INVEGA® (paliperidone ER)
INVEGA SUSTENNA® (paliperidone palmitate 1-month)
INVEGA TRINZA® (paliperidone palmitate 3-month)
INVEGA HAFYERA® (paliperidone palmitate 6-month)
Use of INVEGA, INVEGA SUSTENNA, INVEGA TRINZA, and INVEGA HAFYERA in Pregnancy or Lactation

Exposure in Pregnancy[a-g]

General Information[a-d]

- Untreated schizophrenia and exposure to antipsychotics, including paliperidone, PP1M, PP3M, and PP6M, during pregnancy pose **risks** to the mother.
- The clinical significance of paliperidone, PP1M, PP3M, and PP6M administered before pregnancy or anytime during pregnancy is not known.

PP1M

Paliperidone is detected in plasma in adult subjects up to **126 days** after a single-dose administration of PP1M

PP3M

Paliperidone is detected in plasma in adult subjects up to **18 months** after a single-dose administration of PP3M

- Paliperidone (9-OH-risperidone) is the major active metabolite of risperidone.

Placental Passage[a-e]

- A prospective observational study including 6 women treated with risperidone (the parent compound of paliperidone) demonstrated **placental passage** of **risperidone** and **paliperidone**.

Congenital Birth Defects/Cardiac Malformations[a-d, f, g]

- A retrospective cohort study from a Medicaid database of 9258 women evaluated exposure to antipsychotics during pregnancy.
  - Results did not indicate an overall increased risk for major birth defects.
  - There was a **small increase** in the risk of **major birth defects** and **cardiac malformations** in a subgroup of women exposed to the parent compound of paliperidone, risperidone, during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

RR of Congenital Birth Defects or Cardiac Malformations on Exposure to Risperidone During Pregnancy

Defects/Malformations	Subgroup of Women Exposed to Risperidone (n=1566)
Major birth defects, RR (95% CI)	1.26 (1.02-1.56)
Cardiac malformations, RR (95% CI)	1.26 (0.88-1.81)

Click on the following links to related sections within the document: Clinical Data - Use During Pregnancy.

Note: There is a pregnancy registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including INVEGA, INVEGA SUSTENNA, INVEGA TRINZA, and INVEGA HAFYERA, during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/[a-d]

Abbreviations: CI, confidence interval; OH, hydroxy; PP1M, paliperidone palmitate 1-month; PP3M, paliperidone palmitate 3-month; PP6M, paliperidone palmitate 6-month; RR, relative risk.

[a]INVEGA SUSTENNA [(paliperidone palmitate) Extended-Release Injectable Suspension] [Prescribing Information].[1] [b]INVEGA [(paliperidone) Extended-Release Tablets] [Prescribing Information].[2] [c]INVEGA TRINZA [(paliperidone palmitate) Extended-Release Injectable Suspension] [Prescribing Information].[3] [d]INVEGA HAFYERA [(paliperidone palmitate) Extended-Release Injectable Suspension] [Prescribing Information].[4] [e]Newport (2007).[5] [f]Huybrechts (2016).[6] [g]Data on file (2022).[7] [h]Weggelaar (2011).[8] [i]Aichhorn (2005).[9] [j]Ilett (2004).[10] [k]Hill (2000).[11]

Fetal/Neonatal Adverse Reactions[a-d]

- **Extrapyramidal and/or withdrawal symptoms** have been reported in neonates who were exposed to antipsychotic drugs, including paliperidone, PP1M, PP3M, and PP6M, during the **third trimester** of pregnancy.

Extrapyramidal and/or withdrawal symptoms:			
	• Agitation • Hypertonia • Hypotonia	• Tremor • Somnolence	• Respiratory distress • Feeding disorder

- These symptoms have varied in severity.
- Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.
- Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Lactation[a-d, h-k]

- The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for paliperidone, PP1M, PP3M, and PP6M and any potential adverse effects on the breastfed child from the aforementioned drugs or from the mother's underlying condition.
- **Limited data** from published literature report the presence of paliperidone in **human breast milk**.

