A Systematized Review of Atypical Antipsychotics in Pregnant Women: Balancing Between Risks of Untreated Illness and Risks of Drug-Related Adverse Effects

Sarah Tosato, MD, PhD[a,*]; Umberto Albert, MD, MSc, PhD[b]; Simona Tomassi, MD[a]; Felice Iasevoli, MD[c]; Claudia Carmassi, MD, PhD[d]; Silvia Ferrari, MD[e]; Maria Giulia Nanni, MD[f]; Alessandra Nivoli, MD[g]; Umberto Volpe, MD, PhD[h]; Anna Rita Atti, MD, PhD[i]; and Andrea Fiorillo, MD, PhD[h]

ABSTRACT

Objective: To summarize risks related to (1) illness and (2) second-generation antipsychotic (SGA) treatment in pregnant women and their offspring. Concerning illness-related risks, we focused on bipolar disorder and schizophrenia, psychiatric disorders for which SGAs are preferentially prescribed.

Data Sources: PubMed, Ovid, Scopus, PsycINFO, and Cochrane Library were searched from the date of the first available article to October 2015 using the following key terms: *pregnancy* OR *gestation* OR *bipolar disorder* OR *schizophrenia*. We also included cross-references from identified articles.

Study Selection: We included 49 English-language articles regarding illness-related and SGA-related risks in bipolar disorder and schizophrenia. First, searches were done for epidemiologic or experimental studies (from January 2000 to October 2015), then for systematic reviews and meta-analyses.

Data Extraction: Data were extracted independently, after removing duplicates and studies that were not relevant or not pertinent.

Results: Abrupt discontinuation of treatment-exposed mothers with bipolar disorder or schizophrenia led to a high risk of relapses during pregnancy. Both bipolar disorder and schizophrenia were linked to a slightly increased risk of obstetric complications for mothers (schizophrenia) and the newborn (bipolar disorder and schizophrenia), although data on drug exposure during pregnancy were not given in the majority of studies. Maternal morbidity (schizophrenia but not bipolar disorder) may be associated with the worst neonatal outcomes (stillbirth, neonatal or infant deaths, and intellectual disability). Untreated bipolar disorder and schizophrenia may be considered independent risk factors for congenital malformations, while SGAs were not associated with increased recurring defects in fetuses. Evidence regarding the potential effects of SGAs on child neurodevelopment remains reassuring.

Conclusion: After taking into account the parents' will and after they provide informed consent, the most reasonable and less harmful choice for treating future mothers with bipolar disorder or schizophrenia appears to be maintaining them at the safest minimum dosage.

[a]Section of Psychiatry, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Italy [b]Rita Levi Montalcini Department of Neuroscience, University of Turin, Italy, and San Luigi Gonzaga University Hospital, Orbassano, Turin, Italy [c]Department of Neuroscience, Reproductive Sciences and Odontostomatology, University "Federico II" of Naples, Italy [d]Department of Clinical and Experimental Medicine, University of Pisa, Italy [e]Department of Diagnostic-Clinical Medicine and Public Health, University of Modena and Reggio Emilia, Modena, Italy [f]Institute of Psychiatry, Department of Biomedical and Specialty Surgical Sciences, University of Ferrara, Italy [g]Institute of Psychiatry, University of Sassari, Italy [h]Department of Psychiatry, University of Naples SUN, Naples, Italy [i]Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy

**Corresponding author:* Sarah Tosato, MD, PhD, Section of Psychiatry, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Policlinico GB Rossi, Ple LA Scuro 10, 37134 Verona (VR), Italy (sarah.tosato@univr.it).

Pregnancy and the first 6 months after delivery are vulnerable periods for women with severe psychiatric disorders such as bipolar disorder and schizophrenia, mainly because of the high risk of relapse. Many women affected by these illnesses are increasingly prescribed second-generation antipsychotics (SGAs).[1] Moreover, use of these compounds has increased and the approved indications have expanded beyond psychotic disorders to include major depression, anxiety disorders, and attention-deficit/hyperactivity disorder.[2] As a consequence, at the time of pregnancy or when planning it, women find themselves facing the dilemma of whether to continue or stop taking antipsychotics. Specifically, the potential risks of untreated mental illness for both mothers and newborns should be balanced against known benefits and side effects of pharmacologic interventions.[3–6]

Despite the undoubtedly great clinical relevance of the effects of untreated bipolar disorder and schizophrenia on pregnancy and the adverse outcomes associated with SGA use pregnancy, very little is known about these relationships due to the paucity of available data.[7]

This systematized review aims to summarize the evidence regarding the benefits and potential harms of SGAs in pregnant women affected by bipolar disorder or schizophrenia, taking also into account the potential effects of the illness on pregnant women and on newborns. Concerning risks of untreated illness for mothers and newborns, we focused on bipolar disorder and schizophrenia, psychiatric disorders for which SGAs are preferentially prescribed, although some SGAs are prescribed most often now for other psychiatric disorders such as treatment-resistant depression and, increasingly, anxiety disorders. We restricted our review to SGAs and mention first-generation antipsychotics (FGAs) only when a study reported separately the risks of exposure to SGAs and FGAs.

In women affected by bipolar disorder and schizophrenia we aimed to evaluate in detail (1) the risks of relapse, obstetric complications, and adverse neonatal outcomes due to the untreated

Clinical Points

- Balancing between risks of untreated bipolar disorder and schizophrenia and the risks of adverse outcomes associated with second-generation antipsychotics (SGAs) in pregnancy is complex.
- Available data delineate significant illness-related risks of worst maternal and newborn outcomes; SGAs are associated with neither increased defects in the fetus nor adverse child neurodevelopment.
- The most reasonable and less harmful choice appears to maintain treatment in future mothers with bipolar disorder or schizophrenia.

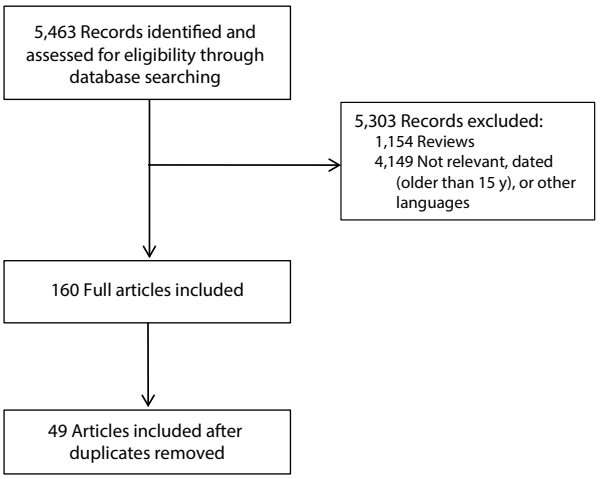
illness and (2) the benefits and potential harms of treatment with SGAs during pregnancy.

