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Endocrine disease history and the risk of postpartum depression

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Background

Previous research has suggested that some women are at increased risk of postpartum depression (PPD) because of an extra sensitivity to fluctuating hormones before and after parturition. This may particularly apply to women with endocrine disease, characterised by a less than optimal capability to self-regulate the hormonal feedback system.

Aims

To investigate if women with endocrine disease history are at increased risk of developing PPD.

Method

Based on information from Danish national registers, this nationwide cohort study included 888 989 deliveries (1995–2018). Endocrine disease history was defined as thyroid disease, pre-pregnancy diabetes, polycystic ovary syndrome and/or previous gestational diabetes within 10 years before pregnancy start. PPD was defined as use of antidepressants and/or hospital contact for depression within 6 months after childbirth.

Results

Among 888 989 deliveries, 4.1% had a history of endocrine disease and 0.5% had a PPD episode. Overall, women with an endocrine disease history had a 42% (risk ratio 1.42, 95% CI 1.24–1.62) higher risk of PPD when compared with women with no endocrine disease. However, we also found the reverse association, whereby women with a PPD history had a 50% (hazard ratio 1.5, 95% CI 1.4–1.6) higher risk of endocrine disease when compared with women with no PPD history.

Conclusions

Women with endocrine disease history had a 40% higher risk of PPD compared with women with no endocrine disease. More attention should be given to pregnant women with endocrine disease history to increase awareness of early signs of PPD. The bi-directionality of the association points to a common underlying factor.

Keywords

Depressive disorders; epidemiology; neuroendocrinology; perinatal psychiatry; antidepressants.

Pregnancy and the early postpartum period constitutes an unparalleled situation with large endocrine alterations.[1] During pregnancy many hormones levels increase markedly, including reproductive hormones such as oestradiol and progesterone, as well as hormones of other biological systems such as thyroid-stimulating hormone, cortisol, corticotropin-releasing hormone and prolactin. After parturition, the hormones return to normal levels (depending on breastfeeding of the baby), some gradually within a few months and others, in particular hormones of the hypothalamic-pituitary-adrenal axis and reproductive hormones, within days of delivery.[2–4] In most women, these drastic changes are counteracted by balancing measures, and do not appear to have consequences for somatic or mental health.[1] However, in some women, they have been suggested to play a role in the development of postpartum depression (PPD).[1,2,5,6] This is partly based on an observed association between various endocrine disorders and depression not related to childbirth,[7,8] and the temporal association of rapid hormonal changes and depressive disorders in the ante- and postpartum period. The latter association has been termed the 'hormone-sensitive' PPD hypothesis.[4,9] In an experimental design, Bloch and colleagues administered gonadal steroids in an on/off design mimicking the hormonal milieu around parturition in women with and without previous PPD history.[6] Based on their findings, the authors concluded that there is a subgroup of women with previous PPD history who are especially responsive to changing levels of gonadal steroids of parturition, as measured by depressive symptoms. This sensitivity was only present in women that had previously experienced a PPD episode.[6] Further, Schiller and colleagues tested a cross-species oestrogen withdrawal model of PPD in rats and pregnant women. The results supported an effect of oestradiol on perinatal depressive symptoms.[10] However, the literature on this topic is still limited, and the findings are conflicting.[6,11–13] Some argue that the inconsistent findings may partly be a result of the wide variety of subtypes encompassed in the PPD definition, and the many different ways hormones have been assessed and examined in relation to PPD.[4,9]

Aims

We hypothesised that if some women are at increased risk of PPD because of an extra sensitivity to fluctuating hormones around parturition, this may particularly apply to women with endocrine diseases, characterised by a malfunction of hormonal regulation. Less than optimal capability to self-regulate the hormonal feedback system may put women with endocrine disease in a vulnerable position when facing the rapid changes of hormones associated with parturition. To address this hypothesis, we used a nationwide register-based cohort design to investigate the association between clinically overt endocrine diseases (polycystic ovary syndrome (PCOS), diabetes, gestational diabetes (GDM) and thyroid disease) diagnosed before conception, GDM in the current pregnancy and the following risk of PPD. We focus on PPD in women without psychiatric history, assuming that an effect of endocrine disease history might be relatively more pronounced for them when compared with women with psychiatric history.

