

## Outcomes of long-acting injectable antipsychotics use in pregnancy: A literature review

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### Abstract

#### BACKGROUND

Women with a history of serious psychotic disorders are at increased risk of disease relapse during pregnancy. Long-acting injectable (LAI) antipsychotics have been widely used to improve adherence and prevent relapse in patients with various severe psychotic disorders, but there is a lack of high-quality data from previous research on the safety of LAI antipsychotics during pregnancy.

**AIM**

To summarize relevant data on maternal, pregnancy, neonatal, and developmental outcomes from published cases of LAI antipsychotic use in pregnancy.

**METHODS**

A literature search was performed through November 11, 2023, using three online databases: PubMed/MEDLINE, Scopus, and Web of Science. Case reports or case series that reported information about the outcomes of pregnancy in women who used LAI antipsychotics at any point in pregnancy, with available full texts, were included. Descriptive statistics, narrative summation, and tabulation of the extracted data were performed.

**RESULTS**

A total of 19 publications satisfied the inclusion criteria: 3 case series, 15 case reports, and 1 conference abstract. They reported the outcomes of LAI antipsychotic use in 74 women and 77 pregnancies. The use of second-generation LAI antipsychotics was reported in the majority ( $n = 47$ ; 61.0%) of pregnancies. First-generation LAI antipsychotics were administered during 30 pregnancies (39.0%). Most of the women (approximately 64%) had either satisfactory control of symptoms or no information about relapse, while approximately 12% of them had developed gestational diabetes mellitus. A minority of cases reported adverse outcomes such as stillbirth, spontaneous abortion, preterm birth, low birth weight, congenital anomalies, and neurological manifestations in newborns. However, there were no reports of negative long-term developmental outcomes.

**CONCLUSION**

Currently available data seem reassuring, but further well-designed studies are required to properly evaluate the risks and benefits of LAI antipsychotic use during pregnancy.

**Key Words:** Antipsychotic agents; Long-acting injectable; Pregnancy; Outcome; Review

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**Core Tip:** Considering that the currently available research on the use of long-acting injectable antipsychotics in pregnancy consists only of case reports and series, additional well-designed studies are needed to properly evaluate the risks and benefits of their use during pregnancy. Currently available data seem reassuring, given that most of the women seemed to have satisfactory control of the symptoms and that a minority of the cases reported adverse outcomes, such as stillbirth, spontaneous abortion, preterm birth, low birth weight, congenital anomalies, and neurological manifestations in newborns, while there were no reported negative long-term developmental outcomes.

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**INTRODUCTION**

Owing to their unique formulations, specific pharmacokinetic properties (*i.e.*, flip-flop kinetics), and accompanying innovations in drug delivery mechanisms, long-acting injectable (LAI) antipsychotics have been widely used in clinical practice for decades to improve adherence and prevent relapse, with the ultimate goal of reducing (re)hospitalization and mortality rates in patients with various severe psychotic disorders[1-3]. In fact, the use of these depot formulations with less frequent, more convenient dosing generally provides several relevant advantages over their oral counterparts[4-6]. By providing slow systemic absorption and continuous drug exposure with more stable blood levels, a potentially greater efficacy and acceptable safety profile are ensured, reflecting the previously mentioned beneficial effects on the main challenges regarding treatment outcomes of chronic diseases such as schizophrenia or bipolar disorder[1,7,8]. To date, several LAI antipsychotics have been approved[9,10], divided into first-generation or typical LAI antipsychotics (*e.g.*, haloperidol, fluphenazine, flupentixol, and zuclopenthixol) and second-generation or atypical LAI antipsychotics (*e.g.*, risperidone, olanzapine, aripiprazole, and paliperidone).

Women with a history of serious psychotic disorders are at increased risk of disease relapse during pregnancy, which can significantly endanger both the mother and the fetus, and satisfactory compliance with antipsychotic medications plays a key role in avoiding treatment failure[11-13]. Therefore, continuation and maintenance of antipsychotic therapy are necessary for pregnant women[14]. However, in daily clinical practice, antipsychotics are likely to be discontinued when pregnancy is confirmed for fear of possible teratogenicity or fetotoxicity[15,16]. Moreover, despite the current evidence showing that the use of oral antipsychotics is not significantly associated with poor pregnancy outcome[17,18], as well as a lack of high-quality data from previous research on the safety of LAI antipsychotics during pregnancy that

does not clearly support their avoidance[19-21], it has been observed that psychiatrists prefer not to start or stop the use of LAI antipsychotics, even in pregnant women with an exceptionally high risk of psychotic symptom recurrence[22].

