CNS Spectrums (2017), **22**, 273–281.
doi:10.1017/S1092852916000699

REVIEW ARTICLE

Neurodevelopmental outcomes in infants exposed in utero to antipsychotics: a systematic review of published data

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The proportion of pregnancies exposed to either second-generation antipsychotics (SGAs) or first-generation antipsychotics (FGAs) varies between 0.3%–2% of all pregnancies, but, until now, little is known about the potential neurobehavioral teratogenicity of antipsychotics. Assessing this safety facet is the aim of this article. PubMed, Scopus, and Google Scholar were searched for eligible articles. PubMed (1954 to May 2016) was searched using several medical subject headings, variously combined. PubMed search results were also limited using the search filter for human studies published in English. Scopus and Google Scholar searches were filtered for article title (antipsychotics/neuroleptics, pregnancy). After excluding duplicates, 9,250 articles were identified and 29 met the following inclusion criteria: only articles that provided original/primary data on neurodevelopmental outcome in human offspring older than 4 months of age, independently of the study design, were selected for review. Indeed, some relevant neurodevelopmental milestones are achieved at this time. Length of study and neurodevelopmental assessment methodology did not influence the study selection. Unfortunately, published data on neurodevelopmental teratogenicity of SGAs mainly derive from case reports and small case-series studies. Even findings emerging from case-control and prospective/retrospective studies are of limited clinical relevance because of their small sample sizes. Limited data are also available on FGAs. Hence, we have to conclude that the long-term neurodevelopmental outcomes for children exposed in utero remain unclear. Low to very low quality evidence of retrieved data makes impossible to confirm or exclude potential long-lasting untoward effects on infant neurocognitive development associate with antenatal exposure to either SGAs or FGAs.

Received 25 May 2016; Accepted 9 September 2016; First published online 21 November 2016

Key words: Antipsychotics, neurodevelopmental teratogenicity, neuroleptics, pregnancy, safety.

Introduction

Until 2005,[1] clinicians and researchers had focused their attention on a single aspect of the reproductive safety of psychotropic medications and, specifically, on the risk of structural teratogenicity. Nevertheless, progress in the field of perinatal psychiatry has suggested that in utero exposure to different classes of psychotropics may have long-term effects on infant development.[2]

However, currently, little is known about the potential neurobehavioral teratogenicity of antipsychotics. Despite the lack of specific safety data, during the last decades the use of second-generation antipsychotics (SGAs) has progressively increased in pregnant women diagnosed with different psychiatric disorders, including bipolar disorder, schizophrenia, unipolar depressive disorder, and other psychiatric disorders. Indeed, in the US there has been a 2.5-fold increase in the use of SGAs in pregnant women.[3] In contrast, in this specific population of patients, the use of first-generation antipsychotics (FGAs) is progressively decreasing.[3] However, nearly 0.5% of pregnancies are still exposed to FGAs.[4] It is interesting to

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Dr. Gentile and Dr. Fusco wish to acknowledge Kay McCauley-Elsom and Christina Wichman for having kindly provided additional relevant information about their articles.

TABLE 1. Main neurodevelopmental milestones at 4 months of age[8]

Social/emotional skills	Language/communication skills	Cognitive skills	Movement/physical development skills
Smiles spontaneously, especially at people	Begins to babble	Recognizes familiar people and things at a distance	Holds head steady, unsupported
Likes to play with people and might cry when playing stops	Babbles with expression and copies sounds he hears	Responds to affection	Pushes down on legs when feet are on a hard surface
Copies some movements and facial expressions, like smiling or frowning	Cries in different ways to show hunger, pain, or being tired	Reaches for toy with one hand	May be able to roll over from tummy to back
		Lets you know if she is happy or sad	Can hold a toy and shake it and swing at dangling toys
		Uses hands and eyes together, such as seeing a toy and reaching for it	Brings hands to mouth
		Follows moving things with eyes from side to side	When lying on stomach, pushes up to elbows
		Watches faces closely	

note that the proportion of pregnancies exposed to SGAs does not vary between countries, being about 2% of all pregnancies both in the US[3–5] and in some Europen countries, such as Italy.[6]

However, the neurobehavioral teratogenicity of both FGAs and SGAs is far from being established.[7] Thus, assessing systematically all published information focused on investigating the neurobehavioral effects of antipsychotics in infants in utero exposed to such medications is the aim of this review.

