Schizophrenia Bulletin vol. 36 no. 3 pp. 518–544, 2010
doi:10.1093/schbul/sbn107
Advance Access publication on September 11, 2008

Antipsychotic Therapy During Early and Late Pregnancy. A Systematic Review

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Objective: **Both first- (FGAs) and second-generation antipsychotics (SGAs) are routinely used in treating severe and persistent psychiatric disorders. However, until now no articles have analyzed systematically the safety of both classes of psychotropics during pregnancy.** ***Data sources and search strategy:*** **Medical literature information published in any language since 1950 was identified using MEDLINE/PubMed, TOXNET, EMBASE, and The Cochrane Library. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from companies developing drugs. Search terms were pregnancy, psychotropic drugs, (a)typical-first-second-generation antipsychotics, and neuroleptics. A separate search was also conducted to complete the safety profile of each reviewed medication. Searches were last updated on July 2008.** ***Data selection:*** **All articles reporting primary data on the outcome of pregnancies exposed to antipsychotics were acquired, without methodological limitations.** ***Conclusions:*** **Reviewed information was too limited to draw definite conclusions on structural teratogenicity of FGAs and SGAs. Both classes of drugs seem to be associated with an increased risk of neonatal complications. However, most SGAs appear to increase risk of gestational metabolic complications and babies large for gestational age and with mean birth weight significantly heavier as compared with those exposed to FGAs. These risks have been reported rarely with FGAs. Hence, the choice of the less harmful option in pregnancy should be limited to FGAs in drug-naive patients. When pregnancy occurs during antipsychotic treatment, the choice to continue the previous therapy should be preferred.**

Key words: antipsychotics/gestational metabolic complications/neuroleptics/neonatal complications/pregnancy/safety

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Introduction

The fertility rate among women suffering from schizophrenic and other severe and persistent psychiatric disorders (SPPDs) has increased since deinstitutionalization.[1,2] This may be as a direct result of availability of sexual partners or concurrent changing attitudes toward conception among those with serious mental illness.[3] The growing diffusion of second-generation antipsychotics (SGAs), except for risperidone, less likely than first-generation antipsychotics (FGAs) to induce hyperprolactinemia, may have also contributed to improved fecundity in this population of patients.

Unfortunately, however, unplanned and unwanted pregnancies occur more frequently in women with SPPDs than in the general population.[4,5] This may result in delayed or poor antenatal care and unhealthy behavior (such as alcohol and street drug consumption) that may be avoided if the woman is made aware of her status.[6]

Evidence regarding the impact of pregnancy on the course of schizophrenia is inconclusive: however, McNeil et al[7] found that in those women with a history of a psychotic disorder, during pregnancy a worsening rather than an improvement of symptoms was more common.[8] Regarding bipolar disorder, there are some peculiar features of bipolar women that set them apart from other patient populations. Women with bipolar disorder are typically in their teens and early 20s at onset of the illness, placing them at risk of mood episodes during childbearing age.[9] The female reproductive cycle also introduces multifactorial complexities into the treatment of the disease.[10] The course of recurrence is often severe and characterized by a relatively high frequency of rapid-cycling forms, mixed mania, and antidepressant-induced mania.[11,12] The issue of whether bipolar disorder improves during pregnancy is controversial[13–16]; however, pregnancy seems not to be protective for all bipolar women. Indeed, during the gestational period, risk of a relapse of the disorder does not decrease.[17]

Consequently, it is particularly important that the mental health of women with SPPDs is stable if they are about to become parents.

Both FGAs and SGAs are known as indispensable effective medications for SPPDs.[18] Until now, however, only one relatively recent systematic review has investigated the safety of SGAs in pregnancy.[19] Nonetheless, data on the reproductive safety of both SGAs have gradually accumulated adding further information on the use of such agents to these vulnerable mothers.

The lack of updated articles on FGAs may reflect reduced scientific interest in clinical safety of this class of medications. However, they should not be considered as a forgotten therapy.[20] Moreover, almost all previous reviews on this topic show a narrative design.[21–23] Regrettably, conclusions emerging from narrative reviews of scientific literature may be biased by a study selection based on subjective methodologies, and some of the analyzed studies might have reflected the authors' personal point of view, rather than reflecting intrinsic scientific validity.[24] Furthermore, a single (nonrecent) meta-analysis was able only to provide statistical analysis of pregnancy outcomes following first trimester exposure of low-potency neuroleptics.[25]

An updated and systematic review of studies focused on investigating safety of both classes of psychotropic agents in pregnancy—the gold standard to obtain evidence, despite lack of randomized controlled trials in pregnant women[26]—is hence the primary aim of this article. A second (but not secondary) aim is to attempt to identify the less harmful treatment option for the mother-infant pair. Beyond classic reproductive risks, we have also taken into consideration risks associated with possible iatrogenic metabolic complications that may affect the physiological course of pregnancy and that have been associated with the use of both FGAs and (prevalently) SGAs (see box 1).

Box 1.

Potential Risks for the Mother-Child Pair Associated With Early and Late Pregnancy Exposure to Antipsychotic Medications

Fetal major malformations (structural teratogenicity)

Perinatal complications (neonatal toxicity)

Postnatal behavioral sequelae (behavioral toxicity)

Gestational complications

Data Selection

Sources

Medical literature information published in any language since 1950 was identified using MEDLINE/PubMed, TOXNET, EMBASE, and The Cochrane Library. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from companies developing drugs.

Search Strategy

MEDLINE/PubMed, TOXNET, EMBASE, and The Cochrane Library search terms were pregnancy, psychotropic drugs, (a)typical-first-second generation antipsychotics, and neuroleptics. A separate search was also conducted to complete the safety profile of each reviewed medication. Searches were last updated on July 24, 2008. More than 2000 articles ($N = 2189$, excluding duplicates) were found through the investigation of such databases.

Selection

Selected on the basis of their abstract or the full-text article when the abstract was unavailable, all articles reporting primary data on the outcome of pregnancies exposed to antipsychotic medications were acquired and analyzed, without methodological limitations ($N = 110$). Data supplied by manufacturers ($N = 2$) and/or obtained from the manual search performed on the reference lists of electronically identified articles ($N = 5$) provided 7 additional sources of information not identified in the initial search. The author was the only reviewer who performed selection and data extraction.

Data Synthesis

Second-Generation Antipsychotics

Amisulpride. To my knowledge, the drug is not approved in the United States as antipsychotic medication. Thus, its pregnancy category has been established by the Congenital Abnormalities Subcommittee of the Australian Drug Evaluation Committee (ADEC),[27] which uses a rating system different to that used by the US Food and Drug Administration (FDA). In accordance with the ADEC system, amisulpride is rated as B3 (drugs which have been taken by only a limited number of pregnant women and women of childbearing age, with no increase in the frequency of malformation).[28] Despite there being no evidence of teratogenicity in embryo-fetal developmental studies in mice and rabbits following oral doses up to 4 times the maximum recommended human dose, no published information on human pregnancies is available.

Aripiprazole. Aripiprazole is rated FDA Pregnancy Category C: this means that there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). In animal studies, aripiprazole demonstrated teratogenicity and developmental toxicity, as well as decreased fetal weight, at doses of 3–10 times the maximum recommended human dose.[29,30] Until now, only 3 case reports have investigated the safety of aripiprazole in human pregnancies (see table 1).[31–33] In 2 cases, the baby showed neither structural anomalies nor neurodevelopmental

Table 1. SGAs and Pregnancy

Study and Sample Size	Drug, Daily Dose, and Timing of Exposure During Pregnancy	Major Malformations	Pregnancy and Neonatal Outcomes
Mendhekar et al[31] ($N = 1$)	ARI, 15 mg (wk 1–8) and 10 mg (wk 20 to delivery)	No	Neonatal tachycardia; no concomitant drug use
Mervak et al[32] ($N = 1$)	ARI, 20 mg (wk 8 to delivery)	No	Healthy
Mendhekar et al[33] ($N = 1$)	ARI, 10 mg (wk 29–31) and 15 mg (wk 32–2 d before delivery)	No	Healthy; no concomitant drug use
Lieberman and Safferman[35] ($N = 14$)	CLZ, dose and timing of exposure: N/A	No	Healthy
Bazire[36] ($N = 84$)	CLZ, dose and timing of exposure: N/A	$N = 8$, further clinical details: N/A; concomitant drug use: N/A	Spontaneous abortions ($N = 7$); concomitant drug use: N/A
Dev and Krupp[37] ($N = 80$)	CLZ, dose and timing of exposure: N/A	$N = 5$, further clinical details: N/A; in some instances, concomitant drug use	Spontaneous abortions ($N = 8$), perinatal complications ($N = 5$), further clinical details: N/A; in some instances, concomitant drug use
Vavrusova and Konikova[38] ($N = 1$)	CLZ, 100 mg (throughout pregnancy)	Atrial septum defect; no concomitant drug use	N/A
Nguyen and Lalonde[39] ($N = 2$—2 successive pregnancies)	CLZ, 350 mg (throughout pregnancy)	No	Gestational diabetes occurring during the first pregnancy; no concomitant drug use
Dickson and Hogg[40] ($N = 1$)	CLZ, 150–250 mg (throughout pregnancy)	No	Gestational diabetes; no concomitant drug use
Waldman and Safferman[41] ($N = 1$)	CLZ, dose and timing of exposure: N/A	No	Gestational diabetes; no concomitant drug use
Mendhekar et al[42] ($N = 1$)	CLZ, 75 mg (throughout pregnancy)	No	Intrauterine death; no concomitant drug use
Rzewuska[43] ($N = 1$)	CLZ, dose and timing of exposure: N/A	No	Infant's retinopathy; concomitant drug use: N/A
Reis and Källén[44] ($N = 18$)	CLZ, dose: N/A (first trimester)	One case of ectopic anus; concomitant drug use: N/A	No cases of gestational diabetes, neonatal complications: N/A
Karakula et al[45] ($N = 1$)	CLZ, 200 mg (throughout pregnancy)	Hernia of the white linea and left testicle atresia; no concomitant drug use	Gestational diabetes and neonatal hypoxemic encephalopathy

