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Impact of Prenatal Exposure to Psychotropic Drugs on Neonatal Outcome in Infants of Mothers With Serious Psychiatric Illnesses

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ABSTRACT

Objective: To assess whether prenatal exposure to 4 major classes of psychotropic drugs compared with no exposure differed with respect to neonatal outcome.

Method: We used the database collected from 13 mother-baby units (MBUs) by the French Network of MBUs. The Marcé Clinical Checklist was used to collect data from maternal interview and clinical record with respect to maternal demographic and clinical characteristics, prenatal exposure to psychotropic drugs, and neonatal outcome (birth weight, preterm birth, neonatal hospitalization). Multivariate logistic regression was used to explore the independent impact of each therapeutic class of psychotropic drug (antipsychotics, antidepressants, mood stabilizers, and anxiolytics/hypnotics) on infant outcomes. All the models were adjusted for maternal confounding factors.

Results: The sample included 1,071 women and their infants. Nearly half (40.2%) used at least 1 psychotropic drug during pregnancy. The risk of low birth weight was increased by antenatal exposure to mood stabilizers (adjusted odds ratio [aOR] = 2.04, 95% confidence interval [CI] = 1.03–4.04, *P* = .04). The risk of neonatal hospitalization was increased by prenatal exposure to antipsychotics (aOR = 1.74, 95% CI = 1.19–2.54, *P* = .004), antidepressants (aOR = 1.59, 95% CI = 1.05–2.41, *P* = .03) or anxiolytics/hypnotics (aOR = 1.89, 95% CI = 1.30–2.75, *P* = .001), independent of birth weight and term delivery status.

Conclusions: Infants exposed to psychotropic drugs during pregnancy have less optimal neonatal outcome than unexposed infants and should be considered as a high-risk population.

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Over the last decades, a large body of literature has been focused on the risks of birth defects related to fetal exposure to psychotropic drugs, whereas studies on the neonatal impact of prenatal exposure remain limited and conflicting. Moreover, the vast majority of recent studies were focused on antidepressant exposure, and few studies assessed the risks associated with prenatal exposure to other psychotropic drugs.[1–3]

With regard to antipsychotics, exposure to first-generation antipsychotics (FGAs)[4] or second-generation antipsychotics (SGAs)[5–10] was associated with low birth weight, preterm birth, extrapyramidal symptoms, and jaundice. Poor neonatal adaptation (neurologic, autonomic, respiratory, and/or gastrointestinal abnormalities) is also more frequent in infants prenatally exposed to antipsychotics. With respect to antidepressants, meta-analyses[11,12] showed a slight significant association between prenatal antidepressant exposure and low birth weight, or preterm delivery. The risk of poor neonatal adaptation was increased specifically with tricyclic antidepressants (TCAs) compared to selective serotonin reuptake inhibitors (SSRIs) in some,[7,11,13] but not all, studies.[14] An increased risk of preterm birth in infants prenatally exposed to mood stabilizers was reported in a single study.[15] The risk of low birth weight, preterm birth, and neonatal complications is well documented in infants prenatally exposed to valproate or carbamazepine.[16–18] Lithium toxicity is a well-established risk for newborns, although the impact on birth weight and gestational age remains controversial.[7,19] Lastly, an increased risk of low birth weight and preterm birth,[17,20,21] as well as poor neonatal adaptation,[7,22] was found after prenatal exposure to anxiolytics/hypnotics.

These studies demonstrated that infants prenatally exposed to psychotropic drugs are at high risk for poor neonatal outcome. However, interpretation of the findings is often limited by the fact that most studies did not adjust for the prescription of other psychotropic drugs. Furthermore, other potential confounders, especially maternal psychiatric diagnoses, were not always considered. The present study was carried out in a sample of infants admitted with their mothers to psychiatric mother-baby units (MBUs), which are psychiatric inpatient units dedicated to hospitalization of women with their babies. Such units usually contain a limited number of beds (1–10 beds) that may be integrated in general or in child psychiatric wards. They are aimed at favoring psychiatric care of women during the postpartum period concomitantly with the promotion of the quality of parent-infant interactions and of the development of the infant.