METHODS

Literature for this systematized review[8] was identified by searching PubMed, Ovid, Scopus, PsycINFO, and Cochrane Library databases from the date of the first available article to October 2015. Original searches were done, in the first instance, for epidemiologic or experimental studies and, in second instance, for systematic reviews and meta-analyses by using the following search terms: *pregnancy* OR *gestation* OR *bipolar disorder* OR *schizophrenia*. These search terms were combined with specific terms for illness-related risks in bipolar disorder and schizophrenia and for treatment-related risks with SGAs, with date limits based on the amount of recent research output in each area. In particular, regarding the risk of relapse, obstetric complications, and neonatal outcome in bipolar disorder and schizophrenia, we used the following terms: *discontinuation* OR *recurrence risk*, *obstetric complications* OR *obstetric* OR *preterm birth* OR *low birth weight*, and *neonatal outcome* OR *offspring outcome* OR *child outcome* OR *fetal outcome* OR *developmental outcome* OR *pregnancy outcome* OR *stillbirth* OR *neonatal mortality/death* OR *infant mortality/death* OR *neonatal morbidity*. Regarding the risks associated with psychotropic treatment, we searched the literature using the following terms: *antipsychotics* OR *antipsychotic agents* OR *second-generation antipsychotics* OR *atypical antipsychotics* AND *teratogenesis* OR *teratogens* OR *abnormalities, drug-induced*; AND *obstetric complications* OR *obstetric*; AND *outcome* OR *pregnancy complications*. An additional search with individual SGAs (amisulpride, aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, zotepine) was also added.

We also examined cross-references from the articles identified. Unpublished studies, conference abstracts, or poster presentations were not included. The database search was restricted to English language articles. Studies that reported only data on FGA exposure were excluded from the review, and, consequently, FGAs were mentioned in the text only when the same study reported separately risks due to SGAs and to FGAs. Articles were identified and assessed for eligibility by 2 independent reviewers (S. Tosato and A.F.). The titles of all studies identified (5,463 articles) as a result of the search strategy were examined, and studies that clearly did not pertain to our topic of interest were excluded (5,303 articles). The 160 full-text articles of the remaining studies were included, and, after duplicates were removed, data extraction was conducted on 49 articles (Figure 1).

Figure 1. Process of Studies Selection



ILLNESS-RELATED RISKS IN BIPOLAR DISORDER AND SCHIZOPHRENIA

Risk of Relapse

In spite of up to a quarter of women with bipolar disorder presenting with recurrence of symptoms during pregnancy,[9] remarkably little is known about the impact of pregnancy on the course and treatment of the disorder.[10] Some epidemiologic studies[11–14] suggest that pregnancy itself may not be associated with an increased risk of onset of affective illness, while other studies[9,15–18] consider pregnancy as a factor associated with higher recurrence rate. Among factors associated with a higher risk of relapse during pregnancy, abrupt discontinuation of mood stabilizers seems to be critical: data show that at least 50% of women with bipolar disorder who had interrupted their therapy became symptomatic during pregnancy, with up to 2-fold greater recurrence risk, a shorter time to recurrence, and a proportionately increased time of illness burden during pregnancy,[15,17] when compared with nonpregnant women with bipolar disorder. Treatment guidelines on women with bipolar disorder during pregnancy are also, to some extent, controversial. Nevertheless, a worldwide warning[19] states that there is a high risk of relapse in affective disorders if medication is discontinued during pregnancy, and adverse outcomes from inadequate pharmacologic prophylaxis have been documented for both the mother and the baby.[20] Studies show that 52% of women who discontinued lithium during pregnancy relapsed, and 70% of the women who remain stable after lithium discontinuation relapse in the

postpartum period.[15] In a more recent prospective cohort study,[9] the overall risk of at least 1 recurrence in pregnancy was 71%, and rapid discontinuation was associated with a higher risk of relapses, which were mainly depressive or mixed (74%); 47% of them occurred during the first trimester. Presently, due to insufficient data, it is difficult to estimate a definitive and comprehensive account of the risks of untreated bipolar disorder during pregnancy.[5]

In conclusion, continuation of psychopharmacologic treatment to maintain stability during pregnancy is often necessary for optimal care,[21] and a balanced consideration of the entire spectrum of risks and benefits involved in the clinical management of pregnant women with bipolar disorder is recommended.[9]

Pregnancy is also associated with a high risk of symptom exacerbation and relapse in women with schizophrenia.[3] This risk appears to increase if ongoing antipsychotics are discontinued. Notably, a 13-fold increased relapse risk occurs within 3 months from typical antipsychotic discontinuation, and rapid withdrawal after detection of pregnancy is one of the most relevant predictors of relapse.[22] Discontinuation of antipsychotics during pregnancy, however, appears to be a frequent phenomenon: in a recent survey[23] on a large UK-based primary care database, only a minority of women taking antipsychotics before pregnancy was found to continue their medications at the start of the third trimester (39% and 19% for atypical and typical antipsychotics, respectively). These results are substantially concordant with those from another UK-based cohort study.[24] However, studies on the effects of atypical antipsychotic withdrawal during pregnancy are lacking or limited to case reports. These case reports suggest that atypical antipsychotic discontinuation is also associated with a high risk of relapse; for example, one case report[25] describes a pregnant woman who stopped taking olanzapine at week 20 of gestation and was subsequently hospitalized at week 36 for a psychotic relapse.

On the basis of the available evidence, the American Congress of Obstetricians and Gynecologists recommends avoiding stopping antipsychotics during pregnancy since severe psychotic relapses may be caused by medication discontinuation.[26]

Obstetric Complications

Having a diagnosis of bipolar disorder has been linked to a slightly increased risk of pregnancy and obstetric complications, as shown in Tables 1 and 2, including preterm birth (< 37 weeks of gestation),[27–29] giving birth to small for gestational age infants (< 10th percentile),[27–30] and low birth-weight (< 2,500 g) infants.[16,29] Among pregnancy complications, data showed an increased risk for placental abnormalities, particularly placenta previa, antepartum hemorrhages,[16] gestational diabetes mellitus,[29,31,32] chronic hypertension,[29] and preeclampsia.[31,32] Only 1 large study,[30] a national cohort study in Sweden involving 332,137 mothers, investigated the impact of untreated bipolar disorder on pregnancy and birth outcomes, while in the majority of studies,[27–29] data on drug exposure during pregnancy were not given.

A slightly increased risk for adverse pregnancy outcomes such as preterm birth has been detected in newborns to mothers with both untreated and treated bipolar disorder (adjusted odds ratio [aOR] = 1.48 [95% CI, 1.08–2.03] vs aOR = 1.50 [95% CI, 1.01–2.24], respectively).[30] More recently, similar results emerged in a large population-based cohort study[29] in Canada of 1,859 women hospitalized for bipolar disorder within a 5-year period, even though data were not controlled for drug treatment, smoking, and illness severity. Results showed that newborns of mothers with bipolar disorder had up to 2 times higher risk for adverse perinatal outcomes than newborns of women without a documented mental illness (n = 432,358), including preterm birth (aOR = 1.95; 95% CI, 1.68–2.26) and severe large for gestational age (aOR = 1.29; 95% CI, 1.08–1.54).[29] Moreover, in another nationwide population-based study[28] from Taiwan, 337 women with bipolar disorder were compared with women with no history of mental illness and showed an increased risk of small for gestational age (aOR = 1.47; 95% CI, 1.14–1.91) and low birth weight (aOR = 1.66; 95% CI, 1.16–2.38), even though data were not controlled for drug treatment, substance and alcohol use disorder, smoking and illness severity, and comorbid chronic medical conditions.