Table 1. Continued

Study and Sample Size	Drug, Daily Dose, and Timing of Exposure During Pregnancy	Major Malformations	Pregnancy and Neonatal Outcomes
Stoner et al[46] (N = 2)	CLZ, 350 mg in the first case and 625 mg in the second case (throughout pregnancy)	No	Seizures and mild gastroesophageal reflux (N = 1); concomitant drug use; postpartum low-grade fever in the newborn (N = 1); no concomitant drug use
Di Michele et al[47] (N = 1)	CLZ, 300 mg (throughout pregnancy)	No	Floppy infant syndrome; concomitant drug use
Yogev et al[48] (N = 1)	CLZ, dose: N/A (throughout pregnancy)	No	Decreased fetal heart rate variability; no concomitant drug use
Barnas et al[50] (N = 1)	CLZ, 100 mg (conception to wk 37) and 50 mg (last 4 wk)	No	No
Gupta and Grover[51] (N = 2)	CLZ, 100–200 mg (throughout pregnancy)	No	Pregnancy-induced hypertension (N = 1); no concomitant drug use
Tényi and Trixler[52] (N = 6)	CLZ, dose and timing of exposure: N/A	No	Healthy
Mendhekar[53] (N = 1)	CLZ, 100 mg (throughout pregnancy)	No	Healthy
Duran et al[54] (N = 3)	CLZ, 200 mg (throughout pregnancy)	No	Healthy
Biswas et al[56] (N = 18)	OLA, dose: N/A (first trimester: N = 11, last semester: N = 3, N/A: N = 4)	Lumbar myelomeningocele in the aborted fetus; concomitant drug use: N/A	Spontaneous abortions (N = 2)
Goldstein et al[57] (N = 34)	OLA, 5–25 mg (most cases during the first trimester or semester)	Dysplastic kidney (N = 1), Down syndrome (N = 1); no concomitant drug use	Gestational diabetes (N = 2), spontaneous abortions (N = 3), perinatal complications (N = 5), SIDS (N = 1); in some instances, concomitant drug use
Manufacturer information (N = 248)	OLA, dose and timing of exposure: N/A	Kidney malformation (N = 5), additional thumb digit (N = 2), bilateral talipes (N = 1), spontaneous abortion of severe deformed fetus (N = 1), pretragus fibrochondroma (N = 1), clubfoot (N = 1), anencephaly (N = 1), absent heart (N = 1), cleft palate (N = 1), ventricular septum defect (N = 1), albino infant (N = 1), esophageal atresia (N = 1), myelomeningocele plus hydrocephalus (N = 1), absent fingers (N = 1); in some instances, concomitant drug use	Spontaneous abortions (N = 24), perinatal complications (N = 49); in some instances, concomitant drug use

Table 1. Continued

Study and Sample Size	Drug, Daily Dose, and Timing of Exposure During Pregnancy	Major Malformations	Pregnancy and Neonatal Outcomes
Reis and Källén[44] (N = 79)	OLA, dose: N/A (first trimester)	Craniosynostosis plus ureteral reflux (N = 1), hand/finger reduction (N = 1), ventricular septum defect plus unspecified upper alimentary tract malformation (N = 1); concomitant drug use: N/A	Gestational diabetes (N = 3); concomitant drug use: N/A; neonatal complications: N/A
Newport et al[67] (N = 14)	OLA, 8.9 ± 8.0 mg—mean, SD—(last 4 mo)	No	Respiratory complications (N = 4), cardiovascular complications (N = 3), hypotonia (N = 1); in some instances, concomitant drug use
Sharma et al[73] (N = 3)	OLA, 5–10 mg (throughout pregnancy: N = 1, a couple of weeks before delivery: N = 2)	No	N/A
McKenna et al[58] (N = 60)	OLA, dose: N/A (first trimester)	Multiple anomalies (N = 1) (midline defects, cleft lip, encephalocele, and aqueductal stenosis); no concomitant drug use	Healthy
Arora and Praharaj[59] (N = 1)	OLA, 10 mg (throughout pregnancy)	Meningocele and complete ankyloblepharon; no concomitant drug use	Healthy
Spryropoulou et al[60] (N = 1)	OLA, 10 mg (first trimester) and 5 mg (last semester)	Hip dysplasia; no concomitant drug use	Healthy
Yeshayahu[61] (N = 1)	OLA, 10 mg (throughout pregnancy)	Atrioventricular canal defect and unilateral clubfoot, no concomitant drug use	N/A
Littrell et al[62] (N = 1)	OLA, 20 mg (wk 1–4) and 15 mg (last 8 mo)	No	Gestational diabetes; no concomitant drug use
Vemuri and Rasgon[63] (N = 1)	OLA, 2.5–5.0 mg (throughout pregnancy)	No	Gestational diabetes; concomitant drug use
Aichhorn et al[64] (N = 1)	OLA, 15 mg (throughout pregnancy)	No	Gestational diabetes; concomitant drug use
Friedman and Rosenthal[65] (N = 1)	OLA, 5 mg (wk 32 to delivery)	No	Baby large for gestational age, Erb's palsy, jaundice; no concomitant drug use
Kirchheiner et al[66] (N = 1)	OLA, 10 mg (wk 18 to delivery)	No	Temporary impairment of motor development; no concomitant drug use
Nagy et al[68] (N = 1)	OLA, dose: N/A (wk 25 to delivery)	No	Healthy
Neumann and Frasch[69] (N = 2)	OLA, dose: N/A (throughout pregnancy)	No	Healthy

Table 1. Continued

Study and Sample Size	Drug, Daily Dose, and Timing of Exposure During Pregnancy	Major Malformations	Pregnancy and Neonatal Outcomes
Mendhekar et al[70] (*N* = 1)	OLA, 10 mg (wk 24–8 d prior delivery)	No	Healthy
Malek-Ahmadi[71] (*N* = 1)	OLA, 15 mg (throughout pregnancy)	No	Healthy
Lim[72] (*N* = 1)	OLA, 25 mg (titrated from wk 8–20 and continued to wk 32)	No	Healthy
Dervaux et al[74] (*N* = 1)	OLA, 7.5 mg (first 2 wk and from wk 16 to delivery)	No	No
Kulkarni et al[75] (*N* = 1)	OLA, 20 mg (wk 1–6)	No	See table 3 (the baby was also exposed to high doses of chlorpromazine during late pregnancy)
Manufacturer's information (*N* = 151) (last update: March 2005)	QUE, dose and timing of exposure: N/A	*N* = 8, further clinical details: N/A; in some instances, concomitant drug use	N/A
Newport et al[67] (*N* = 21)	QUE, 336.9 ± 272.3 mg—mean, SD—(last 7 mo)	No	Cardiovascular complications (*N* = 2), respiratory complications (*N* = 2); in some instances, concomitant drug use
Klier et al[76] (*N*= 1)	QUE, 300 mg (throughout pregnancy)	No	No
Reis and Källén[44] (*N* = 4)	QUE, dose: N/A (first trimester)	No	No cases of gestational diabetes, neonatal complications: N/A
Twaites et al[77] (*N* = 6)	QUE, dose: N/A (first trimester: *N* = 5; last semester: *N* = 1)	No	Spontaneous abortions (*N* = 2); no concomitant drug use
Balke[78] (*N* = 1)	QUE, 25 mg (throughout pregnancy)	No	Healthy
Tényi et al[79] (*N* = 1)	QUE, 300 mg (wk 1–20), 200 mg (wk 20–22), 150 mg (wk 22 to delivery)	No	Healthy
Pace and D'Agostino[80] (*N* = 1)	QUE, 200 mg (last trimester)	No	Healthy
Taylor et al[81] (*N* = 1)	QUE; 300 mg (wk 1–21) and 200 mg (wk 21–35)	No	Healthy
Lee et al[82] (*N* = 1)	QUE, 200 mg (throughout pregnancy)	No	Healthy
Gentile[83] (*N* = 1)	QUE, 400 mg (throughout pregnancy)	No	Healthy
Kruninger et al[84] (*N* = 1)	QUE, 200 mg (throughout pregnancy)	No	Healthy
Cabuk et al[85] (*N* = 1)	QUE, 1200 mg (wk 21 to delivery)	No	Healthy