Apart from a significantly lower potential for overdose, LAI antipsychotics appear to share an overall safety profile similar to that of their oral counterparts[23,24]. An exception is the depot formulation of olanzapine[25], which requires strict monitoring for delirium or excessive sedation for a few hours immediately after intramuscular injection[26,27]. In addition, the women with pharmacokinetic changes reflected in the increased clearance of these drugs during pregnancy may require an increase in their doses[28]. Therefore, the decision to use and the choice of an appropriate LAI antipsychotic with an optimal benefit-risk ratio for an individual pregnant woman is challenging because numerous factors need to be considered, such as: Previous compliance to drug therapy (especially psychotropic drugs); use of antipsychotics/LAI antipsychotics in previous pregnancies if any, as well as the outcomes of such pregnancies; history of recurrent psychotic manifestations, especially if they led to long and frequent hospitalizations; history of licit or illicit abuse of psychoactive substances; compliance with the approved indication related to the psychotic or affective disorder; differences in the safety profile of individual LAI antipsychotics (*e.g.*, metabolic side effects among atypical antipsychotics); need for dose escalation and length of the dosing interval during pregnancy; and a pregnant woman's decision to breastfeed[29-31].

Previous reviews published several years ago identified 12 relevant case reports of both first- and second-generation LAI antipsychotic use during pregnancy[19] and 8 case reports/series of second-generation LAI antipsychotic use during pregnancy[32]. Considering that these reviews included only selected cases published before January and March 2021, respectively, and that several case reports/series reporting outcomes of pregnancy in women using LAI antipsychotics were published in the meantime[20,33,34] or were published earlier but not included in previous reviews[35], there is a need for an updated review. Therefore, our review aims to provide an up-to-date summary of the relevant data on maternal, pregnancy, neonatal, and developmental outcomes from available published cases of LAI antipsychotic use in pregnancy to help inform clinical decision-making. We also aimed to identify whether there are ongoing clinical studies assessing LAI antipsychotic use during pregnancy.

## MATERIALS AND METHODS

Electronic literature searches were conducted using three online databases: PubMed/MEDLINE, Scopus, and Web of Science. A literature search was performed from the beginning of indexing until November 11, 2023, without language or date restrictions. A detailed search strategy for each database is presented in Table 1.

Case reports or case series that reported information about the outcomes of pregnancy in women who used LAI antipsychotics at any point in pregnancy, with available full texts, were included. LAI antipsychotics included first- (fluphenazine, haloperidol, zuclopenthixol, and flupentixol) and second-generation (aripiprazole, olanzapine, paliperidone, and risperidone) antipsychotics. Conference abstracts were included only if they contained sufficient data for analysis. Reviews, meta-analyses, commentaries, guidelines, “*in vitro*” studies, and animal studies were excluded. The eligibility of the retrieved publications was reviewed based on their titles and abstracts. When the title and information available in the abstract were insufficient for evaluating whether the publication properly corresponded to the research topic, we tried to retrieve and evaluate the full text. Publications were included that all the authors agreed met the eligibility criteria. Disagreements between the individual judgments were resolved by consensus.

Additionally, backward and forward citation searches were performed for publications that met the eligibility criteria. Backward citation searching was performed by inspecting the references cited in these publications, while forward citation searching was performed using the Google Scholar citation index on November 21, 2023, to identify publications that cited these publications.

We extracted the following data: type of publication, country, number of women, number of pregnancies, maternal age, information about alcohol/tobacco/illicit drug use during pregnancy, psychiatric diagnosis, information about LAI antipsychotic medication (name, dosage, and duration of treatment during pregnancy) and other medications used during pregnancy, maternal treatment outcomes (information about efficacy of LAI antipsychotic use and relapse of symptoms), gestational diabetes mellitus, pregnancy hypertension, premature rupture of membranes, delivery mode, live birth, stillbirth, spontaneous abortion, preterm birth, gestational age at birth, gender of the newborn, birth weight, Apgar score (at 1, 5, and 10 minutes), admission of the newborn to special care nursery or neonatal intensive care unit, neonatal and developmental outcomes, and main conclusions. Descriptive statistics, narrative summation, and tabulation of the extracted data were performed.

To identify ongoing clinical studies aimed at assessing the use of LAI antipsychotics during pregnancy, we searched the ClinicalTrials.gov database on January 23, 2024. We performed a search by entering previously mentioned LAI antipsychotics in the intervention/treatment search field, and pregnancy in the condition/disease search field.

## RESULTS

### Results of the literature search

Our search strategy identified 142 publications in PubMed/MEDLINE, 67 publications in Scopus, and 47 publications in Web of Science, and 200 total publications were screened for eligibility after duplicates were removed. Of these 200 publications, 17 met the inclusion criteria, and 183 were excluded (172 irrelevant publications, 6 review/consensus