Method

Study population

Using the unique personal identification number assigned to all Danish citizens, we linked individual-level data from various Danish national registers. We established a nationwide cohort

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encompassing all deliveries from 1 January 1996 to 7 June 2018. Based on information from national registers, we excluded deliveries by women not born in Denmark (197 296 deliveries); deliveries with missing information on gestational age (12 607 deliveries) and/or maternal educational level (11 986 deliveries); and deliveries by women with a psychiatric history (284 324 deliveries), including previous PPD episodes (defined in Supplementary Table 1 available at https://doi.org/10.1192/bjp.2022.173). A total of 888 989 eligible deliveries were included in the cohort.

Identification of women with endocrine disease

For this study, we defined endocrine disease history as a diagnosis of diabetes or thyroid disease, or GDM in a previous pregnancy, or PCOS within 10 years of start of pregnancy (for ICD-8 and ICD-10 codes see Supplementary Table 2). The investigated endocrine diseases were chosen based on frequency in our cohort, and so a number of endocrine diseases were not included because there were too few cases. Pregnancy start was defined as the date of the delivery minus the gestational age in days. GDM in the current pregnancy was defined as a diagnosis given from the start of the pregnancy to the delivery (for more detailed information see Supplementary Table 2)/ Information on endocrine disease history and pregnancy duration was based on information in the Medical Birth Registry,[14] the Danish National Prescription Registry[15] and the National Patient Registry.[16]

Identification of women with PPD

We defined PPD as an episode of an in- or out-patient hospital contact for a depressive episode and/or use of an antidepressant medication within 6 months after delivery. Episodes in the Danish National Prescription Registry were identified as women filling at least one prescription for antidepressant medication. Episodes in the National Patient Registry and Psychiatric Central Research Registry[17] were identified as women having an in- or out-patient contact for a depressive episode, using main diagnoses only (for ICD-8 and ICD-10 codes see Supplementary Table 3).

Covariates

Covariates included in this study were parity, calendar year, maternal age at delivery, maternal education, cohabitation, employment status, multiple pregnancy and length of follow-up (see Supplementary Table 4). All covariates, except for length of follow-up, were chosen based on available information in the registers and the potential as a confounder between the endocrine disease and risk of PPD. Strong independent risk factors for PPD were also included. An interaction between maternal age and calendar year was included in the model. This interaction captures that there are few age-related differences in risk of PPD in the first years of the study, but an increased risk of PPD in younger mothers in the later years of the study.

Statistical analysis

For the main analysis, we estimated risk ratio of PPD modelled by log-linear binomial regression. SAS software, version 9.4 (Windows), was used for all analyses. The model was adjusted for all the previous mentioned covariates. In analyses involving a specific disease and subclassifications, the reference group was women with no history of that specific disease, e.g. women with type 1 diabetes are compared with women without type 1 diabetes who may, however, have type 2 diabetes or other endocrine diseases.

Rates of endocrine diseases (diabetes, thyroid disease and PCOS) according to PPD history were investigated in a cohort of women with no psychiatric history or history of endocrine disease before first delivery. The definitions of PPD and endocrine disease and the exclusion criteria were investigated in the women with deliveries in the main study population and no history of endocrine disease before first delivery. Follow-up started at first birth and ended at first diagnosis of endocrine disease, 7 June 2018, death or emigration, which ever came first. Time to first diagnosis of endocrine disease was modelled by a Cox proportional hazards model, using time since first delivery as timescale and allowing PPD history as a time-dependent covariate. Hazard ratio according to PPD history (yes/no) was adjusted for birth year, maternal age, maternal education, cohabitation and employment status, categorised as described in Supplementary Table 4.

The combined endocrine disease category used in the main analyses (Table 1, Fig. 1) includes diabetes, thyroid disease, GDM in a previous pregnancy and PCOS, but not GDM in the current pregnancy. In contrast, in the analysis of time since latest diagnosis or prescription (Table 2) and the analysis of hazard ratios of endocrine disease by PPD history (Table 3), none of the GDM classifications were included in the combined endocrine disease category. As per definition, GDM episodes only occur in the context of a pregnancy, and thus the timing of a GDM episode reflects other factors than the disease itself. GDM in the current pregnancy was not included in the combined endocrine disease category as the overall aim of the study was to study endocrine disease history before pregnancy. However, to investigate the risk of PPD when exposed to more imminent endocrine disease, we also presented a risk ratio according to GDM in the current pregnancy.

