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ORIGINAL ARTICLE

Impact of a prenatal episode and diagnosis in women with serious mental illnesses on neonatal complications (prematurity, low birth weight, and hospitalization in neonatal intensive care units)

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Abstract

Pregnancy in women with mental disorders is increasingly common. The aim of this study was to determine, in women with severe mental illnesses, whether a prenatal episode was related to neonatal complications and if a specific disorder was associated with a higher risk. A population of infants and their mothers ($n = 1439$) jointly admitted to psychiatric Mother-Baby Units in France and Belgium (2001–2010) was assessed respectively for prematurity, low birth weight (LBW), hospitalization in neonatal intensive care units (NICUs), and maternal mental health during pregnancy. Logistic regression was used to explore the association between neonatal complications and a prenatal episode of mental illness and if the presence of a specific disorder was related to a higher risk, taking into account maternal socio-demographic characteristics, pregnancy data, and antenatal exposure to psychotropic drugs. Among the children, 145 (10.2%) were premature, 226 (15.8%) had a LBW, and 348 (24.3%) have been hospitalized in neonatology. The presence of an episode of mental illness during pregnancy was linked to LBW (OR = 2.21 [1.44–3.38]; $p = 0.003$) and NICU hospitalizations (OR = 1.53 [1.06–2.19], $p = 0.002$). Among diagnoses, the presence of a severe substance use disorder in these women was related to LBW (OR = 2.96 [1.49–5.85]; $p = 0.002$) and NICU (OR = 2.88 [1.56–5.29]; $p = 0.04$). Our results underline the importance of systematic and early detection of psychiatric symptoms and substance use disorders during pregnancy in preventing neonatal complications in women with serious mental illness.

Keywords Low birth weight · NICU hospitalization · Pregnancy · Prematurity · Psychiatric disorder · Substance use disorder

Introduction

Women's mental health disorders (psychiatric or severe substance use disorders) during pregnancy are quite frequent with 15–20% of pregnant women presenting a mental disorder (Howard et al. 2014), whether a relapse or a first occurrence.

Both maternal psychiatric and substance use disorders have a major impact on fetal development during pregnancy and on

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premature childbirth, low birth weight (LBW), and hospitalizations in neonatal intensive care units (NICUs), which may also engender long-term negative health consequences for the child, from infancy to adulthood (Singh et al. 2013). LBW seems to be the most important risk factor for perinatal mortality and impairment in later development (Boardman et al. 2002; Walhovd et al. 2012).

In the general population, risk factors for prematurity and LBW are mainly maternal factors linked to the gynecological and/or obstetrical past history (short intervals between pregnancies, previous preterm delivery and intrauterine growth retardation), socio-demographic factors (maternal age less than 18 years or more than 35 years of age, celibacy, low socio-economic status, low level of education, violence during pregnancy, stress, low social support...), nutritional factors (anemia, omega-3 deficiency, low body mass index (BMI) or obesity, low weight gain during pregnancy...), and medical factors (antenatal exposure to toxics or pharmacological treatments, pre-eclampsia, bacterial and viral infections, physical trauma...) (Moutquin 2003). In developed countries, the most important factor for LBW has been reported to be cigarette smoking, followed by poor gestational nutrition and low pre-pregnancy weight (Kramer 1987).

Finally, risk factors for NICU hospitalization are primarily related to the infant and are mainly prematurity and low birth weight (Harrison and Goodman 2015).

Few studies have been conducted within the population of pregnant women with mental illness, and most of them have focused on the impact of fetal exposure to psychotropic drugs (Sutter-Dallay et al. 2015; Mitchell and Goodman 2018). However, maternal mental disorder in itself may lead to perinatal complications independently from prenatal exposure to psychotropic drugs. Yet, few studies have considered maternal psychiatric pathology or severe substance use disorders themselves as independent factors for perinatal complications and these studies were conducted within the general population (Kelly et al. 2002; Bodén et al. 2012; Wiencrot et al. 2012). In addition, a maternal episode of mental illness occurring during pregnancy could participate to explain the occurrence of neonatal complications rather than the mental disorder by itself.