Clinical Points

- Among a population of mothers and their infants hospitalized postpartum in mother-baby units, the risk of infant's low birth weight was increased by antenatal exposure to mood stabilizers. The risk of neonatal hospitalization was increased by prenatal exposure to antipsychotics, antidepressants, or anxiolytics/hypnotics, independent of birth weight and term delivery status.
- Pregnant women with severe psychiatric illness need treatment. Their infants, exposed to psychotropic drugs during pregnancy, have less optimal neonatal outcome than unexposed infants and should be considered as a high-risk population.

The aim of the present study was to explore the independent impact of prenatal exposure to each therapeutic class of psychotropic drugs (antipsychotics, ADs, mood stabilizers, and anxiolytics-hypnotics) on the following neonatal outcomes: preterm birth, low birth weight, and neonatal hospitalization. Such outcomes were explored as preterm birth and low birth weight are major predictors of children's future physical and mental health,[23] and as neonatal hospitalization is a proxy for poor neonatal adaptation to extrauterine life.

METHOD

Data Source

The present study explored the database collected by the French Network of Mother-Baby Units (Société Marcé Francophone). The database has been previously described.[24,25] Briefly, data about women with postpartum psychiatric disorders, jointly admitted with their child, were collected over 10 years (2001–2010) in 13 French MBUs. Women consecutively admitted were eligible for data collection if they fulfilled the following criteria: aged 18 years and over; jointly admitted with their child (< 1 year); hospitalized for at least 5 consecutive days (time to collect relevant information); and gave informed consent for data collection. The medical team collected information during the hospital stay with the French version of the Marcé Clinical Checklist.[24] This tool was originally developed in the United Kingdom to collect standardized clinical data in MBUs and to develop large data sets aimed at supporting multisite research. Data collection was made using all available sources of information (clinical interviews with the patients, psychiatrists, medical records, and child health record booklets).

We used the following information collected in the database: mother's demographic characteristics, maternal diagnoses (made by the treating psychiatrist of the MBUs) using criteria of the *International Statistical Classification of Diseases and Related Health Problems, 10th revision* (*ICD-10*),[26] and information about the course of pregnancy and infant postnatal health collected from the mother and from the child's health record. This study was performed in accordance with the ethical standards of the French National Data Protection Authority.

Assessment of Prenatal Exposure to Psychotropic Drugs

Information on psychotropic drug use during pregnancy was collected from maternal recall and medical records. Psychotropic drugs were categorized into therapeutic and pharmacologic classes. The therapeutic classes included the following categories: antipsychotics, antidepressants, mood stabilizers, and anxiolytics/hypnotics. The pharmacologic classes were created by subdividing the therapeutic class categories (with the exception of anxiolytics/hypnotics) into: (1) antipsychotics: FGAs (phenothiazines, butyrophenones, diazepines, oxazepines, and thioxanthenes) versus SGAs (amisulpride, risperidone, olanzapine, aripiprazole, and clozapine), (2) antidepressants: SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs) versus others antidepressants (TCAs, mianserin, tianeptine, viloxazine, mirtazapine), and (3) mood stabilizers: lithium versus anticonvulsants (valproate, divalproate, carbamazepine, and lamotrigine).

Trimester of exposure to psychotropic drugs was categorized as (1) never exposed, (2) exposed in the first or second trimesters with no exposure during the third trimester, and (3) exposed during the third trimester regardless of exposure during the first and second trimesters. This categorization was aimed at differentiating the impact of late exposure (third trimester) on neonatal outcomes from that of earlier pregnancy exposure.

Assessment of Newborn Outcome

We considered the 3 following neonatal infant outcomes: low birth weight (< 2,500 g), preterm birth (< 36 weeks of gestation, as defined in the Marcé Checklist), and neonatal hospitalization during the first month of life.

Other Variables

ICD-10 maternal diagnoses were categorized into (1) mood disorders (bipolar affective disorders and depressive disorders), (2) psychotic disorders (schizophrenia, schizoaffective disorders, and other nonaffective psychotic disorders), and (3) other disorders (substance use, personality disorders, and anxiety disorders). The type of MBUs were categorized as adult versus child psychiatry units in order to take into account that French MBUs are integrated in either adult or child psychiatric wards, leading to differences in recruitment.