Infants exposed to paliperidone, PP1M, PP3M, and PP6M through breastmilk should be monitored for:		

	• Excess sedation
	• Failure to thrive
	• Jitteriness
		• Extrapyramidal symptoms
		  ○ Tremors
		  ○ Abnormal muscle movements

Infertility in Females[a-d]

- Based on the pharmacologic action of paliperidone (D_2 receptor antagonism), treatment with paliperidone, PP1M, PP3M, and PP6M may result in an increase in serum prolactin levels, which may lead to a **reversible reduction in fertility** in females of reproductive potential.

Click on the following links to related sections within the document: Clinical Data - Use in Lactation Data.

Abbreviations: CI, confidence interval; OH, hydroxy; PP1M, paliperidone palmitate 1-month; PP3M, paliperidone palmitate 3-month; PP6M, paliperidone palmitate 6-month; RR, relative risk.

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PRODUCT LABELING

Please refer to the following section of the Full Prescribing Information[1-4] which is relevant to your inquiry: USE IN SPECIFIC POPULATIONS.

CLINICAL DATA - USE DURING PREGNANCY

Observational, Retrospective, and Prospective Studies

Cicala et al (2023)[12] conducted a real-world, retrospective study analyzing Individual Case Safety Report (ICSR) data from the EUDRAVigilance database between 2011 and 2022 for the use of INVEGA SUSTENNA and INVEGA TRINZA.

A total of 8,152 ICSRs for INVEGA SUSTENNA and INVEGA TRINZA were reported for the 20,226 second-generation antipsychotic (AP) long-acting injectable (LAI) cases examined. The frequency of disorders related to pregnancy, puerperium, and perinatal conditions reported as adverse drug reactions in the ICSRs was 0.4% (n/N=24/6,332) for INVEGA SUSTENNA and 0.2% (n/N=4/1,731) for INVEGA TRINZA.

Onken et al (2018)[13] conducted a prospective cohort study analyzing the outcomes of all pregnancies with paliperidone exposure. Data was gathered from the German Embryotox pharmacovigilance institute from January 2007 to June 2016. Of the 17 assessed pregnancies, 14 resulted in 15 live births (1 set of twins), 2 were spontaneously aborted at 6 weeks and 11 weeks, and 1 elective termination occurred due to personal reasons.

Fifteen of the women were exposed to paliperidone during the first trimester, 7 throughout the pregnancy, and 2 only during the second and third trimester. Risks in this patient population included smoking (65%), alcohol consumption (17%), concomitant teratogenic medication (17%), >35 years (42%), >40 years (29%), and 1 patient with a hepatitis C infection.

None of the infants presented with major congenital malformations. Five infants were born prematurely (<37 gestational weeks), including the twins, which exceeds the expected rate of 9% in Germany's general population. Three of the infants born prematurely were exposed to paliperidone up until the time of delivery. Four infants were small for gestational age.

Paliperidone Palmitate - Case Reports

Pinci et al (2024)[14] described a case report of a 30-year-old patient with schizophrenia who had been in continuous symptomatic remission for the previous 6 years when she presented as 9 weeks pregnant. She had been treated with INVEGA TRINZA (546 mg/3 months) for the past 3 years, and the last dose of INVEGA TRINZA was administered when the patient was 5 weeks pregnant. The patient was also taking lorazepam (2.5 mg). The patient did not have a history of substance and alcohol abuse or any other medical comorbidities; additionally, fetal psychomotor development was reported to be normal, and peripartum depression was ruled out. Due to the patient's concern over past experiences of adverse effects related to the use of LAI APs, including oculogyric crises and fear of excessive weight gain and potential harm to the fetus's health, INVEGA TRINZA was discontinued and oral aripiprazole (15 mg/day) was initiated. The clinical course was uneventful, with a stable remission of psychotic symptoms and the absence of metabolic side effects and excessive weight gain. The fetal development was normal, and a healthy infant was born at 39 weeks with no developmental or congenital abnormalities detected at birth and 4 months after delivery. The patient showed complete clinical remission and stability, with no symptoms of postpartum depression, and was recommended to continue treatment with oral aripiprazole (15 mg/day).