Furthermore, infants of mothers with untreated bipolar disorder were at increased risk of congenital malformations such as microcephaly when compared with women without bipolar disorder (aOR = 1.68; 95% CI, 1.07–2.62).[30] Interestingly, there was no increased risk of congenital malformations in offspring of women with treated bipolar disorder compared with offspring of women without bipolar disorder.[30]

Mothers with schizophrenia and their offspring seemed also to present a higher risk of obstetric complications (see Tables 3 and 4). In most studies analyzing obstetric complications in schizophrenia, however, data on drug exposure,[16,32–37] smoking[32–35] and illness severity,[32–37] substance and alcohol use disorder,[33,34,36,37] and comorbid chronic medical conditions[16,32,36,37] during pregnancy were not given.

Newborns of mothers with schizophrenia were smaller for gestational age (< third centile) (OR = 1.49; 95% CI, 1.19–1.86)[33] and presented a low birth weight (OR = 3.6; 95% CI, 1.8–7.1).[34] Furthermore, the rate of preterm birth was significantly increased (aOR = 1.75; 95% CI, 1.46–2.08),[33] up to 5 times higher ($P = .02$)[32] in children born to affected mothers when compared with those born to nonaffected mothers. Psychiatric illnesses, including schizophrenia, during pregnancy have been proved to represent an independent risk factor for congenital malformations (OR = 1.40; 95% CI, 1.01–1.90).[35] Women affected by schizophrenia presented a course of pregnancy characterized by a 72% greater risk (aOR = 1.72; 95% CI, 1.04–2.85) of thromboembolic disease than did controls.[33] When compared with nonaffected mothers, they also presented higher rates (3.9% vs 1.2%) of preexisting type 2 diabetes mellitus[33] and

Table 1. Obstetric Complications in Newborns of Mothers With Bipolar Disorder

Study	Type of Study	Notes	Small for Gestational Age		Low Birth Weight (<2,500 g)		Preterm Birth (<37 wk gestation)		Congenital Malformations	
			%	OR (95% CI)[a]	%	OR (95% CI)[a]	%	OR (95% CI)[a]	%	OR (95% CI)[a]
Jablensky et al, 2005[16]	Population-based, case-control study	1,301 Women with bipolar disorder compared to 1,831 unaffected women Data on drug exposure during pregnancy not given	9.9[b]	1.1 (0.8–1.4)	6.8	1.0 (0.8–1.4)	6.2	0.8 (0.6–1.1)	4.8[c]	1.0 (0.7–1.3)[d]
MacCabe et al, 2007[27]	Population-based, case-control study	Mothers with affective psychosis (not only bipolar disorder) (N = 5,618) Data on drug exposure during pregnancy not given	3.7	**1.4** (1.2–1.6)[d] 1.1 (0.9–1.3)[e]	4.9	**1.5** (1.3–1.7)[d] **1.2** (1.0–1.4)[e]	5.9	**1.4** (1.2–1.6)[d] **1.3** (1.1–1.4)[e]		
		Births occurring after ≥1 episode of affective psychosis (N = 2,317)	NA	**1.6** (1.3–2.0)	NA	**1.6** (1.3–2.0)	NA	**1.5** (1.2–1.8)		
		Mothers who had episode during pregnancy (N = 226)	NA	**2.4** (1.3–4.2)	NA	**2.2** (1.3–3.8)	NA	**2.7** (1.7–4.2)		
Lee and Lin, 2010[28]	Nationwide, population-based	337 Women with bipolar disorder (among 528,398 singleton births) Data on drug exposure during pregnancy not given	22.3	**1.5** (1.2–2.0)[d] **1.5** (1.1–1.9)[f]	9.8	**1.8** (1.3–2.6)[d] **1.7** (1.2–2.4)[f]	14.2	**2.3** (1.7–3.1)[d] **2.1** (1.5–2.8)[f]		
Bodén et al, 2012[30]	National cohort study	320 Women with treated bipolar disorder[g] (vs 331,263 with no bipolar disorder)	1.3[h]	1.5 (0.6–4.1)[d] 1.1 (0.4–3.1)[i]			8.1	**1.8** (1.2–2.6)[d] **1.5** (1.01–2.2)[i]	3.3[j]	1.5 (0.8–2.7)[d] 1.3 (0.7–2.4)[i]
		554 Women with untreated bipolar disorder (vs 331,263 with no bipolar disorder)	1.8[h]	**2.2** (1.2–4.2)[d] 1.8 (0.97–3.5)[i]			7.6	**1.6** (1.2–2.2)[d] **1.5** (1.1–2.0)[i]	3.9[j]	**1.8** (1.1–1.7)[d] **1.7** (1.1–2.6)[i]
Nguyen et al, 2013[31]	Retrospective review, no control group	56 Women with bipolar disorder who attended a specialist multidisciplinary antenatal clinic 76.8% Exposed to antipsychotics (mostly atypicals) during pregnancy					8.9			
Judd et al, 2014[32]	Retrospective review, with control group	112 Women with schizophrenia or bipolar disorder (data aggregated) referred to a "high-risk pregnancies" unit Data on drug exposure during pregnancy not given					17.9 in the study group			
Mei-Dan et al, 2015[29]	Population-based cohort study	1,859 Women with bipolar disorder hospitalized within 5 y preceding the index pregnancy compared with women without documented mental illness (n = 432,358) Data on drug exposure during pregnancy not given	4.6[k]	1.2 (0.95–1.5)[d] 1.2 (0.9–1.4)[l]	3.8		11.4	**1.9** (1.7–2.2)[d] **1.95** (1.7–2.3)[l]	5.0	**1.5** (1.2–1.8)[m]

[a]Boldface values indicate statistical significance.
[b]Percentage of estimated birth weight (100% represents the population norm, adjusted for gestational age, sex, maternal height tercile, and parity) <10th percentile.
[c]Any birth defects.
[d]Crude OR.
[e]Odds ratios adjusted for maternal age, parity, cohabitation, education level, immigrant status, pregnancy-induced hypertensive disease, and smoking were included.
[f]Odds ratio adjusted for maternal age, education level, marital status, and gestational hypertension, and infant's sex and parity, family monthly income, parental age difference, and paternal education level.
[g]Filling a prescription for lithium, antipsychotics, carbamazepine, lamotrigine, or valproate during pregnancy.
[h]Small for gestational age (including low birth weight and short length) defined as being in ≤2.3 centile (2 SDs) of total population in cohort.
[i]Odds ratio adjusted for birth order, maternal age, cohabitation, smoking, height, and diagnosis of alcohol or substance misuse disorder.
[j]Microcephaly.
[k]Birth weight < 3rd percentile.
[l]Odds ratio adjusted for maternal age, parity, infant sex, obesity prior to pregnancy, substance or alcohol use disorder, diabetes mellitus, hypertension, venous thromboembolism, gestational diabetes mellitus, gestational hypertension, and preeclampsia or eclampsia.
[m]Odds ratio adjusted for maternal age and parity.
Abbreviations: NA = not available, OR = odds ratio.