Table 1 A detailed search strategy for each database

Database	Search strategy
PubMed/MEDLINE	("antipsychotic agents" [Pharmacological Action] OR "antipsychotic agents" [MeSH Terms] OR ("antipsychotic" [All Fields] AND "agents" [All Fields]) OR "antipsychotic agents" [All Fields] OR "antipsychotic" [All Fields] OR "antipsychotics" [All Fields] OR "antipsychotics" [All Fields] OR "antipsychotically" [All Fields] OR "antipsychotically" [All Fields] OR "antipsychotic agents" [Pharmacological Action] OR "antipsychotic agents" [MeSH Terms] OR ("antipsychotic" [All Fields] AND "agents" [All Fields]) OR "antipsychotic agents" [All Fields] OR "antipsychotic" [All Fields] OR "antipsychotics" [All Fields] OR "antipsychotic s" [All Fields] OR "antipsychotically" [All Fields] OR "antipsychotic agents" [Pharmacological Action] OR "antipsychotic agents" [MeSH Terms] OR ("antipsychotic" [All Fields] AND "agents" [All Fields]) OR "antipsychotic agents" [All Fields] OR "antipsychotic agents" [All Fields] OR "neuroleptic" [All Fields] OR "neuroleptics" [All Fields] OR "neuroleptical" [All Fields] OR "neuroleptical" [All Fields] OR "neuroleptization" [All Fields] OR ("antipsychotic agents" [Pharmacological Action] OR "antipsychotic agents" [MeSH Terms] OR ("antipsychotic" [All Fields] AND "agents" [All Fields]) OR "antipsychotic agents" [All Fields] OR "neuroleptic" [All Fields] OR "neuroleptics" [All Fields] OR "neuroleptical" [All Fields] OR "neuroleptical" [All Fields] OR "neuroleptization" [All Fields] OR ("aripiprazole" [MeSH Terms] OR "aripiprazole" [All Fields] OR "aripiprazol" [All Fields] OR "aripiprazole s" [All Fields]) OR ("fluphenazine" [MeSH Terms] OR "fluphenazine" [All Fields] OR "haloperidol" [MeSH Terms] OR "haloperidol" [All Fields] OR "haloperidol s" [All Fields] OR "haloperidole" [All Fields] OR "flupenthixol" [MeSH Terms] OR "flupenthixol" [All Fields] OR "flupentixol" [All Fields] OR "flupentixol" [All Fields] OR "clopenthixol" [MeSH Terms] OR "clopenthixol" [All Fields] OR "zuclopenthixol" [All Fields] OR ("olanzapine" [MeSH Terms] OR "olanzapine" [All Fields] OR "olanzapin" [All Fields] OR "olanzapine s" [All Fields]) OR ("paliperidone palmitate" [MeSH Terms] OR "paliperidone" [All Fields] AND "palmitate" [All Fields]) OR "paliperidone palmitate" [All Fields] OR "paliperidone" [All Fields] OR "paliperidone s" [All Fields]) OR ("risperidon" [All Fields] OR "risperidone" [MeSH Terms] OR "risperidone" [All Fields] OR "risperidone s" [All Fields]) AND ("long-acting" [All Fields] OR "inject" [All Fields] OR "injectability" [All Fields] OR "injectant" [All Fields] OR "injectants" [All Fields] OR "injectate" [All Fields] OR "injectates" [All Fields] OR "injected" [All Fields] OR "injectible" [All Fields] OR "injectibles" [All Fields] OR "injecting" [All Fields] OR "injections" [MeSH Terms] OR "injections" [All Fields] OR "injectable" [All Fields] OR "injectables" [All Fields] OR "injection" [All Fields] OR "injects" [All Fields] OR "depot" [All Fields] OR "depots" [All Fields]) AND ("pregnancy" [MeSH Terms] OR "pregnancy" [All Fields] OR "pregnancies" [All Fields] OR "pregnancy s" [All Fields] OR "pregnant" [All Fields] OR "pregnants" [All Fields]) NOT ("mice" [MeSH Terms] OR "mice" [All Fields] OR "mouse" [All Fields] OR "mouse s" [All Fields] OR "mouses" [All Fields] OR "mice" [MeSH Terms] OR "mice" [All Fields] OR "rats" [MeSH Terms] OR "rats" [All Fields] OR "rat" [All Fields])
Web of Science	In all databases and all collections (Web of Science Core Collection; KCI-Korean Journal Database; Preprint Citation Index; ProQuest™ Dissertations & Theses Citation Index; SciELO Citation Index): TS = (antipsychotic OR antipsychotics OR neuroleptic OR neuroleptics OR aripiprazole OR fluphenazine OR haloperidol OR flupenthixol OR flupentixol OR zuclopenthixol OR olanzapine OR paliperidone OR risperidone) AND TS = (long-acting OR injectable OR depot) AND TS = (pregnancy OR pregnant)
Scopus	TITLE-ABS-KEY ((antipsychotic OR antipsychotics OR neuroleptic OR neuroleptics OR aripiprazole OR fluphenazine OR haloperidol OR flupenthixol OR flupentixol OR zuclopenthixol OR olanzapine OR paliperidone OR risperidone) AND (long-acting OR injectable OR depot) AND (pregnancy OR pregnant))

guidelines, 3 publications with unavailable full text, 1 conference abstract of an already included publication, and 1 conference abstract with incomplete data on pregnancy and delivery outcomes). We identified 2 additional publications *via* citation search; therefore, 19 publications satisfied the inclusion criteria: 3 case series[20,21,33], 15 case reports[34-48], and 1 conference abstract[49]. One case series reported aggregate data[20], while all others reported individual data.