Effect modifications were evaluated by including an interaction term in the regression. Risk ratios and hazard ratios in the supplementary analyses were estimated by the same approach as in the main analyses. Body mass index (BMI) as a potential confounder was evaluated by external adjustment.[18] In a supplementary analysis, we accounted for repeated deliveries by the same woman by generalised estimating equations, using an exchangeable working correlation structure. No ethical approval is needed for this type of register-based cohort study.

Results

Table 1 shows the number and distribution of deliveries with endocrine disease history and PPD, according to covariates used in the study. In total, from 1 January 1996 to 7 June 2018, we included 888 989 deliveries by women with no previous psychiatric disease in the study. Overall, women had a history of endocrine disease history in 4.1% of the deliveries, and women experienced a GDM episode within the current pregnancy in 1.7% of the deliveries. The proportion of deliveries by women with a history of endocrine disease and GDM (both in a previous pregnancy and in the current pregnancy) increased markedly over the study period, with increasing maternal age and parity. The proportion of PPD deliveries in the cohort was highest in the middle part of our study period, in younger mothers, among women with short education and women who were unemployed/outside the labour market.

Figure 1 shows the risk ratio of PPD by endocrine disease history within the past 10 years in women with no psychiatric history. Overall, women with an endocrine disease history had a 40% (risk ratio 1.42, 95% CI 1.24–1.62) higher risk of a PPD episode. The higher risk of PPD was evident for all types of endocrine diseases (thyroid disease: risk ratio 1.37, 95% CI 1.13–1.66; diabetes: risk ratio 1.28, 95% CI 1.02–1.6; PCOS: risk ratio 1.48, 95% CI 1.11–1.97; previous GDM: risk ratio 1.5, 95% CI 1.09–2.06; current GDM: risk ratio 1.33, 95% CI 1.09–1.62).

The higher risk of PPD in women with endocrine disease history compared with women with no such history was unrelated

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Table 1 Total number and distribution of deliveries with endocrine disease history within the past 10 years before pregnancy and postpartum depression, according to covariates

Covariates		Deliveries, *n*	History of endocrine disease, %						
			Any1	Thyroid disease	Diabetes	PCOS	GDM, previous pregnancy	GDM, current pregnancy, %	PPD, current pregnancy, %
All		888 989	4.1	1.9	1.4	0.7	0.6	1.7	0.5
Birth year	1996–1999	200 801	1.7	1.0	0.4	0.1	0.2	0.8	0.3
	2000–2004	224 746	2.5	1.5	0.5	0.3	0.4	1.0	0.5
	2005–2009	200 159	4.4	2.0	1.7	0.7	0.6	2.0	0.7
	2010–2014	159 710	6.6	2.6	2.7	1.3	1.0	2.6	0.6
	2015–2018	103 573	7.6	3.4	2.6	1.7	1.2	3.2	0.3
Maternal age	<20 years	11 007	0.7	0.3	0.2	0.1	0.0	0.7	1.2
	20–24 years	95 227	2.0	0.9	0.7	0.5	0.2	1.1	0.8
	25–29 years	312 047	3.4	1.4	1.3	0.7	0.4	1.3	0.5
	30–34 years	323 621	4.6	2.1	1.6	0.8	0.7	1.8	0.4
	35–39 years	127 120	5.9	3.1	1.8	0.7	1.1	2.7	0.4
	≥40 years	19 967	7.1	4.1	2.0	0.6	1.4	4.2	0.4
Parity	0 previous deliveries	403 242	3.3	1.5	1.4	0.8	0.0	1.6	0.5
	1 previous delivery	342 868	4.7	2.1	3.2	0.7	1.0	1.7	0.5
	≥2 previous deliveries	142 879	4.9	2.5	1.3	0.5	1.3	2.0	0.4
Education	Short education	129 875	3.1	1.4	0.9	0.5	0.6	1.8	0.9
	Intermediate education	419 439	3.8	1.7	1.3	0.7	0.6	1.8	0.5
	Long education	339 675	4.8	2.3	1.7	0.9	0.6	1.6	0.6
Cohabitation	Living alone	92 209	3.1	1.6	1.0	0.5	0.3	1.6	0.7
	Cohabitating/married	796 780	4.2	1.9	1.4	0.7	0.6	1.7	0.5
Employment status	Not working	219 648	3.4	1.6	1.2	0.6	0.6	1.6	0.7
	Working	669 341	4.3	2.0	1.5	0.8	0.6	1.8	0.4
Multiple delivery	Singleton delivery	870 609	4.0	1.9	1.4	0.7	0.6	1.7	0.5
	Multiple delivery	18 380	7.1	2.6	3.2	1.8	0.6	2.8	0.6