The primary aim of this study was to determine whether, in women with severe mental illnesses hospitalized in a MBU after delivery, the presence of a maternal episode during pregnancy was associated with neonatal complications (prematurity, LBW, or NICU admission) independently from maternal socio-demographic characteristics, pregnancy characteristics, and antenatal exposure to psychotropic drugs. The second aim was to explore if the presence of a specific maternal mental health disorder (regarding ICD-10 criteria) was significantly related to a higher risk of infant neonatal consequences.

Material and methods

Data source

The present study explored the multi-center database founded by the French Network of Mother-Baby Units (MBUs) (Societe Marce Francophone). The database has been previously described (Glangeaud-Freudenthal et al. 2011; Gressier et al. 2017). To summarize, data from women with severe psychiatric or substance-related disorders, jointly admitted with their single child in one of 16 MBUs (13 in France and 3 in Belgium), was collected over a 10-year period (between January 1, 2001 and December 31, 2010).

Women with a serious mental diagnosis jointly admitted with their child (< 1 year) to one of the units were eligible for inclusion in the database if they fulfilled the following criteria: hospitalized for at least five consecutive days (time to collect relevant information); with a single baby. The medical team collected information on the hospital stay using the Marce Clinical Checklist (Glangeaud-Freudenthal et al. 2011). This tool was originally developed in the UK to collect standardized clinical data in UK MBUs and to develop large datasets intended to support multi-site research (Salmon and Appleby 2000; Salmon et al. 2004). The data collection used all available sources of information (clinical interviews with the patients and psychiatrists, medical records).

All selected women provided informed consent for their inclusion in the database. The study was performed in accordance with the ethics standards of the French National Data Protection Authority (CNIL) which the CNIL approved the study. Because no intervention was involved, no additional approval was required by French law. The three outcome variables presently studied were occurrence of low birth weight (< 2500 g), preterm birth (under 37 weeks gestation), and NICU hospitalization (during the first month).

Maternal psychiatric diagnoses were assessed by clinical examination by a clinical psychiatrist and were categorized (ICD-10) into the following: (1) anxiety disorders (general anxiety disorder, obsessive and compulsive disorder), (2) bipolar disorders, (3) depressive disorders, (4) psychotic disorders, (5) personality disorders, and (6) severe substance use disorders. Information on the presence of a maternal episode of mental illness during pregnancy (decompensation or relapse) was collected from maternal report and medical records.

The following risk factors identified from the literature were also extracted from the database: maternal socio-demographic characteristics (age, education, infant gender, absence of the child's father), pregnancy characteristics (primiparity, physical complications during pregnancy, prenatal alcohol, and illicit drugs and tobacco consumptions, including number of cigarettes per day), inadequate obstetrical

monitoring (fewer than the recommended 7 prenatal appointments and 3 obstetric ultrasounds), and maternal intake of psychotropic drugs during pregnancy (antidepressants, mood stabilizers, antipsychotics, anxiolytics).

Statistical analyses

The statistical analyses were performed using R software version 2.14.1. A descriptive analysis was first carried out on the entire study population. Quantitative variables were described by means and standard deviations (SD) and qualitative variables by percentages (Table 1).

Logistic regressions were then carried out in order to evaluate the association between a specific maternal diagnosis (categorized in anxiety disorder, chronic psychotic disorder, depressive disorder, bipolar disorder, personality disorder, and severe substance use disorder), presence of a maternal episode of mental illness during pregnancy (assessed from maternal reports and medical records), and infant neonatal outcomes (prematurity, LBW, and NICU admission), giving odds ratios (OR) and 95% confidence intervals (CI). All the models were adjusted a priori for socio-demographic data: maternal age, education level, infant gender, child's father absence, pregnancy characteristics: primiparity, physical complications during pregnancy, low medical follow-up, smoking during pregnancy, and antenatal psychotropic exposure: antidepressants, antipsychotics, mood stabilizers, or anxiolytic agents. Three sensitivity analyses were performed: the first one considering illicit drug or not (severe alcohol use disorder) for severe substance use disorder, the second considering the number of cigarettes per day instead of tobacco consumption (yes or no), and the third considering drug use (tobacco, alcohol, and illicit drugs).