Table 1. Continued

Study and Sample Size	Drug, Daily Dose, and Timing of Exposure During Pregnancy	Major Malformations	Pregnancy and Neonatal Outcomes
McKenna et al[58] (N = 36)	QUE, dose: N/A (first trimester)	No	N/A
Newport et al[67] (N = 6)	RIS, 3.0 ± 1.8 mg—mean, SD—(last 5 mo)	No	Healthy
McKenna et al[58] (N = 49)	RIS, dose: N/A (first trimester)	No	No differences in the prevalence rate of poor pregnancy outcome and perinatal complications between the exposed group and a control group exposed to nonteratogens
MacKay et al[88] (N = 7)	RIS, dose and timing of exposure: N/A	No	N/A
Ratnayake and Libretto[89] (N = 2)	RIS, 4–6 mg (throughout pregnancy)	No	Healthy
Kato et al[90] (N = 1)	RIS, low dose, unspecified, (wk 1–35) and 6 mg (last month)	No	Healthy
Physician's Desk Reference[93] (N = 1)	RIS, dose and timing of exposure: N/A	Agenesis of corpus callosum; concomitant drug use	N/A
Grover and Avasthi[94] (N = 1)	RIS, 4 mg (throughout pregnancy)	No	Oligohydramnios; no concomitant drug use
McCauley-Elsom and Kulkarni[95] (N = 1)	RIS, 4 mg (throughout pregnancy)	No	Small-for-date baby, hyperbilirubinemia, thermoregulation, and feeding problems; concomitant marijuana and nicotine use
Dabbert and Heinze[92] (N = 1)	RIS, 25 mg every fortnight, long-acting injectable formulation (wk 4–20)	No	Small-for-date baby; no concomitant drug use
Reis and Källén[44] (N = 51)	RIS, dose: N/A (first trimester)	Anal atresia plus lung malformation (N = 1); concomitant drug use: N/A	Gestational diabetes (N = 1); concomitant drug use: N/A; neonatal complications: N/A
Kim et al[91] (N = 1)	RIS; 25 mg every fortnight, long-acting injectable formulation (throughout pregnancy)	No	Healthy

Table 1. Continued

Study and Sample Size	Drug, Daily Dose, and Timing of Exposure During Pregnancy	Major Malformations	Pregnancy and Neonatal Outcomes
Coppola et al[96] (N = 201 —previously unpublished data)	RIS, dose: N/A (various stages of pregnancy)	Cleft lip/palate (N = 2); esophageal atresia, ear pinna hypoplasia, and slight facial dysmorphia (N = 1); Ivemark syndrome (N = 1); Moyamoya disease (N = 1); ventricular cyst in the brain (N = 1); patent foramen ovale (N = 1); hypoplastic left heart (N = 1); dilated cardiomyopathy (N = 1); right auricular achondroplasia (N = 1); mild talipes equinovarus (N = 1); gastroschisis (N = 1); Pierre-Robin syndrome (N = 1); in some instances, concomitant drug use	Spontaneous abortions (N = 42), stillbirth (N = 4), perinatal complications (N = 40) (including withdrawal syndromes, respiratory difficulties, seizures, prematurity and intrauterine growth retardation, birth trauma, and jaundice); in some instances, concomitant drug use

Note: ARI: aripiprazole; CLZ: clozapine; N/A: data not available; OLA: olanzapine; QUE: quetiapine; RIS: risperidone; SIDS: sudden infant death syndrome.

impairment; conversely, transient symptoms attributable to poor neonatal adaptation phenomena were observed.[31] In the third case, the outcome was fully healthy. However, in 2 of these 3 cases, the fetus was exposed to the drug only after week 20 of gestation.[31,33]

Clozapine. Clozapine is rated FDA Pregnancy Category B, despite paucity of data. Reproductive studies performed in rats and rabbits at doses of approximately 2–4 times the human dose revealed no harm to the fetus.[34] In humans, information on the safety of clozapine in human pregnancies (reassumed in table 1) has been available since the early 1990s.[35] Single cases of major malformations, gestational metabolic complications, poor pregnancy outcome, and perinatal adverse reactions associated with exposure to clozapine during various stages of pregnancy have been subsequently reported, though they derive solely from case reports and/or small case series studies.[36–48] However, clozapine overdose during pregnancy may cause fatal poisoning of the newborn.[49] On the other hand, clinical observations suggesting safe use of clozapine in pregnant women are limited.[50–54]

Olanzapine. Olanzapine is rated FDA Pregnancy Category C. Reproductive studies show no evidence of fetal harm in animals.[55] Unfortunately, however, large, prospective studies in humans are presently unavailable. A postmarketing surveillance study on 8858 patients in England identified a small number of olanzapine-exposed pregnancies. One case of therapeutic abortion was due to a fetal malformation identified prenatally.[56] The first report from the Lilly Worldwide Pharmacovigilance Safety Database identified no cases of fetal malformations but some cases of perinatal adverse reaction and complicated pregnancy outcome.[57] Conversely, further expansion of this registry has recorded anecdotal cases of major structural anomalies; however, the manufacturer states that the prevalence of such events does not differ from that found in the general population. (Eli Lilly Italia, written communication, December 2006). Nonetheless, sporadic cases of olanzapine-associated fetal major malformations, gestational metabolic complications (such as the onset or worsening of gestational diabetes), neonatal adverse reactions, self-remitted neurodevelopmental impairment are now being recorded.[44,58–66] Very recently, Newport et al[67] investigated the placental passage (defined as the ratio between umbilical cord and maternal plasma concentrations) of different antipsychotic agents. Olanzapine showed a higher amount of placental passage (mean 72.1%, SD = 42.0%) and, also, higher rates of either low birth weight and/or perinatal complications as compared with other antipsychotics. In contrast, there are a number of reports describing healthy outcomes in infants exposed to olanzapine during early, late, and throughout pregnancy.[68–75] Data on the use of olanzapine in pregnancy are shown in table 1.

Quetiapine. Quetiapine is rated FDA Pregnancy Category C. Preclinical safety data from the Summary of Product Characteristic report no teratogenic effects in animals (Astra Zeneca SpA, Medical Science and

Communication, Basiglio, Milan, Italy, written communication). In human studies, quetiapine showed the lowest amount of placental passage (mean = 23.8%, SD = 11.0) when compared with both FGAs (haloperidol) and SGAs (risperidone and olanzapine).[65] Moreover, drug maternal serum levels and pharmacokinetic properties do not show relevant changes during pregnancy.[76] A number of case reports have described healthy outcomes in babies exposed in utero to quetiapine despite the fact that, in some of these occasions, the pregnant mothers had also been treated with other psychotropic medications.[44,77–85] McKenna et al[58] recently reported manufacturer's updated information reassuming spontaneous reports of outcomes of pregnancies exposed to quetiapine. In many cases ($N = 295$), the outcome was unknown, and there were other medications also taken during pregnancy. Despite some cases of major malformations occurring, no recurrent pattern of anomalies was recorded. The authors also identified prospectively 36 women treated with quetiapine during early pregnancy: these patients were compared with a control group of women exposed to nonteratogenic agents. Primary outcome of interest was the presence or absence of major fetal malformation. Secondary outcome of interest included a range of maternal conditions and neonatal health outcomes. Quetiapine was not associated with an increase of the teratogenic risk, and both maternal and neonatal health was apparently unaffected by this treatment. However, one of the limitations of this study was its small sample size; therefore, it only had an 80% power to detect a 4-fold increase in the rates of fetal malformations, which is an α of .05. Hence, this finding requires large, prospective confirmations.

Risperidone. Risperidone is rated FDA Pregnancy Category C, and the drug has shown no direct teratogenic effects in animal studies.[86,87] In humans, the amount of placental passage of risperidone was estimated at 49.2% ± 33.9% (SD).[67] The prospective study by McKenna et al[58] showed quite reassuring results, which substantially replicated those emerging from a postmarketing safety surveillance study and case reports.[88–92] In fact, only sporadic clinical observations have described fetal malformations and complicated pregnancy outcomes following in utero exposure to the drug.[44,93–95] Very recently, a comprehensive review assembled all prospective and retrospective reports of pregnancies exposed to risperidone received by the Benefit Risk Management (a division of Johnson & Johnson Pharmaceutical Research & Development, LLC)[96]: 201 unpublished cases of risperidone-exposed pregnancies were identified. A number of cases of birth defects and peri- and postnatal complications have been reported, but most reports were confounded by the concomitant use of other psychotropic medications (some of which are known teratogens). The authors concluded that an increased risk of spontaneous abortions and fetal teratogenicity could not be identified in pregnant women administered with risperidone. However, such results did not derive from incidence rates but, rather, from percentages of voluntarily reported prospective cases or retrospectively identified cases where the subsequent outcome was known or reported.

Sertindole. Sertindole is rated FDA Pregnancy Category C, though no human data are available on this drug that, however, has not demonstrated any teratogenic effects in animal reproduction studies.[97]

Ziprasidone. Ziprasidone is rated FDA Pregnancy Category C. In animal studies, ziprasidone demonstrated developmental toxicity, including possible teratogenic effects (mainly represented by ventricular septum defects and kidney malformations), at doses similar to the human therapeutic dose.[98] At present, no human data are available.

