies the maternal immune system has already had the opportunity to develop tolerance to paternally inherited antigens expressed by the fetus. This pathophysiological model elegantly accounts for the well-replicated findings of decreased risk of pre-eclampsia during subsequent pregnancies, compared with a woman's first pregnancy in which the risk is highest (Sargent *et al.* 2006; Steegers *et al.* 2010). Consistent with this epidemiological finding, increasing intervals and/or a new partner have been shown to reduce maternal tolerance and thereby increase pre-eclampsia risk (Tandberg *et al.* 2015).

In theory, maternal–fetal incompatibility could potentially explain many of the similarly enigmatic clinical characteristics of acute postpartum episodes, including the substantially increased risk of first pregnancies and an increasing risk with longer intervals between subsequent pregnancies. However, one important difference between postpartum disorders and pre-eclampsia is the timing of onset of clinical symptoms. Pre-eclampsia is a disease of pregnancy, in which delivery resolves the pathophysiological process, whereas the highest known risk factor for the onset of psychiatric disorders falls within the early postpartum interval following delivery. Accordingly, maternal immune-related pathophysiological changes early in pregnancy could only lead to acute

postpartum episodes several months later if there is a second trigger around the time of delivery.

Vascular damage

When considering pathophysiological changes later in pregnancy and closer to the postpartum onset of psychiatric episodes, the second pathophysiological stage of pre-eclampsia might be of interest. This stage is characterized by excessive endothelial activation and a generalized hyperinflammatory state compared with normal pregnancy (Redman & Sargent, 2001; Sargent *et al.* 2006; Steegers *et al.* 2010). Widespread endothelial dysfunction establishes a high vulnerability to disruption of the blood–brain barrier (Amburgey *et al.* 2010). An increased permeability of the blood–brain barrier, in the setting of a hyperinflammatory state, is known to broadly influence brain function, including neurotransmitter metabolism, neuroendocrine function and synaptic plasticity (Capuron & Miller, 2011; Bergink *et al.* 2014). Together, vascular inflammation as observed in pre-eclampsia could be seen as a candidate neurobiological vulnerability mechanism for psychiatric disorders. The systemic consequences of this vascular inflammation, such as renal and liver dysfunction (including insulin resistance), could further influence brain function. Under this model, psychiatric episodes could be seen as the direct consequence of the later-stage pathophysiological changes of pre-eclampsia.

Methodological considerations

The present study is based on data from Danish population registers covering the entire nation, thereby providing information on a large, unselected group of women during pregnancy. However, there are certain limitations to the data, including the definition of our main outcome of interest: any type of psychiatric disorder treated at an in-patient or out-patient psychiatric treatment facility. The present study included primiparous pregnancies and first-onset psychiatric episodes as exposure and outcome variables. It is likely that women in our cohort are less likely to continue reproducing (Laursen & Munk-Olsen, 2010), and hence generalizability to multiparous women can be questioned. As this information is obtained from women who actively sought care, the rates of psychiatric episodes presented in the present study may be an underestimation of the true population incidence. Furthermore, our results do not provide information on less severe mental health problems treated through primary care providers. In an effort to avoid bias by clinical heterogeneity, the present study focused exclusively on primiparous mothers with no previous evidence of psychiatric history. Importantly, we acknowledge that this decision also potentially limits the generalizability of our findings. Residual confounding factors cannot be excluded since unmeasured patient characteristics may have influenced our results, including the lack of information regarding diseases of milder severity not captured by the Charlson co-morbidity index, lifestyle factors such as obesity and smoking, as well as aspects regarding infant health.

Conclusion

This population-based cohort study demonstrates that primiparous women are at high risk of first-onset psychiatric episodes particularly during the early postpartum period. The present study confirms a link between pre-eclampsia and postpartum psychiatric episodes, mainly representing unipolar depression and adjustment disorders. Additionally, our findings suggest a particularly elevated risk of postpartum episodes in women with somatic and obstetric co-morbidities, compared with women without these co-morbidities. Explanatory models linking pre-eclampsia and postpartum episodes could include exogenous and/or endogenous factors:

(1) The psychological impact of a serious medical condition such as pre-eclampsia might have contributed to the vulnerability for psychiatric episodes.
(2) An underlying immune-mediated pathophysiological mechanism could lead to both pre-eclampsia and postpartum psychiatric episodes. In particular, vascular pathology and hyperinflammation are important candidate vulnerability triggers for postpartum psychiatric episodes.

The clinical relevance of our findings is most importantly found among pregnant primiparous patients with somatic co-morbidities including pre-eclampsia, in whom clinicians should be aware of the increased risk of first-onset postpartum psychiatric episodes.

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