In order not to exclude all the cases for which some of the inputs are missing, we have used the Gibbs sampling method for missing data imputation; Gibbs sampler is an algorithm used to obtain observations that approximate a specified multivariate probability distribution when a subset of variables is unknown (Yang et al. 2005). All tests were two-tailed. The significance level was set at 0.05.

Table 1 Characteristics of the sample

Sample characteristics	
Mother's age (mean [sd]) ($n = 1438$)	31.25 [6.21]
	n (%)
Maternal education level ($n = 1392$)	
Primary/secondary	621 (44.60)
Infant gender ($n = 1422$)	
Male	734 (51.60)
Child's father ($n = 1422$)	
Absence	506 (35.58)
Pregnancy characteristics	
Primiparity ($n = 1427$)	
Yes	629 (44.08)
Pregnancy physical complications ($n = 1405$)	
Yes	212 (15.10)
Smoking during pregnancy ($n = 1265$)	
Yes	351 (27.25)
Alcohol during pregnancy ($n = 1376$)	
Yes	115 (8.40)
Illicit drug during pregnancy ($n = 1308$)	
Yes	124 (9.48)
Low medical follow-up ($n = 1381$)	
Yes	131 (9.50)
Psychotropic treatment during pregnancy	
Antidepressants ($n = 1411$)	
Yes	206 (14.60)
Antipsychotics ($n = 1426$)	
Yes	343 (24.05)
Mood stabilizers ($n = 1425$)	
Yes	76 (5.33)
Anxiolytics ($n = 1419$)	
Yes	312 (21.99)
Child's characteristics at birth	
Prematurity < 37 SA ($n = 1428$)	
Yes	145 (10.20)
Low birth weight < 2500 g ($n = 1430$)	
Yes	226 (15.80)
NICU hospitalization ($n = 1433$)	
Yes	348 (24.30)
Episode of mental illness during pregnancy ($n = 1282$)	
Yes	611 (47.66)
Anxiety disorder ($n = 1381$)	
Yes	133 (9.63)
Chronic psychotic disorder ($n = 1381$)	
Yes	377 (27.30)
Depression ($n = 1381$)	
Yes	445 (32.22)
Bipolar disorder ($n = 1381$)	
Yes	282 (20.42)
Personality disorder ($n = 1381$)	
Yes	350 (25.34)
Severe substance use disorder ($n = 1381$)	
Yes	90 (6.52)

Results

Sample characteristics

The sample that included 1439 women with serious mental illness and their child admitted to a mother baby unit in France and in Belgium is described in Table 1.

Concerning diagnosis, 133 of women had anxiety disorder, 445 unipolar disorder, 282 bipolar disorder, 377 psychotic disorder, 350 personality disorder, and 90 severe substance use disorder. Diagnosis was missing for 57 women (3.96%). Concerning severe substance use disorder, substance was classified as follows: alcohol ($n = 34$), opioid ($n = 13$), cocaine ($n = 3$), THC ($n = 14$), and poly-consumption ($n = 23$) (not available for 3). Two hundreds and seventy eight women had more than one diagnosis.

A maternal episode of mental illness occurred during pregnancy for 611 (47.66%) women.

Prematurity

Of the 1439 women, 145 (10.2%) gave birth prematurely, and data were unavailable for 11 of them.

No specific association was reported between prematurity and the presence of a maternal episode during pregnancy or a specific mental health diagnosis (Table 2). Same results were found distinguishing illicit drug and not (alcohol) for severe substance use disorder (Suppl S1). The second sensitive analysis, considering the number of cigarettes per day (Suppl S2), reported also consistent results. In the third sensitive analysis, taking into account drug use during pregnancy (tobacco, alcohol, and illicit drugs, yes or no), no association was found (illicit drugs OR = 1.06 [0.53–2.13], $p = 0.86$; alcohol 0.94 [0.48–1.85], $p = 0.87$; tobacco 1.02 [0.64–1.62], $p = 0.94$).

Low birth weight

Among the 1439 women, 226 (15.8%) gave birth to a child with a birth weight < 2500 g, 1204 to a child with a weight ≥ 2500 g; birth weight was unavailable for nine newborns.