Table 2. Obstetric Complications in Mothers With Bipolar Disorder

Study	Type of Study	Notes	Thromboembolic Disease		Gestational Diabetes		Gestational Hypertension		Preeclampsia/ Eclampsia	
			%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
Jablensky et al, 2005[16]	Population-based, case-control study	1,301 Women with bipolar disorder compared to 1,831 unaffected women Data on drug exposure during pregnancy not given					12.5[a]	1.17 (0.93–1.48)[b]		
Bodén et al, 2012[30]	National cohort study	320 Women with treated bipolar disorder[c] (vs 331,263 with no bipolar disorder)			1.9	1.2 (0.6–2.6)[b] 1.1 (0.5–2.4)[d]				
		554 Women with untreated bipolar disorder (vs 331,263 with no bipolar disorder)			1.8	1.1 (0.6–2.0)[b] 1.01 (0.5–1.9)[d]				
Nguyen et al, 2013[31]	Retrospective review, no control group	56 Women with bipolar disorder who attended a specialist multidisciplinary antenatal clinic 76.8% Exposed to antipsychotics (mostly atypical) during pregnancy			12.5				10.7	

[a]Hypertension including preeclampsia.
[b]Crude OR.
[c]Filling a prescription for lithium, antipsychotics, carbamazepine, lamotrigine, or valproate during pregnancy.
[d]Odds ratio adjusted for birth order, maternal age, cohabitation, smoking, height, and diagnosis of alcohol or substance misuse disorder.
Abbreviation: OR = odds ratio.

an increased risk for gestational diabetes (12.7% vs 6.4%, $P = .007$).[32] In addition, higher rates of preexisting chronic hypertension (3.7% vs 1.9%) and an enhanced risk for gestational hypertension (OR = 1.45; 95% CI, 1.05–1.99)[33] differentiated mothers affected by schizophrenia from controls. Finally, they showed higher rates of preeclampsia (11.0% vs 2.6%, $P < .001$),[32] with an 84% increased risk (OR = 1.84; 95% CI, 1.28–2.66),[33] even if it was not confirmed.[38]

Neonatal Outcomes

Studies[16,27,29,31,32] that investigated neonatal outcomes of mothers with bipolar disorder failed to show an increased risk of stillbirth (fetal death at 28 completed gestational weeks or later), neonatal death (mortality < 28 days of life), and infant death (mortality within 1 year after birth). On the contrary, 2 studies[39,40] from the same Danish national registers found increased risks of stillbirth (in 1 study[40] risk was due only to congenital malformations) and neonatal death in babies of women with affective disorders (data not available on women with bipolar disorder only). According to the authors,[39,40] one possible explanation for the increased risks might be the use of prescribed psychotropic drugs during pregnancy, although data or dosage were not available from the study registers. No study has specifically examined neonatal mortality in offspring of women with untreated bipolar disorder during pregnancy.

Similarly, findings regarding stillbirth and infant death of offspring of mothers with schizophrenia point out heterogenic conclusions.[16,31,32,35,37,40] A significantly increased risk for stillbirth (OR = 2.1; 95% CI, 1.3–3.5) and infant death (OR = 2.1; 95% CI, 1.3–3.5) has been shown.[36] Schizophrenia in both fathers and mothers seemed to confer a higher risk for infant death (OR = 1.9 and 2.4, respectively).[37] At the same time, other studies[16,40] showed no significant differences among groups with regard to stillbirths, neonatal deaths, and infant deaths.

Neonatal morbidity (inclusive of jaundice and hypoglycemia) in infants of mothers with bipolar disorder was investigated in a large population-based cohort study,[30] which was controlled for medication treatment during pregnancy, even if dosage of antipsychotics was not given. Results showed an increased risk of neonatal morbidity in the infants of untreated (during pregnancy) women with bipolar disorder (OR = 1.51; 95% CI, 1.04–2.43) when compared with infants of women without bipolar disorder but failed to demonstrate any significant difference between newborns of women with treated and untreated bipolar disorder (OR = 1.18; 95% CI, 0.64–2.16). This is particularly relevant, as recurrent episodes of neonatal hypoglycemia are correlated with persistent neurodevelopmental and physical growth deficit until 5 years of age, severe mental retardation, and epilepsy.[41]

The specific risks of untreated bipolar disorder during pregnancy in terms of psychological and developmental disturbances in children are poorly understood and have received little attention; untreated depressive episodes are known to pose risks to the fetus and are associated with increased risk of psychological and developmental disturbances in children.[42] We could not find any study investigating the effect of untreated bipolar disorder during pregnancy on children's neurodevelopmental and cognitive outcome. A recent population-based cohort study[43] found that children of mothers with bipolar disorder are at significant increased risk of intellectual disability (OR = 3.1; 95% CI, 1.9–4.9); children with intellectual disability have increased rates of both pregnancy and labor and delivery complications. Of note, the risk of intellectual disability is significantly increased only if onset of maternal illness predated the index birth; the authors[43] interpret their findings as a reflection of the role of

