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Evaluating the Postmarketing Experience of Risperidone Use During Pregnancy

Pregnancy and Neonatal Outcomes

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Abstract

Background: A significant number of women of childbearing age have schizophrenia or other psychoses. This means that there is a considerable risk of *in utero* exposure to risperidone due to maternal use.

Objective: To determine whether *in utero* exposure to the atypical antipsychotic risperidone is associated with poor pregnancy and fetal/neonatal outcomes.

Methods: A search of the Benefit Risk Management Worldwide Safety database, using a selection of preferred terms from the Medical Dictionary of Regulatory Activities, was performed to identify all cases of pregnancy or fetal/neonatal outcomes reported in association with risperidone treatment from its first market launch (international birth date, 1 June 1993) to 31 December 2004. The main measures were the patterns and reporting rates of pregnancy (stillbirth and spontaneous and induced abortion) and fetal/neonatal outcomes (congenital abnormalities, perinatal syndromes and withdrawal symptoms) for women administered risperidone during pregnancy.

Results: Overall, 713 pregnancies were identified in women who were receiving risperidone. Data were considered prospective in 516 of these, and retrospective in the remaining 197 cases. The majority of the known adverse pregnancy and fetal/neonatal outcomes were retrospectively reported. Of the 68 prospectively reported pregnancies with a known outcome, organ malformations and spontaneous abortions occurred 3.8% and 16.9% (when the 15 induced abortions were excluded from the denominator, as they were predominantly undertaken for nonmedical reasons), respectively, a finding consistent with background rates of the general population. There were 12 retrospectively reported pregnancies involving major organ malformations, the most frequently reported of which affected the heart, brain, lip and/or palate. There were 37 retrospectively reported pregnancies involving perinatal syndromes, of which 21 cases involved behavioural or motor disorders. In particular, there was a cluster of cases reporting tremor, jitteriness, irritability, feeding problems and somnolence, which may represent a withdrawal-emergent syndrome.

Conclusion: This comprehensive review of the Benefit Risk Management Worldwide Safety database for case reports of risperidone exposure during pregnancy represents the largest ever published dataset documenting pregnancy outcomes for women taking the atypical antipsychotic risperidone. It indicates that *in utero*

exposure to risperidone does not appear to increase the risk of spontaneous abortions, structural malformations and fetal teratogenic risk above that of the general population. Self-limited extrapyramidal effects in neonates were observed after maternal exposure to risperidone during the third trimester of pregnancy. Risperidone should only be used during pregnancy if the benefits outweigh the potential risks.

Background

A significant number of women of childbearing age have schizophrenia or other psychoses.[1] The rapid emergence of new antipsychotic medications, coupled with an increased emphasis on rehabilitation and community-based care for psychotic patients, have led to an increase in fertility rates among women with psychoses. However, their fertility rate remains lower than women of child-bearing age in general.[2]

The management of psychosis during pregnancy requires a careful evaluation of the relative risks and benefits, which can be quite challenging.[3] Physicians must weigh the benefits of controlling severe psychiatric illnesses in pregnant patients and the possible risks to the mother and the fetus of withdrawing treatment, versus the risks to the fetus of continuing antipsychotic treatment.[4-6] Although knowledge of the risk to the fetus from *in utero* exposure to psychotropic medications is incomplete, two comprehensive reviews of the literature have demonstrated that psychotropic medications diffuse readily across the placenta.[7,8] Thus, initiating and/or maintaining medical therapy during pregnancy raises concern regarding obstetric, teratogenic, neurobehavioural and neonatal toxic effects.[9] Available data indicate that first-trimester exposure to low-potency phenothiazines, lithium, certain anticonvulsants and benzodiazepines all increase the relative risk for congenital anomalies.[9-15] Atypical antipsychotic agents were first developed in the mid-1990s, but few studies have examined their safety during pregnancy, since pregnant women are generally not recruited for clinical trials and women usually withdraw from studies if they become pregnant. Nonetheless, results from a recent prospective, comparative study documenting pregnancy outcomes in women exposed to olanzapine (n = 60), risperidone (n = 49), quetiapine (n = 36) and clozapine (n = 6) suggest that the atypical antipsychotics, as a group, do not appear to be associated with an increased risk of major malformations.[16]

Risperidone, which belongs to the chemical class of benzisoxazole derivatives, is indicated for the treatment of acute and chronic schizophrenia and the management of mania in bipolar disorder. Risperidone is available in various oral formulations (0.25, 0.5, 1, 2, 3 and 4mg tablets, a 1 mg/mL oral solution and 0.5, 1 and 2mg orally disintegrating tablets) and, more recently, as a long-acting formulation for intramuscular injection, which is given at dosages of 25, 37.5 and 50mg once every 2 weeks. Clinical studies have demonstrated that oral and long-acting risperidone are both effective and well tolerated in patients with schizophrenia, as demonstrated by significant improvements in total Positive and Negative Syndrome Scale and Clinical Global Impression of Severity scores and reductions in relapse and rehospitalisation rates.[17-19] Similarly, oral risperidone has been shown to be effective in patients with acute bipolar mania, as assessed by improvements in the Young Mania Rating Scale and the Montgomery-Asberg Depression Rating Scale.[20-22]

Although the actual number of women who have been exposed to risperidone during pregnancy is unknown, it has been estimated that 22% of risperidone prescriptions written between January 2002 and January 2005 were for women of child-bearing age.[23] Animal studies have shown that risperidone does not cause direct reproductive toxicity or teratogenic effects;[24,25] however, its safety during human pregnancy has not been established. Consequently, risperidone, like other antipsychotic agents (except clozapine, identified as pregnancy category B), has been identified by the US FDA as being pregnancy category C ("risk cannot be ruled out: adequate well controlled human studies are lacking and animal studies have shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is

Table I. Unique pregnancies in women receiving risperidone

Pregnancy outcome	Prospective	Retrospective	Total
Known outcome	68	197	265
Live births	43	145	188
abnormal outcomes in uninterrupted pregnancies	6	56	62
major organ malformation[a]	2	12	14
minor organ malformations	0	3	3
other[b]	4	41	45
normal outcome	37	89	126
Interrupted pregnancies	25	52	77
induced abortion	15	16	31
spontaneous abortion[a]	9	33	42
stillbirth[a]	1	3	4
Unknown outcome	448	NA	448
Total	516	197	713

a In the general population, major birth defects have been estimated to occur in 3.6% of all pregnancies, spontaneous abortions in 10–25% of all pregnancies and stillbirth in 0.5% of all pregnancies.[27,28]

b Includes perinatal syndromes, prematurity, abnormal laboratory results and long-term developmental syndromes.