LBW was associated with a maternal episode of mental illness during pregnancy (OR = 2.21 [1.44–3.38], $p = 0.003$) and to the presence of a diagnosis of severe substance use disorder (OR = 2.96 [1.49–5.85], $p = 0.002$), independently of the other variables included in the model for regression analysis such as prematurity, psychotropic treatments, and tobacco use.

In the first sensitive analysis distinguishing illicit and non-illicit drugs, LBW was both associated with illicit and non-illicit (alcohol) drug severe substance use disorder (Suppl S1).

In the second sensitive analysis, considering the mean of cigarettes per day instead of tobacco consumption (yes or no), the association with a maternal episode during pregnancy and severe substance use disorder remained significant (S2).

In the third sensitive analysis, considering substance use during pregnancy, LBW was significantly associated with tobacco (OR = 1.95 [1.22–3.11], $p = 0.005$), but not illicit drug consumption (OR = 1.51 [0.81–2.81], $p = 0.19$) or alcohol consumption (OR = 1.21 [0.65–2.26], $p = 0.55$).

NICU hospitalization

Among 1439 women, 348 (24.3%) had their baby transferred and admitted to NICU; data on NICU hospitalization was unavailable in six files.

NICU hospitalization was significantly associated with the presence of a maternal episode during pregnancy (OR = 1.53 [1.06–2.19], $p = 0.002$) and the presence of severe substance use disorders (2.88 [1.56–5.29]; $p = 0.04$), independently of the other variables including in the model such as prematurity, LBW, psychotropic drugs, and tobacco use.

In the sensitive analysis distinguishing illicit and non-illicit drugs, NICU was associated with both non-illicit drug and illicit severe drug disorder (Suppl S1).

In the sensitive analysis taking into account the mean of cigarettes per day, the associations with tobacco, severe substance use disorder, and decompensation during pregnancy remained significant (S2).

Considering substance use during pregnancy, NICU was significantly associated with tobacco (1.64 [1.11–2.42], $p = 0.008$) and illicit drug (OR = 2.06 [1.22–2.43], $p = 0.01$) but not alcohol (OR = 1.56 [0.92–2.64], $p = 0.10$), independently of the others variables.

A logistic regression satisfies the conditions of statistical validity if there are at least five events per explanatory variable (Vittinghoff and McCulloch 2007). In our main logistic regression model, we included 19 explanatory variables for prematurity, 20 for LBW, and 21 for NICU hospitalizations. With 145, 226 and 348 events (respectively the number of prematurity, LBW, and NICU), we are in the conditions of validity.

Discussion

The prevalence of prematurity was 10.2% in our sample of women with serious mental illnesses admitted postnatally to francophone mother-baby units, which is higher than the 7.4% described in general population in France (Sentilhes et al. 2017). Prevalence of LBW was 15.8% which is also higher than the 7% observed in countries with a high socio-economic level, including France, according to the WHO report (2005).

NICU admissions accounted for 24.3% of children, a high percentage compared to 7.8% in the general population in the USA in 2012 (Harrison and Goodman 2015) and 8.7% in France in 2015 (Combier et al. 2014).

Thus, our results highlight a globally higher morbidity of newborns of patients with psychiatric or severe addictive disorders. This is in line with previous studies (Kelly et al. 2002; Schneid-Kofman et al. 2008; Wiencrot et al. 2012).

A maternal episode of mental illness during pregnancy was associated with LBW and NICU hospitalization independently of other risk factors. To our knowledge, our study is the first to consider the presence of a maternal episode during pregnancy, whereas others have only taken into account mental health diagnosis.

In addition, our results reported this association taking into account the independent effect of psychotropic drugs as potential confounding factors. In previous studies, data on prenatal exposure to psychotropic drugs were not taken into account. Indeed, psychotropic treatment during pregnancy has been associated with LBW and NICU hospitalization (due to a cumulative effect of treatment and subsequent withdrawal).