Statistical Analyses

Statistical analyses were carried out using SAS statistical software 9.3.[27] Univariate analyses (χ^2 test and Student *t* test) were used to compare the characteristics of women with and without missing data for the variables of interest, and mothers with and without psychotropic drugs during pregnancy. We used logistic regression models giving odds ratios (ORs) and 95% confidence intervals (CIs) to explore the associations between prenatal exposure to psychotropic drugs and the infant outcomes. All the models were adjusted a priori for maternal age, education level (< 12 years vs ≥ 12

Table 1. Characteristics of Dyads With and Without Missing Data

	No Missing Data (N = 1,071)	With Missing Data (n = 169)	Statistics		
Mother's characteristic	Mean (SD)	Mean (SD)	*t* Test	*df*	*P* Value
Age, y	31.50 (6.1)	31.11 (6.0)	−0.21	1,237	.83
	n (%)	n (%)	χ^2	*df*	*P* Value
Education level (< 12 y)	456 (42.6)	49 (29.0)	0.86	1	.35
Primiparity	480 (44.8)	67 (39.6)	0.01	1	.92
No partner	254 (23.7)	38 (22.5)	0.12	1	.73
Maternal mental illness[a]			9.39	2	.009
Mood disorders	421 (39.3)	46 (27.2)			
Psychotic disorders	243 (22.7)	51 (30.2)			
Other disorders	407 (38.0)	68 (40.2)			
Tobacco during pregnancy	376 (35.1)	59 (34.9)	8.9	1	.003
Adult psychiatry unit[b]	504 (47.1)	71 (42.0)	1.5	1	.22
Newborn's characteristic	n (%)	n (%)	χ^2	*df*	*P* Value
Prematurity (< 36 wk)	97 (9.1)	23 (13.6)	3.82	1	.05
Low birth weight (< 2,500 g)	159 (14.9)	25 (14.8)	0.008	1	.93
Neonatal hospitalization	240 (22.4)	32 (18.9)	0.92	1	.34

[a]Mood disorders = bipolar affective disorders and depressive disorders; psychotic disorders = schizophrenia and other psychotic disorders; and other disorders = substance use, personality disorders, anxiety disorders, disorders associated with the puerperium, and other disorders.
[b]Versus child psychiatry unit.

years), parity (primiparity vs multiparity), presence of partner, maternal diagnosis, and type of unit. The models exploring the impact of prenatal exposure to psychotropic drugs on birth weight and prematurity were adjusted for prenatal exposure to tobacco.

The same modeling strategy was used for each outcome. First, we explored the impact of prenatal exposure to psychotropic drugs categorized into therapeutic classes. All the therapeutic classes were simultaneously entered into the same model to explore the independent effect of each class. When an association was found between exposure to a therapeutic class and an infant outcome at a significant level ($P < .05$), we further explored the associations with the corresponding pharmacologic classes by using the same model but substituting the variables "pharmacologic classes" for the variable "therapeutic class."

The 3 infant outcomes considered were not independent; that is, infants with low birth weight or with preterm birth are at increased risk of being hospitalized during the neonatal period, and infants with premature birth are also more likely to have low birth weight. Considering the strong associations between these outcomes leading to lack of convergence, they could not be entered in the same model. When an association was found between exposure to a therapeutic class and a given infant outcome, we explored whether the association was explained by an association between this class of psychotropic drug and another outcome by performing stratified analyses according to the presence or absence of the other outcome.

Lastly, we conducted sensitivity analyses to examine whether missing data could have biased any findings. For each therapeutic class, we substituted missing data regarding prenatal use in such a way that the extremes of any bias could be quantified. First, all missing data were assigned to "use of the therapeutic class," and we observed the possible impact in the multivariate model; all the other variables remaining unchanged. Second, all missing data were assigned to "no use of the therapeutic class."