Methods

Sources

PubMed, Scopus, and Google Scholar were searched for eligible articles.

Search strategy

PubMed (1954 to April 2016) was searched using medical subject headings (MeSH): ("antipsychotic agents" [Pharmacological Action] OR "antipsychotic agents" [MeSH Terms] OR "neuroleptics" [All Fields]) ("antipsychotic" [All Fields] AND "agents" [All Fields]) OR "antipsychotic agents" [All Fields] OR "antipsychotics" [All Fields]) AND ("pregnancy" [MeSH Terms] OR "pregnancy" [All Fields]). The PubMed search results were also limited using the search filter for human studies published in English. Scopus and Google Scholar searches were filtered for article title (antipsychotics/neuroleptics, pregnancy). After excluding duplicates, 9,250 articles were identified.

Selection

Only articles that provided original/primary data on neurodevelopmental outcome in human offspring older than 4 months of age, independent of the study design, were selected for being reviewed. This age was selected as some relevant neurodevelopmental milestones are achieved at this time[8] (see Table 1).

For those articles that did not specify to which antipsychotic the infants were exposed, we contacted the authors to obtain this information. Length of study and neurodevelopmental assessment methodology did not influence the of study selection process.

Twenty-nine articles met the inclusion criteria. Both authors searched, selected, and rated the studies independently. The retrieved articles were rated in accordance with the GRADE literature rating system (GRADE working group, update 2016).[9] Figure 1 shows a flow-chart detailing the study selection process.

Results

Case reports and case-series studies (see Table 2)

Amisulpride

Only one case is available on amisulpride.[10] A 35-year-old woman diagnosed with schizophrenia had a history of 2 hospitalizations for acute exacerbation of psychotic symptoms. There were no current psychotic symptoms except residual transient reference thoughts for the last 5 years while she was taking combined therapy with amisulpride (400 mg/day) and aripiprazole (15 mg/day). The patient stopped the medication at the fifth gestational week. However, 1 month later, reference delusion relapsed. Thus, amisulpride, together with FGAs, were re-administered throughout pregnancy. The mother wished to breastfeed her baby, despite the fact that she continued the combined pharmacological treatment postpartum. No signs of neurodevelopmental delay were detected in the baby.

https://doi.org/10.1017/S1092852916000699 Published online by Cambridge University Press