An explanation for the association between a maternal episode of mental illness during pregnancy and certain neonatal

Table 2 Logistic regression on neonatal complications (prematurity, LBW, and NICU hospitalization) and prenatal episode of mental illness and diagnosis

	Prematurity				LBW[a]				NICU hospitalization[b]			
n = 1439	Prematurity	No prematurity	OR [95%CI]	*p*	LBW	No LBW	OR [95%CI]	*p*	NICU hospitalization	No NICU hospitalization	OR [95%CI]	*p*
Episode of mental illness during pregnancy			1.48 [0.98–2.23]	0.06			2.21 [1.44–3.38]	*0.003*			1.53 [1.06–2.19]	*0.002*
Yes	73 (57.94)	532 (46.30)			121 (61.73)	487 (45.09)			212 (67.09)	398 (41.33)		
No	53 (42.06)	617 (53.70)			75 (38.27)	593 (54.90)			104 (32.91)	565 (58.67)		
Mental health diagnosis												
Anxiety disorder			1.17 [0.58–2.33]	0.66			0.85 [0.40–1.79]	0.67			1.11 [0.58–2.09]	0.76
Yes	17 (12.41)	115 (9.32)			20 (9.30)	112 (9.68)			29 (8.66)	103 (9.90)		
No	120 (87.59)	1119 (90.68)			195 (90.70)	1045 (90.32)			306 (91.34)	937 (90.10)		
Psychotic disorder			0.53 [0.26–1.08]	0.08			1.07 [0.54–2.10]	0.85			1.66 [0.94–2.94]	0.08
Yes	23 (16.79)	352 (28.52)			46 (21.40)	328 (38.35)			91 (27.16)	284 (27.31)		
No	114 (83.21)	882 (71.48)			169 (78.60)	829 (71.65)			244 (72.84)	756 (72.69)		
Depression			0.99 [0.55–1.77]	0.97			0.84 [0.46–1.52]	0.56			1.06 [0.63–1.78]	0.83
Yes	45 (32.85)	395 (32.00)			62 (28.84)	379 (32.76)			85 (25.37)	357 (34.33)		
No	92 (67.15)	839 (68.00)			153 (71.16)	778 (67.24)			250 (74.63)	683 (65.67)		
Bipolar disorder			1.14 [0.57–2.24]	0.71			0.91 [0.45–1.83]	0.79			1.17 [0.64–2.13]	0.82
Yes	31 (22.63)	251 (20.34)			40 (18.60)	242 (20.92)			67 (23.76)	268 (24.52)		
No	106 (77.37)	983 (79.66)			175 (81.40)	915 (79.08)			215 (76.24)	825 (75.48)		
Personality disorder			1.01 [0.60–1.64]	0.96			1.55 [0.94–2.54]	0.08			1.51 [0.97–2.33]	0.07
Yes	43 (31.39)	304 (24.64)			73 (33.95)	276 (23.85)			103 (30.75)	246 (23.65)		
No	94 (68.61)	930 (75.36)			142 (66.05)	881 (76.15)			232 (69.25)	794 (76.35)		
Severe substance use disorder			1.25 [0.60–2.61]	0.54			2.96 [1.49–5.85]	*0.002*			2.88 [1.56–5.29]	*0.04*
Yes	11 (8.03)	76 (6.16)			32 (14.88)	55 (4.75)			54 (16.12)	35 (3.37)		
No	126 (91.97)	1158 (93.84)			183 (85.12)	1102 (95.25)			281 (83.88)	1005 (96.63)		
Smoking during pregnancy			1.07 [0.70–1.64]	0.83			1.60 [1.05–2.44]	*0.03*			1.82 [1.28–2.57]	*0.001*
Yes	40 (32.26)	307 (27.14)			81 (41.12)	269 (25.36)			137 (44.92)	214 (22.38)		
No	84 (67.74)	824 (72.86)			116 (58.88)	792 (74.65)			168 (55.08)	742 (77.62)		

italicized values: $p<0.05$

LBW low birth weight, *NICUs* neonatal intensive care units

Adjusted for socio-demographic characteristics: mother's age, maternal education level, infant, child's father presence; pregnancy characteristics: primiparity, physical complications, smoking, low medical follow-up; psychotropics during pregnancy: antidepressants, antipsychotics, mood stabilizers, anxiolytics

Data from the multi-center database formed by the French Network of Mother-Baby Units (MBUs) (Societe Marce Francophone), collected over a 10-year period (between January 1, 2001 and December 31, 2010) from 16 MBUs (13 in France and 3 in Belgium)

[a] Adjusted also for prematurity

[b] Adjusted also for prematurity and low birth weight

outcomes can be found in the stress levels commonly associated to the occurrence of symptoms.