RESULTS

Characteristics of the Sample

Characteristics of dyads with and without missing data are presented in Table 1. Data were missing for at least one of the variables of interest for 169 dyads (13.6%). In the dyads with missing data compared with the dyads without, infants more frequently had a preterm birth, mothers smoked more frequently during pregnancy, and a higher proportion presented with a diagnosis of psychotic disorder. No information was available on the number and characteristics of mothers admitted to MBUs over the period of interest who were not included in the database. The sample included 1,071 women, primarily multiparous, well educated, and presenting mood disorders (Table 1).

Characteristics of Exposure to Psychotropic Drugs During Pregnancy

In the sample, 431 women (40.2%) used at least 1 psychotropic drug during pregnancy. Compared to mothers without psychotropic drug use during pregnancy (Table 2), mothers with psychotropic drug use during pregnancy had a higher education level, were less frequently primiparous, presented more frequently with psychotic disorders and tobacco use, and were more frequently hospitalized in adult psychiatric units.

The frequently prescribed therapeutic classes of drugs were antipsychotics (n = 267, 25.0%; FGAs: 17.1%, SGAs: 5.2%) and anxiolytics/hypnotics (n = 257, 24.0%), then antidepressants (n = 154, 14.4%; SSRIs/SNRIs: 10.8%, other antidepressants: 3.4%, among which 2.8% were TCAs). Use

Table 2. Characteristics of Mothers With and Without Psychotropic Drug Use During Pregnancy

Mother's Characteristic	No Drug Use (n = 640) Mean (SD)	Drug Use (n = 431) Mean (SD)	Statistics *t* Test	*df*	*P* Value
Age, y	30.79 (6.08)	32.46 (5.92)	−4.46	1,069	.55
	n (%)	n (%)	χ^2		
Education level (< 12 y)	253 (39.53)	203 (47.10)	6.03	1	.01
Primiparity	324 (50.63)	156 (36.19)	21.68	1	< .0001
No partner	141 (22.03)	113 (26.22)	2.50	1	.11
Maternal mental illness[a]			26.88	2	< .0001
Mood disorders	262 (40.94)	159 (36.89)			
Psychotic disorders	111 (17.34)	132 (30.63)			
Other disorders	267 (41.72)	140 (32.48)			
Tobacco during pregnancy	160 (25.00)	216 (50.12)	71.31	1	< .0001
Adult psychiatry unit[b]	280 (43.75)	224 (51.97)	6.99	1	.01

[a]Mood disorders = bipolar affective disorders and depressive disorders; psychotic disorders = schizophrenia and other psychotic disorders; and other disorders = substance use, personality disorders, anxiety disorders, disorders associated with the puerperium, and other disorders.
[b]Versus child psychiatry unit.

Table 3. Associations Between Prenatal Exposure to Psychotropic Drugs and Infant Outcomes: Multivariate Analyses

	Birth Weight			Term			Neonatal Admission		
	≥ 2,500 g (n = 909) n (%)	< 2,500 g (n = 159) n (%)	aOR (95% CI)[a]	≥ 36 wk (n = 970) n (%)	< 36 wk (n = 97) n (%)	aOR (95% CI)[a]	No (n = 828) n (%)	Yes (n = 240) n (%)	aOR (95% CI)[a]
Antipsychotics	219 (24.1)	48 (30.2)	0.98 (0.62–1.55) *P* = .92	241 (25.0)	26 (26.8)	1.00 (0.56–1.78) *P* = .99	172 (20.8)	95 (39.6)	1.74 (1.19–2.54) *P* = .004
Antidepressants	121 (13.3)	33 (20.7)	1.39 (0.85–2.28) *P* = .19	131 (13.5)	22 (22.7)	1.73 (0.96–3.12) *P* = .07	96 (11.6)	58 (24.2)	1.59 (1.05–2.41) *P* = .03
Mood stabilizers	41 (4.5)	15 (9.4)	2.04 (1.03–4.04) *P* = .04	47 (4.8)	9 (9.3)	1.92 (0.84–4.40) *P* = .12	33 (4.0)	23 (9.6)	1.68 (0.90–3.12) *P* = .10
Anxiolytics/hypnotics	201 (22.2)	56 (35.2)	1.40 (0.89–2.19) *P* = .15	225 (23.2)	31 (32.0)	1.17 (0.66–2.07) *P* = .58	158 (19.1)	99 (41.2)	1.89 (1.30–2.75) *P* = .001

[a]Adjusted odds ratio (95% confidence intervals); adjusted for the 3 other types of psychotropic drugs, mother's age, education level, parity, presence of partner, maternal diagnosis (mood disorders/psychotic disorders/other disorders), type of unit (adult/child psychiatry unit), and prenatal exposure to tobacco.

of mood stabilizers was rare (n = 56, 5.2%; lithium: 3.0%, anticonvulsants: 2.2%). Among the 431 women who used psychotropic drugs during pregnancy, 205 (47.6%) were on monotherapy and 226 (52.4%) on polytherapy.