### Main characteristics of included pregnant women

An overview of the included publications/cases is presented in Table 2. They reported the outcomes of LAI antipsychotic use in 74 women and 77 pregnancies. The age of the pregnant women ranged from 20 to 43 years, and most were diagnosed with schizophrenia ( $n = 43$ ; 58.1%), followed by schizoaffective disorder ( $n = 8$ ; 10.8%), bipolar disorder ( $n = 5$ ; 6.8%), and psychosis ( $n = 3$ ; 4.0%). The exact diagnosis in 15 women (20.3%) reported by Eleftheriou *et al*[33] was not specified (either a bipolar or psychotic disorder). The majority of the women were from Australia ( $n = 39$ ; 52.7%), followed by Italy ( $n = 15$ ; 20.3%), Spain ( $n = 9$ ; 12.2%), Turkey ( $n = 3$ ; 4.0%), the United States ( $n = 3$ ; 4.0%), Japan ( $n = 1$ ; 1.3%), Portugal ( $n = 1$ ; 1.3%), Serbia ( $n = 1$ ; 1.3%), South Korea ( $n = 1$ ; 1.3%), and Sweden ( $n = 1$ ; 1.3%). Smoking, alcohol consumption, and the use of illicit drugs some point during pregnancy were reported in 33 (44.6%), 3 (4.0%), and 3 (4.0%) women, respectively.

### Characteristics of prescribed LAI antipsychotics

In the majority ( $n = 47$ ; 61.0%) of pregnancies, the use of second-generation LAI antipsychotics was reported [aripiprazole was used in 26 (33.8%); paliperidone in 14 (18.2%); risperidone in 6 (7.8%); and olanzapine in 1 (1.3%)]. First-generation LAI antipsychotics were used in 30 (39.0%) pregnancies [zuclopenthixol in 14 (18.2%); flupentixol in 9 (11.7%); fluphenazine in 5 (6.5%); and haloperidol in 2 (2.6%)]. The dosage and duration of LAI antipsychotic treatment during pregnancy varied considerably among individual medications, and this information is presented in Table 2. During more than half of the pregnancies, women reported using medications other than LAI antipsychotics ( $n = 46$ ; 59.7%).

### Maternal outcomes

Relapse/worsening of the patients' condition during pregnancy, after delivery, and both during pregnancy and after delivery were reported in 15 (19.5%), 7 (9.1%), and 1 (1.3%) pregnancies, respectively. One patient (1.3%) required hospitalization for psychosis relapse after stillbirth, while another patient (1.3%) discontinued LAI antipsychotic use without consulting a clinician and was hospitalized for an acute psychotic attack. Improvement or partial control of symptoms was reported in 3 (3.9%) pregnancies. The remaining 49 (63.6%) had satisfactory symptom control or no information about relapse. Gestational diabetes mellitus was reported in nine (11.7%) pregnancies (two during the use of first-generation LAI antipsychotics and seven during the use of second-generation LAI antipsychotics). Elevated blood

Table 2 An overview of included publications/cases

No.	Ref.	Maternal age (yr)	Type of publication, No. of women/pregnancies	Psychiatric diagnosis	LAI-AP medication (dosage, duration of treatment during pregnancy); other medications used during pregnancy	Maternal treatment outcomes	Pregnancy and delivery outcomes (gestational age, gender, birth weight, Apgar score 1/5/10 min)	Neonatal and developmental outcomes
1	Donaldson and Bury[36], 1982	29	Case report, 1/1	Hebephrenic schizophrenia	Fluphenazine enanthate (25 mg/month, entire pregnancy); dicyclomine hydrochloride, doxylamine succinate and pyridoxine hydrochloride (from 45 to 101 d of gestation), ferrous sulphate, folic acid (from day 101 to near delivery), paracetamol (from day 165 to near delivery), sodium amytal (from day 250 to 255)	Her symptoms improved during pregnancy	Labor was induced surgically and proceeded to forceps delivery (36 wk, male, 2520 g, 9/NR/NR)	Born with a short sloping forehead, wide metopic suture, persistent metopic fontanelle, telecanthus, ocular hypertelorism, nystagmoid eye movements, bilateral cleft lip and palate, imperforate anus, rectourethral fistula, bifid scrotum, unusual penis with hypospadias, and neutrophil polymorphs with numerous nuclear projections. His overall progress was good, with the rectourethral fistula divided and anoplasty performed soon after delivery and the cleft lip and palate repaired at 7 months
2	Cleary[37], 1977	32	Case report, 1/1	Schizophrenia	Fluphenazine decanoate (2 cc every 3 wk, entire pregnancy); benzotropine mesylate sporadically	Latent homicidal ideas were noted late in pregnancy, and her behavior continued to be bizarre, explosive, and unpredictable. Two months after delivery, she developed somatic delusions, became agitated and paranoid, and was readmitted to a psychiatric hospital. After discharge and some months later, she indicated the persistence of a schizophrenic thought disorder	Delivered by cesarean section 9 d after the expected date following the failure of oxytocin to induce labor (40 wk and 9 d, male, 3380 g, 8/10/NR)	Born healthy. Possible minor extrapyramidal manifestations 4 wk after delivery (or withdrawal symptoms from fluphenazine) that responded to diphenhydramine elixir. Apparently well-nourished, well-developed, and alert child at 24 months
3	O'Connor <i>et al</i> [38], 1981	22	Case report, 1/1	Schizophrenia	Fluphenazine decanoate (50 mg fortnightly from 14 to 24 wk /increased over three wk to this dose/, then 100 mg fortnightly from 24 wk to delivery); chlorpromazine (from 12 <sup>th</sup> week of pregnancy to delivery)	Her suicidal behavior gradually abated after the LAI-AP dosage increase, but she continued to exhibit denial of pregnancy, extreme unpredictability, and total resistance to obstetric examination	Delivered by cesarean section after spontaneous onset of labor (39 wk, male, 3530 g, 10/10/NR)	Excellent condition at delivery. Initial progress was good. On the 21 <sup>st</sup> d after birth, he developed many neurological signs ( <i>e.g.</i> , excessive irritability, choreiform and dystonic movements involving mainly the upper limbs, jittery behavior, and hypertonicity) which persisted for 9 months and were mainly treated with diphenhydramine. The symptoms were consistent with LAI withdrawal effects. Follow-up at 15 months of age revealed no abnormalities
4	Collins and Comer[39], 2003	35	Case report, 1/1	Schizoaffective disorder	Haloperidol decanoate (200 mg/2 wk, throughout the pregnancy – last dose 3 wk before delivery); not specified	She had an acute psychotic episode before induced delivery	Induced vaginal delivery (full term, female, 3880 g, 9/9/NR)	At birth was noted to be “jittery”, then developed diarrhea and metabolic acidosis, and was transferred to NICU at 3 <sup>rd</sup> d. She became increasingly irritable, and on day 8 had an episode of tonic-clonic movements in