First-Generation Antipsychotics

Butyrophenone, Diphenylbutylpiperidine, and Thioxathene Derivates. Haloperidol. Haloperidol is rated FDA Pregnancy Category C. In animal studies, haloperidol rarely induced fetal malformations.[99] In humans, the amount of placental passage shown by the drug is 65.5% ± 40.3% (SD).[67] Information describing congenital anomalies (most frequently, limb defects) in neonates born to mothers who took haloperidol while pregnant is available since 1966.[100] Such a concern was identified in further clinical observations[101–103] but remains controversial.[44,104,105] In fact, the safety of haloperidol in pregnancy was assessed in a recent, multicenter, prospective, controlled cohort study.[106] Babies exposed in utero to haloperidol showed congenital malformation rates within the expected baseline risk for the general population. However, because of the small sample size and the ratio between exposed and unexposed subjects, the study had a detection power of 80% to identify a 2.9-fold increase in the overall rate of major malformations (with 95% confidence interval). On the other hand, warning information is available about the risk of perinatal adverse reactions in newborns,[107–110] despite a case of drug overdose during pregnancy that induced transient and self-remitted complications in the neonate.[111] Data on the safety of haloperidol during pregnancy are summarized in table 2.

Penfluridol and Pimozide. Penfluridol and pimozide are both rated FDA Pregnancy Category C. The study by Diav-Citrin et al[106] identified a small number of pregnancies exposed to penfluridol. One case of fetal malformation was recorded, whereas no cases of birth defects have been reported in anecdotal description of human pregnancies exposed to pimozide (see table 2).[44,112]

Flupenthixol, Chlorprothixene, and Zuclopenthixol. Chlorprothixene and zuclopenthixol are both rated

Table 2. Butyrophenone, Diphenylbutylpiperidine, and Thioxathene Derivates and Pregnancy

Study, Drug, and Sample size	Drug, Daily Dose, and Timing of Exposure During Pregnancy	Major Malformations	Pregnancy and Neonatal Outcomes
Dieulangard et al[100] (N = 1)	HAL, dose and timing of exposure: N/A	Limb malformations; concomitant drug use	N/A
Kopelman et al[101] (N = 1)	HAL, 15 mg (wk 1–7)	Limb malformations; concomitant drug use and infectious mononucleosis	Infant's death due to subdural hemorrhage
Council on drugs[102] (N = 1)	HAL, dose and timing of exposure: N/A	Limb malformations; concomitant drug use	N/A
Godet and Marie-Cardine[103] (N = 29)	HAL, dose and timing of exposure: N/A	N = 3, further clinical details: N/A; concomitant drug use: N/A	Increased rates of prematurity (12.3%); concomitant drug use: N/A
Reis and Källén[44] (N = 77)	HAL, doses: N/A (first trimester)	Microphtalmia plus gastroschisis (N = 1), renal dysplasia plus pes equinovarus (N = 1); concomitant drug use: N/A	Gestational diabetes (N = 1); concomitant drug use: N/A; neonatal complications: N/A
Diav-Citrin et al[106] (N = 188)	HAL, 10 mg (wk 34 to delivery) and 12.5 mg/mo, long-acting injectable formulation (wk 1–35), dose: N/A (2 wk during the second trimester) and 150 mg/mo, long-acting injectable formulation (throughout pregnancy), 10 mg (wk 1–30)	Severe bullous emphysema (N = 1); finger's anomalies (N = 1); cystic hygromas (N = 1); carbamazepine syndrome, developmental delay, and congenital heart defect (N = 1); ventricular septum defect and genu varum (N = 1); in some instances, concomitant drug use	Perinatal complications: (N = 9) (including feeding and respiratory problems, arrhythmia, irritability, and hypotonia); in some instances, concomitant drug use
Van Waes and Van de Velde[105] (N = 96)	HAL, 1.2 ng—median—(first trimester)	No	Spontaneous abortions (N = 4), stillbirths (N = 4); concomitant drug use: N/A
Sexson and Barak[107] (N = 1)	HAL, 2–6 mg (wk 1–34)	No	Continue tongue thrust (withdrawal emergent syndrome); probable concomitant drug use (primidone, phenytoin)
Mohan et al[108] (N = 1)	HAL, dose and timing of exposure: N/A	No	Severe hypothermia; concomitant benztropine use
O'Collins and Comer[109] (N = 1)	HAL, 200 mg every 2 wk, long-acting injectable formulation (throughout pregnancy)	No	Continue tongue thrust, torticollis, and tonic-clonic movements; no concomitant drug use
Walloch et al[110] (N = 1)	HAL, 5 mg (wk 27 to prior delivery)	No	Healthy

Table 2. Continued

Study, Drug, and Sample size	Drug, Daily Dose, and Timing of Exposure During Pregnancy	Major Malformations	Pregnancy and Neonatal Outcomes
Hansen et al[111] (N = 1)	HAL, 300 mg (single overdose during the last month)	No	Fetal akinesia and neuromuscular depression; no concomitant drug ingestion
Newport et al[67] (N = 13)	HAL, 2.25–10 mg—range— (last 3 mo)	No	Cardiovascular complications (N = 2), respiratory complications (N = 1), hypotonia (N = 1); in some instances, concomitant drug use
Diav-Citrin et al[106] (N = 27)	PEN, 2.9 mg—median— (wk 1–13)	Limb deformities (N = 1); no concomitant drug use	N/A
Reis and Källén[44] (N = 5)	PMZ, dose: N/A (first trimester)	No	No
Bjarnason et al[112] (N = 1)	PMZ, 1 mg (throughout pregnancy)	No	Premature birth; concomitant drug use
Reis and Källén[44] (N = 98)	FPX, dose: N/A (first trimester)	Situs inversus plus patent ductus arteriosus (N = 1), cerebral cyst plus malformation of large veins (N = 1), cleft palate plus accessory thumb (N = 1); concomitant drug use: N/A	Gestational diabetes (N = 1); concomitant drug use: N/A; neonatal complications: N/A
Reis and Källén[44] (N = 5)	CPX, dose: N/A (first trimester)	No	No cases of gestational diabetes; neonatal complications: N/A
Reis and Källén[44] (N = 75)	ZPX, dose: N/A (first trimester)	Hypospadias plus urinary tract malformations (N = 3), ventricular septum defects in one case complicated by pylorostenosis and in another case by atrial septum defect (N = 4), congenital cataract plus undescended testis (N = 1), congenital heart block plus tracheomalacia (N = 1); concomitant drug use: N/A	Gestational diabetes (N = 5); concomitant drug use: N/A; neonatal complications: N/A

Note: HAL: haloperidol; N/A: data not available; PMZ: pimozide; FPX: flupenthixol; CPX: chlorprothixene; ZPX: zuclopenthixol; PEN: penfluridol.

FDA Pregnancy Category C, while to the best of my knowledge FDA Pregnancy Category for flupenthixol has still not been established. Recently, Reis and Källén[44] identified retrospectively a number of pregnancies exposed to flupenthixol, chlorprothixene, and zuclopenthixol. Some cases of birth defects and gestational metabolic complications were recorded in both zuclopenthixol- and flupenthixol-exposed pregnancies (see table 2).

Table 3. Phenothiazines and Pregnancy

Study and Sample Size	Drug, Daily Dose, and Timing of Exposure During Pregnancy	Major Malformations	Pregnancy and Neonatal Outcomes
Favre-Tissot and Broussolle[114] (*N* = 362)	PHE as a group, dose: N/A (first trimester: *N* = 310, second trimester: *N* = 52)	Cardiac anomalies (*N* = 4), club foot (*N* = 3), complex malformations (*N* = 2), hydronephrosis (*N* = 1), unspecified anomalies (*N* = 1); concomitant drug use: N/A	Spontaneous abortions (*N* = 8), premature delivery (*N* = 4), stillbirths (*N* = 2); concomitant drug use: N/A
Rawlings et al[115] (*N* = 341)	PMZ and TFP, dose and timing of exposure: N/A	*N* = 11, further clinical details: N/A; concomitant drug use: N/A	Spontaneous abortions (*N* = 80), perinatal deaths (*N* = 11); concomitant drug use: N/A
Milkovich and van den Berg[116] (*N* = 976)	PHE as a group, dose: N/A (first trimester)	*N* = 35, further clinical details: N/A; concomitant drug use: N/A	N/A
Romeau-Rouquette et al[117] (*N* = 315)	PHE as a group, dose: N/A (first trimester)	Single malformations (*N* = 153) (including central nervous system, heart, pharynx, palate, digestive system, urinary system, genital system, skeletal system, muscle, and sense organ defects), multiple malformations (*N* = 37); no concomitant drug use	N/A
Slone et al[118] (*N* = 1309)	PHE as a group, dose: N/A (first 4 mo)	*N* = 94, possible increased risk of cardiac malformations (RR: 1.00, 95% CI: 1.49–1.94); concomitant drug use: N/A	Stillbirths (*N* = 79) (no differences between the exposed and the control group regarding perinatal mortality rate, birth weight, and IQ measured at 4 y of age); concomitant drug use: N/A
Scokel and Jones[121] (*N* = 686)	PHE as a group, dose: N/A (during labor)	N/A	Increased risk of jaundice in preterm infants (statistical significance: N/A); concomitant drug use
Štika et al[122] (*N* = 63)	PHE as a group, dose: N/A (wk 20 to delivery)	N/A	No differences between the exposed and the control groups regarding school behavior