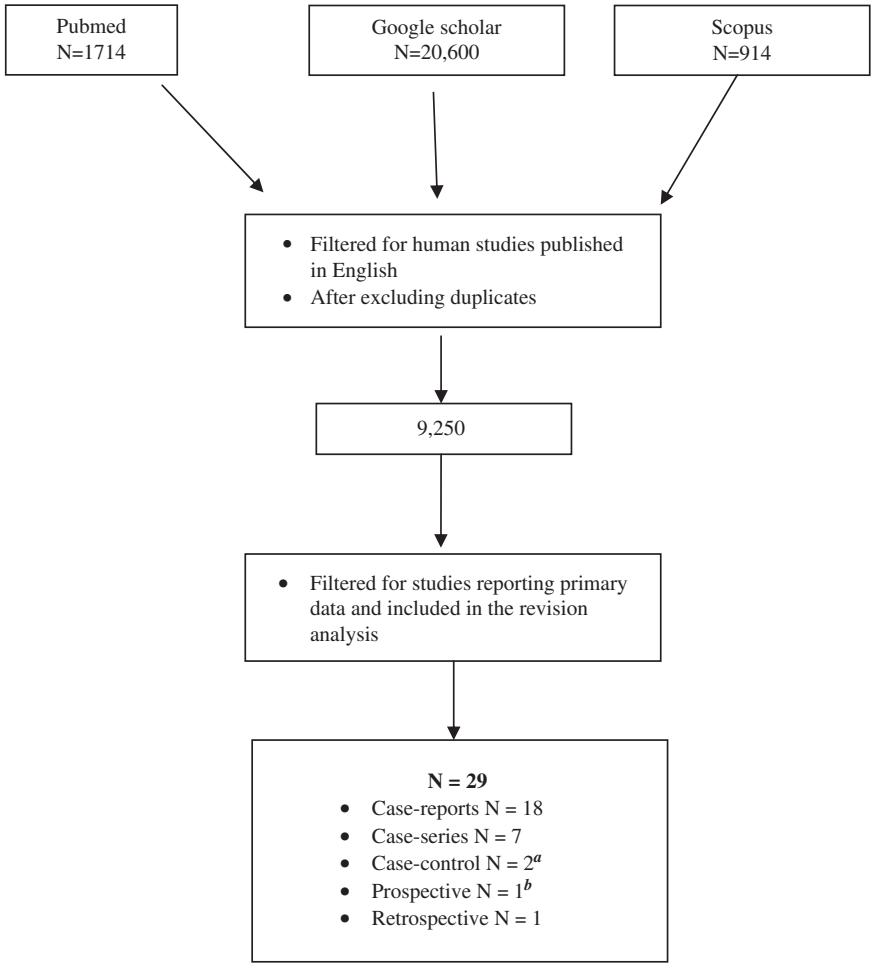

FIGURE 1. Flow chart detailing the study selection process. [a]In one case-controlled, prospective study,[35] analyses designed to compare groups were performed for all enrolled infants (intent-to-treat analyses using the last observation carried forward method for missing data). The difference was considered statistically significant if a two-tailed P value was less than 0.05. [b]In a prospective study,[36] Pearson correlations, independent *t*-tests, 1-way analyses of variance, and χ^2 analyses tested associations between the dependent variables (Infant Neurological International Battery composite and habituation measures) and potential covariates. Analyses of covariance were performed to test study hypotheses. Multiple regression/partial correlation analyses were conducted to examine treatment duration effects within each exposure group, and post-hoc χ^2 analyses and logistic regression were conducted to further clarify group differences with respect to published clinical cutoffs. All results reflect 2-tailed tests.

Aripiprazole

Two cases of neurodevelopmental outcome following aripiprazole exposure during pregnancy are available. The first case involved a woman diagnosed with schizoaffective disorder,[11] and the second one involved a woman suffering from paranoid schizophrenia.[12] In both cases, the babies showed no neurodevelopmental problems.

Clozapine

Conflicting results are available on clozapine. Anecdotal reports describe healthy neurodevelopmental outcomes in infants born to schizophrenic mothers antenatally exposed to clozapine in combination with other psychotropic medications[13]; however, other clinical vignettes report selective neurodevelopmental delay, even in the case of very low dose exposure.[14]

Olanzapine

A relatively large amount of information is available on olanzapine. In one case, the exposed baby showed temporary neurodevelopmental problems.[15] In another case, the authors reported motor retardation in infants born to a mother with bipolar disorder who required polypharmacotherapy during pregnancy to maintain euthymic conditions. Of note, some pregnancy complications occurred, such as preterm birth and gestational diabetes.[16] However, several cases of healthy outcome are available. The first one involved a 41-year-old woman diagnosed with paranoid schizophrenia at the age of 27 years.[17] She was on olanzapine treatment for about 3 years when she became pregnant. The pregnancy proceeded without complications except for significant weight gain (64 to 88 kg at delivery). She continued to

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TABLE 2. Neurodevelopmental outcome following antenatal exposure to antipsychotics: case reports and case-series studies