NA = not applicable.

administered during pregnancy; but the potential benefits may outweigh the potential risk").[26]

The objective of this study was to determine whether exposure to risperidone during pregnancy is associated with poor fetal and neonatal outcomes in patients with psychotic disorders by examining prospective spontaneous reports of abnormal outcomes, as well as by clinically evaluating all case reports (prospective and retrospective) of organ malformations or other congenital abnormalities, perinatal syndromes and long-term developmental syndromes.

Methods

All prospective and retrospective reports of risperidone exposure during pregnancy received by Benefit Risk Management, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, from any source or country are entered into the Benefit Risk Management Worldwide Safety database, regardless of outcome, on an ongoing basis. A search of this database was undertaken to identify all cases of pregnancy exposure, as well as all adverse maternal or fetal/neonatal outcomes, in women prescribed any dose or formulation of risperidone, regardless of indication, reported to the company from its first market launch (international birth date, 1 June 1993) to 31 December 2004. This was performed by identifying maternal and child cases based on database-record attributes, by searching the database for cases that contained selected preferred terms (PTs) from MedDRA (the Medical Dictionary for Regulatory Activities), an internationally approved medical technology designed to support the classification, retrieval, presentation and communication of medical information between countries. Maternal cases were identified by searching the database for records that had the classification attribute 'pregnancy exposure/pregnancy', contained the PT 'Drug exposure during pregnancy', contained the characters 'preg' in the narrative, or contained PTs that included the word-phrase '*abortion*'. Child cases were identified by searching the database for records that contained a patient age of ≤1 month or a designated age group of 'Neonate' or 'Infant' and by searching retrieved maternal cases for linked child records. To ensure that all relevant maternal and child cases were retrieved, the database was also searched for cases that contained the following PTs: 'Stillbirth', 'Intra-uterine death', 'Death neonatal', 'Caesarian section', 'Chromosome abnormality', 'Fetal disorder' and 'Developmental delay'. Searches included reports from clinical trials as well as spontaneous postmarketing reports from the following sources: physicians, the literature, registries, consumers and health authori-

ties. For the purpose of this analysis, clinical study reports for which the treatment allocation was still blinded were assumed to involve risperidone. Unblinded clinical study reports that were determined to not involve risperidone were excluded. A report of pregnancy exposure was considered to be prospective if the earliest report of pregnancy contained no pregnancy outcome information, whereas a report was considered to be retrospective if the earliest report of pregnancy also contained pregnancy outcome information.

Results

A total of 713 unique pregnancies in women with psychiatric illness receiving oral or long-acting risperidone were identified. Altogether, 516 cases were classified as prospectively reported and 197 as retrospectively reported. Of all the pregnancies, 188 were categorised as live births, 77 as interrupted pregnancies and 448 as pregnancies with an unknown outcome. The majority of unique pregnancy reports documented either a live birth with a healthy outcome (n = 126) or provided no outcome information (n = 448) [table I].

Prospectively Reported Cases

Overall, there were 516 prospective reports of pregnancies in women receiving risperidone. However, 448 of these cases reported an unknown outcome, leaving just 68 cases reporting on fetal and neonatal outcomes. In 37 cases, a normal outcome was reported. Of the 68 prospectively reported pregnancies with a known outcome, organ malformations and spontaneous abortions occurred in 3.8% and 16.9%, respectively (when the 15 induced abortions were excluded from the denominator as they were predominantly undertaken for nonmedical reasons).

Interrupted Pregnancies

Prospectively reported interrupted pregnancies occurred in 25 patients receiving oral risperidone (n = 18), long-acting risperidone (n = 3) and oral plus long-acting risperidone (n = 3) for schizophrenia, psychotic symptoms, bipolar disorder and other mood disorders or symptoms (formulation data were not available for one patient). In the 22 cases that reported maternal age, the mean age was 30.6 years. Of the 21 cases that provided information on the trimester of exposure, all confirmed first-trimester exposure to risperidone. In the 11 cases that reported the duration of exposure, the mean duration of risperidone exposure was 11.3 weeks.

Induced Abortion

Amongst prospective reports of interrupted pregnancy, 15 involved an induced abortion, the majority of which involved elective abortions for nonmedical reasons or provided no medical indication for the interruption of pregnancy. Only one case reported a fetal abnormality (tricuspid atresia).

Spontaneous Abortion and Stillbirth

There were nine prospectively reported cases of spontaneous abortion (occurring between 8 and 14 weeks in the four cases reporting gestational age at the time of abortion). No fetal abnormalities were reported for these pregnancies. One pregnancy resulted in stillbirth at 27 weeks due to placental abruption.

Uninterrupted Pregnancies with Abnormal Outcomes

Major Organ Malformations

Two uninterrupted pregnancies involving major organ malformations were prospectively reported. A 35-year-old woman with gestational diabetes mellitus who took risperidone daily throughout pregnancy gave birth at 40 weeks' gestation to a 2.9kg boy who had grade III oesophageal atresia, hypoplasia of the pinna of the ear and slight facial dysmorphia. These events were confounded by the patient's concomitant use of tropatepine, dipotassium clorazepate (known to be teratogenic), chlorpromazine and buprenorphine throughout pregnancy. The reason for risperidone treatment was not reported in this case. A 39-year-old woman with schizophrenia who took risperidone daily for 1 month during the first trimester, concomitantly with lormetazepam, gave birth to a 2.8kg girl with multiple congenital abnormalities (pulmonary artery stenosis, abdominal heterotaxy and splenic agenesis), consistent with Ivemark's Syndrome.