Iwata et al (2021)[15] described a case report of a 30-year-old female diagnosed with schizophrenia. At the time of presentation, the patient was 12 weeks pregnant with uncontrolled symptoms. The patient had a worsening of symptoms due to poor adherence to her oral AP medication and was involuntarily admitted to the hospital at 24 weeks pregnant. The patient was continued on oral olanzapine 20 mg/day but remained hostile, guarded, and withdrawn. Olanzapine was discontinued, and the patient was started on oral risperidone for 7 days to assess efficacy and tolerability before transitioning to INVEGA SUSTENNA at 34 weeks gestation. At 38 weeks gestation, she electively gave birth through cesarean delivery, which was uneventful, and was discharged in 8 days. The newborn showed transient tachypnea managed by nasal continuous positive airway pressure and was discharged 29 days after delivery. Since discharge, her symptoms were controlled on INVEGA SUSTENNA 234 mg every month plus 3 to 6 mg of oral paliperidone. There were no notable complications in the development of the baby. Breastfeeding was abandoned after a discussion of the risks and benefits associated with INVEGA SUSTENNA.

de Azevedo Avelar et al (2020)[16] discussed a case report of a 26-year-old female with schizophrenia who presented to the emergency room with a chief complaint of abdominal pain. After examination, it was determined that the patient was pregnant and actively in labor. The pregnancy was not planned or monitored.

The patient's medical history included a diagnosis of schizophrenia at the age of 20 when she was hospitalized and presented with paranoid delusional ideas, perplexity, disorganized

speech, inappropriate laughs, and absence of insight. During hospitalization, the patient was initiated on oral olanzapine but, after no improvement, switched to clozapine 600 mg. The clozapine dose was reduced to 400 mg due to transaminase elevation and fever and further reduced to 200 mg due to weight gain, somnolence, and amenorrhea. Subsequently, the patient began to miss follow-up appointments after reducing clozapine by herself. Oral risperidone 6 mg/day was initiated; however, the patient maintained weight gain and amenorrhea. Ten months after risperidone was started, the patient was hospitalized due to an increase in schizophrenic symptoms due to noncompliance. Treatment with risperidone was resumed, and INVEGA SUSTENNA 156 mg monthly injection was added. The patient continued to maintain a history of noncompliance, and after 1 year, the patient was reinitiated on INVEGA SUSTENNA 156 mg along with quetiapine 300 mg for emotional instability and irritability. After a year and a half, the quetiapine was stopped, and the dosage of INVEGA SUSTENNA was reduced to 117 mg. After a total of 17 monthly injections of INVEGA SUSTENNA 117 mg, the patient was switched to INVEGA TRINZA 410 mg every 3 months to increase compliance.

INVEGA TRINZA was administered twice, with the second dose given 2 months before the patient arrived at the emergency room in labor. The patient gave birth to a healthy newborn male weighing 2,420 g with an appearance, pulse, grimace, activity, and reflexes (APGAR) score of 9-10-10 with no complications. The patient decided against breastfeeding. Approximately 1 year after birth, the baby showed no health or developmental problems, and the patient remained on treatment with INVEGA TRINZA with no symptoms.

Binns et al (2017)[17] measured paliperidone concentrations in both maternal and cord blood of a 28-year-old Australian aboriginal woman who was pregnant with her second child. The patient had a history of chronic paranoid schizophrenia with onset after her first pregnancy, alcohol and marijuana use, and obesity. Following poor adherence with oral APs and lack of access to community mental health services due to remote living, the patient was initiated on INVEGA SUSTENNA and gained satisfactory symptom control under doses of 234 mg every 4 weeks. The patient and her family decided to continue INVEGA SUSTENNA treatment throughout the pregnancy. While good psychosis control was achieved, the pregnancy was complicated by continued use of marijuana and alcohol along with polyhydramnios. Fetal development was otherwise normal except for bilateral talipes equinovarus (clubfoot), suspected at the 20-week ultrasound. The patient's last INVEGA SUSTENNA dose was 13 days before delivery. Due to fetal distress, labor was induced at 39 weeks, and a 3,840 g newborn male was delivered via cesarean section (APGAR scores 9 at 1 and 5 minutes).