For all therapeutic classes, exposure was less frequent in the first and second trimesters than in the third trimester: 31 (3.0%) versus 199 (18.6%) mothers taking antipsychotics, 40 (3.7%) versus 107 (9.9%) taking antidepressants, 10 (0.9%) versus 43 (4.0%) taking mood stabilizers, and 25 (2.3%) versus 200 (18.7%) taking anxiolytics/hypnotics. Most mothers were exposed in the third trimester: 199 (86.5%) taking antipsychotics, 107 (72.8%) taking antidepressants, 43 (81.1%) taking mood stabilizers, and 200 (88.9%) taking anxiolytics/hypnotics. Separate analyses by trimester of exposure were not conducted due to the preponderance of late pregnancy exposures and as it was not possible to know whether this late exposure was due to cessation of treatment in chronically ill patients, relapse of disorders stabilized before pregnancy, or first episode.

Associations Between Exposure to Psychotropic Drugs During Pregnancy and Infant Outcomes

The associations between prenatal psychotropic drug exposure and infant outcomes are given in Table 3. After adjustment for the other characteristics, low birth weight was twice as likely in infants with prenatal exposure to mood stabilizers. The association between the 2 pharmacologic classes of mood stabilizers and low birth weight was not significant. No association was found between exposure to the other therapeutic classes (antipsychotics, antidepressants, and anxiolytics/hypnotics) and low birth weight. The risk of preterm birth was not significantly increased in infants prenatally exposed to psychotropic drugs, irrespective of the therapeutic class (Table 3).

The rate of neonatal hospitalization was increased in infants prenatally exposed to antipsychotics, antidepressants, or to anxiolytics/hypnotics (Table 3). The significant association between exposure to antipsychotics and neonatal hospitalization was also observed for the 2 pharmacologic classes of antipsychotics—FGAs: aOR = 1.78, 95% CI = 1.18–2.69; *P* = .01; SGAs: aOR = 2.21, 95% CI = 1.16–4.21; *P* = .02. With respect to antidepressants, the association with neonatal hospitalization was restricted to other antidepressants (aOR = 2.45, 95% CI = 1.19–5.03; *P* = .01). The association with SSRIs or SNRIs was not significant (aOR = 1.27, 95% CI = 0.79–2.04, *P* = .32).

The stratified analyses exploring the association between psychotropic drug exposure and neonatal hospitalization

Table 4. Associations Between Prenatal Exposure to Psychotropic Drugs and Infant Outcomes: Multivariate Stratified Analyses