Withdrawal and Other Perinatal Syndromes

Four cases of perinatal syndromes were prospectively reported, involving behavioural and motor disorders (considered a possible withdrawal syn-

drome) [n = 1], birth trauma (n = 1) and prematurity (n = 2). In the case involving a possible withdrawal syndrome, a 35-year-old primigravid woman with schizophrenia, who occasionally drank alcohol during pregnancy and who took risperidone on a daily basis, concomitantly with imipramine and clonazepam throughout pregnancy, gave birth to a boy who was sleepy for the first few days, then jittery for 10 days and slow to suckle. There was no information on breastfeeding in this case report. No specialised care or specific intervention was mentioned. The remaining three cases of perinatal syndromes described prematurity, prematurity and erythroderma, and a nuchal cord. One of the cases of prematurity was described in the context of a single day of maternal therapy with risperidone during pregnancy for delusional disorder and was not considered to be related to risperidone exposure. This case was complicated by a history of cigarette smoking and illicit drug use, as well as *Escherichia coli* septicaemia during pregnancy. For the other case of prematurity (with erythroderma), maternal alcohol abuse was also reported; the case reporting a nuchal cord was confounded by polysubstance abuse, including alcohol, intravenous drugs and daily amphetamine use. None of the cases of perinatal syndromes described congenital anomalies or long-term complications.

Retrospectively Reported Cases

Overall, there were 197 retrospective reports of pregnancies in women receiving risperidone. By definition, the birth outcome for all of these reports is known.

Interrupted Pregnancies

Retrospectively reported interrupted pregnancies in patients receiving oral risperidone (n = 44), long-acting risperidone (n = 2) or oral plus long-acting risperidone (n = 1) occurred in 52 cases (formulation data were not available for five patients). The characteristics of these cases are shown in table II.

Induced Abortion

There were 16 retrospectively reported pregnancies that resulted in an induced abortion, the majority of which involved elective abortions for nonmedical reasons or provided no medical indication for the interruption of pregnancy. Fetal abnormalities were observed in two cases, but these were considered unrelated to risperidone exposure. The first case, which described lumbar myelomeningocele, a lemon shaped head, dilated ventricles and a banana-shaped cerebellum, lacked a temporal relationship to oral risperidone treatment since the drug had been discontinued 1 month prior to conception. The second case, which reported severe deformation of the fetus, was thought by the reporting physician to be caused by illicit drug use.

Spontaneous Abortion and Stillbirth

There were 33 retrospectively reported cases of spontaneous abortion, of which two were associated with fetal abnormalities that were described only as unspecified chromosomal abnormalities and that resulted in fetal loss at 10 and 12 weeks' gestation, respectively. Three pregnancies resulted in stillbirth. In one case, the reporting physician suspected this to be the result of placental abruption, whereas another case noted the presence of maternal-fetal toxoplasmosis, other, rubella, cytomegalovirus and herpes simplex syndrome. In the third case of stillbirth, no information about the condition of the fetus was provided.

Uninterrupted Pregnancies with Abnormal Outcomes

Major and Minor Organ Malformations

There were 12 retrospectively reported pregnancies involving major-organ malformations affecting the face: lip/palate (n = 2); auricle (n = 1); brain (n = 3); heart (n = 3); skeleton (n = 1); mid-gut (n = 1); and one case describing a multi-organ syndrome (Pierre Robin) [n = 1]. No morphological pattern of events describing brain or heart abnormalities could be detected. Four cases reported risperidone use only in the first trimester, one only in the second trimester and one in the second and third trimesters. Five reports described maternal use throughout the first, second and third trimesters. One case did not report on the trimester of exposure to risperidone. Patients were being treated for a range of psychiatric illnesses, including schizophrenia, psychosis, delusions, depression and hypomania. In 10 of 12 cases, concomitant or co-suspect medications included one or more other antipsychotic agents, an antiepileptic drug and/or a benzodiazepine; in the remaining two cases, no in-

Table II. Characteristics of retrospectively reported interrupted pregnancies in women receiving risperidone

Parameter	Spontaneous abortion	Induced abortion	Stillbirth	Total[a]
Total cases	33	16[a]	3	52[a]
Maternal age (years)				
n	25	13	3	41[a]
mean	32.5	27.5	36.3	31.1
median (range)	33 (20–48)	25 (19–38)	36 (32–41)	32 (19–48)
Duration of exposure (weeks)				
n	21	4	3	28
mean	6.7	7.4	18.7	8.2
median (range)	6 (0.14–17.5)	5.5 (0.14–26)	16 (15–25)	6.5 (0.14–26)
First-trimester exposure				
n	27	13	3	43
yes	27	11	2	40
no	0	2	1	3
Risperidone formulation				
n	31	13	3	47
oral	30	12	2	44
LAI	1	1	0	2
oral + LAI	0	0	1	1
Indication				
n	24	13	2	39
schizophrenia and psychotic symptoms	18	13	2	33
bipolar and other mood disorders or symptoms	5	0	0	5
other (anxiety)	1	0	0	1

a Includes one patient who discontinued risperidone 1 month prior to conception.

LAI = long-acting injectable formulation; **n** = the number of cases contributing information.

formation was reported with respect to concomitant medications (table III).

There were also three retrospectively reported pregnancies involving minor organ malformations affecting the vascular system (capillary haemangioma in the leg), inguinal canal (undescended testis and hydrocele) and skeleton (unspecified, but requiring a 'Craig splint' to prevent hip displacement). The report of hydrocele was confounded by maternal use of other antipsychotic agents, an anti-epileptic, a benzodiazepine and alcohol throughout pregnancy.