Table 3. Obstetric Complications in Newborns of Mothers With Schizophrenia

Study	Type of Study	Notes	Small for Gestational Age		Low Birth Weight (<2,500 g)		Preterm Birth (<37 weeks of gestation)		Congenital Malformations	
			%	OR (95% CI)[a]	%	OR (95% CI)[a]	%	OR (95% CI)[a]	%	OR (95% CI)[a]
Nilsson et al, 2002[36]	Population-based, case-control study	2,096 Births by 1,438 mothers diagnosed with schizophrenia (of whom 696 mothers were antenatal diagnosed and 188 admitted during pregnancy) 1,555,975 Births in the general population Data on drug exposure during pregnancy not given	4.2	**1.6** (1.3–2.0)[b] 1.1 (0.9–2.0)[c]	6.0	**1.8** (1.5–2.2)[b] **1.3** (1.1–1.6)[c]	6.7	**1.7** (1.4–2.0)[b] **1.4** (1.2–1.7)[c]		
			2.1[d]	**1.9** (1.4–2.5)[b] 1.2 (0.8–1.6)[c]	3.1[d]	**2.2** (1.7–2.8)[b] **1.4** (1.1–1.8)[c]	2.0[d]	**2.0** (1.5–2.5)[b] **1.5** (1.2–2.0)[c]		
			0.5[e]	**2.2** (1.2–4.1)[b] 1.1 (0.6–2.0)[c]	1.2[e]	**4.3** (2.9–6.6)[b] **2.3** (1.5–3.5)[c]	1.0[e]	**3.4** (2.1–5.4)[b] **2.4** (1.5–3.8)[c]		
Jablensky et al, 2005[16]	Population-based, case-control study	382 Women with schizophrenia and 1,449 women with affective psychosis 3,129 Births of 1,831 comparison mothers 618 Births of 382 mothers with schizophrenia Data on drug exposure during pregnancy not given	12.6	**1.4** (1.03–1.9)	8.9	1.4 (0.9–1.9)	8.6	1.1 (0.8–1.6)	6.0[f]	1.2 (0.9–1.8)
									0.5[g]	1.5 (0.4–5.5)
									1.6[h]	**2.5** (1.2–5.4)
									0.3[i]	1.5 (0.3–6.9)
Nilsson et al, 2008[37]	Population-based, case-control study	3,119 Mothers with schizophrenia and 1,880,976 control mothers delivering singleton births	3.9	**1.4** (1.2–1.7)[b] 0.9 (0.7–1.2)[j]	5.6	**1.6** (1.4–1.9)[b] 1.1 (0.9–1.4)[j]	6.4	**1.6** (1.4–1.8)[b] 1.2 (1.0–1.4)[j]		
		2,829 Fathers with schizophrenia and 1,865,434 control fathers Data on drug exposure during pregnancy not given	4.1	**1.5** (1.3–1.9)[b] 1.2 (1.0–1.6)[j]	4.5	**1.3** (1.1–1.6)[b] 1.1 (0.9–1.3)[j]	4.7	1.1 (1.0–1.4)[b] 1.0 (0.8–1.2)[j]		
Schneid-Kofman et al, 2008[35]	Population-based, case-control study	607 Mothers with mental illnesses (n = 67, 11% affected by schizophrenia) 180,872 Control mothers Data on drug exposure during pregnancy not given							7.1[f]	**1.3** (1.2–1.4)[b] **1.4** (1.01–1.9)[k]
Lin et al, 2009[34]	Population-based, case-control study	191 Mothers with schizophrenia who received inadequate prenatal care vs 258 mothers with schizophrenia who received appropriate prenatal care Data on drug exposure during pregnancy not given	29.3	**2.2** (1.4–3.5)[b] **2.1** (1.3–3.4)[k]	16.8	**3.5** (1.8–6.8)[b] **3.6** (1.8–7.1)[k]	16.3	**2.4** (1.3–4.5)[b] **2.6** (1.4–5.0)[k]		
Vigod et al, 2014[33]	Retrospective review, with control group	1,391 Women with schizophrenia 432,358 Control women Data on drug exposure during pregnancy not given	6.0	**1.6** (1.3–1.9)[b] **1.5** (1.2–1.9)[l]			11.2	**1.9** (1.6–2.2)[b] **1.8** (1.5–2.1)[l]		
Judd et al, 2014[32]	Retrospective review, with control group	112 Women with schizophrenia or bipolar disorder (63 women with schizophrenia, data aggregated) vs 19,755 controls referred to as a "high-risk pregnancies" unit Data on drug exposure during pregnancy not given	17.9 vs 1.9 in controls $\chi^2 = 5.5$ $P = .02$							

[a]Boldface values indicate statistical significance.
[b]Crude OR.
[c]Odds ratio adjusted for maternal age, parity, maternal education, cohabiting with infant's father, mother's country of birth, maternal smoking, and pregnancy-induced hypertensive diseases.
[d]Infants of women diagnosed with schizophrenia before childbirth compared to women without schizophrenia.
[e]Infants of women admitted to hospital for schizophrenia during pregnancy compared to women without schizophrenia.
[f]Any birth defects.
[g]Nervous system birth defect.
[h]Cardiac birth defect.
[i]Chromosomal birth defect.
[j]Odds ratio adjusted for schizophrenia in spouse, maternal age, parity, maternal and paternal education, cohabitation status, and maternal smoking.
[k]Odds ratio adjusted for maternal age, pregestational diabetes, and fertility treatment.
[l]Odds ratio adjusted for maternal age (continuous in years), parity (0, 1, ≥2), income quintile, community size, diabetes mellitus prior to pregnancy, hypertension prior to pregnancy, thromboembolic disease prior to pregnancy, and infant sex.
Abbreviation: OR = odds ratio.

Table 4. Obstetric Complications in Mothers With Schizophrenia

Study	Type of Study	Notes	Thromboembolic Disease		Gestational Diabetes		Gestational Hypertension		Preeclampsia/Eclampsia	
			%	OR (95% CI)[a]	%	OR (95% CI)	%	OR (95% CI)[a]	%	OR (95% CI)[a]
Bennedsen et al, 2001[38]	Population-based, case-control study	2,212 Births to 1,537 schizophrenic women 122,931 Births to 72,742 control women Data on drug exposure during pregnancy not given							NA	**0.4** (0.2–0.9)
Vigod et al, 2014[33]	Retrospective review, with control group	1,391 Women with schizophrenia 432,358 Control women Data on drug exposure during pregnancy not given	1.2	**2.2** (1.4–3.6)[b] **1.7** (1.0–2.9)[c]	2.5	1.2 (0.9–1.5)[b] 1.1 (0.9–1.4)[c]	2.8	**1.5** (1.1–2.0)[a] 1.4 (0.9–1.9)[b]	2.2	**1.9** (1.3–2.8)[b] **1.8** (1.3–2.7)[c]
Judd et al, 2014[32]	Retrospective review, with control group	112 Women with schizophrenia or bipolar disorder (63 women with schizophrenia, data aggregated) vs 19,755 controls referred to as a "high-risk pregnancies" unit Data on drug exposure during pregnancy not given			12.7 vs 6.4 in controls $P = .007$				11 vs 2.6 in controls $P < .001$	

[a]Boldface values indicate statistical significance.
[b]Crude OR.
[c]Odds ratio adjusted for maternal age (continuous in years), parity (0, 1, ≥ 2), income quintile, community size, diabetes mellitus prior to pregnancy, hypertension prior to pregnancy, thromboembolic disease prior to pregnancy, and infant sex.
Abbreviations: NA = not available, OR = odds ratio.

medication taken during pregnancy (although data on dosage and type of medication during pregnancy were not available).

Children born to mothers with schizophrenia were at significantly increased risk of intellectual disability (OR = 3.2; 95% CI, 1.8–5.7).[43] Conversely, children of affected mothers were not at higher risk when compared with control offspring, neither for epilepsy (OR = 1.4; 95% CI, 0.9–2.1) nor for convulsions (OR = 0.7; 95% CI, 0.2–2.3).[43] Similarly, no significant association was found between being born to mothers with schizophrenia and the onset of pervasive developmental disorders (such as autism) (OR = 5.1; 95% CI, 0.3–81.2). However, another recent study[44] showed a significant association between both maternal and paternal diagnosis of schizophrenic spectrum disorder and the presence of an autism spectrum disorder in offspring (OR = 2.5 [95% CI, 1.9–3.2] and OR = 2.2 [95% CI, 1.7–3.0], respectively). Data regarding drug treatment were not given.