	Birth Weight ≥ 2,500 g (n = 909)			Birth Weight < 2,500 g (n = 159)		
	Neonatal Admission			Neonatal Admission		
	No (n = 785), n (%)	Yes (n = 124), n (%)	aOR (95% CI)[a]	No (n = 43), n (%)	Yes (n = 116), n (%)	aOR (95% CI)[a]
Antipsychotics	163 (20.8)	56 (45.2)	1.91 (1.17–3.10) *P* = .01	9 (20.9)	39 (33.6)	2.98 (1.01–8.84) *P* = .05
Antidepressants	88 (11.2)	33 (26.6)	1.63 (0.96–2.76) *P* = .07	8 (18.6)	25 (21.5)	1.48 (0.50–4.36) *P* = .48
Mood stabilizers	30 (3.8)	11 (8.9)	1.34 (0.59–3.02) *P* = .49	3 (7.0)	12 (10.3)	1.38 (0.31–6.16) *P* = .68
Anxiolytics/hypnotics	143 (18.2)	58 (46.8)	2.41 (1.50–3.87) *P* = .0003	15 (34.9)	41 (35.3)	0.55 (0.19–1.56) *P* = .26
	Term ≥ 36 weeks (n = 970)			Term < 36 weeks (n = 97)		
	Neonatal Admission			Neonatal Admission		
	No (n = 818), n (%)	Yes (n = 152), n (%)	aOR (95% CI)	No (n = 10), n (%)	Yes (n = 87), n (%)	aOR (95% CI)
Antipsychotics	171 (20.9)	70 (46.0)	2.11 (1.36–3.27) *P* = .001	1 (10.0)	25 (28.7)	2.13 (0.17–26.79) *P* = .56
Antidepressants	94 (11.5)	37 (24.3)	1.48 (0.90–2.43) *P* = .12	2 (20.0)	20 (23.0)	0.57 (0.08–4.05) *P* = .57
Mood stabilizers	33 (4.0)	14 (9.2)	1.49 (0.72–3.07) *P* = .29	0 (0.0)	9 (10.3)	∞ (< 0.001–∞) *P* = .97
Anxiolytics/hypnotics	157 (19.2)	68 (44.7)	2.08 (1.34–3.21) *P* = .001	1 (10.0)	30 (34.5)	3.76 (0.28–49.95) *P* = .31

[a]Adjusted odds ratio (95% confidence intervals); adjusted for the 3 other types of psychotropic drugs, mother's age, education level, parity, presence of partner, maternal diagnosis (mood disorders/psychotic disorders/others), type of unit (adult/child psychiatry unit); prenatal exposure to tobacco.

according to birth weight and delivery status are given in Table 4. The analysis stratified according to birth weight showed that prenatal exposure to antipsychotics was associated with an increased risk of neonatal admission irrespective of the birth weight. Prenatal exposure to anxiolytics/hypnotics increased the risk of neonatal admission only in infants with birth weight > 2,500 g. The analysis stratified by term status showed that prenatal exposure to antipsychotics or anxiolytics/hypnotics increased the risk of neonatal admission only in infants born at ≥ 36 weeks. Stratified analysis of birth weight according to term did not reveal a significant association (data not shown).

Sensitivity analyses on missing data showed that the strength of the associations was unchanged for the 2 extreme biases.

DISCUSSION

Nearly half of the women of our sample had been exposed to at least 1 psychotropic medication during pregnancy. The risk of low birth weight was increased by prenatal exposure to mood stabilizers independently from exposure to other psychotropic drugs and from maternal characteristics. A higher frequency of neonatal hospitalization was found in infants prenatally exposed to antipsychotics and/or antidepressants and/or anxiolytics/hypnotics.

As most prior studies explored the specific impact of each class of psychotropic drug on neonatal outcome, we will use this framework for discussion, keeping in mind that we assessed the independent effects of each class. In our sample, prenatal exposure to antipsychotics was associated with an increased risk of postnatal hospitalization, irrespective of birth weight and term. The increased rate of admission in infants prenatally exposed to an antipsychotic might be due to the high frequency of poor neonatal adaptation in these infants. We did not confirm the findings of prior studies reporting an increased risk of low birth weight with FGAs and SGAs, and of preterm birth with SGAs.[5,8–10] However, these findings were not adjusted for maternal psychiatric disorder, although maternal schizophrenia is a risk factor for low birth weight and/or for preterm birth independent from antipsychotics exposure.[28]

We found that the risk of neonatal hospitalization increased in infants prenatally exposed to antidepressants, particularly for those exposed to "other antidepressants." The risk for poor neonatal adaptation after prenatal exposure to antidepressants is well documented, especially for TCA,[7,11,13,29] although the proportion of poor neonatal adaptation leading to neonatal admission is unknown. The findings of meta-analyses[11,12] showing an association between exposure to antidepressants and preterm birth and low birth weight were not replicated in the present study, even if the associations were in the same direction.