Withdrawal and Other Perinatal Syndromes

Altogether, there were 37 retrospectively reported pregnancies involving perinatal syndromes in women treated with oral or long-acting risperidone for a wide range of psychiatric illnesses including schizophrenia, psychotic disorder, depression, anxiety, bipolar disorder and phobia. Of these cases, 21 involved behavioural or motor disorders, that either referred explicitly to drug withdrawal or described events that possibly represented a withdrawal-emergent syndrome (WES) [see table IV, along with the single prospective report of such a case]. Among these cases, third-trimester exposure to risperidone was present in 13, whereas only first-trimester exposure was reported in one case. Seven cases did not report the trimester of exposure. Adverse events reported amongst the cases of WES included: reported drug withdrawal (n = 13), movement disorder or tremors (n = 9), jitteriness or irritability (n = 8), feeding problems (n = 8), somnolence and lethargy (n = 4) and convulsions or seizures (n = 3). Of the 13 cases reporting drug withdrawal, five were attributed to withdrawal of concomitant medications by the reporting physician. A further two cases attributed withdrawal symptoms to be possibly related to risperidone, including a case that attributed the events to both risperidone and the concomitant medica-

Table III. Retrospectively reported pregnancies in women receiving risperidone that resulted in major organ malformations

Characteristics of the mothers	Organ-system malformation	First trimester risperidone exposure (yes/no)	Concomitant benzodiazepines, antidepressants, antiepileptics or other antipsychotic agents	Comments
Face, auricle				
27 years old, schizophrenia	Cleft lip and palate	Y	Chlorpromazine	Cleft lip and palate detected on ultrasound evaluation at 25 weeks. No past obstetric or family history provided
33 years old, psychosis, history of type II diabetes mellitus, smoked cigarettes until 30th week of pregnancy	Thoracic vertebra injury and cleft lip and palate	Y	Diazepam	Child also experienced neonatal convulsions, prolonging hospitalisation. No family history of congenital malformations or hereditary disorders
30 years old, schizophrenia and affect lability, history of cigarette and alcohol consumption	Right-auricular achondroplasia	Y	Carbamazepine 400 mg/day throughout pregnancy	At 3-month follow-up examination, infant was well with no abnormal findings on physical examination. No family history of congenital anomalies or hereditary disorders
Multiorgan syndromes				
33 years old, schizophrenia	Pierre Robin syndrome, manifest with micrognathia, glossoptosis and cleft palate	Y	Clobazam after first trimester	Unknown medical, obstetric, family or social history
Brain				
34 years old, schizophrenia	Corpus callosum agenesis	Y	Perphenazine, zuclopenthixol, haloperidol, temazepam	Caesarean section was performed at 32 weeks due to pre-eclampsia. Condition of infant was stable
35 years old, delusions	Moyamoya disease	N	Pipamperone 50 mg/day for 14 days during first trimester. Ethyl loflazepate 2 mg/day for 49 days during first trimester. Brotizolam 0.25 mg/day intermittently. Bromazepam 4–6 mg/day during the second and third trimesters	Female infant experienced a cerebral infarction causing hemiplegia on the left side 8 months after birth. Infant required surgery, after which paralysis disappeared and she recovered completely
35 years old, schizoaffective psychosis	Ventricular cyst in the brain	N	Carbamazepine 600 mg/day, paroxetine 20 mg/day, flupentixol 50mg every 2 weeks throughout pregnancy	Infant born 10 weeks pre-term with bleeding from the ventricular cyst. Afterwards, child developed normally although head circumference was above the 97th percentile
Heart				
Age unknown, schizophrenia	Patent foramen ovale	Y	Flunitrazepam	Severity of defect and outcome was not reported

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Table III. Contd

Characteristics of the mothers	Organ-system malformation	First trimester risperidone exposure (yes/no)	Concomitant benzodiazepines, antidepressants, antiepileptics or other antipsychotic agents	Comments
24 years old, paranoid psychosis	Hypoplastic left heart	Y	Not reported	
Age unknown, depression	Dilated cardiomyopathy and 'congenital abnormality' (not otherwise specified)	Unknown	Not reported	Child was awaiting heart transplantation at the time of reporting
Skeleton				
30 years old, psychotic disorder, history of anti-phospholipid syndrome and three spontaneous abortions	Mild talipes equinovarus	Y	Haloperidol, chlorpromazine, clonazepam	Infant had a favourable outcome with physiotherapy
Midgut				
30 years old, hypomania	Gastroschisis	Y	Haloperidol	Anomaly had been detected by ultrasound at 12 weeks. Infant required surgical correction of the anomaly

tions. A single case attributed the withdrawal symptoms as likely to be related to risperidone therapy. The remaining five cases provided no causality attribution by the reporter. Eighteen of the 21 retrospectively reported cases of possible withdrawal syndromes were confounded by concomitant use of antidepressants, benzodiazepines, other antipsychotics, narcotics, alcohol or illicit drug use. Of these 18 cases, 14 specifically reported that one or more of these classes of medications were used during the third trimester. The use of general anaesthesia or narcotics during delivery was reported in one and three cases, respectively.

The age at onset of withdrawal symptoms was reported to be from birth to 13 days. Although several cases described onset within 1–3 days after birth, and others within weeks, more than half reported some symptoms at birth, such that a distinction could not be definitively made between potential drug toxicity and possible withdrawal symptoms. Moreover, although risperidone is excreted into human breast milk,[24] 19 of 21 cases did not provide information about whether the infant was breast-fed, making it difficult to determine if or when risperidone was completely withdrawn. When time to resolution was specified, events were generally self-limiting, as indicated by resolution of the reported events without documented intervention, and with the exception of one case, resolved within a matter of days or weeks. This case, which described 4–5 months of typical symptoms (irritability, hypotonia, poor sucking ability), was confounded by concomitant benzodiazepine use by the mother during the third trimester of pregnancy and by the baby as treatment for symptoms and documented delayed myelination of the brain. The postnatal course was particularly suggestive of WES since improvement was seen following neonatal therapy with risperidone. Three case reports explicitly stated that the infants required intensive care. An additional seven case reports indicated that special care was required because patients were 'admitted' or 'transferred' to paediatric 'units' or required prolonged hospitalisation. The majority of cases (n = 15) did not report specific remedial measures. However, in the remaining six cases, infants received treatment with oxygen, feeding through a catheter or treatment with anticonvulsants (phenobarbital/phenobarbitone),

Table IV. Pregnancies exposed to risperidone that resulted in possible withdrawal syndromes[a]