TREATMENT-RELATED RISKS WITH SECOND-GENERATION ANTIPSYCHOTICS

Teratogenesis

McKenna and colleagues[45] assessed 151 women exposed to SGAs during pregnancy (olanzapine, n = 60; risperidone, n = 49; quetiapine, n = 36; clozapine, n = 6), compared them to the same number of nonexposed mothers, and found no increased risk for major malformations. A study[46] of the Swedish Medical Birth Register assessed exposure to antipsychotic drugs or lithium in 958,729 pregnancies: 460 women had taken FGAs and 101, SGAs. An overall OR of 1.5 was calculated for increased risk of teratogenicity (cardiovascular defects mostly) (overall OR = 1.52; 95% CI, 1.05–2.19), but only in the FGA group: no significant teratogenic action was hypothesized for SGAs.[46] In 57 pregnant women taking SGAs (olanzapine, n = 32; risperidone, n = 49; quetiapine, n = 15), no pattern of defect was observed.[47] Pregnant women exposed to SGAs (n = 133) were compared to as many nonexposed women; 96 in the exposed group were also taking other psychotropic medications. The rate of major malformations in the exposed group was higher than that in the control group, although this difference was not significant (6.2% vs 2.6%, $P = .211$).[1] A prospective cohort study[48] compared 561 women who were exposed during pregnancy to SGAs to 1,122 nonexposed mothers. Exposure to SGAs resulted in a higher risk of congenital major malformations in comparison to nonexposed pregnancies (aOR = 2.17; 95% CI, 1.20–3.91), with post hoc analysis that revealed an increased incidence of cardiovascular malformations (atrial and ventricular septal defects: OR = 3.21; 95% CI, 1.34–7.67).[48] Notably, 3 of 12 infants with cardiovascular malformations were reported after maternal comedication with lithium throughout pregnancy. Moreover, infants exposed to SGAs had isolated septal defects in contrast to 3 of 5 nonexposed infants having multiple malformations including septal defects. A detection bias cannot be ruled out since women exposed to medication like SGAs, especially for which there are sparse reproductive safety data, may be more likely to receive more prenatal and postnatal care.[48] Recently, the Massachusetts General Hospital (MGH) National Pregnancy Registry for Atypical Antipsychotics[6] compared 214 women who were exposed to SGAs during the first trimester to 89 nonexposed mothers with psychiatric illnesses and found the risk of a major malformation for SGAs (OR = 1.25; 95% CI, 0.13–12.19) was not significantly different between the 2 groups.[49]

Interestingly, after adjusting for potential likely confounders (eg, alcohol, bupropion use, bipolar disorder diagnosis, planned pregnancy, maternal body mass index [BMI]), with the exception of cigarette and anticonvulsant use, the OR estimate became closer to the null.

A very recent review[50] analyzing data from over 6,000 pregnancies provides a somewhat more negative picture of potential risks related to antipsychotic exposure than previous works: risk of congenital malformations was higher for pregnancies exposed to antipsychotics in general (OR = 2.12; 95% CI, 1.25–3.57), with no statistical difference between FGAs and SGAs.

Concerning the single atypical antipsychotics, clozapine, the oldest one has been associated with minor and major malformations, though evidence derives almost entirely from low-strength studies.[51,52]

Olanzapine showed the highest amount of placental passage compared to other antipsychotic agents[53]; despite this, no significant evidence of a role of olanzapine in causing major congenital malformation has been found.[51,52,54] Single case reports[45,55,56] of hip dysplasia, meningocele, ankyloblepharon, and neural tube defects have been described. However, a review[57] of 610 prospectively identified pregnancies during which olanzapine was used (data from the Eli Lilly and Company global safety database) did not find a higher congenital anomaly rate (4.4%) as compared to that in a historic control of the general population (3%–5%).

Quetiapine, which has the lowest amount of placental passage in comparison to other antipsychotic agents,[53] similarly has never been found to be associated with increased risk of birth defects or teratogenicity.[45,51,58] A postmarketing surveillance study[59] reported 6 pregnancies with quetiapine, 5 of which had exposure during the first trimester only, with 4 live births without congenital abnormalities. A review[60] of the Benefit Risk Management Worldwide Safety database on case reports of risperidone exposure during pregnancy assessed a total of 713 pregnancies (516 prospectively and 197 retrospectively assessed) and concluded that this medication was not associated with an increase in the risk of teratogenicity. A case report[61] of the use of long-acting risperidone in pregnancy described no consequences on the fetus and in the baby. No literature data are available so far about the use in pregnancy of paliperidone, the active metabolite of risperidone. A recent review[62] of the literature reported no congenital abnormalities in 15 women exposed to aripiprazole during pregnancy. Exposure to aripiprazole during embryogenesis has been recently studied[63] in 87 women compared to 172 controls, and no significantly increased rate of malformation was found (OR = 2.30; 95% CI, 0.32–16.7). A single case report[64] of cleft palate (palatoschisis) with ziprasidone use during the entire course of pregnancy has been reported.

No reports are available on other SGAs, such as amisulpride, sertindole, zotepine, lurasidone, or asenapine.[51,65]

Obstetric Complications

As for the overall risk of obstetric complications, a recent review[66] on the topic reported that the risk was increased after SGA use. Stillbirth or abortion represents the greater risk for a fetus exposed to SGAs. In a cohort of 151 pregnant women,[45] 24% of the cases exposed to SGAs (olanzapine, quetiapine, risperidone, and clozapine) reported abortion, either spontaneous or therapeutic (9.9% for SGA users vs 1.3% for non-SGA users, $P = .003$), and stillbirth (2.6% for both SGA and non-SGA users, $P = 1.0$). A review[67] highlights that among SGAs, olanzapine and quetiapine had the lowest risk for stillbirth or abortion; however, these drugs were also those with highest risks for gestational diabetes (which, in turn, may cause further pregnancy and delivery complications).[30] Within the available literature, no significant differences have emerged concerning the impact of any specific SGAs on pregnancy course and delivery,[50] although olanzapine, quetiapine, and clozapine are often considered more favorably with respect to risperidone, aripiprazole, and amisulpride.[53,67] One clinical case description[68] reports that ziprasidone is associated with a normal pregnancy course.

Gestational exposure to SGAs seems to be associated with an increased risk of other pregnancy adverse outcomes, although the whole picture seems not clear yet: while some authors[30,45,53,69] report lower birth weight or length, others[70,71] report a significantly higher incidence of "large for gestational age." Complications during delivery have also been reported: different studies find that using SGAs may increase the risk for preterm delivery,[1,72] instrumental labor,[1] Cesarean section,[71] and postnatal admission to intensive care unit,[1,52] particularly for respiratory distress.[72] An increased risk of obstetric complications after maternal exposure to SGAs has been associated with higher SGA doses[1,23] and use of multiple drugs, particularly, if SGAs are associated with mood stabilizers.[72]

Finally, a prospective cohort study[72] reported an SGA withdrawal syndrome at birth happened in 15% of the cases, with quetiapine followed by olanzapine as the most commonly prescribed SGAs. Since the rate of polytherapy was high (43% of women also took antidepressants and 11% took 2 antipsychotics), it is hard to establish an association between a specific compound with the withdrawal syndrome.[72] Moreover, for all SGAs except clozapine, since animal studies show evidence of adverse fetal effects, the US Food and Drug Administration (FDA) reports a safety warning regarding risk of abnormal muscle movements and withdrawal syndrome in neonates.[73] These warnings were based on cases reported in the FDA Adverse Event Reporting System database. Most of withdrawal syndrome cases involved potential confounding factors, including the presence of obstetric complications and concomitant exposure to other drugs associated with withdrawal syndrome (eg, antidepressant, benzodiazepines).[73]

Effects on Child From In Utero Exposure

Peng and colleagues[74] assessed 76 in utero–exposed infants (clozapine, n = 33; risperidone, n = 16; sulpiride,

n = 13; olanzapine, n = 8; quetiapine, n = 6) at the age of 2 months and compared them to as many nonexposed infants using the Bayley Scales of Infant and Toddler Development (BSID-III).[75] Exposure to SGAs resulted in a short-term (at 2 months) delayed development in cognitive, motor, social/emotional functioning, and adaptive behavior ($P < .001$), but not in language. A recent prospective case-control (drug vs drugs) study[76] compared 33 infants exposed to clozapine in utero versus 30 infants exposed to other SGAs (risperidone, n = 16; olanzapine, n = 8; quetiapine, n = 6) using BSID-III scale and failed to observe major differences among diverse drugs. It highlighted a delayed adaptive behavior in infants exposed to clozapine ($P = .001$) but found no significant differences between groups with respect to short-term (at 2 months) development in cognitive, motor, and social/emotional functioning and language.