Blood samples were collected from the mother at 15 and 9 hours before delivery. Cord blood was collected from the umbilical vein at the time of delivery. Paliperidone concentrations were measured via a novel liquid chromatography-tandem mass spectrometry assay for very small blood volumes. Results are found in the Table: Maternal and Cord Paliperidone Concentrations 13 Days Following Last 234 mg Paliperidone Palmitate Injection.

Maternal and Cord Paliperidone Concentrations 13 Days Following Last 234 mg Paliperidone Palmitate Injection[17]

Patient	Collection Time	Paliperidone, ng/mL
Mother	15 hr before delivery	12.7
Mother	9 hr before delivery	15.0
Baby	Delivery	7.3

Post-delivery, neonatal examination confirmed bilateral talipes equinovarus but was otherwise normal. The authors noted that the relationship between the talipes and paliperidone exposure is uncertain. Overall, the postnatal course was uncomplicated, and the mother elected not to breastfeed for reasons unrelated to her medication use.

Zomara-Rodriguez et al (2017)[18] described the case of a 34-year-old female patient with bipolar schizoaffective disorder and multiple substance dependence treated with INVEGA SUSTENNA during pregnancy. At the time of presentation, she had a daily tobacco use of approximately 40 cigarettes/day and alcohol (beer) consumption of about 8-10 UBE (1 UBE in Spain = 10 g of pure alcohol). Her medications included olanzapine 10 mg/day, venlafaxine 150 mg/day, and clonazepam 4 mg/day. Due to weight gain, noncompliance, and occasional AP medication abuse, olanzapine was discontinued, and INVEGA SUSTENNA 156 mg every 4 weeks was started. Three weeks after the initial dose, the patient discovered she was 5 weeks pregnant. INVEGA SUSTENNA was reduced to 78 mg every 4 weeks, venlafaxine was replaced by fluoxetine 20 mg/day, and clonazepam was replaced by lorazepam 2 mg/day. Tobacco use was halved during pregnancy, and alcohol consumption was reduced to 3-5 UBE. Except for slight anxiety immediately after discovering she was pregnant and postpartum depression (days 7-9), both of which were self-limiting, the patient remained clinically stable throughout her pregnancy with no psychotic or affective symptoms. At 40 weeks, she gave birth to a healthy (APGAR 9/10 at 1 min after birth; 10/10 at 5 and 10 mins after birth) newborn male 47 cm in length, weighing 2,440 g. The baby was not breastfed. Three weeks postpartum, her INVEGA SUSTENNA dosage was increased to 156 mg every 4 weeks with good treatment compliance. In the first year of follow-up, no abnormalities or malformations were detected in the infant, and psychomotor development (Haizea-Lievant Scale of Infant Development) was age-appropriate. At 12 months, the child's weight and height were 11.5 kg and 77 cm, respectively (65th percentile).

Özdemir et al (2015)[19] discussed a case report of a 37-year-old female with an 8-year history of schizophrenia presenting with persecutory delusions and disorganized behavior. She was 29 weeks pregnant upon admission to the clinic. Her schizophrenia symptoms were in remission for the past year on INVEGA SUSTENNA 156 mg monthly. However, despite regular injections, psychotic symptoms had developed over the last 2 weeks. Symptoms subsided within 3 weeks following the addition of haloperidol 5 mg administered orally once a day. Her treatment regimen remained unaltered during the remaining weeks of her pregnancy and postpartum.

Regular gynecological exams, including ultrasounds, were conducted during the patient's pregnancy with no abnormal findings. Following a normal and healthy pregnancy period, a C-section was performed at week 39 with no complications. The newborn weighed 3,000 g and had an APGAR score of 9. No malformations or growth retardation were detected during the infant's 4-month follow-up period.