Characteristics of the mothers	Third trimester risperidone exposure (yes/no)	Risperidone dose	Relevant concomitant drug exposure during the third trimester or where the trimester of use was unknown	Relevant adverse events	Time to onset from birth	Time to resolution	Reported treatments
35 years old, schizophrenia, occasional alcohol consumption[b]	Y	12 mg/day from 3 days prior to delivery, daily dose ↓ to 10mg for 2 days, then to 8mg	TCAs (imipramine 80 mg/day), BDZs (clonazepam 1mg), alcohol	Somnolence Jitteriness Poor sucking reflex (slow to suckle)	At birth	Few days 10 days Unknown	None reported
32 years old, schizophrenia, smoked 1.5–2 packs of cigarettes a day	Y	4 mg/day (long-term treatment)	SSRI (sertraline 100 mg/day), narcotic analgesic during labour and delivery (pethidine), cigarette smoking	Hypertonia Jitteriness	19 hours	Unknown ↓ 27 hours post-delivery	None reported
Age and condition unknown	Y	Dose unknown	SSRI (sertraline)	Neonatal tremors, 'jitteriness' Hypertonia	At birth 19 hours	Unknown (↓ and intermittent at 72 hours) Unknown	None reported
Age and condition unknown, alcohol consumption during pregnancy, already had 3 children; youngest had developmental disorder	Y	1 mg/day throughout	TCA (clomipramine), BDZ (flunitrazepam 2 mg/day), alcohol	Cyanosis, deterioration in tonus of the extremities Tachypnoea, hyperreflexia Muscle contractions, involuntary twitching, irritability Tremor Nystagmus Drug withdrawal syndrome	At birth 24 hours 15 days	15+ days 1 day 'Long time after birth' 15 days Same day Unknown	Placed in an incubator and given oxygen
24 years old, schizophrenia	Y	1 mg/day during the last 4 months	SSRI (sertraline 50 mg/day)	Hypersensitivity, choking, drug withdrawal syndrome (signs of hyper-responsiveness, irritability and 'jitteriness')	2–3 days	24 hours post-event	None reported
Age and condition unknown, smoked five cigarettes a day during pregnancy, cocaine and marijuana use in the second and third trimester	Y	Dosage uncertain (2 or 4mg day)	BDZs (unspecified), cigarette smoking, illicit drug use (cocaine, marijuana)	Cyanosis, pallor, drug withdrawal syndrome, 'slow to cry', hyperreflexia Convulsions	At birth Soon after delivery	Not reported	None reported

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Table IV. Contd

Characteristics of the mothers	Third trimester risperidone exposure (yes/no)	Risperidone dose	Relevant concomitant drug exposure during the third trimester or where the trimester of use was unknown	Relevant adverse events	Time to onset from birth	Time to resolution	Reported treatments
39 years old, unknown medical history	Not documented	Dose unknown	BDZs (nitrazepam), other antipsychotics (levomepromazine)	Poor suckling reflex[c]	Birth	Not reported	None reported
30 years old, psychotic disorder	Not documented	Dose unknown	BDZs (unspecified), other antipsychotics (thioridazine), SSRI (unspecified)	Drug withdrawal syndrome (restlessness and fussy feeding)[d]	13 days	Not reported	None reported
33 years old, schizophrenia, history of cigarette smoking	N	2 mg/day during first and second months	Opioid analgesic (methadone), cyamemazine, cigarette smoking	Drug withdrawal syndrome	Birth	Not reported (outcome favourable, baby showed healthy psychomotor development)	Not reported
Age and condition unknown, history of cigarette smoking	Y	4 mg/day during last 12.5 weeks	BDZs (cloxazolam), other antipsychotics (chlorpromazine/ promethazine), AEDs (phenobarbital, carbamazepine), cigarette smoking	Fetal distress syndrome, drug withdrawal convulsions, dysphagia, bradycardia, haemorrhage intracranial	Birth	Discharged at 3 weeks and made a full recovery	Aspiration, phenobarbital suppository for 1 week, antibacterials
Unknown age, severe psychosis	Y	Dose unknown for first 6.5 weeks. At 36 weeks restarted on 8 mg/day	BDZs (diazepam), other antipsychotics (chlorpromazine, sulpiride, haloperidol), AEDs (clonazepam)	Hypotonia, somnolence Feeding disorders	Birth	13 days Not reported	None reported, baby was fed with a catheter
Unknown age, schizophrenia and depression	Not documented	4 mg/day	SSRI (paroxetine 40 mg/day)	'Jitteriness' Drug withdrawal syndrome	At birth	Was still jittery after 18 days Not reported (recovered)	None reported, phenobarbital
				Convulsion	40 hours		
29 years old, schizophrenia	Not documented	Dose unknown	Narcotic during delivery (unspecified)	Feeding problems[e]	1 day	7 days	None reported

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Table IV. Contd

Characteristics of the mothers	Third trimester risperidone exposure (yes/no)	Risperidone dose	Relevant concomitant drug exposure during the third trimester or where the trimester of use was unknown	Relevant adverse events	Time to onset from birth	Time to resolution	Reported treatments
22 years old, acute psychosis	Y	8 mg/day during last 4 months	BDZs (diazepam), other antipsychotics (alimemazine)	Hypotonia, somnolence	At birth	1 week	None reported
33 years old, severe depression with paranoia	Y	4 mg/day from 20 weeks to birth	SSRI (sertraline), opioid analgesic during delivery (unspecified)	Drug withdrawal syndrome	2 days	2 days	None (resolved spontaneously)
Unknown age and condition	Not documented	Oral risperidone 4 mg/day, long-acting risperidone 25mg every 2 weeks	None reported	Diarrhoea, lethargy, agitation, possible withdrawal syndrome	Unknown	Not reported	None reported
35 years old, schizophrenia	Y	1 mg/day throughout pregnancy	General anaesthesia during delivery	Somnolence, depressed level of consciousness Hypersalivation Drug withdrawal syndrome[e]	Birth	24 hours, 12 hours 12 hours 2 days	Oxygenation, breast feeding discontinued after 24 hours
30 years old, psychotic disorder	Not documented	3 mg/day	Other antipsychotics (clozapine 100 mg/day)	Withdrawal syndrome due to clozapine (shivering)	At birth	Not reported	None reported
Unknown age, depression	Not documented	0.25 mg/day	SSRI (sertraline 150mg/day)	Drug withdrawal syndrome, irritability,[f] muscle spasms,[f] tremor,[f] laryngomalacia[f]	24 hours	8 days	None reported