No pattern of delay was observed at the 6 and 12 months of age assessments among infants exposed to SGAs in utero when compared with nonexposed infants[74] in terms of cognitive, motor, social/emotional functioning; language; and adaptive behavior. Again, different antipsychotics showed similar effects on neurodevelopment, as estimated at 6 and 12 months of age by the BSID-III scale.[76]

DISCUSSION

At present, any comfort we may have in prescribing antipsychotics during pregnancy comes mainly from the absence of negative data rather than the presence of positive data.[66] To date, there is a paucity of information regarding SGA congenital malformation risk[72]: the most recent data[49] conclude that these drugs are not major teratogens. It should be noted that, since the malformation rate in the general population is 1%–3%,[66] at least 500 cases are needed for each individual medication to determine differences in occurrence of major malformation and larger numbers are required to control for other potential confounders.[77] In fact, to be sure that a specific malformation is related to the use of a specific SGA, several confounders should be taken into account, such as maternal age,[29] BMI,[29] parity,[46] comorbid chronic medical conditions,[29,34] behaviors associated with psychiatric illness such as alcohol or substance misuse[32] or cigarette smoking,[32] illness severity,[49] and SGA dosage and polypharmacotherapy.[48] Results from the recently established MGH National Pregnancy Registry for Atypical Antipsychotics[6] show that after adjusting for such potential confounders, the OR estimate for major malformations becomes closer to the null.[49] Even if the size of the registry at present may be a limitation for the assessment of specific types of malformations and the confidence intervals around the odds ratio estimate remain very wide, with the probability for change over the course of the study, it is unlikely that the risk will rise to that of major teratogens such as valproate.[49] Moreover, when consideration is given to the risk-benefit profile of treatment with SGAs during pregnancy, equal weight should be given to the risks of not treating with SGAs.

In the present systematized review, we chose to focus on the 2 psychiatric disorders for which SGAs are most frequently prescribed, bipolar disorder and schizophrenia, although we acknowledge that SGAs are often used (in many circumstances off-label) in other disorders such as, for example, treatment-resistant depression, anxiety disorders, obsessive-compulsive disorders, and posttraumatic stress disorders.

For both bipolar disorder and schizophrenia, abrupt discontinuation of treatment seems to be critical for relapses during pregnancy. Data show that at least 50% of women with bipolar disorder who have interrupted therapy become symptomatic during pregnancy,[15,17] and, in schizophrenia, a 13-fold increased relapse risk occurs within 3 months following antipsychotic discontinuation.[22] These findings suggest that untreated bipolar disorder and schizophrenia expose mothers to a very high risk of relapse during pregnancy and in the immediate postpartum; mothers with bipolar disorder and schizophrenia should then be treated during pregnancy, choosing the medication with less side effects and paying particular attention to the proper dosage necessary for clinical stability. In much of the general clinical practice, it is thought that psychotropic doses should be decreased in pregnancy, with the idea of protecting the fetus from exposure to potential harm. However, this common clinical practice does not take into account the physiological changes occurring during pregnancy and the changes in metabolism that reduce the concentration and sometimes efficacy of the drug. The dynamic physiological changes that occur in the maternal-placental-fetal unit during pregnancy influence the pharmacokinetic processes of drug absorption, distribution, and elimination (eg, increased glomerular filtration rate with enhanced renal drug elimination, increase in total body water—approximately 8 L—which alters drug distribution and results in decreased peak serum concentrations, pregnancy-related hypoalbuminemia leading to decreased protein binding and then increased free-drug concentration, etc). For these reasons, more often drug doses must be increased across pregnancy to maintain efficacy and reduced in the postpartum to prevent toxicity; one drug that has been extensively studied and is known for this is lamotrigine.[78] Pregnancy also influences drug metabolism in a metabolic enzyme–specific manner: elimination rates of drugs metabolized by some cytochrome P450 enzymes (eg, CYP2A6, CYP2C9, CYP2D6, and CYP3A4) are increased, leading to decreased plasma concentrations. Antidepressants, for example, are metabolized at a higher rate in pregnancy; antipsychotics may be subject to the same increase in metabolism because they are also metabolized by the P450 system, although further data are required for antipsychotics. To maintain the same plasma concentration during pregnancy, then, it may be necessary to increase the dose of an antipsychotic, as maintaining the same dose or even decreasing it could lead to a relapse, exposing the mother and the fetus to the risks of untreated illness.

Regarding obstetric complications, both bipolar disorder and schizophrenia have been linked to a slightly increased

risk of preterm birth, small for gestational age, and low birth-weight infants.[16,27,28,30] Unfortunately, in most of the studies analyzing obstetric complications in bipolar disorder and schizophrenia, data on drug exposure during pregnancy are not given, limiting our capacity to balance the treatment-related versus the illness-related risk. One study,[30] on the contrary, suggests that the risk is reduced in treated mothers as compared to untreated ones, suggesting that risks of obstetric complications are more illness related than treatment related.

Considering the potential explanatory factors for the increased occurrence of obstetric complications among women with bipolar disorder, several biological and psychosocial risk factors for adverse perinatal outcomes, such as underlying genetic susceptibility, comorbid substance use, and increased maternal body weight, may be shared among women with mood disorders in general. It remains to be elucidated whether risk for adverse pregnancy and neonatal outcomes among women with bipolar disorder is specific to bipolar disorder or characteristic of severe mood disorders in general.

As with bipolar disorder, a variety of biological, psychological, social, and behavioral elements in schizophrenia have also been taken into account. Older age, excessive smoking, use of illicit drugs and alcohol, and less antenatal care in women with schizophrenia appear to contribute to the higher risk of obstetric complications.[16,31,32,36,79–82] The situation may be aggravated by low socioeconomic status and low social support.[38,82] Other studies[35–37] emphasize the biological components of the obstetric complications in mothers affected by schizophrenia, stressing that the enhanced risk remained in the schizophrenic population even after adjusting for the above confounders.

Although some guidelines[83,84] concerning the use of SGAs during pregnancy have been developed to avoid obstetric complications, these articles have been outdated by further evidence and, to date, no definitive indications concerning the use of SGAs during pregnancy exist.