Review

Reinstein et al (2020)[20] published a review and guidance for the use of LAIs during pregnancy.

Women with a history of psychotic and affective illness are at a higher risk for psychiatric symptoms during pregnancy. The continuation of LAIs may be appropriate in women with a history of significant psychiatric illness who either wish to become pregnant or recently have become pregnant unless there is a compelling reason for discontinuation. Clinical risk factors to be considered are nonadherence with oral AP medication, history of frequent and extended psychiatric hospitalization associated with schizophrenia, previous psychiatric decompensation during pregnancies, and illicit substance abuse.

Before prescribing an LAI for a patient who is pregnant or wishes to become pregnant, it is important to engage in an informed consent discussion with the patient and to fully discuss the potential risks and benefits of LAI treatment during pregnancy.

When selecting LAIs for pregnant women, clinicians should consider the metabolic profiles of medications, the potential for an increase in dose during pregnancy, length of dosing intervals, consistent plasma drug levels, approved indications, and plans for breastfeeding.

9-OH-Risperidone Concentrations Case Reports

Oriolo et al (2015)[21] reported the case of a 28-year-old female diagnosed with paranoid schizophrenia. The patient was receiving INVEGA 3 mg/day. Treatment was stopped when the patient realized she was in her 8th week of pregnancy. Around the 24th week of pregnancy, the patient's family reported behavioral changes, suspicious attitudes, and irritable mood. The patient was hospitalized during the 36th week of pregnancy with delusion of reference, thought broadcasting, intrusive mental images of her son's violent death, and delusion of biomorphism (delusion that organic dead matter [eg, food and water] are living things) with rejection of food intake and hydration.

Risperidone oral solution titrated up to 4 mg/day, was administered by nasogastric tube. Predose levels of risperidone and 9-hydroxyrisperidone, measured on the 8th day of treatment, were subtherapeutic. A Caesarean delivery occurred during the 38th week of pregnancy. APGAR scores were 9 at the 1st minute and 10 at the 5th minute. The patient showed worsening negativism. The patient received electroconvulsive therapy (ECT). After 2 sessions of ECT, the patient started to accept food and oral medication. Predose levels of risperidone and 9-hydroxyrisperidone increased to therapeutic levels. The patient experienced mild bradykinesia with facial hypomimia and mild upper limb joint rigidity. Risperidone was titrated down as the patient experienced akathisia.

Newport et al (2007)[5] conducted a prospective observational study assessing the placental passage of AP medications (haloperidol, olanzapine, quetiapine, or risperidone) in 54 pregnant females.

Maternal and umbilical cord plasma was collected at delivery to determine AP concentrations via high-performance liquid chromatography (HPLC). Placental passage was defined as the ratio of plasma umbilical cord concentration (ng/mL) to maternal plasma concentration (ng/mL) for both parents and, in the case of risperidone, metabolite. In addition, obstetrical outcomes were assessed.

Before delivery, 6 patients were receiving oral risperidone (mean dose at delivery: 3.0 mg/day) for at least 2 weeks, with a mean duration of 25.9 continuous weeks. Concomitant selective serotonin reuptake inhibitors (SSRIs)/serotonin and norepinephrine reuptake inhibitors (SNRIs) were utilized by 50% of the risperidone group. The mean placental passage ratio was 49.2% for risperidone (95% confidence interval [CI], 13.6-84.8%), with a range of 16.8-105.2%. Umbilical cord plasma concentrations were 0.36 ng/mL for risperidone and 1.31 ng/mL for its active metabolite (9-OH-risperidone). Maternal plasma concentrations were 0.32 ng/mL for risperidone and 3.57 ng/mL for its active metabolite. The risperidone to metabolite ratio was 0.58 in umbilical cord plasma and 0.12 in maternal plasma. Obstetrical outcomes in the risperidone group included birth weight <2,500 g (n=1) and mean APGAR scores (n=6) of 8.7 at 1 minute and 9.2 at 5 minutes.