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Table IV. Contd

Characteristics of the mothers	Third trimester risperidone exposure (yes/no)	Risperidone dose	Relevant concomitant drug exposure during the third trimester or where the trimester of use was unknown	Relevant adverse events	Time to onset from birth	Time to resolution	Reported treatments
24 years old, unknown medical condition, smoked 10 cigarettes a day	Y	3 mg/day for last 2 weeks of pregnancy	BDZs (prazepam), other antipsychotics (zuclopenthixol), cigarette smoking	Hypotonia,[g] dyskinesia,[g] hypertonia, developmental coordination disorder (hyperirritability, hyperexcitability, poor eye pursuit, poor sucking ability, primitive reflexes),[g] brain malformation (delayed myelination diagnosed at 5 months)[g]	8–10 days	Dystonias recovered at 4–5 months of age	Trihexyphenidyl with no improvement, diazepam started, then risperidone was introduced and clinical improvement observed; within 15 days of discontinuation of risperidone treatment, hyperexcitability persisted and patient had episodes of dystonia
40 years old, 'heavy' psychiatric history, bipolar I disorder	Y	Dose unknown	BDZs (diazepam)	Hypotonia, dystonia, feeding problems (poor suckling)	At birth	Not reported	None reported
Unknown age and condition	Y	1 mg/day during latter half of pregnancy	BDZs (lorazepam), SSRI (paroxetine 20 mg/day), AED (valproate sodium 600 mg/day)	Drug withdrawal syndrome (increased muscle tone and irritability, overactive Moro reflex, involuntary facial movements around the mouth)[h]	24 hours	Improved at 1 month and eventually recovered	None reported

a All cases, bar one, were retrospectively reported.

b Prospectively reported.

c Investigator suspected the event to be related to concomitant nitrazepam and levomepromazine.

d Reporter considered event likely related to concomitant benzodiazepine exposure.

e Reporting physician considered the event to be possibly related to risperidone.

f Events were interpreted by the reporting physician as withdrawal symptoms associated with the abrupt withdrawal of sertraline.

g Differential diagnoses considered by the reported included overdose of neuroleptic, neuroleptic withdrawal syndrome and benzodiazepine withdrawal.

h Reporting physician considered events to be related to risperidone, valproate and paroxetine.

AED = anitepileptic drug; **BDZ** = benzodiazepine; **SSRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant; ↓ indicates decreased.

Table V. Retrospectively reported pregnancies in women receiving risperidone that resulted in perinatal syndromes during pregnancy

Characteristics of the mothers	Medical diagnosis	Risperidone[a] dose and exposure during pregnancy	Co-suspect/concomitant medications during pregnancy	Fetal and neonatal outcomes (infant full term, 38–41 weeks, unless otherwise specified)
Respiratory difficulties				
23 years old	Unknown	2 mg/day during the second and third trimesters	Pentazocine, diazepam, methylergometrine, oxytocin and mepivacaine during labour and delivery (co-suspect medications). Pipamperone, diazepam, trihexyphenidyl and promethazine (concomitant medications)	2.9kg male with transient tachypnoea requiring oxygen therapy. Physician considered event to be unrelated to risperidone
Unknown	Unknown	2 mg/day during the fifth and sixth months of pregnancy	Not reported	4.9kg male presented with polypnoea, which resolved spontaneously
24 years old	Unknown	Unknown	Fluphenazine, citalopram and fluoxetine (concomitant medications)	Premature (31.5 weeks) 1.4kg infant required oxygen therapy for 1 week and nasogastric feeding for 2–3 weeks
31 years old; 'allergic to recreational drugs'	Schizophrenia	6 mg/day during the second and third trimesters	Co-suspect medications included intramuscular haloperidol and biperiden during labour	3.6kg male with a low respiratory rate. According to the physician, the event was not related to risperidone
37 years old	Depression	2 mg/day (duration unknown)	Not reported	Male infant with polypnoea, which resolved spontaneously
Seizures				
28 years old; pregnancy was complicated by toxemia	Phobia	2mg, one day before delivery of twins	Clomipramine (for last 7 weeks of pregnancy) and fluvoxamine (co-suspect medications). Trihexyphenidyl, 1 day before delivery, phenobarbital, valproic acid (sodium valproate) and antibacterials (concomitant medications)	First twin was born immature (1.8kg) with apnoeic episodes followed by convulsions, tachypnoea and hyperbilirubinemia. When the apnoeic episodes subsided, chronic convulsions persisted for 5 weeks. Second twin was healthy. Physician considered the mother's underlying disease to be a possible cause for the events
Prematurity and intra-uterine growth retardation				
25 years old	Unknown	2.5 mg/day (duration unknown)	Paroxetine 20 mg/day, levothyroxine sodium 0.75 mg/day and lorazepam 0.5mg every 4 hours as needed (concomitant medications)	Male infant born prematurely (26 weeks' gestation) with oligohydramnios
35 years old	Unknown	4 mg/day (duration unknown)	Not reported	'A premature infant'
42 years old; no prenatal care during pregnancy	Unknown	10 mg/day throughout pregnancy	Concomitant medications included paroxetine 20 mg/day	Male infant born in a toilet. Infant's temperature was 30°C on admission and he was small for gestational age (40 weeks). Temperature stabilised and he was discharged as a well baby