5	Janjić <i>et al</i> [40], 2013	35 at 1 <sup>st</sup> pregnancy, 38 at 2 <sup>nd</sup> pregnancy	Case report, 1/2	Schizophrenia	Zuclopenthixol decanoate (in 1 <sup>st</sup> pregnancy initially 400 mg/2 wk, then upon discovery of the pregnancy at 13 wks' gestation dose was decreased to 200 mg/month and this dose was also used during entire 2 <sup>nd</sup> pregnancy); not specified	Maternal psychiatric status during both pregnancies, after each delivery, and during the follow-up period was favorable (continued to be rated as "borderline mentally ill"), with no exacerbations	Delivery method not specified for both pregnancies. 1 <sup>st</sup> pregnancy/child: (39 wk, female, 3750 g, 9/NR/NR); 2 <sup>nd</sup> pregnancy/child: (40 wk, female, 3700 g, 9/NR/NR)	all extremities with tongue thrusting and torticollis (possible tardive dyskinesia or withdrawal dyskinesia). Tonic-clonic episodes continued up to the 14 <sup>th</sup> d of life (successfully treated with clonazepam). On day 21, she was discharged to foster care with no tremulous movements noted
6	Ballester-Gracia <i>et al</i> [41], 2019	43	Case report, 1/1	Bipolar disorder	Aripiprazole LAI (400 mg/month for first 2-3 wk of pregnancy, then decreased to 300 mg/month, entire pregnancy); not specified (probably none)	No recurrence of her illness or significant mood fluctuations during pregnancy. Two days after hospital discharge after delivery, she came as an outpatient and was euthymic, so LAI-AP dose was increased to 400 mg/4 wk	Spontaneous vaginal delivery without complications (40 wk and 4 d, female, 3500 g, 9/10/10)	No congenital malformations at birth or development abnormalities at five months after delivery
7	Sole <i>et al</i> [49], 2020	30	Conference abstract, 1/1	Schizophrenia	Aripiprazole LAI (400 mg/28 d, entire pregnancy), not specified	No psychiatric complications due to pregnancy and puerperium were reported. No bounding disorder was detected	Delivered without obstetric complications (41 wk, female, 3465 g, 9/10/NR)	No neonatal complications
8	Fernández-Abascal <i>et al</i> [21], 2021	35 (table), 39 (text)	Case series, 1/1	Paranoid schizophrenia	Aripiprazole LAI (400 mg/28 d from beginning of pregnancy to 8 <sup>th</sup> week, 300 mg/28 d from 8 <sup>th</sup> week until delivery); not specified	Throughout pregnancy, the patient remained psychopathologically stable, and treatment adherence was maintained	Uncomplicated eutocic/vaginal delivery (38 wk and 5 d, gender?/male in text; female in table/, 3300 g, 9/10/NR)	During the first 6 wk of follow-up postural plagiocephaly and hypertonia were noted, that finally were resolved with physiotherapy. He developed normally during a 3-yr follow-up
9	Fernández-Abascal <i>et al</i> [21], 2021	29 (table), 32 (text)	Case series, 1/1	Schizophrenia, schizotypal personality disorder	Aripiprazole LAI (400 mg/28 d from beginning of pregnancy to 20 <sup>th</sup> week, 300 mg/28 d from 20 <sup>th</sup> week until delivery); not specified	Adherence was maintained throughout the pregnancy with psychopathological stability and good adherence. She had clinical worsening 3 months after delivery	Admitted to ED for spontaneous delivery - eutocic/vaginal delivery, right medial episiotomy (31 wk and 5 d, female, 1800 g, 10/10/NR)	Remained in an incubator for 1 month due to prematurity. No congenital malformations were observed at delivery or during the postpartum period. She developed normally during a 2-yr follow-up
10	Fernández-Abascal <i>et al</i> [21], 2021	35 (table), 36 (text)	Case series, 1/1	Paranoid schizophrenia	Aripiprazole LAI (400 mg/28 d from beginning of pregnancy to 5 <sup>th</sup> week, 300 mg/28 d from 5 <sup>th</sup> week until delivery); not specified	Psychopathological stability and proper treatment adherence were maintained throughout the pregnancy	Eutocic/vaginal delivery (39 wk and 6 d, male, 3140 g, 9/10/NR)	No congenital malformations were observed at birth, and the postpartum period proceeded without relevant events. Normal development at 2 months
11	Fernández-Abascal <i>et al</i> [21], 2021	31	Case series, 1/1	Schizophrenia	Aripiprazole LAI (160 mg/28 d from beginning of pregnancy until delivery); occasional budesonide inhalation	Throughout the pregnancy, the patient remained psychopathologically stable, and treatment adherence was maintained	Uncomplicated eutocic/vaginal delivery (39 wk and 5 d, male, 3102 g, 10/10/NR)	Born healthy. In the 2-yr follow-up he remained in good health and developed normally