Table 3. Continued

Study and Sample Size	Drug, Daily Dose, and Timing of Exposure During Pregnancy	Major Malformations	Pregnancy and Neonatal Outcomes
Romeau-Rouquette et al[117] (*N* = 43)	CPZ, dose: N/A (first trimester)	Syndactyly (*N* = 1); endocardial fibroelastosis and finger anomalies (*N* = 1); microcephaly (*N* = 1); microcephaly, clubhand, clubfoot, and muscular abdominal aplasia (*N* = 1); in 2 cases, concomitant drug use	N/A
Crombie, personal communication (*N* = 43)	CPZ, dose: N/A (first trimester)	No	N/A
Kris and Carmichael[125] (*N* = 8)	CPZ, 50–200 mg (throughout pregnancy)	No	Healthy
Ayd[126] (*N* = 16)	CPZ, 150–900 mg (throughout pregnancy)	No	Healthy
Kris[127] (*N* = 2)	CPZ, 50–150 mg (throughout pregnancy)	No	Healthy
Sobel[128] (*N* = 52)	CPZ, 100–600 mg (various stages of pregnancy)	No	Respiratory distress, convulsions, and neurodevelopmental delay (*N* = 1); spontaneous abortions (*N* = 1); stillbirths (*N* = 1); respiratory distress (*N* = 3), followed by postnatal death in one case; concomitant drug use: N/A
O' Leary and O'Leary[129] (*N* = 1)	CPZ, 50 mg (throughout pregnancy)	Omphalocele, absence of one lower extremity; concomitant meclizine use	Stillbirth
Kulkarni et al[75] (*N* = 1)	CPZ, 750 mg (wk 28 to delivery)	No	Small-for-date baby, postnatal pneumonia; concomitant dilantin use
Falterman and Richardson[130] (*N* = 7)	CPZ, 200 mg (last semester)	No	Small left colon syndrome; concomitant benztropine use
Ben-Amital and Merlob[131] (*N* = 1)	CPZ, 200 mg (throughout pregnancy)	No	Fever and cyanotic spells; no concomitant drug use

Table 3. Continued

Study and Sample Size	Drug, Daily Dose, and Timing of Exposure During Pregnancy	Major Malformations	Pregnancy and Neonatal Outcomes
Ergenkon et al[132] (*N* = 1)	CPZ, dose and timing of exposure: N/A	No	Transient heart block and respiratory problems; concomitant haloperidol and biperiden use
Auerbach et al[133] (*N* = 6)	CPZ, 25–250 mg (last trimester)	No	Perinatal complications, including hypertonia, startles, and poor motor maturity (*N* = 4); in some instances, concomitant drug use
Levy and Wisniewski[134] (*N* = 1)	CPZ, 600 mg (throughout pregnancy)	No	Hypertonia, tremor, hyperreflexia, and facial edema. EPS persisted for 6 mo and required specific pharmacological management (diphenhydramine); concomitant drug use: N/A
Nielsen et al [135] (*N* = 1)	CPZ, 2000 mg (wk 25 to delivery)	No	Severe neurological depression; concomitant lithium use (1800 mg/d)
Meut et al[136] (*N* = 1)	CPZ, 200 mg (wk 29 to delivery)	No	Necrotizing enterocolitis; concomitant nitrazepam and biperiden use
Hill et al[137] (*N* = 2)	CPZ, 50–400 mg (throughout pregnancy)	No	Extrapyramidal symptoms persisting up to 12 mo of age (*N* = 2); in one case, concomitant thioridazine use
O'Connor et al[138] (*N* = 1)	CPZ, 1200 mg (throughout pregnancy)	No	Extrapyramidal symptoms persisting up to 9 mo of age and requiring specific therapy; the mother also was on fluphenazine and ECT treatments
Tamer et al[139] (*N* = 2)	CPZ, 600 mg (last 22 d) and 200 mg (last 5 mo)	No	Jaundice and opisthotonus (*N* = 1), persistent tremor and borderline mental retardation (*N* = 1); in one case, concomitant phenobarbital and phenytoin use
Falterman and Richardson[140] (*N* = 2)	CPZ, 200 mg (first semester—7 h before delivery) and 100 mg (single dose 1 h before delivery)	No	Functional intestinal obstruction (*N* = 1); concomitant benztropine use
Reis and Källén[44] (*N* = 98)	CPZ, dose: N/A (first trimester)	No	Gestational diabetes (*N* = 1); concomitant drug use: N/A; neonatal complications: N/A
Farag and Ananth[141] (*N* = 1)	PCZ, multiple doses of 10 mg (first trimester)	Thanatophoric dwarfism; no concomitant drug use	Neonatal death
Mellin[142] (*N* = 76)	PCZ, dose: N/A (wk 1–20)	*N* = 14 (preauricalar sinus, hydrocele, undescended testis, bifid uvula, micrognathia, congenital deafness, accessory spleen, multiple cardiac anomalies); concomitant drug use: N/A	N/A
Rafla[143] (*N* = 3—1 pair of twins)	PCZ, dose: N/A (wk 1–12)	Limb deformities (*N* = 2); concomitant drug use: N/A	N/A

Table 3. Continued

Study and Sample Size	Drug, Daily Dose, and Timing of Exposure During Pregnancy	Major Malformations	Pregnancy and Neonatal Outcomes
Freeman[144] (*N* = 1)	PCZ, 15 mg (1 wk during the first trimester)	Limb deformities; concomitant drug use: N/A	N/A
Ho et al[145] (*N* = 1)	PCZ, 10 mg (2 wk during the first trimester)	Limb deformities, cleft palate, and congenital heart disease; concomitant drug use	N/A
Reis and Källén[44] (*N* = 224)	PCZ, dose: N/A (first trimester)	No	No cases of gestational diabetes, neonatal complications: N/A
Moriarty and Nance[146] (*N* = 480)	TFP, dose and timing of exposure: N/A	*N* = 5 (1 case of hydrocele, 1 hydrocephalus, 2 cases of polydactylism, 1 case of multiple anomalies); concomitant drug use: N/A	Spontaneous abortion (*N* = 12), stillbirths (*N* = 5); concomitant drug use: N/A
Canadian Department of National Health and Welfare, Food and Drug Directorate[147] (*N* = 8)	TFP, dose and timing of exposure: N/A	*N* = 8 (hydrocele, hydrocephaly, polydactylism, clubbed foot, mongoloid features); concomitant drug use: N/A	N/A
Hall[148] (*N* = 1)	TFP, 1–3 mg (first trimester)	Phocomelia; concomitant prochlorperazine use	Healthy
Corner[149] (*N* = 2)	TFP, 4 mg (first semester)	Limb malformations in one pair of twins; concomitant drug use	N/A
Vince[150] (*N* = 1)	TFP, 4 mg (first 4 mo)	Complete transposition of great vessels and parent foramen ovale; concomitant thioridazine use	Cyanosis, respiratory distress, and cardiac decompensation due to the cardiac malformation
Wheatley[151] (*N* = 59)	TFP, doses: N/A (first trimester)	*N* = 3, further clinical details: N/A; concomitant drug use: N/A	N/A
Auerbach et al[133] (*N* = 1)	TFP, 9 mg (last trimester)	No	Healthy
Schrire[152] (*N* = 478)	TFP, dose: N/A (first trimester)	No	Spontaneous abortion (*N* = 2); concomitant drug use: N/A
King et al[153] (*N* = 244)	FLU, 1–4 mg (1–2 wk during the first trimester)	Talipes (*N* = 2), polydactylism (*N* = 2), spina bifida (*N* = 1), syndactylism (*N* = 1); concomitant drug use: N/A	Stillbirths (*N* = 6), spontaneous abortion (*N* = 19); concomitant drug use: N/A
Reis and Källén[44] (*N* = 17)	FLU, dose: N/A (first trimester)	No	Gestational diabetes (*N* = 1); concomitant drug use: N/A; neonatal complications: N/A