Perceived maternal life event stress has been associated with negative infant outcomes (Austin and Leader 2000) and maternal psychological stress and distress have been associated with LBW, prematurity, and intrauterine growth retardation (Rondó et al. 2003).

Our secondary aim was to determine whether a specific disorder was associated with a higher risk for these neonatal complications, in women with serious mental illness, independently of other variables, such as antenatal exposure to psychotropic drugs.

We found a significant association between the presence of severe substance use disorders and LBW and NICU hospitalization, after adjusting for potential bias including tobacco consumption. These associations, independently of other variables, may be even more important since the frequency of under-reporting substance use during pregnancy is high. In the sensitive analysis, analyzing separately illicit drug and not, LBW, and NICU were associated both with illicit and non-illicit (alcohol) drug.

Several studies reported higher risk for adverse health outcomes in infants born to mothers with substance use disorder (Hwang et al. 2017). However, the association between LBW, substance use disorders, and mental illness has only been tested in a few studies that led to similar conclusions. In a population-based retrospective cohort analysis (Kelly et al. 2002), women with psychiatric diagnoses or substance use diagnoses had significantly higher risk of infant low birth weight than women without those diagnoses. This risk was higher with substance use (OR = 3.7 [3.4–4.0]) than psychiatric diagnoses (OR = 2.00 [1.7–2.3]) compared to control group. The same pattern was observed in a retrospective cohort in Massachusetts: mental illness (OR = 1.6 [1.4–1.8]) and substance abuse (OR = 3.8 [3.1–4.7]) were associated with LBW compared to controls (Wiencrot et al. 2012). In a recent study taking into account 22,193 pregnant women in Australia, the strongest predictor of LBW was poly or illicit substance use (OR = 2.73, 2.15–3.47). The regression reported that history of mental illness was also a predictor but weaker (1.39, 1.19–1.63) as well as tobacco (1.21, 1.03–1.41) (Zhao et al. 2017). In primiparous mothers hospitalized for mental and behavioral disorders due to substance use during pregnancy, alcohol, opioids, and cannabinoids were associated with LBW and NICU hospitalizations, after adjusting for potential bias including tobacco consumption (Bonello et al. 2014). Illegal drug use in pregnancy appears to increase the risk of adverse outcomes, over and above that related to cigarette smoking (Black et al. 2013).

Future studies should explore the role of each substance in neonatal outcomes, taking into account quantity ingested and drug dependence. Association between alcohol and neonatal outcomes is well known with a strong effect of alcohol use during pregnancy on neonatal outcomes (Thibaut et al. 2018). The literature on tobacco during pregnancy is even more vast and a recent meta-analysis confirmed that active maternal smoking is associated to LBW (OR = 2.00 (95% CI: 1.77–2.26) (Pereira et al. 2017). Moore et al. showed that quitting smoking early during pregnancy negates the risk of preterm birth (Moore et al. 2016). Opioid is strongly associated with neonatal complications like neonatal abstinence syndrome (NAS) and infants with NAS are more likely to be born at a LBW than others (21.2% vs 11.8% vs 9.9%; $p = 001$; Patrick et al. 2015). Few studies reported an association between prematurity, LBW, and cocaïne (Behnke et al. 2001) and metamphetamine (Wright et al. 2015). A systematic review and meta-analysis of maternal marijuana use during pregnancy was not related to any neonatal outcomes, which were attributable to concomitant tobacco use and other confounding factors (Conner et al. 2016).

Monitoring on substance use disorders should be implemented. Certain biomarkers, such as ethylgluronide in urines as a marker of alcohol consumption (Ferraguti et al. 2017), and CDT carbohydrate-deficient transferrin (CDT) and phosphatidylethanol (PEth) to identify heavy drinking (Howlett et al. 2017) may complement self-report. Urinary tobacco-specific nitrosamine metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-a1-butanol (NNAL) might be a useful biomarker as smoking status in association with adverse pregnancy outcomes (Lee et al. 2018). Screening could be proposed more systematically. Increased monitoring for substance use disorders could enable timely interventions and improve birth outcomes.