12	Fernández-Abascal <i>et al</i> [21], 2021	38 (table), 39 (text)	Case series, 1/1	Schizophrenia	Aripiprazole LAI (300 mg/28 d from beginning of pregnancy until delivery); not specified	Throughout the pregnancy, she remained psychopathologically stable, and treatment adherence was maintained	Eutocic/vaginal delivery (39 wk, male, 2940 g, 8/10/NR)	Born healthy. In the 1-yr follow-up, he remained in good health and developed normally
13	Fernández-Abascal <i>et al</i> [21], 2021	30	Case series, 1/1	Schizophrenia	Aripiprazole LAI (400 mg/28 d from beginning of pregnancy to 8 <sup>th</sup> week); when pregnancy was confirmed the prescription dose of benzodiazepines was adjusted downwards until they were withdrawn along 4 wk, levothyroxine	To ensure psychopathological stability and to detect warning signs of decompensation, the patient was closely monitored weekly during pregnancy (no worsening was reported)	Eutocic/vaginal delivery (40 wk, male, 3400 g, 9/10/NR)	Born healthy. He has been followed for 18 months, and no malformation, developmental abnormalities, or growth retardation were detected
14	Eleftheriou <i>et al</i> [33], 2023	38	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (400 mg/month, pregnancy started on LAI treatment, interruption of treatment at 23 wk); folic acid	Postpartum hospitalization for psychosis relapse	Cesarian section (31 wk, NR, 1995 g, 6/8/NR)	Down's syndrome, fetal hydrops complicated by septic shock, massive anuria, and death in 10 d. This syndrome cannot be considered a drug-induced malformation
15	Eleftheriou <i>et al</i> [33], 2023	25	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (400 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid	Postpartum hospitalization for psychosis relapse	Vaginal delivery (40 wk, female, 3300 g, 9/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
16	Eleftheriou <i>et al</i> [33], 2023	31	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (200 mg/month, pregnancy started on LAI treatment, interruption of treatment at 14 wk); folic acid, haloperidol (first trimester)	No hospitalization for psychosis relapse	Spontaneous abortion (miscarriage) at 15 <sup>th</sup> week	Not applicable
17	Eleftheriou <i>et al</i> [33], 2023	35	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (200 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid, haloperidol (first trimester)	No hospitalization for psychosis relapse	Spontaneous abortion (miscarriage) at 9 <sup>th</sup> week	Not applicable
18	Eleftheriou <i>et al</i> [33], 2023	34	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (200 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid, carbamazepine (in first trimester, stopped at 10 wk)	Postpartum hospitalization for psychosis relapse	Cesarian section (40 wk, male, 2900 g, 9/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
19	Eleftheriou <i>et al</i> [33], 2023	28	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (400 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid, oral aripiprazole (in first trimester)	No hospitalization for psychosis relapse	Cesarian section (40 wk, female, 3140 g, 7/9/NR)	Live birth with no malformations. No adaptation disorders after delivery