Reference number/ GRADE rating	Drug, daily dose, timing of exposure during pregnancy, concomitant drug exposure	Neurodevelopmental outcome	Age of assessment and assessment instruments
10 ($N = 1$) Very low	AMI 400 mg (weeks 1–5; week 9–delivery) Haloperidol (5 mg)	Healthy	15 months Pediatrician's report
11 ($N = 1$) Very low	ARI 20 mg (week 8–delivery) No	Healthy	12 months Pediatrician's report
12 ($N = 1$) Very low	ARI 10 mg (weeks 29–31) 15 mg (week 32–2 days before delivery) No	Healthy	6 months N/A
13 ($N = 1$) Very low	CLO 300 mg (before conception–delivery) Lithium: N/A	Healthy	24 months Clinical evaluation
14 ($N = 1$) Very low	CLO 100 mg (before conception–delivery)	Delayed speech acquisition until 48 months	60 months By the end of 5 years, she had gained normal fluent speech.
15 ($N = 1$) Very low	OLA 10 mg (week 18–delivery) No	Temporary motor developmental delay	7 months At 11 months and during further regular examinations, there were no abnormal findings. Pediatrician' report
16 ($N = 1$) Very low	OLA 25 mg (before conception–delivery) Fluoxetine 60 mg Lithium 1250 mg	Motor developmental delay	18 months The baby was not able to walk. Gross motor skills were at the level of a 9.5-month-old baby. Pediatrician's report.
17 ($N = 1$) Very low	OLA 15 mg (before conception–delivery) No	Healthy	6 months N/A
10 ($N = 1$) Very low	OLA 10 mg (week 8–delivery) HAL (5 mg)	Healthy	10 months Pediatrician's report
18 ($N = 1$) Very low	OLA 10–20 mg (before conception–delivery) Promethazine (75 mg) Diazepam (15 mg) Lithium (800 mg)	Healthy	5 months Pediatrician's report
19 ($N = 1$) Very low	OLA 10 mg (before conception–week 20; week 36–delivery) Valproate (500–1000 mg)	Healthy	6 months Parental report
20 ($N = 1$) Very low	OLA 7.5 mg (before conception–delivery)	Healthy	6 months N/A
21 ($N = 4$) Very low	Case 1: OLA 5 mg (before conception–delivery) No Case 2: OLA 5 mg (before conception–delivery) No Case 3: OLA 20 mg (before conception–delivery) No Case 4: ORAL RIS 2–4 mg (before conception–delivery) Fluoxetine 20 mg	Healthy Motor developmental delay Healthy Healthy	12 months Clinical observation
22 ($N = 2$) Very low	1st child: ORAL RIS 3 mg (before conception–delivery) 2nd child: ORAL RIS 2 mg (before conception–delivery)	Healthy Healthy	36 months N/A 18 months N/A
23 ($N = 1$) Very low	RIS-LAI 37.5 mg/2 weeks (before conception–delivery)	Healthy	8 months N/A
24 ($N = 1$) Very low	RIS-LAI 37.5 mg/2 weeks (before conception–delivery) QUE 50 mg	Healthy	12 months N/A

https://doi.org/10.1017/S1092852916000699 Published online by Cambridge University Press

TABLE 2. Continued

Reference number/ GRADE rating	Drug, daily dose, timing of exposure during pregnancy, concomitant drug exposure	Neurodevelopmental outcome	Age of assessment and assessment instruments
25	PP 100 mg monthly	Healthy	4 months
(*N* = 1)	(before conception–delivery)		N/A
Very low	HAL (5 mg)		
26	QUE 300 mg (before conception–breastfeeding)	Healthy	12 months
(*N* = 1)	Venlafaxine extended release (75 mg)		Clinical evaluation
Very low	Trazodone extended release (150 mg)		
27	Case 1: QUE 50 mg (week 18–breastfeeding)	Healthy	Case 1: 9 months
(*N* = 2)	Paroxetine 40 mg	Healthy	Case 2: 12 months
Very low	Case 2: QUE 75 mg (week 18–breastfeeding)		*Bayley Scales of Infant Development*, 2nd Edition
	Venlafaxine (75 mg)		
	Trazodone (75 mg)		
28	QUE 200 mg (before conception–breastfeeding)	Healthy	4.5 months
(*N* = 1)			Clinical evaluation
Very low			
29	QUE 400 mg (before conception to week 32; 300 mg	Healthy	4 months
(*N* = 1)	(week 32–delivery)		Clinical evaluation
Very low	Trazodone (200 mg: before parturition–week 30)		
	Flurazepam (30 mg: before parturition–week 30)		
	Mirtazapine (30 mg: before conception–delivery)		
	Lorazepam (7.5 mg: before conception–week 30; 1 mg until delivery)		
30	1st child: QUE 225 mg (before conception–delivery)	Healthy	1st child: 24 months
(*N* = 2)	2nd child: QUE 250 mg (before conception–delivery)	Healthy	2nd child: 9 months
Very low			Clinical evaluation
31	ZIP 40 mg (before conception–breastfeeding)	Healthy	12 months
(*N* = 1)	Citalopram (60 mg)		Pediatrician's report
Very low			
32	1st child: HAL 7.5–10 mg (before conception–delivery)	Healthy	84 months the oldest, 16 the youngest
(*N* = 3)	2nd child: HAL 7.5–10 mg (before conception–delivery	Healthy	Clinical evaluation
Very low	3rd child: HAL 15 mg (before conception–delivery	Healthy	
	Trihexyphenidyl (4 mg: before conception–delivery) in all 3 children		
	Oral RIS (2 mg: weeks 14–18 in the third child)		
33	Both children: ZPX DEC 400–200 mg once monthly	Healthy	6 and 42 months
(*N* = 2)	(before conception–delivery)		Clinical evaluation
Very low			