Some recent initiatives aimed at developing specific registries in the United States,[6] Australia,[72] and low- and middle-income countries[85,86] give, on one hand, new hopes for the systematic study of this issue; on the other, such initiatives highlight the urgent need to acquire more robust data to draw definitive conclusions on this relevant area of clinical psychiatry. Moreover, bipolar disorder in pregnancy, whether in pharmacologic treatment or not, seems not to be associated with increased risks of stillbirth or neonatal or infant deaths.[38–40] These conclusions, however, are preliminary, as few studies are available and most of them consider mothers with affective psychoses and disorders as a unique group. It remains to be understood whether bipolar disorder per se or depressive episodes within a longitudinal diagnosis of bipolar disorder[9] (this condition is dominated by depressive episodes during pregnancy) account for the observed increased risk of adverse neonatal outcomes. Perinatal episodes, in fact, are very important, with suicide a leading cause of maternal death. For this reason, obstetric factors, including pregnancy and delivery complications, cesarean section, sex of baby, and gestation period, have been investigated in relation to risk of postpartum psychosis, but the only consistent finding is a strong association with primiparity.[7,87–89] Untreated bipolar disorder in the peripartum is associated with higher risk of relapse, particularly in the postpartum, and this might impact children's mental health. Children of mothers admitted to mother and baby units with severe postnatal disorders are at increased risk of a psychiatric (mainly emotional) disorder in adulthood compared with siblings who are not exposed to a postnatal episode.[90] No data are available, however, considering offspring of mothers affected by bipolar disorder who have an affective episode during pregnancy.

Conversely, children born to mothers with schizophrenia are at significantly increased risk of intellectual disability.[43] Interestingly, another recent study[44] shows a significant association between both maternal and paternal diagnosis of schizophrenic spectrum disorder and the presence of an autism spectrum disorder in offspring (OR = 2.5 [95% CI, 1.9–3.2] and OR = 2.2 [95% CI, 1.7–3.0], respectively). Maternal morbidity (schizophrenia but not bipolar disorder) may be then associated with the worst neonatal outcomes. This conclusion, however, is drawn from studies that did not provide information on drug exposure during pregnancy.

To ascertain the teratogenicity of a given medication, not only the incidence of birth defects after exposure should be increased but also a "pattern of defect" (little or no variations in the defect) must be recognized.[91] The most critical period is the first trimester of pregnancy, when women may not be aware yet of their state.[92–94] Infants of mothers with untreated bipolar disorder are at increased risk of congenital malformations such as microcephaly when compared with infants of women without bipolar disorder. Interestingly, there is no increased risk of congenital malformations in offspring of women with treated bipolar disorder compared with those of women without bipolar disorder.[30] Strength of evidence on this topic is limited by methodological shortcomings (the retrospective, observational designs and the difficulty in controlling for confounding variables such as psychiatric diagnosis, maternal age, use of alcohol and other substances or medication, smoking, gravidity history, previous pregnancy loss, genetic history, and dose and timing of drug exposure); nonetheless, schizophrenia and related altered behaviors may be considered risk factors for congenital malformations.[51,60,94,95] To date, although the evidence either against or for the potential risk of teratogenesis with SGA use is limited,[4,96] SGAs, as a class and singularly, are not strongly associated with increased recurring defects in fetuses. This conclusion comes from studies that examined antipsychotic exposure during pregnancy irrespective of the psychiatric diagnosis for which mothers were prescribed SGAs (not only bipolar disorder or schizophrenia but also major depression or anxiety disorders); thus, it is not limited to mothers with bipolar disorder or schizophrenia exposed during the first trimester of pregnancy to antipsychotics.

Evidence regarding the use of SGAs during pregnancy and their potential effects on both short-term and long-term child neurodevelopment remains overall reassuring. No pattern of delay was observed at the 6 and 12 months of age assessments among infants exposed in utero to SGAs when compared with nonexposed infants[74] in terms of cognitive, motor, and social/emotional functioning; language; and adaptive behavior.

Before achieving any definitive conclusions, however, some critical issues deserve attention: first, the lack of clinical trials, which is ethically unacceptable, and second, the availability of observational studies or manufacturer reports, mainly with retrospective design. Cases retrospectively identified lack a denominator for the number of exposures, and this makes comparison of prevalence rates between exposed and unexposed difficult. Recall bias might also occur: women who had children with birth defects or neurodevelopmental difficulties, for example, are more likely to report having taken a drug during pregnancy than women who have had healthy babies. On the other side, adherence to prescribed antipsychotics is especially challenging during pregnancy. For example, a patient who had an antipsychotic prescribed but did not ingest the pills would be misclassified as being exposed.[97] Third, given the possibility that the effect on children is the result of other in utero exposures (eg, smoking, alcohol, illicit drugs) that may influence neurodevelopment,[53] further studies should adequately control for possible confounders. Furthermore, as we have described previously, parental mental illness,[98] especially schizophrenia,[99,100] may play a relevant role in modulating neurodevelopment[44] and should be systematically taken into account. Fourth, the use of birth registries and administrative data might result in imprecise information for recording or misclassifying stressors (eg, domestic violence, poor vitamin intake, smoking) that are especially associated with mental illness and delays in child development. Last, length of follow-up is crucial. Future studies with longer follow-up are desirable to survey child growth and get a widespread range of rigorous measures with good predictive validity. Rigorous pharmacoepidemiologic studies are also needed[65] together with the establishment of an accurate national pregnancy registry[6,101,102] for drugs to collect widespread and accurate data on offspring's safety related to in utero exposition.

CONCLUSIONS

On the basis of our systematized review, we may tentatively draw some preliminary conclusions:

1. Untreated bipolar disorder and schizophrenia expose mothers to a very high risk of relapses during pregnancy and in the immediate postpartum period.
2. Maternal morbidity (both bipolar disorder and schizophrenia) is associated with obstetric complications for both mothers (schizophrenia) and the newborn (bipolar disorder and schizophrenia); data on drug exposure during pregnancy, however, are not given in the majority of studies. One study,[30] on the contrary, suggests that the risk is reduced in treated mothers as compared to untreated ones.
3. Maternal morbidity (schizophrenia but not bipolar disorder) may be associated with the worst neonatal outcomes. This conclusion, however, is drawn from studies that did not provide information on drug exposure during pregnancy.
4. SGAs, as a class and singularly, are not associated with increased recurring defects in fetuses.[49] Evidence regarding the potential effects of SGAs on both short-term and long-term child neurodevelopment remains overall reassuring.

The available data appear, then, to delineate a significant illness-related risk of worst maternal and newborn outcomes, especially with regard to schizophrenia, although a proper evaluation of the specific contribution of the exposure to medications during pregnancy is still lacking. Similarly, a rigorous and methodologically founded assessment of the treatment-related risks for teratogenesis, obstetric complications, and long-term child neurodevelopment, independent from the illness, is needed.

To date, it appears fair enough to affirm that maintaining future mothers with bipolar disorder or schizophrenia on their drug regimen (the safest, at the minimum dosage required to maintain clinical stability, which may imply increasing the dosage as compared to that before pregnancy due to physiological changes occurring during pregnancy) represents the most reasonable and less harmful choice, taking into strong account the parents' will and after they provide a thorough informed consent subsequent to an exhaustive description of known risks and benefits.

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Drug names: aripiprazole (Abilify and others), asenapine (Saphris), bupropion (Wellbutrin and others), carbamazepine (Tegretol, Epitol, and others), clozapine (Clozaril, FazaClo, and others), lamotrigine (Lamictal and others), lurasidone (Latuda), olanzapine (Zyprexa and others), paliperidone (Invega and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

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