Continued next page

Table V. Contd

Characteristics of the mothers	Medical diagnosis	Risperidone[a] dose and exposure during pregnancy	Co-suspect/concomitant medications during pregnancy	Fetal and neonatal outcomes (infant full term, 38–41 weeks, unless otherwise specified)
Unknown age, heavy cigarette smoker	Unknown	2–3 mg/day throughout pregnancy	Haloperidol, zopiclone and nitrazepam (concomitant medications)	2.5kg male with fetal growth retardation. Reporter considered event to be related to mother's heavy nicotine use
Birth trauma				
Unknown age	Schizophrenia	12 mg/day (duration unknown)	Bromperidol, clotiazepam, trihexyphenidyl and zotepine (co-suspect medications)	3.7kg male with neonatal asphyxia, subarachnoid/subdural haemorrhage and shoulder dystocia. Infant required intensive care for cyanosis, shock, retractive breathing, decreased muscle tone, congenital brain damage, unilateral facial palsy, metabolic acidosis and hyperbilirubinemia
Jaundice				
31 years old	Psychosis	2 mg/day for 2 months during early pregnancy	Not reported	3.6kg infant who required phototherapy for jaundice
33 years old, enrolled in a clinical trial to evaluate the efficacy of risperidone injection in the treatment of acute exacerbation of schizophrenia	Schizophrenia	Risperidone injection (dose and duration unknown)	Not reported	3.87kg male who required phototherapy for jaundice. Physician reported that a causal association with risperidone was doubtful
Other				
Unknown age	Unknown	1–2 mg/day throughout pregnancy	Not reported	Infant has experienced a low red blood cell count since birth (infant was 1 year old at the time of this report)
Unknown age	Unknown	Unknown	Concomitant medication included olanzapine during second and third trimesters	2.7kg infant experienced transient tachycardia, which resolved spontaneously
38 years old	Psychosis	2 mg/day during the first 2 months of pregnancy	Haloperidol 2 mg/day started 3 weeks after discontinuation of risperidone (concomitant medications)	Infant died immediately after birth. Fetus had no visible malformations and cause was not specified

a Oral risperidone unless otherwise stated.

ECG = electrocardiogram; **MRI** = magnetic resonance imaging.

benzodiazepines (diazepam), risperidone or antiparkinsonian agents (trihexyphenidyl).

The remaining 16 of 37 cases of retrospectively reported perinatal adverse events lacked a discernible pattern of anomalies and provided no evidence to implicate risperidone as their cause. The events included respiratory difficulties, seizures, prematurity and intra-uterine growth retardation, birth trauma, jaundice and other complications such as low red blood cell count and tachycardia. These additional perinatal syndromes are shown in table V.

Long-Term Developmental Syndromes

There were four retrospectively reported pregnancies that resulted in poorly defined long-term developmental syndromes. A 28-year-old woman who took risperidone with fluoxetine and benzotropine (trimester unspecified) gave birth to a boy who experienced seizures from birth and had a degree of developmental delay. A woman of unknown age who took risperidone concomitantly with pipotiazine, procyclidine, temazepam, diazepam and sertraline (trimester unspecified) gave birth to a boy with significant neurodevelopmental problems. The mother had used illicit drugs, including amphetamines and cannabis, before and throughout pregnancy and drank heavily in the early stages of pregnancy. An 18-year-old woman who was treated with risperidone for a nervous breakdown during the ninth month of pregnancy gave birth to a boy who at 8 months was experiencing motor problems. Finally, a woman of unknown age who was receiving risperidone for the treatment of psychosis during her pregnancy (trimester unspecified), concomitantly with fluoxetine and sertraline, gave birth to a male infant who presented at birth with some degree of myotonia and who continued to have muscle problems at 6 months of age.

Discussion

A significant number of women of childbearing age experience psychiatric disorders requiring treatment with antipsychotic drugs. Indeed, results from a sample of patients receiving community mental heath services in the UK reported that >60% of women with psychotic disorders were mothers.[29] The management of these women during pregnancy presents a therapeutic dilemma. Treatment must always take into consideration the potential effect of therapy on the fetus. However, avoiding medications can present a threat to both the mother and fetus by impairing the mother's ability to care for herself and comply with prenatal care, or by distorting her perspective on pregnancy.[30] Furthermore, stopping antipsychotic treatment during pregnancy may trigger a relapse of psychosis in up to 65% of affected pregnant women,[31] resulting in poor maternal nutrition, increased use of over-the-counter remedies, and alcohol and substance abuse, thereby exposing the fetus to risk factors for adverse pregnancy outcomes.[30] It has been suggested that such stress during pregnancy may affect the learning abilities of the infant and result in developmental delays.[30] As such, clinicians must carefully weigh the risks and benefits for each patient on an individual basis. Atypical antipsychotic agents have been extensively used for the long-term management of schizophrenia and other psychoses, since the most unwelcome effects of conventional antipsychotics (i.e. movement disorders) are less frequent with the atypical agents.[32-34] However, data regarding fetal outcomes following treatment of pregnant women with atypical antipsychotics remain limited. To address this, a cumulative review of the Benefit Risk Management Worldwide Safety database on the use of the atypical antipsychotic risperidone during pregnancy was undertaken to identify the fetal and neonatal outcomes following *in utero* exposure to risperidone. To the best of our knowledge, this is the largest dataset ever published concerning the pregnancy and neonatal outcomes for women receiving risperidone therapy whilst pregnant.

Although pharmacovigilance databases are generally used to collect voluntary adverse-event reports for company drugs from any source (including physicians, the literature, registries, consumers and health authorities), Benefit Risk Management, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, follows a defined procedure to collect, document and follow up reports of pregnancy exposure to risperidone, regardless of whether or not an adverse outcome is reported. In many aspects, this process is consistent with the procedures used by a pregnancy registry. However, due to the nature of voluntary reports, there are limitations to the quality of the data received; impor-

tant follow-up information can often not be obtained despite the most diligent efforts and the analysis is largely dependent on the clinical evaluation of individual well documented case reports.

Overall, 713 pregnancies in women with psychiatric illnesses who received oral or long-acting risperidone were identified, of which 516 cases were prospectively reported and 197 retrospectively reported. A pregnancy was considered to be prospectively reported if the earliest report of pregnancy contained no pregnancy-outcome information, whereas a report was considered to be retrospective if the earliest report of pregnancy also contained pregnancy outcome information. For this analysis, searches included all spontaneous, postmarketing reports from physician, literature, registry, consumer and health authority sources. Although reports from clinical trials were also included, the vast majority of cases were voluntarily reported to Benefit Risk Management, with over half providing no information with respect to the pregnancy outcome.