Table 3. Continued

Study and Sample Size	Drug, Daily Dose, and Timing of Exposure During Pregnancy	Major Malformations	Pregnancy and Neonatal Outcomes
Clearly[154] (*N* = 1)	FLU, 50 mg every 3 wk, long-acting injectable formulation (throughout pregnancy)	No	Minor extrapyramidal manifestations; concomitant benztropine use
Hill et al[137] (*N* = 1)	TIO, 100–200 mg (throughout pregnancy)	No	Healthy
Brougher[155] (*N* = 21)	TIO, 40 mg (timing of exposure: N/A)	No	Healthy
Auerbach et al[133] (*N* = 1)	TIO, 40 mg (last trimester)	No	Hypertonia; concomitant drug use: N/A
Reis and Källén[44] (*N* = 35)	TIO, dose: N/A (first trimester)	Tetralogy of Fallot (*N* = 1); concomitant drug use: N/A	No cases of gestational diabetes, eonatal complications: N/A
New Zealand Committee on Drug Reactions[156] (*N* = 1)	TPZ, dose: N/A (mo 3–4)	Hydrocephalus, meningomyelocele, and hypospadias; concomitant drug use: N/A	N/A
Puhó et al[157] (*N* = 33)	TPZ, dose: N/A (first trimester)	Cleft/lip palate (*N* = 26); concomitant drug use	N/A
Wheatley[151] (*N* = 165)	PMT, dose: N/A (first trimester)	*N* = 7, further clinical details: N/A; concomitant drug use: N/A	N/A
Idänpään-Heikkilä and Saxen[158] (*N* = 2)	PPZ, dose: N/A (first trimester)	Micrognathia (*N* = 1), hydrocephalus (*N* = 1); both mothers took concomitant medications	Hydrocephalus was complicated by subarachnoid hemorrhage leading to infant's death
Reis and Källén[44] (*N* = 90)	PPZ, dose: N/A (first trimester)	Spina bifida plus testis aplasia (*N* = 1), ventricular septum defect plus undescended testis (*N* = 1); concomitant drug use: N/A	Gestational diabetes (*N* = 1); concomitant drug use: N/A; neonatal complications: N/A
Reis and Källén[44] (*N* = 50)	LPZ, dose: N/A (first trimester)	Hypospadias (*N* = 1), spina bifida plus polysyndactyly (*N* = 1), concomitant drug use: N/A	Gestational diabetes (*N* = 1), concomitant drug use: N/A; neonatal complications: N/A

Note: PHE: phenothiazines; N/A: data not available; PMZ: phenmetrazine; TFP: trifluoperazine; RR: relative risk; CI: confidence interval; CPZ: chlorpromazine; PCZ: prochlorperazine; FLU: fluphenazine; TIO: thioridazine; TPZ: thiethylperazine; PMT: promethazine; PPZ: perphenazine; LPZ: levomepromazine.

Phenothiazines. Studies Investigating Phenothiazine Agents as a Group. The teratogenic effect of phenothiazines as a group has been proved in mice and rats.[113] The amount of placental passage of these drugs is unknown. In humans, Favre-Tissot and Broussolle[114] investigated the outcomes of a relatively large number of phenothiazine-exposed pregnancies, most of them exposed to chlorpromazine. Although some cases of fetal major malformations were recorded, the authors concluded that the rate of these anomalies was not statistically different from that shown by unexposed populations. Rawlings et al[115] reported similar findings. However, a relatively high rate (23.4%) of spontaneous abortion was recorded in this study. Quite reassuring results also emerged from a prospective study on the use of phenothiazines as a short-term treatment of nausea and vomiting in pregnancy.[116] In contrast, a statistically significant increase in the rate of birth defects associated with first trimester exposure to phenothiazines with 3-carbon aliphatic side chain (specifically, chlorpromazine, methotrimeprazine, trimeprazine, and oxomemazine) was demonstrated in 2 prospective surveys.[117,118] However, in the first of these studies, phenothiazines were also used for controlling threat of abortion. Because early pregnancy loss may be due to an embryo affected by chromosomal or structural anomalies,[119,120] the reported association between pregnancy exposure to this class of antipsychotics and birth defects seems to be the result rather than the cause of birth defects.[117] Scokel and Jones[121] also suggested an increased risk of neonatal jaundice in preterm infants whose mothers had been treated with phenothiazines during labor. The long-term behavioral outcome of children exposed in utero to phenothiazines after week 20 of pregnancy was investigated in a single case-control study.[122] These children, aged 9–10 years, showed no behavioral anomalies. However, the development of such children was assessed by their teachers using an oversimplified, semistructured formulary; neither specific instruments of evaluation nor qualified intervention by specialized staff was actually provided. Studies investigating phenothiazine agents collectively are shown in table 3.

Studies on Specific Phenothiazine Agents. *Chlorpromazine.* Chlorpromazine is rated FDA Pregnancy Category C. In animal studies, chlorpromazine has been associated with an increased risk of congenital malformations (involving skeletal and central nervous systems, eye, cleft palate, fetal death, and reduced fetal weight gain) but at doses many times higher than the human-recommended dose.[123,124] Regarding human teratogenicity, Rumeau-Rouquette et al[117] reported a personal communication by Crombie, who found no case of fetal malformations in a small number of babies born to mothers who had been treated with chlorpromazine during the first trimester of pregnancy. Such reassuring results were confirmed retrospectively by subsequent case reports and case series studies on drug exposure during early and late pregnancy.[44,125–128] However, it was hypothesized that chlorpromazine might be associated with an increased risk of neonatal respiratory distress if used at daily doses higher than 500 mg.[126] Until now, only one case of either fetal malformations or gestational diabetes has been reported,[44,129] whereas perinatal complications seem to be relatively common when the drug is used in late pregnancy (see table 3).[75,130–140]

Prochlorperazine. Prochlorperazine is rated FDA Pregnancy Category C. One case of rare and mortal fetal anomaly was described in a woman who needed prochlorperazine during pregnancy because of suffering from a severe form of hyperemesis gravidarum.[141] Prospective investigations and case reports also suggested an increased risk of major and minor congenital malformations after exposure to prochlorperazine during the first 20 weeks of gestation.[142–145] Conversely, Reis and Källén[44] found no cases of fetal malformations in a relatively large number of retrospectively identified prochlorperazine-exposed pregnancies. Data on prochlorperazine are shown in table 3.

Trifluoperazine. Trifluoperazine is rated FDA Pregnancy Category C. More than 40 years ago, Smith Kline and French reexamined its database to determine whether there was evidence of a causal relationship between trifluoperazine therapy in pregnancy and an increased risk of fetal malformations.[146] No evidences of teratogenicity were found. However, most of these women (87%) received the drug to control nausea and vomiting in pregnancy; only 13% of women had been on long-term treatment because of psychiatric disorders. Nonetheless, in December 1992, the Canadian Food and Drug Directorate stated that trifluoperazine might be associated with sporadic cases of congenital anomalies, including skeletal and multiple internal deformities.[147] Indeed, some cases of limb defects and other unspecified malformations following early in utero exposure to trifluoperazine during the first trimester had been observed,[148–151] although anecdotal clinical reports and one relatively large retrospective investigation (this last study conducted on women who took the drug for nausea and vomiting in pregnancy) did not confirm such observations.[132,152] Data on trifluoperazine in pregnancy are summarized in table 3.

Fluphenazine. To the best of my knowledge, fluphenazine has not been formally assigned to a pregnancy category by the FDA. The effects of fluphenazine on pregnancy outcomes were studied extensively only in women who took the drug for treating hyperemesis gravidarum.[153] Delivery and neonatal records revealed that the rates of spontaneous abortions, perinatal mortality, premature delivery, and fetal malformations were similar between the fluphenazine group and a control group of women treated with placebo.[153] Sporadic case reports and information from retrospective investigation of birth registers have also suggested that maternal fluphenazine treatment may be relatively safe for the developing fetus and rarely induce gestational metabolic complications but may induce neonatal adverse reactions.[44,154] These studies are summarized in table 3.

Thioridazine and Thiethylperazine. Thioridazine and thiethylperazine have not, as yet, been assigned a formal FDA Pregnancy Category. A small number of women who have needed low doses of thioridazine during pregnancy have showed uncomplicated deliveries.[137,155] Conversely, late in utero exposure to the drug might be associated with an increased risk of extrapyramidal symptoms in neonates.[133] Until now, only one case of fetal malformations following placental exposure to the drug has been reported.[44] One study suggested an increased risk of fetal major malformations associated with early in utero exposure to thiethylperazine.[156] Very recently, a relatively large, observational, case-control study has also hypothesized that the drug might be associated with a statistically significant increase (odds ratio: 1.7; 95% confidence interval: 1.1–2.5) in the risk of cleft and lip palate if used during early pregnancy (see table 3).[157] Data on thioridazine and thiethylperazine are shown in table 3.

Promethazine, Perphenazine, and Levomepromazine. Promethazine, perphenazine, and levomepromazine are all rated FDA Pregnancy Category C. In the case of promethazine, a relatively large number of women exposed early in pregnancy were prospectively and retrospectively identified. Despite some cases of birth defects being observed in babies born to these mothers, the rate of major structural malformations (4.3%) did not differ from that expected (see table 3).[150] Two case reports described fetal malformations in infants whose mothers took perphenazine (but amitriptyline too) during early pregnancy (see table 3).[158] Sporadic cases of both fetal malformations and gestational metabolic complications also emerged from a recent retrospective study investigating the use of perphenazine during pregnancy.[44] Anecdotal cases of birth defects and gestational metabolic complications have been reported among a relatively small number of women who had taken levomepromazine during early pregnancy.[44] Data on these 3 antipsychotic medications are shown in table 3.