PCOS, polycystic ovary syndrome; GDM, gestational diabetes; PPD, postpartum depression.
1 'Any history of endocrine diseases' includes history of thyroid disease, diabetes, PCOS and previous GDM episodes.

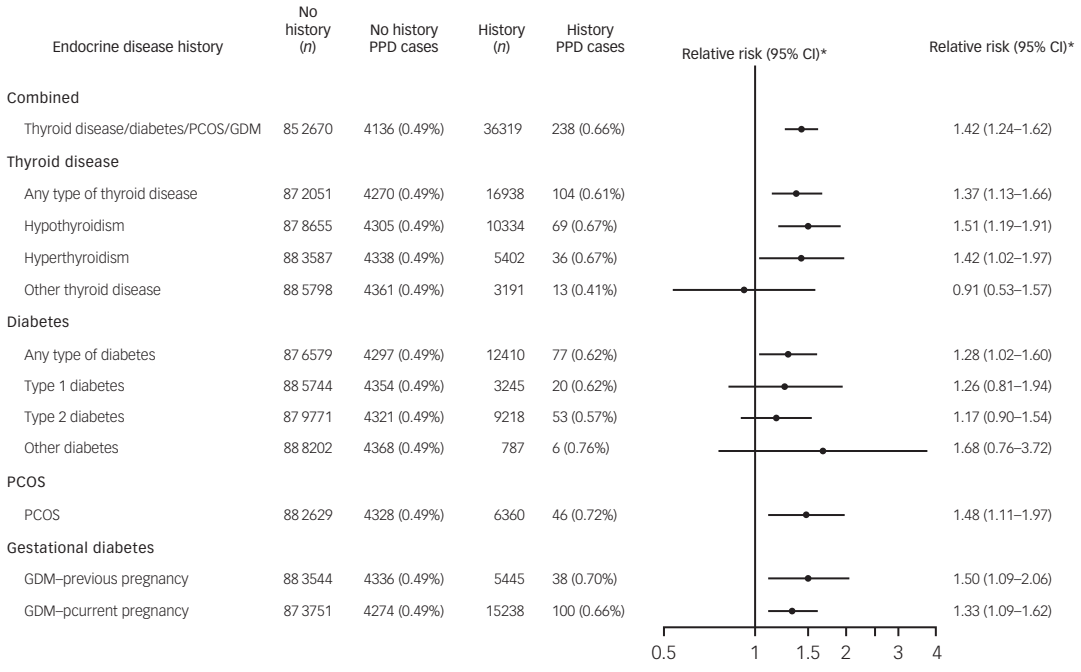

Fig. 1 Risk ratio (RR) of postpartum depression by endocrine disease history.

*Adjusted for calendar year, length of follow-up, parity, multiple delivery, maternal education, cohabitation, employment status and calendar year × maternal age. PPD, postpartum depression; PCOS, polycystic ovary syndrome; GDM, gestational diabetes.

to a specific postpartum period (0–7 weeks after delivery: risk ratio 1.27, 95% CI 0.96–1.68; 8–26 weeks after delivery: risk ratio 1.47, 95% CI 1.26–1.70) (Table 2). Likewise, the higher risk of PPD in women with endocrine disease history compared with women with no such history was not related to the timing of the endocrine disease before delivery (<1 year: risk ratio 1.37, 95% CI 1.16–1.62; 1–10 years: risk ratio 1.37, 95% CI 1.08–1.75) (Table 2).