The first limit of this work is that we analyzed a population of patients hospitalized in MBUs, which does not allow extrapolation of data to all women with a severe psychiatric or substance-related disorder during the puerperal period. In general, women hospitalized in MBUs have more severe symptoms and probably higher levels of medication.

Secondly, no description of the symptoms of maternal episode during pregnancy was available.

Thirdly, the quantities of alcohol and other toxic substances consumed were missing. In addition, the amount of tobacco use was not screened for each trimester. Indeed, tobacco use during the 3rd trimester could be associated with neonatal outcomes. Yet, there is a likely bias in responses regarding consumption with under-reporting expected in the context of pregnancy. However, we completed our analyses with a sensitive analysis distinguishing illicit drug use and non (severe alcohol use disorder) considering the item severe substance use disorder. We also performed a second sensitive analysis taking into account the number of cigarettes smoking and a third with drug use for alcohol, illicit drug, and tobacco (qualitative variables).

Fourthly, psychotropic drug use during the third trimester was not differentiated from the rest of pregnancy. Fifthly, no

data were available on birth defects which could also be associated to neonatal complications and NCIU.

Despite these limitations, this study has several strengths. The first one is the large size of this sample of mothers with severe mental illnesses ($n = 1439$). To our knowledge, this is the first study in a population of more than a thousand women with serious mental health disorders. Indeed, even if the comparison group should be the general population or pregnant women without maternal mental health conditions, it would have been very difficult to include them on the same population as were selected the cases, and if so, the number of cases would have been smaller, with a lack of statistical power for analyses. The interest of our work is to focus on the presence of a maternal episode of mental illness during pregnancy, which is not possible with the general population. The significant positive association between the presence of a maternal episode during pregnancy and neonatal outcomes (LBW and NICU hospitalization) independently from antenatal exposure to psychotropic drugs has clinical implications and highlights the need to treat mental health symptoms in women with severe mental illness.

Pregnancy in women with mental disorders is increasingly common, hence the interest in determining in these women the type of diagnosis associated to highest neonatal complications. To our knowledge, this is the first statistical study taking all the relevant variables in account in a regression model to explain prematurity, LBW, and NICU hospitalization considering psychiatric and addictive disorder diagnoses as independent risk factors. One of the main strength is to take into account tobacco and psychotropic drugs as potential confounding factors and to consider several classes of medication (antidepressants, mood stabilizers, antipsychotics, and anxiolytics).

Conclusion

Our results point out the importance for perinatal professionals to systematically explore maternal mental health and especially occurrence of a recent maternal episode of mental illness and/or drug consumption. Pregnancy is a privileged period to start medical and social care, keeping in mind that patients under-report psychiatric symptoms as well as toxic consumption, due to guilt and anxiety about the risk of placement of the child, but also may be motivated by the health of their infant. Thus, the identification of mental health disorders requires a training of perinatal health professionals to enable them at the systematic screening for substance consumption and psychiatric symptoms from pre-conception to birth. Once the screening is done, monitoring with regard to assessing the evolution of the disease and the need for psychotropic treatment, taking into account the benefit/risk balance, should be multidisciplinary and specialized. Partnerships between psychiatric, addictive, gynecological, and pediatric follow-up, as well as maternal and child protection and general practitioners should be implemented.

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Compliance with ethical standards

All selected women provided informed consent for their inclusion in the database. The study was performed in accordance with the ethics standards of the French National Data Protection Authority (CNIL) which the CNIL approved the study.

Conflicts of interest Regarding potential conflicts of interest, all of them were indirect:

Reda Boukakiou, Nine Glangeaud-Feudenthal, and Anne-Laure Sutter-Dallay report no financial relationships with commercial interests.

Bruno Falissard has been a consultant, expert, or has given talks for E. Lilly, BMS, Servier, Sanofi, GlaxoSmithKline, HRA, Roche, Boeringer Ingelheim, Bayer, Almirall, Allergan, Stallergene, Genzyme, Pierre Fabre, Astra Zeneca, Novartis, Janssen, Astellas, Biotronik, Daiichi-Sankyo, Gilead, MSD, and Lundbeck. Florence Gressier has given talks for Lundbeck and Servier and received a grant from Servier for a post-doctoral degree (2011–2012).

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