Discussion

Previously published guidelines, editorials, and narrative reviews have rightly highlighted the necessity to start or continue antipsychotic therapy in vulnerable mothers because either the relapse or the recurrence of psychotic symptoms represents medical and obstetrical emergencies.[25] However, these studies provided no information about the best treatment option for the mother-infant pair because they frequently concluded that, when available, reassuring findings on structural teratogenicity of all antipsychotics, either of first or second generation, were preliminary and too limited for recommending safe use in pregnancy.[25,159–162] Moreover, the majority of studies on the reproductive safety of antipsychotic medications are also characterized by single-dimension experimental design, which is unable to individuate all the factors that, in pregnant women with SPPD, may lead to increase in the risk of birth defects and poor pregnancy outcomes independent of the drugs (malnutrition, poor antenatal cares, episodes of domestic and/or sexual violence, gynecological infectious diseases, and unhealthy behaviors).[163] This situation is not surprising: it is indeed unethical to include pregnant women in randomized controlled trials because this would involve deliberate exposure of the fetus to a potential teratogen.[164]

Table 4. Fetal Malformations Related to Prepregnancy Obesity With Statistical Significance[172]

Fetal Malformation	OR (95% CI)
Spina bifida	2.19 (1.69–2.85)
Anorectal atresia	1.68 (1.12–1.52)
Omphalocele	1.42 (0.81–2.51)
Cardiac defects	1.33 (1.17–1.52)
Limb reduction defects	1.26 (0.93–1.71)
Hypospadias	1.25 (0.96–1.63)
Diaphragmatic hernia	1.20 (0.82–1.76)

Note: OR: odds ratio; CI: confidence interval.

As a result, the best available data on antipsychotic drug usage in pregnant women that can be used to support clinical decisions come from nonrandomized, prospective, and observational studies, and, more often, single case reports or small case series studies thus also suffer from being methodologically poor. It must be stressed, however, that the lack of data on the use of psychotropic medications in women is not limited to this specific phase of the female reproductive cycle: despite the urgent need to identify major gaps in our knowledge of how gender may influence psychiatric diagnoses and treatment outcomes,[165] it was not until 1990 that the National Institute of Health in the United States issued guidelines mandating the inclusion of women in clinical trials.[166] Nevertheless, in the absence of more controlled researches, reviewed studies provide the only information source potentially useful in clinical practice, and it is reassumed below.

Premise

When investigated collectively, antipsychotic medications have been associated with a statistically significant increase in the risk of birth defects as a whole, with no significant differences in malformation risk between classes and/or single medications[44]; thus, it is possible that underlying pathology or unidentified confounding factors may explain the increased risk.[44] In addiction, the use of both SGAs and FGAs during late pregnancy has been associated with increased rates of perinatal complications. However, the following findings (including specific comments on the specificity of iatrogenic metabolic complications in this phase of the female reproductive cycle) need to be highlighted.

SGAs and Structural/Behavioral Teratogenicity

Because of the lack of any human data, the teratogenic risk of amisulpride, ziprasidone, and sertindole should be considered unknown. Only 3 case reports are available on aripiprazole: in one of these cases, transient unwanted effects on the neonatal cardiac rhythm were observed.[31] Hence, these drugs should be avoided in pregnant women because either no or limited anecdotal data are available about their own structural and behavioral teratogenicity.

Approximately, 200 babies exposed in utero to clozapine have been investigated. Fifteen cases of fetal malformations have been reported, as well as cases of poor pregnancy outcomes and perinatal complications (including transient floppy infant syndrome, retinopathy, and severe neonatal hypoxemic encephalopathy).[36–38,42,44–48,56,57] However, in most of these cases no information was available about the kind of the malformation; hence, possible recurrent patterns of anomalies cannot be ascertained. Moreover, on some occasions the mothers took concomitant medications. In addiction, Pinkofsky et al[167] have raised the issue of potential clozapine-induced fetal agranulocytosis. Thus, white blood cell counts of all newborn infants whose mothers have received clozapine during pregnancy should be monitored weekly for the first 6 months to detect agranulocytosis that may result in life-threatening infectious diseases.[168]

Olanzapine is the SGA with the highest number of reports regarding its use during pregnancy ($n = 419$), but the attempt to analyze the possible teratogenicity of the drug is impaired by the fact that these mothers were exposed concomitantly to other psychotropic medications. Twenty-six cases of congenital malformations have been reported (fully described in all cases). Neural tube defects were diagnosed in 4 of these cases.[56,58,59] Thus, some signals seem to exist suggesting that the drug may increase the risk of this specific anomaly.[59,169] 63 cases of perinatal complications following inuter exposure to olanzapine have been reported. However, clinical information on these untoward events was rarely available (Eli Lilly Italia, wriiten communication[47,57])

At the time of writing, 227 reports of pregnancies exposed to quetiapine are available, in 8 cases complicated by the occurrence of fetal malformations of unknown typology. For this reason, no conclusions can be drawn about the safety of this drug in early pregnancy. Moreover, the first reports of perinatal complications are now being released.[67]

Three hundred twenty-one cases of pregnancy exposure to risperidone are available. Fifteen cases of fetal malformations (all with known typology) have been observed, with no recurrent patterns of anomalies. Perinatal complications of various degrees of severity may also occur, ranging from withdrawal reactions to seizures.[58,92,95,96] Finally, sporadic cases of poor pregnancy outcome and neonatal complications have been recorded.[92,94–96]

SGAs and Gestational Metabolic Complications

Most SGAs (with the possible exception of aripiprazole and ziprasidone) are likely to induce obesity and other metabolic complications, especially during long-term treatments.[170,171] This risk seems to be higher in women with childbearing potential.[19,21] It must be stressed that women who become obese prior to pregnancy are more likely to deliver malformed babies than nonobese women (see table 4); the mechanism underlying such an association may be related to an undiagnosed diabetes.[172] Gestational diabetes has also been associated with an increased risk of developing breast cancer later in the mother's life.[173] In addition, a recent prospective study has demonstrated that infants exposed in utero to SGAs might show a significantly higher incidence of being large for gestational age and a mean birth weight significantly heavier than those exposed to FGAs.[174] Besides neonatal hypoglycemia, infants who are born large for gestational age show increased lipolysis and a propensity for decreased insulin sensitivity already at birth; such infants are also at risk of developing obesity, cardiovascular disease, and diabetes later in life.[175] Among SGAs, clozapine[39–41,43,45,51,57] and olanzapine[44,57,62–64] should definitively be considered as drugs associated with an increase in the risk of metabolic complications in pregnancy (prevalently gestational diabetes). Until now, amisulpride, aripiprazole, quetiapine, sertindole, and ziprasidone have not been associated with occurrence of gestational metabolic complications, whereas a single case of gestational diabetes has been reported during therapy with risperidone.[44]

FGAs and Fetal/Behavioral Teratogenicity

Despite approximately 40 years of clinical use and a safety database recently defined as "reasonably extensive,"[66] we have found only 411 published cases of pregnancies exposed to haloperidol. Overall, 14 cases of fetal anomalies were reported (3 were limb malformations[100–102]). Thus, the risk of limb anomalies associated with early in utero exposure to haloperidol cannot be excluded. One case of limb deformity has also been detected among 27 penfluridol-exposed babies.[106] Finally, the risk of perinatal complications associated with late in utero exposure to haloperidol (ranging from withdrawal symptoms to instability of body temperature) should be stressed.

Early pregnancy exposure to thioxathenes have been sporadically associated with birth defects,[44] whereas only anecdotal, despite reassuring, descriptions of human pregnancies exposed to pimozide are available.[44]

A relatively large number of babies exposed in utero to phenothiazine agents (as a group) have been investigated (4060 cases). However, most of these babies were exposed to such agents for only a short period; indeed, their mothers were not psychiatric patients but needed such drugs for treating hyperemesis gravidarum. In addition, because these studies lump together different neuroleptics, their results provide no significant information about the teratogenicity of specific drugs.[118,176] In any case, the overall rate of birth defects was about 10% (N = 406). The suggested risk of fetal cardiac malformations cannot be confirmed[118] also because published data are impaired by incomplete reporting.[116]

More than 400 cases of pregnancies exposed to chlorpromazine have been published. Only 5 cases of fetal malformations have been described.[117,129] Conversely, the use of this drug during late pregnancy seems to be inevitably associated with an increased risk of perinatal complications (including extrapyramidal signs, which may persist up to 1 year of age; respiratory distress; seizures; and transient neurodevelopmental delay).[132–140]

Whereas reports on pregnancies exposed to prochlorperazine show contradictory findings,[44,141–145] more than 1000 cases of pregnancy exposed to trifluoperazine are known. Nineteen cases of major malformations have been described. The poor methodology of such reports makes it impossible to confirm or exclude the doubtful finding that the drug may be associated with an increased risk of fetal skeletal and internal anomalies if used during early pregnancy.[146–152]

The theoretical risk of increased rates of cleft lip palate associated with the use of thiethylperazine early in pregnancy has been hypothesized in only one study, based however on a very small sample size.[157]

Further, no conclusions can be drawn about the teratogenicity of fluphenazine, thioridazine, and promethazine, despite the first 2 drugs being definitively associated with an increased incidence of neonatal extrapyramidal reactions.

FGAs and Gestational Metabolic Complications

Although recent researches suggest that FGAs may also induce clinically relevant weight gain during long-term therapy,[177] until now the number of reports describing FGA-induced gestational metabolic complications is limited. Early pregnancy exposure to thioxathenes and chlorpromazine have been sporadically associated with the onset or worsening of gestational diabetes.[44]

Box 2.