Finally, we investigated the reverse association: does an episode of PPD increase a woman's risk of a subsequent endocrine disease? We found that reverse association was indeed also present, hence women with a PPD episode had a 50% higher risk of a subsequent

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Table 2 Risk ratio of postpartum depression first by endocrine disease history according to time since latest diagnosis and/or prescription before pregnancy, and by time since delivery according to endocrine disease history

Endocrine disease history[a]	Deliveries	Number of PPD cases (%)	Risk ratio (95% CI)
By time since latest diagnosis and/or prescription before pregnancy			
No endocrine disease history	856 426	4163 (0.49%)	Reference
Within the past year	21 989	144 (0.65%)	1.37 (1.16–1.62)[b]
Within 1–10 years	10 574	67 (0.63%)	1.37 (1.08–1.75)[b]
By time since delivery			
0–7 weeks			
No endocrine disease history	852 670	1010 (0.12%)	Reference
Endocrine disease history[a]	36 319	52 (0.14%)	1.27 (0.96–1.68)
8–26 weeks			
No endocrine disease history	851 660	3126 (0.37%)	Reference
Endocrine disease history[a]	36 267	186 (0.51%)	1.47 (1.26–1.70)

PPD, postpartum depression.
a. Endocrine disease history includes diabetes, thyroid disease, polycystic ovary syndrome and previous gestational diabetes episodes.
b. Adjusted for calendar year, length of follow-up, parity, multiple delivery, maternal education, cohabitation, employment status and calendar year × maternal age.

Table 3 Hazard ratios of endocrine disease by history of postpartum depression

	PPD history		No PPD history		PPD history versus no PPD history
	Incidence rate/1000 person-years	Endocrine disease cases	Incidence rate/1000 person-years	Endocrine disease cases	Hazard ratio (95% CI)[a]
Endocrine disease[b]	9.8	507	6.3	40,925	1.5 (1.4–1.6)
Thyroid disease	6.3	332	4.6	30,433	1.4 (1.2–1.5)
Diabetes	3.5	190	1.6	10,759	1.8 (1.6–2.1)
PCOS	0.5	30	0.3	2,127	1.3 (0.9–1.8)

PPD, postpartum depression; PCOS, polycystic ovary syndrome.
a. Adjusted for birth year, maternal age, maternal education, cohabitation and employment status.
b. Endocrine disease includes diabetes, thyroid disease, PCOS and previous gestational diabetes episodes.

endocrine disease (risk ratio 1.50, 95% CI 1.40–1.60) compared with women with no PPD episode. The higher risk was observed in all types of endocrine disease studied (see Table 3).

Supplementary analyses

First, we found that two control diseases, fractures in extremities and appendicitis, that *a priori* were not expected to be associated with PPD, were indeed not associated with PPD (Supplementary Table 5). Second, in a cohort of women with psychiatric history, we found that endocrine disease history was not markedly associated with the risk of PPD (risk ratio 1.11, 95% CI 1.00–1.23). Only women with type 2 diabetes history had a higher risk of PPD (Supplementary Fig. 1). Third, in a cohort of women with no psychiatric disease history (psychiatric disease defined as a hospital contact and/or two or more prescriptions of psychotropic drugs), we found that the estimates resembled those of the main analyses (Supplementary Table 5). Fourth in a generalised estimating equations model, we found that accounting for repeated observation did not change the main estimate (endocrine disease history: risk ratio 1.42, 95% CI 1.24–1.62). Finally, we did not have information on the women's BMI, which could be a potential confounder. However, using external information on the association between BMI and endocrine disease, and the association between BMI and PPD, we estimated that the observed association between endocrine disease and PPD (observed risk ratio 1.42, 95% CI 1.24–1.62) would only change slightly (adjusted risk ratio 1.41, 95% CI 1.23–1.60) after adjustment for BMI (for details see Supplementary Table 6).