20	Eleftheriou <i>et al</i> [33], 2023	43	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (400 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid.	No hospitalization for psychosis relapse	Vaginal delivery (40 wk, male, 2300 g, 10/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
21	Eleftheriou <i>et al</i> [33], 2023	31	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (400 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid	No hospitalization for psychosis relapse	Vaginal delivery (40 wk, male, 3500 g, 8/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
22	Eleftheriou <i>et al</i> [33], 2023	20	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (400 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid, haloperidol (in first trimester)	Hospitalization for psychosis relapse after stillbirth	Stillbirth at 26 <sup>th</sup> week	Not applicable
23	Eleftheriou <i>et al</i> [33], 2023	31	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (400 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid, paroxetine (in first trimester)	No hospitalization for psychosis relapse	Vaginal delivery (38 wk, female, 3120 g, 9/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
24	Manouilenko <i>et al</i> [42], 2018	35	Case report, 1/1	Psychosis	Olanzapine pamoate (405 mg/4 wk, from 25 <sup>th</sup> week, reduced to 300mg/4 wk from 29 <sup>th</sup> week and ultimately due to sedation to 210 mg/2 wk at 39 <sup>th</sup> week, exposure until delivery); oral olanzapine for 4 d and promethazine injections before initiation of LAI-AP	Improved rapidly on LAI-AP, but she was hospitalized at pregnancy week 40 since she reported fatigue and depression	Vaginal delivery was induced by amniotomy (40 wk, female, 2930 g, 9/10/10)	Fully developed infant. The child's somatic and psychomotor development up to 3 yr of age was normal
25	de Azevedo Avelar <i>et al</i> [43], 2020	26	Case report, 1/1	Schizophrenia	Paliperidone palmitate (263 mg every three months twice during pregnancy, the last one approximately 2 months before birth - exposure during entire pregnancy); none	She was doing well on this LAI-AP (asymptomatic on follow-up)	Presented to ED with abdominal pain, found to be in labor - pregnancy was not planned nor monitored (unknown gestational age, male, 2420 g, 9/10/10)	Approximately 1 yr after birth no health or developmental issues
26	Zamora Rodríguez <i>et al</i> [44], 2017	34	Case report, 1/1	Bipolar schizoaffective disorder	Paliperidone palmitate (100 mg/4 wk initially, then reduced to 50 mg/4 wk, she was pregnant for 2 wk when it was initiated, and dosage reduced at 5 wk of pregnancy and remained at this dosage until and after delivery); venlafaxine and clonazepam for first 5 wk, which were then changed to fluoxetine and	No psychotic or affective symptoms except for a slight period of anxiety in the days immediately after discovering she was pregnant, and a mild and self-limited depressive relapse from days 7 to 9 after giving birth	Term birth, delivery mode not specified (40 wk, male, 2440 g, 9/10/10)	Clinical status of the newborn was normal. No diseases or malformations were detected in the first year of follow-up



27	Özdemir <i>et al</i> [45], 2015	37	Case report, 1/1	Schizophrenia	lorazepam, omeprazole and yodocefol Paliperidone palmitate (100 mg monthly, from beginning until week 28 of gestation – last dose given at the 28 <sup>th</sup> week); haloperidol orally from 29 <sup>th</sup> week until delivery	Developed psychotic symptoms despite regular injections of LAI-AP 2 wk before a change to haloperidol was made (her symptoms subsided 3 wk afterwards)	Cesarean section without complications (39 wk, male, 3000 g, 9/NR/NR)	The baby has been followed for 4 months, and no malformation or growth retardation was detected
28	Binns <i>et al</i> [46], 2017	28	Case report, 1/1	Chronic paranoid schizophrenia	Paliperidone palmitate (150 mg/4 wk, entire pregnancy); not specified	Good control of psychosis was maintained	Pregnancy was complicated by polyhydramnios, induced labor followed by cesarean section due to fetal distress (39 wk, male, 3840 g, 9/9/NR)	Neonatal clinical examination confirmed a minor correctable congenital anomaly, bilateral talipes equinovarus, which was managed conservatively but was otherwise normal. The early postnatal course was uncomplicated
29	Iwata <i>et al</i> [34], 2021	30	Case report, 1/1	Schizophrenia	Paliperidone palmitate (150 mg/monthly, first dose was given at 34 wks' gestation, and she electively gave birth at 38 wks' gestation); initially from beginning of pregnancy olanzapine orally (problems with adherence) up to 32 <sup>nd</sup> week, then risperidone orally for 7 d during 33 <sup>rd</sup> week of pregnancy	Doing well on LAI-AP (after its initiation at the third trimester she had a notable improvement in positive and negative symptoms, and the delivery was performed without any issues)	Uneventful cesarean section (38 wk, male, NR, NR/NR/NR)	Transient tachypnea of the newborn that was managed with nasal continuous positive airway pressure. He was discharged 29 d after the delivery. Normal growth and neuropsychological development at 12 months after birth
30	Erdoğan <i>et al</i> [35], 2017	25	Case report, 1/1	Schizophrenia	Paliperidone palmitate (150 mg/monthly, from beginning of pregnancy, last dose given at 22 <sup>nd</sup> week); not specified	She discontinued LAI-AP use without consultation with a clinician. At the 29 <sup>th</sup> week of pregnancy, she was hospitalized with an acute psychotic attack	Normal vaginal delivery (40 wk, male, 3200 g, 9/10/NR)	Born healthy baby. Normal neurobehavioral development according to BSID-III (subscales of cognitive, motor, and language developments were in normal ranges at 2, 6, 12, 18, and 24 months of age)
31	Erdoğan <i>et al</i> [35], 2017	32	Case report, 1/1	Schizophrenia	Paliperidone palmitate (150 mg/monthly, entire pregnancy); not specified	No information about worsening of her condition during treatment. Four months after delivery she gave baby to ward of state	Normal vaginal delivery (41 wk, female, 2980 g, 9/10/NR)	Normal neurobehavioral development according to BSID-III (subscales of cognitive, motor and language developments were in normal ranges at 2, 6, 12, and 18 months of age)
32	Eleftheriou <i>et al</i> [33], 2023	26	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Paliperidone LAI (50 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid, lorazepam (first trimester)	Postpartum hospitalization for psychosis relapse	Cesarian section (39 wk, female, 3020 g, 9/9/NR)	Live birth with no malformations. No adaptation disorders after delivery
33	Eleftheriou <i>et al</i> [33], 2023	32	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Paliperidone LAI (100 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid	No hospitalization for psychosis relapse	Cesarian section (40 wk, male, 3250 g, 9/10/NR)	Live birth with no malformations. No adaptation disorders after delivery