Oral Risperidone Case Reports

Huybrechts et al (2016)[6] conducted an analysis of a United States Medicaid database from 2000 to 2010 to examine the risk of overall congenital malformations and cardiac malformations associated with first-trimester exposure to APs in females aged 12 to 55 years. The study cohort included 1,341,715 women who met the inclusion criteria and whose pregnancies resulted in live births (mean age: 24 years). Pregnancies with known exposure to teratogenic medications during the first trimester or pregnancies with chromosomal abnormalities were excluded. Women who filled at least 1 prescription for an AP during the first trimester were considered exposed to an AP. Potential confounders included the calendar year, age, race, smoking, multiple gestation, indications for APs, maternal morbidity, concomitant medication use, and general markers of the burden of illness and were accounted for as part of the adjusted analyses.

The most frequently used atypical AP was quetiapine (n=4,221), followed by aripiprazole (n=1,756), risperidone (n=1,566), olanzapine (n=1,394) and ziprasidone (n=697). The

unadjusted analysis implied a significantly increased risk of malformations in atypical APs. In the fully adjusted analysis, the relative risk (RR) shifted to the null for both typical (0.90; 95% CI, 0.62-1.31) and atypical APs (1.05; 95% CI, 0.96-1.16) but remained elevated for risperidone (1.26; 95% CI, 1.02-1.56) (Table: Maternal Exposure to Antipsychotics and RR for Malformations in Infants). The authors commented that the findings for risperidone will require confirmation in additional studies.

Maternal Exposure to Antipsychotics and RR for Malformations in Infants[6]

Cohort	RR for Congenital Malformations			RR for Cardiac Malformations		
	Unadjusted Analysis (RR)	Adjusted for Psychiatric Conditions (RR)	Fully Adjusted (RR)	Unadjusted Analysis (RR)	Adjusted for Psychiatric Conditions (RR)	Fully Adjusted (RR)
Typical APs	1.17	1.00	0.90	1.18	0.94	0.75
Atypical APs	1.36	1.12	1.05	1.40	1.15	1.06
Aripiprazole	1.31	1.04	0.95	1.33	1.06	0.93
Olanzapine	1.30	1.05	1.09	1.24	0.96	0.99
Quetiapine	1.32	1.09	1.01	1.43	1.18	1.07
Risperidone	1.56	1.31	1.26	1.60	1.39	1.26
Ziprasidone	1.14	0.90	0.88	1.12	0.88	0.85
Abbreviations: APs, antipsychotics; RR, relative risk.						

CLINICAL DATA - USE IN LACTATION DATA

9-OH-Risperidone Concentrations - Oral Risperidone Use in Nursing Mothers

Weggelaar et al (2011)[8] published a case report of a 40-year-old woman with bipolar disorder, treated with risperidone 1 mg/day daily during 8 months of pregnancy and 2 mg/day during the final month. The infant was fed breast milk only, and the mother volunteered to measurements of risperidone levels both in the serum and breast milk. Samples were taken over the 24-hour post-dose period. The resulting serum level in the infant was also to be measured.

Risperidone and the metabolite, 9-OH-risperidone could be detected in the serum of the mother. The highest level of risperidone detected in the serum was approximately 4 µg/L, 1 hour post-dose; at 2 hours post-dose, the level was approximately 1 µg/L. Only the active metabolite 9-OH-risperidone could be detected in the breast milk; concentrations recorded between the 3 and 20 hours post-dose were approximately 4 µg/L. No risperidone could be detected in the serum of the infant. The product of the average drug concentration in the breast milk and the milk intake of the infant (150 mL/kg per day) was used to calculate the exposure of the infant to the drug and the metabolite. The authors calculated that the total intake of 9-OH risperidone by the infant was 4.7% of the weight-adjusted oral intake of the mother.