We also conducted supplementary analyses of the reverse association of PPD and later risk of endocrine disease. First, maternal age did not modify the association between PPD and endocrine disease (<40 years: hazard ratio 1.5, 95% CI 1.3–1.7; ≥40 years hazard ratio 1.5, 95% CI 1.3–1.7). Second, we investigated if time since PPD onset modified the risk of subsequent endocrine disease; however, it did not (<1 year: hazard ratio 2.0, 95% CI 1.5–2.5; ≥1 year: hazard ratio 1.4, 95% CI 1.3–1.6).

Discussion

Main findings

In this study we found that women with endocrine disease history had a 40% higher risk of a subsequent PPD episode compared with women with no such history. The higher risk of PPD was evident for all types of endocrine disease studied. We also found evidence of the reverse association, as women with a PPD episode had a 50% higher risk of subsequent endocrine disease compared with women with no PPD history.

Interpretation

This is, to our knowledge, the first study linking endocrine disease history up to 10 years before childbirth to PPD. In contrast, prior studies on endocrine disease and PPD have focused on hormonal events during the pregnancy and immediate postpartum period.[3,19,20] However, the aim of this study was to investigate a more general malfunction of hormonal regulation and a potential stressor, endocrine disease history, rather than to investigate the direct effect of endocrine and hormonal alterations on the risk of PPD. Congruently, acknowledging the many different aetiologies and pathogenic mechanisms behind PPD, we only included women with no psychiatric history, to obtain a more homogenous

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cohort. We found that a history of endocrine disease increased the risk of PPD among women without psychiatric history. Interestingly, in a supplementary analysis of a cohort of women with psychiatric history, we found that endocrine disease history did not have the same effect on PPD risk as in women without psychiatric disease (Supplementary Fig. 1). Thus, recognising PPD as a heterogenic disease with several different aetiological backgrounds and separating women according to psychiatric history seem highly relevant when studying endocrine factors and PPD.

In an effort to further elucidate the link between endocrine disease and PPD, we also found that having an episode of PPD increased the risk of subsequent endocrine disease. One interpretation of this bi-directionality of the association is that different mechanisms are in play, and that endocrine disease increases the risk of PPD by, for example, a hormone-sensitive pathway, whereas PPD increases the risk of endocrine disease by other pathways. Another possibility is that the observation is caused by a common underlying factor, which predisposes women to both PPD and endocrine disease. This interpretation is supported by the lack of temporal effect of endocrine disease history on PPD risk, as one would have expected if the instigating factor had been changing levels of hormones around parturition. Supplementary analyses showed that the association between PPD and risk of endocrine diseases was not affected by maternal age or time since PPD onset. Also, an episode of GDM in the current pregnancy did not increase the risk of PPD comparably more than an episode of GDM in previous pregnancies.

Previous studies have found a bi-directionality of endocrine disease and general depression.[21,22] An example of a common underlying factor might be chronic low-grade inflammation. Inflammatory processes are the body's natural response to infections, physical injury or psychological stress. An acute inflammation is often beneficial, whereas a chronic inflammation can have a harmful effects on brain homeostasis.[23] Chronic low-grade inflammation causes activation of the peripheral macrophages, central microglia and hypercortisolaemia, and is linked to both depression and various endocrine disorders.[24,25] Obesity is often linked to chronic low-grade inflammation. In a sensitivity analyses, we estimated the effect of adjusting for BMI, and found no support for BMI explaining the observed association.

The endocrine system does not work alone, but rather is part of an intricate feedback system in which the hypothalamus and the pituitary gland regulates and is regulated by the response of the peripheral glands of the body, which together constitute the neuroendocrine system. Advances in the understanding of the neuroendocrine system have shown that steroid hormones not only regulate hypothalamic function, but also influence receptors in the brain outside the hypothalamus, such as the hippocampus,[26] which plays a central role in depressive illness.[27] Thus, it is possible that abnormalities in either of the systems markedly increase the risk of pathophysiological conditions in the corresponding system,[26] potentially explaining the bi-directionality of associations observed in this study.

In women with psychiatric disease history, we did not find that endocrine disease history was associated with PPD. Women with psychiatric disease history have a higher risk of PPD.[28] This is in accordance with the kindling hypothesis of recurrent depression.[29] Some evidence suggests that the depressed brain does not fully recover, and that recurrent episodes of depression are triggered by progressively weaker stress episodes.[30] Thus, this higher risk of PPD in women with psychiatric disease history, potentially induced by such neurobiological changes, may lessen the relative importance of endocrine disease in these women.