Our results show a 2-fold higher risk of low birth weight in infants prenatally exposed to mood stabilizers. We found no impact of mood stabilizer use during pregnancy on preterm birth. To our knowledge, the only prior study exploring the specific impact of mood stabilizers[15] showed no increased risk of low birth weight and a higher risk of preterm birth in children of women with bipolar disorder exposed to mood

stabilizers during pregnancy compared to children of healthy women. This prior study considered antipsychotics in the mood stabilizers class and did not adjust for the prescription of other psychotropic drugs, which may explain the discrepancy with our results. We cannot exclude that these differences may be explained by environmental factors not measured in the studies, such as nutritional factors. In our sample, the risk of neonatal admission after exposure to mood stabilizers was not different between exposed and unexposed children. The literature on this issue is rather heterogeneous, making the reported findings difficult to compare with those obtained here. Studies exploring neonatal adaptation of infants prenatally exposed to lithium[19,30] have reported a large range of dose-dependent adverse events or were based upon case reports of specific events. With regard to anticonvulsants, several types of perinatal complications have been reported by studies conducted in samples of mothers with epilepsy or in general population samples without information about the reason for prescription.[17,18]

In our study, antenatal use of anxiolytic/hypnotics leads to an about 2-fold higher risk of being hospitalized after birth, regardless of birth weight and term. We further confirm the potential severity of poor neonatal adaptation induced by these drugs in the specific context of severe maternal psychiatric disorder.[17,20,22] We did not find any impact of anxiolytic/hypnotic use on the risk of low birth weight or on preterm birth. Few recent studies showed an association between prenatal exposure to anxiolytics/hypnotics and low birth weight or preterm birth,[17,20,21] but some did not take into account coprescriptions,[17,21] and none considered maternal psychiatric diagnosis.

The present study has several strengths. To our knowledge, no prior study has simultaneously explored the independent impact of prenatal exposure to multiple classes of psychotropic drugs on the health of the newborn. The findings were also adjusted for maternal characteristics often not included in such studies, especially maternal psychiatric diagnosis. We have conducted stratified analyses to take into account associations between neonatal hospitalization and low birth weight or prematurity. These factors are frequently underlined as a bias of previous studies exploring the risk factors for neonatal hospitalization.

These findings also have to be interpreted in the light of potential methodological limitations. Our study was carried out in a sample of women hospitalized postpartum in psychiatric settings, which limits the generalizability of our results to the whole population of babies with prenatal exposure to psychotropic drugs. The retrospective collection of data may have resulted in recall bias. We cannot exclude that more detailed information was collected on maternal drug exposure during pregnancy for babies with a poor neonatal outcome or conversely that exposed infants might be more likely to be admitted after birth. However, as this information was collected in medical records by investigators unaware of the hypotheses tested in the present study, we do not suspect a selective bias for a specific therapeutic or pharmacologic class of psychotropic drugs. If such a bias were operating, it would have been more marked for infants prenatally exposed to antipsychotics, as the stigma of taking these drugs in pregnancy is greater than taking antidepressants or anxiolytics. Other limitations are related to the lack of information about psychotropic drug dosages as maternal serum levels may influence neonatal outcome.[30] As prematurity was defined in the MBU database as delivery < 36 weeks, we could not use the international definition of prematurity, ie, delivery < 37 weeks.[31] As a consequence, the generalization of our findings is limited. We also had no information on reasons for neonatal hospitalizations.

These data do not clarify the mechanisms responsible for poor neonatal outcomes. Women who are psychiatrically hospitalized represent a subgroup that is likely most ill. Maternal severe psychiatric illnesses such as schizophrenia or bipolar disorder are associated with specific adverse effects on neonatal adjustment (including an increased risk of obstetric complications), as well as with a myriad of bio-psychosocial risk factors. Hence, the severity of maternal psychiatric illness is a potential confounder by indication with regard to the association between exposure to psychotropic drugs and poor neonatal outcome.[15,32,33] Lastly, no reliable information was available in the database on mother's prior psychiatric history.

Pregnant women with severe psychiatric illness do need treatment with psychotropic medications. Our results underline the necessity for close follow-up of this particular population and especially for further prospective studies on large cohorts to examine the independent impact of each pharmacologic class of drugs. Another important issue is to examine the occurrence and the severity of poor neonatal adaptation of exposed infants, and the link between poor neonatal adaptation and subsequent child development in the context of maternal severe mental illness.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), risperidone (Risperdal and others).

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