AMI: amisulpride, ARI: aripiprazole, CLO: clozapine, OLA: olanzapine, RIS: risperidone, LAI: long-acting injections, PP: paliperidone palmitate, QUE: quetiapine, ZIP: ziprasidone, HAL: haloperidol, ZPX DEC: zuclopenthixol decanoate, N/A: data not available.

take the drug during breastfeeding, but the infant showed no signs of neurodevelopmental delay. A second case involved a 35-year-old patient with bipolar disorder.[9] The patient ceased any psychotropic medication when she became aware of her pregnancy. However, at week 8 she was hospitalized because of the occurrence of a manic episode; she was therefore successfully treated with olanzapine and FGAs. The mother wished to breastfeed her baby, despite the fact that she continued pharmacological treatment postpartum. No signs of neurodevelopmental delay were detected in the baby. Other cases with healthy developmental outcomes were described in a baby born to a woman diagnosed with bipolar I disorder, despite the fact that the neonate had suffered from severe hypoglycemia after birth;[18] in a baby antenatally exposed to olanzapine and "classic" mood stabilizing agents[19]; and in a baby born to a mother with schizoaffective disorder exposed in utero to olanzapine monotherapy.[20] In a case-series study of 10 babies born to women with a history of serious mental illness and who were exposed to antipsychotics,[21] data on neuro behavioral outcomes were available for 4 infants, 3 of them exposed to olanzapine. One infant exposed to olanzapine showed motor delay (McCauley-Elsom, personal communication).

Oral risperidone, risperidone LAI, and paliperidone palmitate

A few of reports are available on oral risperidone, risperidone long-acting injection (LAI), and paliperidone palmitate. One report[22] describes a case of a 23-year-old woman who presented a 2-year history of undifferentiated

https://doi.org/10.1017/S1092852916000699 Published online by Cambridge University Press

schizophrenia with predominant symptoms of incongruent affect, bizarre delusions, and auditory hallucinations wherein oral risperidone was used successfully in 2 consecutive pregnancies. Two reports are available on neurodevelopmental outcome following in utero exposure to risperidone LAI. The first[23] describes a 35-year-old woman with schizophrenia treated with the drug before and throughout her pregnancy. She gave birth to a female infant weighing 2230 g at 36 weeks and 6 days of pregnancy, following premature rupture of the membranes. The baby was healthy several months postnatally. The second case[24] involved a 29-year-old woman with schizophrenia and comorbid obesity. Her son was born at week 36 of gestation by elective caesarean section. He was admitted to the neonatal intensive care unit due to abstinence syndrome and neonatal hypoglycemia. Despite such problems, his neurodevelopment was healthy. One case is also available following antenatal exposure to paliperidone palmitate.[25] A 37-year-old schizophrenic patient developed persecutory delusions and disorganized behavior at week 29 of pregnancy. She had been using the drug for a year. The last dose was given at the 28th week of pregnancy. The patient had been in remission for 1 year but developed psychotic symptoms for the last 2 weeks despite regular injections. Therefore, a FGA was added to the existing treatment. No neurodevelopmental problems were detected in her baby.

Quetiapine

A 17-year-old pregnant adolescent suffered from pseudotumor cerebri. The neurological illness was treated with acetazolamide and lumbar puncture. She also had a bipolar II disorder (which had been successfully treated with quetiapine and antidepressants) and a history of alcohol abuse. When the patient became aware of her pregnant status, she decided to carry out the pregnancy despite the risk deriving from her neurological condition and the potential iatrogenic risks for the fetus. No signs of developmental impairment were detected in her baby.[26] In the 2 cases described by Misri *et al*,[27] the drug was used as add-on treatment in patients with treatment-resistant major depression. The infant neurodevelopment, assessed by specific instruments such as the Bayley Scales of Infant Development, 2nd Edition, was normal. Other cases of healthy neurodevelopmental outcomes are also available,[28,29] and even in successive pregnancies.[30]

Ziprasidone

One case is available on ziprasidone. A 26-year-old African American woman with psychotic depression and post-traumatic stress disorder started, 11 months prior to parturition, treatment with ziprasidone and selective serotonin re-uptake inhibitors (SSRIs) to treat mood symptoms, suicidal thoughts, and olfactory hallucinations. The patient responded well. During the course of therapy, she became pregnant. The risks and benefits of continuing ziprasidone and SSRI were discussed with her. As a result of significant relapse risk, she chose to continue both medications. At 34 and 35 weeks of gestation, the woman was hospitalized with exacerbation of depressive and psychotic symptoms as a result of medication nonadherence. During her hospitalization, SSRIs and ziprasidone were successfully reinstated. Upon discharge, breastfeeding was initiated after birth and maintained postnatally through 6 months, when the baby had reached normal neurodevelopmental milestones.[31]