Managing Psychotic Symptoms During Pregnancy

Antipsychotic therapy should be considered mandatory in pregnant patients with psychotic features

When a planned or unplanned pregnancy occurs during antipsychotic treatment, privilege the choice to continue the previous therapy, if known as effective Pregnancy is not the best period to experiment the effectiveness of drugs

In the case of occurrence of psychotic symptoms in drug-naïve pregnant patients, privilege the drug showing the highest number of reassuring reports and the lowest reported number of fetal anomalies (eg, chlorpromazine)

Provide strict gynecological surveillance (tritest, regular clinical follow-up, and ultrasound monitoring) during therapy with both first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs)

Provide strict endocrinological surveillance (Hb1Ac, glycemia, cholesterol and triglycerides serum levels, bodyweight gain) during therapy with FGAs but, especially, with SGAs

Take into consideration the possibility to taper both FGAs and SGAs during the last trimester in order to reduce the risk of neonatal extrapyramidal reactions and seizures Match this decision with the risk of a relapse of psychotic symptoms

Provide strict cooperation between gynecologists, neonatologists, and pediatricians in order to warrant optimal maternal antenatal cares and promptly diagnose and manage eventual perinatal complications during the first hours after delivery

Provide regular follow-up of children exposed in utero to either FGAS and SGAs in order to diagnose and manage possible signs of neurodevelopmental delay

Treatment Guidelines

Despite both the lack of methodologically valid safety data and the presence of possible reproductive safety concerns specified above, antipsychotic therapy must be considered mandatory in women with SPPDs even during pregnancy because the risks associated with pharmacological intervention may outweigh the risks of an untreated mental illness for the mother-infant pair.[178,179] Independent of any safety considerations, it should be stressed that most of these pregnant women require admission to psychiatric emergency services for pharmacological management of psychotic breakdown episodes: in such conditions, antipsychotics are the more frequently administered drugs.[180] Moreover, some SPPDs seem to be an independent risk factor for adverse pregnancy outcomes (higher rates of prenatal hospitalization due to maternal medical problems, placental anomalies, eclampsia, antepartum hemorrhages, premature delivery, lower birth weight and Apgar scores, shorter length at delivery, fetal distress, stillbirth, perinatal mortality, and congenital anomalies).[181–184] The existing correlation between unfavorable perinatal circumstances (such as low birth weight) and increased rates of suicide of offspring as young adults should also be highlighted.[185] This seems to be especially true for schizophrenia, which has also been specifically associated with an increase in risk of major neurological malformations, preterm delivery, low birth weight, and small-for-gestational age babies.[186,187] In contrast, these findings remain controversial for affective psychosis.[188] It has been recently confirmed that increased risk of obstetrical complications in schizophrenic patients seems to be due to engagement in health risk behaviors during pregnancy, whereas genetic susceptibility to the disorder, by itself, does not appear to influence the natural course of pregnancy.[189]

In any case, maternal SPPDs may have a devastating impact on the quality of the mother-infant bonding and on the infant's neurodevelopment. Mothers with schizophrenia are likely to have their attachment to the baby compromised by the maternal psychopathology and the reality of their psychosocial situation.[190] These women are also more likely to experience difficulties with parenting and thus to lose custody of their children.[8] Maternal bipolar disorder is associated with increased rates of memory and attention disturbances, impaired social functioning, behavioral and emotional problems, and even severe psychiatric disorders in the offspring.[191–194]

Managing SPPDs in Pregnant, Drug-Naïve Women

Given this background, when clinicians have to manage psychotic symptoms in pregnant, drug-naïve women, the less harmful pharmacological option should be selected within FGAs. In contrast with Trixler et al[22] who suggest to privilege high-potency agents (such as haloperidol) as first-line management of psychotic disorders during pregnancy,[23] in our opinion chlorpromazine should be considered as a possible first-line option because the drug evidences less-worrying teratogenic data. In fact, the association between first trimester exposure to phenothiazines and congenital anomalies reported in other narrative reviews and a single meta-analysis[25,195–197] seem to be unconfirmed for chlorpromazine.[24] Moreover, among both FGAs and SGAs, phenothiazines are the only medications that show some, albeit preliminary and methodologically not impeccable, findings suggesting no impact on later infants' school behavior.[122] Moreover, only anecdotal reports have described an increased risk of clinically significant episodes of orthostatic hypotension in pregnant women on chlorpromazine treatment,[75] a clinical concern previously emphasized.[23] Further, the reported increased height in children born to mothers on FGA therapy during pregnancy compared with those born to untreated mentally impaired mothers (this difference, however, disappeared at 7 years of age)[198] seems to have no clinical relevance; this finding might be simply due to the improvement of maternal mental conditions secondary to antipsychotic treatment. Restoration of patient sound contact with reality and the pharmacological control of other positive symptoms might have facilitated a good adherence to antenatal care and reduced unhealthy lifestyle and behaviors, with obvious favorable effects on infant development. It must be stressed, however, that chlorpromazine may induce neonatal extrapyramidal reactions, respiratory distress, and transient neurodevelopmental delay (see box 2). However, use of central acting anticholinergic drugs for controlling extrapyramidal adverse events should be avoided whenever possible. Information on the safety of such medications is available neither in animal nor in human pregnancies.

Managing SPPDs in Patients Who Incur in an Unplanned Pregnancy During Antipsychotic Treatment

Given the increasing use of SGAs in clinical practice, most of these women could be on SGA treatment at the time of conception; unfortunately, no evidence-based information allows to individuate the safest SGA in pregnancy. However, the risk of polypharmacotherapy, either concomitant and/or consecutive, has not been established in pregnancy, despite nearly one-third of women with SPPDs filled prescriptions for up to 10 medications during their pregnancy.[199] Thus, when an unplanned pregnancy occurs during antipsychotic treatment, the choice to continue the previous therapy (if known as effective, even when based on SGAs) should be preferred. Pregnancy is not the best period to attempt pharmacological shifts and experiment on the effectiveness of drugs. However, such women should be carefully monitored to prevent or manage metabolic complications (such as excessive weight gain, increased serum triglyceride and cholesterol levels, glucose intolerance, and/or gestational diabetes—see box 2).

Managing SPPDs in Patients on Antipsychotic Treatment Who Wish to Become Mothers

In the light of these considerations, in this situation clinicians should evaluate the general reproductive safety of the current antipsychotic treatment. If the patient is already prescribed chlorpromazine, no changes are needed. Conversely, these patients and their partners should be carefully counseled to plan effective anticonception measures until pharmacological shift from previously prescribed antipsychotic drug to the lowest effective dose of chlorpromazine is complete.

Conclusions

The desire of women with SPPD to have a child should be taken into great consideration, for as many as 50% of them are mothers, which almost equals the figure for the general population.[200] Hence, in these women pharmacological management of the underlying illness is only part of an integrated multidisciplinary approach. Other indispensable tools must include the implementation, before conception, of educational programs finalized to reduce unhealthy behaviors that may contribute to increase in risk of fetal malformations independently of drug use (alcohol, nicotine, and street drug) and unprotected sexual practices (which amplify risk of sexually transmitted diseases).

However, the main clinical concern of pregnant women with SPPDs is probably psychotic relapse due to nonadherence to neuroleptic medications, which may lead to poor outcomes such as termination of pregnancy, obliged cesarean section, and institutionalization of their offspring due to reduced child-care capabilities.[201,202] Hence, clinicians should make all possible effort to inform these vulnerable mothers about the advantage of accepting a possible, modest increase in teratogenic risk in comparison with the need to maintain stable mental health during pregnancy.[21] These women should be made aware that fetal malformation is a relatively common pregnancy complication even in general health population.[203] Approximately, 150 000 children with malformations are born annually in the United States.[204] Ethical and legal concerns regarding the validity of informed consent from severely mental ill patients are beyond the scopes of this article (see resource documents issued by American Psychiatry Association[205] and Royal Pharmaceutical Society[206]): however, it should be stressed that most patients with serious mental illness have abilities similar to healthy persons when making treatment decision, and deficits in their decision-making performance may be temporary and may improve with treatment.[207] Nonetheless, the decision to start or continue antipsychotic therapy during pregnancy should be shared with partners and/or other family members because evidence is that women usually involve (or are influenced by) these people in their reproductive decisions.[178,179] Indeed, expectant fathers and patient relatives may also have prejudices about teratogenic risks of those medications deemed indispensable by clinicians for maintaining stable mental conditions or obtaining satisfactory recovery after a psychotic storm.[178,179] Thus, the second tool consists of implementing specific consultation services for parents and clinicians, finalized to empower the quality of information about the reproductive safety profile risks of any psychotropic medications. Indeed, pharmacological treatment also remains an indispensable tool for acquiring maternal adherence to alternative interventions.[208]

The third tool is enhancement of all other non–drug-related support programs (which must include psychological support to maternity, implementation of the number of psychiatric mother-baby units for preventing attachment-turmoil and mother-baby division during postpartum period,[209] social support finalized to facilitate community reintegration, and identification of potential alternative caregivers to the children) that may contribute to the maintenance of good, stable mental status[210] and may facilitate construction of sound mother-child bonding.

Acknowledgments

Dr Gentile acknowledges Medical Information Service (Annamaria Desiati, Lucia Fantini, Cristina Mari, Stefania Metafonti, and Luana Salvati), a free-access service of Eli Lilly SpA, Sesto Fiorentino, Italy, for the kind and professional support in providing full-text articles. He dedicates this article to his father. No source of funding was used.

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