The majority of known adverse fetal and neonatal outcomes were reported retrospectively. Only two prospectively reported cases identified major organ malformations, and an additional four cases reported perinatal syndromes (two premature births, one case of a nuchal umbilical cord and a case of a behavioural disorder). Nine prospectively reported cases described spontaneous abortions. Of interest, 22.1% of prospectively reported pregnancies resulted in an elective abortion. This is in line with results from a prospective, follow-up study in which 21.1% of women opted for a termination of pregnancy following first-trimester exposure to atypical antipsychotics,[35] and may reflect concerns about the potential teratogenicity of risperidone. However, when viewed in the context of the total number of prospective reports for which outcome data are available, organ malformations and spontaneous abortions accounted for 3.8% (2/53) and 16.9% (9/53) of prospectively reported outcomes, respectively (induced abortions were excluded from the denominator, since most were undertaken for nonmedical reasons). These results are consistent with those from the general population, in which major birth defects have been estimated to occur in 3.6% of all pregnancies and spontaneous abortions in 10–25% of all pregnancies.[27,28] We acknowledge that these results are not incidence rates but rather percentages of voluntarily reported prospective cases where the subsequent outcome has been reported.

Our pregnancy database is primarily limited to voluntary reports of drug exposure during pregnancy. The actual number of women who have been exposed to risperidone during pregnancy is unknown. As of 31 December 2004, worldwide exposure to risperidone, for any indication, was estimated at 21 million person-years, with 22% of prescriptions written between January 2002 and January 2005 being for women of childbearing age (15–44 years).[23] Therefore, it is likely that a relatively large number of women have been exposed to risperidone during pregnancy. For retrospectively reported pregnancies, incidence rates for adverse outcomes cannot be meaningfully calculated because of an obvious upward bias towards reporting adverse outcomes over normal outcomes once the outcome is known. Consequently, the true prevalence of pregnancy outcomes cannot be determined from this dataset comprised primarily of voluntary reports obtained during postmarketing surveillance. Nevertheless, retrospective case reports can be analysed for apparent patterns of abnormality that may indicate a specific teratogenic effect. With the exception of possible withdrawal symptoms, no such patterns were evident.

Overall, there were 197 retrospectively reported pregnancies in women receiving risperidone. Altogether, there were 12 retrospectively reported pregnancies involving major-organ malformations, three involving minor-organ malformations, 37 involving perinatal syndromes and four involving long-term developmental disorders. Of the 12 cases reporting major-organ malformations, the most frequently reported abnormalities involved the heart (n = 3), brain (n = 3) and the lip and/or palate (n = 3). These various abnormalities are amongst the most frequently reported congenital anomalies occurring in the general population (heart and circulation defects: 1/125 to 1/150 live births, nervous system and eye defects: 1/235 live births, cleft lip with or without cleft palate: 1/1000 live births and club foot: 1/735 live births). Consequently, the observed pattern of abnormalities does not suggest a specific teratogenic effect with risperidone. Furthermore, 8 of these 12 cases involved concomitant maternal use of

antidepressants, benzodiazepines and/or antiepileptics that have been reported to cause neonatal complications,[36-40] and may have been temporally related to the period of risk (i.e. the first trimester). In addition, women with psychiatric illnesses have higher prevalence rates of cigarette smoking and alcohol and drug abuse, all of which are strongly associated with low birth weight, preterm birth, organ malformations and perinatal death in the general population.[41-43] Two case reports of major organ malformations indicated a history of cigarette and alcohol consumption. However, this was insufficiently documented in many of the case reports and was, therefore, likely to have been considerably underestimated, especially since the National Institute of Mental Health reported that 33.7% of patients with schizophrenia have lifetime co-morbid alcohol abuse or dependence.[44]

Of the 37 retrospectively reported cases involving perinatal syndromes, 21 involved behavioural or motor disorders. In particular, there were several cases reporting tremor, jitteriness, irritability, feeding problems, convulsions or seizures and somnolence in neonates born to women taking risperidone. Although this symptomatology may be consistent with a possible toxicity of risperidone, such effects are difficult to evaluate in the neonate, and may instead represent a WES. WES is a subtype of tardive dyskinesia characterised by choreoathetoid and myoclonic movements of the trunk, extremities and orofacial region that has been found to occur in children following withdrawal of antipsychotic therapy[45,46] and that has also been reported in neonates exposed to antipsychotic medications *in utero*.[47] The diagnosis of WES is generally associated with a good prognosis, with most symptoms resolving quickly.[47] This proved to be the case in our analysis, with all but one case of potential WES resolving in a matter of days to weeks. Only a small minority of cases provided information with respect to potential exposure via breast milk after birth. However, since the cases of WES were generally self-limited, it is unlikely that breast-feeding was a contributing factor in these cases. The four cases describing long-term developmental disorders contained poorly defined events and insufficient detail on clinical course for a meaningful assessment to be made.

Exposure to risperidone during pregnancy was not clearly associated with organ malformations or spontaneous abortions among cases reported in this analysis. A major limitation of this study is the lack of information on long-term neurodevelopmental outcomes in the neonate and growing child.

Conclusion

This comprehensive review of the Benefit Risk Management Worldwide Safety database for case reports of risperidone exposure during pregnancy represents the largest ever published dataset documenting pregnancy outcomes for women taking the atypical antipsychotic risperidone. Although exposure to certain psychotropic drugs *in utero* may increase the risk for specific congenital abnormalities, no clear pattern was identified in association with risperidone in this analysis. The majority of reports were confounded by concomitant medications, several of which are known teratogens. On the basis of the evidence presented here, an increased risk of spontaneous abortions, structural malformations and fetal teratogenicity could not be identified in pregnant women administered risperidone. Self-limited extrapyramidal effects have been observed in neonates after maternal exposure to risperidone during the third trimester of pregnancy. Risperidone should only be used during pregnancy if the benefits outweigh the potential risks.

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