Haloperidol

Data on haloperidol are limited. Uneventful use of haloperidol has been described in 3 consecutive pregnancies.[32]

Zuclopenthixol decanoate

The only available cases of antenatal exposure to zuclopenthixol decanoate, a long-acting FGA, involve 2 successive pregnancies in the same woman. No problems were detected in either infant.[33]

Case-control, prospective, and retrospective studies (see Table 3)

The long-term behavioral outcome of school-age children exposed in utero to phenothiazines after week 20 of pregnancy was investigated in a single case-control study.[34] These children showed no behavioral anomalies. However, no specific instruments of evaluation nor qualified intervention by specialized staff were provided.

The study by Peng *et al*[35] aimed to investigate the developmental effects of SGAs in infants born to mothers taking such drugs throughout pregnancy. The developmental progress of 7 infants who experienced fetal exposure to SGAs was compared to that of matched control infants who had no fetal exposure to any antipsychotics. Assessments included cognitive, language, motor, social-emotional, and adaptive behavior composite scores measured by a widely used instrument investigating infant developmental delays. Each child's progress was charted, and parents were taught about their child's development by specific scales. There were no statistically significant differences between the 2 groups in cognitive, language, motor, social-emotional, or adaptive development. A prospective controlled study,[36] conducted December 1999–June 2008 at the Infant Development Laboratory of the Emory Psychological Center (Atlanta, GA, USA), examined a relatively large number of maternal–infant dyads at 6 months postpartum. Women were subdivided into 3 groups: the first exposed

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TABLE 3. Neurodevelopmental outcome following antenatal exposure to antipsychotics: case-control, prospective, and retrospective studies

Reference number/Study design/GRADE rating	Drug, daily dose, timing of exposure during pregnancy, concomitant drug exposure	Neurodevelopmental outcome	Age of assessment and assessment instruments
34 Case-control (*N* = 63) Very low	PHE as a group Dose: N/A (week 20–delivery) N/A	No differences between the exposed and the control groups regarding school behavior	9–10 years Over-simplified, semistructured formulary administered by teachers
35 Case-control (*N* = 76) Low	CLO (n = 33) mean dose 178 mg RIS (n = 16) mean dose 2 mg SUL (n = 13) mean dose 461 mg OLA (n = 8) mean dose 8 mg QUE (n = 6) mean dose 550 mg Throughout pregnancy No	There was no significant difference between the 2 groups in the mean composite scores of cognitive, language, motor, social-emotional, and adaptive behavior scales.	12 months. *Bayley Scales of Infant and Toddler Development*, 3rd edition
36 Prospective (*N* = 22) Low	HAL (n = 10) ARI (n = 1) OLA (n = 5) QUE (n = 5) ZIP (n = 1) The number of gestational weeks exposed ranged from 2–40 (median = 32 weeks) Various psychotropics	Infants exposed prenatally to antipsychotics demonstrated significantly lower scores on a standardized neuromotor screening measure compared with both antidepressant-exposed infants and infants with no psychotropic exposure. Only 19% of infants prenatally exposed to an antipsychotic demonstrated normal neuromotor performance.	6 months The Infant Neurological International Battery
37 Retrospective (*N* = 16) Very low	ARI (n = 2) 2.5–15 mg QUE (n = 10) 25–400 mg RIS (n = 3) 1–6 mg ZIP + RIS (n = 1) 60 mg and 5 mg 14 cases: N/A No	Healthy in 14 cases. 2 children exposed to RIS (throughout pregnancy) and RIS (during the 2nd trimester) and ZIP during the 3 rd trimester) showed behavioral concerns (no further details available).	36 months Clinical observation

PHE: phenothiazines, SUL: sulpiride, CLO: clozapine, OLA: olanzapine, RIS: risperidone, QUE: quetiapine, ZIP: ziprasidone, HAL: haloperidol, ARI: aripiprazole, ZIP: ziprasidone.

to antipsychotics, the second to antidepressants, and the third not exposed to any psychotropic agents. Among 6-month-old infants, a history of intrauterine antipsychotic exposure, compared with antidepressant or no psychotropic exposure, was associated with significantly lower scores on a standard test of neuromotor performance.