Aichhorn et al (2005)[9] published a case report of a 23-year-old female diagnosed with paranoid schizophrenia, second episode, 1 week after the delivery of her son. The patient was initiated on 2 mg/day of risperidone. The dose was increased to 3 mg/day on day 10, secondary to poor clinical response associated with low maternal drug plasma levels. The mother fed her infant 6 times a day. Risperidone levels in the mother's and infant's serum and the breast milk are presented in the Table: Risperidone (R) and 9-OH-risperidone Concentrations (ng/mL). Fore and hind milk were determined separately, based on the presumption that higher lipid content in hind milk would lead to higher concentrations.

Risperidone (R) and 9-OH-risperidone Concentrations (ng/mL)[9]

	Fore Milk R	Fore Milk OH	Hind Milk R	Hind Milk OH	Maternal Plasma R	Maternal Plasma OH	Infant Plasma[a] R	Infant Plasma[a] OH
Day 6[b]	3	11	2	9	10	43	NA	NA
Day 10[c]	0	1.4	0	1.2	0.4	4	0	0.1
Day 20[d]	0.1	3	0.1	2	1	14	NA	NA

Abbreviations: h, hour; R, risperidone; NA, not available.
[a]Body weight of infant was 4.2 kg.
[b]3h post dose.
[c]15h post dose.
[d]16h post dose; daily dose increased to 3 mg.

The infant's psychomotor development in the hospital was normal, and no sedation or adverse events related to risperidone were detected. Two months after discharge and 5 months after risperidone initiation, the mother and baby were well.

Ilett et al (2004)[10] assessed the safety of breastfeeding during maternal risperidone administration by studying the transfer of risperidone and 9-OH-risperidone into the breast milk of 3 women (breastfeeding, n=2; risperidone-induced galactorrhea, n=1). Infant plasma concentrations were measured. Estimates were made with regard to the amount of drug the infant received. The results are listed in the Table: Breast Milk Study Results.

Breast Milk Study Results[10]

	Case 1 (Galactorrhea)	Case 2 (Breastfeeding)	Case 3 (Breastfeeding)
Age (years)	29	31	25
Risperidone dose (mg/day)	3	4	1.5
Risperidone average conc (milk, µg/L)	<1[a]	2.1[b]	0.39[b]
9-OH-risperidone average conc (milk, µg/L)	5.3[a]	6[b]	7.06[b]
Risperidone plasma conc (µg/L)	<1[a]	NA	NA
9-OH-risperidone plasma conc (µg/L)	14[a]	NA	NA
Milk/Plasma ratio (RIS)	NA	NA	0.1
Milk/Plasma ratio (9-OH-risperidone)	0.36	NA	0.5
Absolute infant dose (µg/kg/day, RIS equivalents)	0.88	0.32	0.06
Absolute infant dose (µg/kg/day, 9-OH-risperidone equivalents)	NA	0.9	1.06
Relative infant dose (risperidone equivalents)	2.3%	2.8%	4.7%
Infant plasma conc	NA	Undetectable	Undetectable
Infant Observed Adverse Events/Abnormalities	NA	None	None

Abbreviations: 9-OH-risperidone, 9-hydroxyrisperidone; conc, concentration; NA, not available; RIS, risperidone.
[a]20 hours after last dose.
[b]Average concentration.

The authors concluded that an infant's short-term exposure to risperidone via breast milk is unlikely to be a significant hazard, but due to limited data, an individual risk-benefit

assessment should be made before making the decision on whether or not to breastfeed during risperidone therapy.

Hill et al (2000)[11] discussed a case report of a 21-year-old female with a 2-year history of bipolar disorder. After delivering her baby, she became increasingly withdrawn and depressed, suffering from paranoid delusions and passivity phenomena. She stopped breastfeeding and was started on risperidone. Her risperidone dose was gradually titrated to 6 mg/day. After 1 week on risperidone 6 mg/day, 7 serial samples of plasma and 6 serial samples of breast milk were drawn over a 24-hour period and tested for risperidone and 9-OH-risperidone levels. The researchers concluded that the nursing infant would receive 0.84% of the maternal dose of risperidone and an additional 3.46% from 9-hydroxyrisperidone. The authors concluded that their recommendation to the patient to discontinue nursing was conservative but appropriate.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 09 May 2024.

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