Strengths and limitations

Strengths of this study include the population-based prospective design and the use of high-quality nationwide Danish registers. In Denmark, health data is registered at each visit or contact with health services. Furthermore, the majority of the healthcare system is free of charge. This ensures that all residents, regardless of economic capability, are offered appropriate treatment, and it also ensures a high-quality research resource. It is a strength of the study design that we were able to qualify the research question by reversing the association, and thereby provide more nuanced conclusions of the study.

Although the strength of the design pertains to the use of national registers, so do some of the limitations. By defining endocrine disease history from hospital contacts and use of medication, we only capture clinically overt endocrine disease and not the subclinical cases. However, there is no indication that this misclassification is differential to PPD cases and non-cases, and it will therefore bias the estimate toward one. Another limitation to this study is that we have no indication in the registries as to how well-regulated the observed endocrine disease is. However, as a form of proxy, analysis that included time since latest endocrine hospital contact and/or prescription, a measure of endocrine disease healthcare utilisation, showed that risk of PPD did not seem to differ according to the timing of the latest endocrine contact (see Table 2). Lastly, we use treatment data to identify PPD, which most likely only includes a subgroup of severe PPD cases and could affect the generalisability to milder cases of PPD. Using antidepressants to identify cases of PPD in our study means that the women characterised as having PPD in our study do not necessarily fulfil the ICD-10 diagnostic criteria for depression, as antidepressants are also used for other indications such as anxiety,[31] as well as a number of off-label indications. This may introduce misclassification of PPD cases. A Canadian study from 2017 found that 29% of antidepressants prescribed in primary care were used off-label.[32] However, in our study, antidepressants were used for the first time in the postpartum period, where one must assume the proportion of off-label use is lower and depression the most frequent psychiatric disorder.

Perspectives

In a study by Milgrom et al, 9853 women completed questions on antenatal risk factors such as previous psychiatric conditions, and filled out a Edinburgh Postnatal Depression Scale (EPDS) questionnaire.[33] A total of 372 women with PPD had no psychiatric history, whereas 389 women had a psychiatric history (data from Table 3, Milgrom et al).[33] Thus, almost half of the PPD cases (49%) occurred among women without psychiatric history. This shows that although prior psychiatric history is one of the strongest predictors of PPD risk, almost half of PPD cases occur *de novo* in otherwise seemingly mentally healthy women. The distinction between a first episode of PPD and a PPD episode as part of a general psychopathology is important as preventive capabilities and measures differ. In Denmark, vulnerable pregnant women (e.g. characterised based on their mental history) are offered more visits to the midwife and from the public health nurse outside of the standard antenatal care programme. Thus, to identify risk factors, such as endocrine disease history, for PPD in women with no psychiatric history is of importance as it allows healthcare professionals to target preventive support to women at risk that may not be classified as a vulnerable, and thus currently may not receive the extra help needed.

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Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1192/bjp.2022.173

Data availability

Our study is based on Danish national register data. These data belong not to us but to the Danish Ministry of Health, and we are not permitted to release them, except in aggregate (as, for example, in a publication). However, interested parties can obtain the data on which our study was based by applying to the Ministry of Health's Research Service (Forskerservice) at forskerservice@ssi.dk.

Author contributions

M.-L.H.R. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. M.-L.H.R., G.J.P., P.V., J.W. and M.M. conceived of and designed the study. M.-L.H.R. was responsible for acquisition of data. M.-L.H.R., G.J.P., J.W. and M.M. were responsible for data analysis and interpretation. M.-L.H.R. drafted the manuscript. M.-L.H.R., G.J.P., P.V., J.W. and M.M. provided critical revision of the manuscript for important intellectual content. M.-L.H.R. and G.J.P. provided statistical analysis. M.-L.H.R. and M.M. obtained funding. J.W. and M.M. supervised the study.

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Declaration of interest

M.M. is a cofounder of Mirvie Inc, which creates precise, actionable, non-invasive tests for maternal-foetal health. The other authors report no competing interests.

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