Wichman[37] conducted a retrospective chart review of all pregnant women presenting at her medical center from 1993 to 2007. During that time period, there were 30,092 total deliveries.[37] Of the total number of deliveries, 15 mothers were prescribed atypical antipsychotics at some point during their pregnancy. Two infants, one exposed to risperidone and one exposed to risperidone and ziprasidone, had behavioral problems (Wichman, personal communication).

Discussion

Despite the increasing use of SGAs in pregnancy, data on their neurodevelopmental teratogenicity mainly derive from case reports and small case-series studies. Even findings emerging from case-control and prospective or retrospective studies are of limited clinical relevance due to the small sample sizes of such studies. Likewise, limited data are available on FGAs, despite the fact that such medications were introduced onto the market in the early 1950s and have been in use since then.

However, this situation is not surprising. Difficulties of standardizing amount, timing, pattern of use, puzzling effect of the risk factors, and uncontrolled confounding variables complicate the interpretation of the results of neurodevelopmental outcome studies.[38] Other various factors unite to complicate the problems in conducting neurobehavioral teratology studies. First, useful information on the late teratogenic effects is unlikely to be forthcoming until children are closer to school age. Second, this kind of long-term follow-up is difficult to carry out because many families move or miss follow-up clinical evaluations.[39]

Nevertheless, case reports remain a valued part of the medical literature, despite dramatic changes in the way we receive medical information.[40] Over the past century, case reports have evolved from the arcane purpose of reporting rare or unusual conditions to the more pragmatic role of helping clinicians accurately diagnose and appropriately treat less common clinical conditions.[41] As reported elegantly by Hurd,[41] "Reading case reports of less common clinical situations serves a purpose similar to pilots' flight simulators. If such a situation occurs in real life, the pilot is more likely to respond effectively, even if it is the first time he or she

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has experienced it. Good case reports can prepare clinicians for the unexpected (p. 410)." However, it is important to stress that there was no common or standardized measurement of neurodevelopmental outcome. Each case was actually assessed differently.

Moreover, 2 case-control studies and one prospective study failed to demonstrate any association between antenatal antipsychotic exposure and long-term impacts on infant and child development. However, the study by Johnson *et al*[36] concluded that infants exposed prenatally to antipsychotics demonstrated significantly lower scores on a standardized neuromotor screening measure. However, the small sample, the inclusion of infants exposed to either SGAs or FGAs, the lack of analysis of the effects of single medications, and the concomitant exposure to other psychotropics impair the clinical relevance of such results.

Given this background, we have to conclude that the long-term neurodevelopmental outcomes for children exposed in utero to antipsychotics remain unclear. Indeed, low to very low quality evidence of retrieved data makes it impossible to confirm or exclude whether antenatal exposure to either SGAs or FGAs is associate with potential long-lasting untoward effects on infant neurocognitive development.

However, when considering the risk of these medications in pregnancy, the risk of untreated maternal illness on both maternal and child health outcomes is relevant.[42] Indeed, when the effects of intellectual disability and other neuropsychiatric outcomes was examined on children of mothers with severe psychiatric disorders, including schizophrenia and bipolar disorder, children were found to be at significantly increased risk of intellectual disability.[43] The study also investigated the distribution of rare syndromes (including Hurler, Klinefelter, Moebius, Noonan, Prader–Willi, Rett, Rubinstein-Taybi, VATER association, and Turner syndromes). Such syndromes showed unusually high rates of prevalence in the case children.[43]

Independent of any safety considerations, it should be stressed that most pregnant women with severe psychiatric disorders require admission to psychiatric emergency services for pharmacological management of psychotic breakdown episodes. In such conditions, in order to obtain a prompt recovery from the psychotic crisis, antipsychotics are the more frequently administered drugs[44]; the safety profiles of the medications regarding the mother–fetus dyad is likely to be neglected.[7]

Since the question of whether in utero exposure to antipsychotics negatively affects brain development remains unresolved, future research needs to focus on prospective, longitudinal studies with adequate measures of key confounding variables, including maternal mental illness, other exposures (such as smoking, alcohol, and illicit drug use), and adequate length of follow-up where accurate child developmental measures are obtained.

Disclosures

The authors do not have anything to disclose.

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