34	Eleftheriou <i>et al</i> [33], 2023	30	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Paliperidone LAI (100 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid	Postpartum hospitalization for psychosis relapse	Cesarian section (39 wk, male, 3650 g, 10/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
35	Eleftheriou <i>et al</i> [33], 2023	25	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Paliperidone LAI (100 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid	No hospitalization for psychosis relapse	Cesarian section (40 wk, female, 3255 g, 9/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
36	Eleftheriou <i>et al</i> [33], 2023	33	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Paliperidone LAI (50 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid, haloperidol (first trimester)	No hospitalization for psychosis relapse	Cesarian section (39 wk, female, 3100 g, 9/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
37	Clinebell <i>et al</i> [47], 2017	32	Case report, 1/1	Bipolar disorder	Risperidone LAI (50 mg/2 wk, entire pregnancy); risperidone orally, citalopram, and benztropine (entire pregnancy)	She was doing well	Intrauterine growth restriction, and, due to concerns for placental insufficiency, she had induction of labor (35 wk, male, 2098 g, 8/8/9)	Born healthy, but with bilateral supernumerary nubs/digits on his hands that were removed after birth (this anomaly was a paternal family trait). The child has met developmental milestones at 16 months
38	Kim <i>et al</i> [48], 2007	35	Case report, 1/1	Schizophrenia	Risperidone LAI (25 mg/2 wk, entire pregnancy); not specified	Her psychotic symptoms improved markedly with LAI-AP treatment. No information about relapse	She delivered vaginally 3 h after premature rupture of membranes (36 wk and 6 d, female, 2230 g, 9/9/NR)	No evidence of congenital malformation at birth and no developmental abnormalities were found 8 months postnatally
39	Nguyen <i>et al</i> [20], 2022	Mean±SD: All: 30.3±5.5; FGA: 31.0±6.0; SGA: 29.1±4.5	Case series, 36/38	Schizophrenia (25/69.4%); Schizoaffective disorder (6/16.7%); Bipolar affective disorder (3/8.3%); Unspecified psychosis (2/5.6%)	FGA (24/38): zuclopenthixol- 12 (100 mg fortnightly- 2, 150 mg fortnightly- 2, 200 mg fortnightly- 5, 300 mg monthly- 1, 300 mg fortnightly- 1, 300 mg monthly- 1); flupentixol- 9 (20 mg fortnightly- 1, 30 mg fortnightly- 1, 40 mg fortnightly- 5, 40 mg monthly- 1, 100 mg fortnightly- 1); fluphenazine- 2 (50 mg fortnightly); haloperidol- 1 (dose missing). SGA (14/38): aripiprazole- 8 (300 mg monthly- 1, 400 mg monthly- 7), risperidone- 4 (37.5 mg fortnightly- 1; 37.5 mg monthly- 1, 50 mg fortnightly- 2); paliperidone- 2 (100 mg monthly). First trimester exposure data only on 35/38 pregnancies, with 1/38 having a third	Psychiatric relapse reported in 9 (40.9%) pregnancies in women on FGA and 3 (27.3%) pregnancies in women on SGA LAI-AP. Note: Valid% reported due to missing data	All pregnancies: spontaneous delivery in 13 (34.2%), emergency cesarean section in 11 (28.9%), premature birth (< 37 wk) in 6 (15.8%). Induction in 16 (66.7%) on FGA and 7 (50.0%) on SGA, emergency cesarean section in 8 (33.3%) on FGA and 3 (21.4%) on SGA, premature birth (< 37 wk) in 5 (20.8%) on FGA and 1 (7.1%) on SGA. Note: Valid% reported due to missing data. For all babies the mean gestational age was 38.25 wk (SD = 2.19) and mean birth weight was 3.18 kg (SD = 0.76). Gender and Apgar score were NR	Admission to a special care nursery was reported in a total of 18 <i>i.e.</i> , 47.4% of babies (13 <i>i.e.</i> , 54.2% and 5 <i>i.e.</i> , 35.7% whose mothers received FGA and SGA, respectively). Congenital malformations were recorded in 2 babies, and with data available on first-trimester exposure in only 35 pregnancies, this gives a 5.7% rate. One baby had undescended testes whose mother was treated with risperidone LAI, and the other was a patent ductus arteriosus in a baby of a woman who received flupentixol LAI. Both babies were managed conservatively. The authors were not able to assess for neonatal extrapyramidal syndrome (not recorded in their data)

trimester exposure and first trimester data were missing for 2/38. Nearly half ( $n = 17, 44.7\%$ ) were on LAI-AP as the sole medication while the rest had exposures to other oral medications including olanzapine, quetiapine, diazepam, chlorpromazine, risperidone, benztropine, venlafaxine, aripiprazole, fluoxetine, escitalopram, desvenlafaxine, lamotrigine)

AP: Antipsychotic(s); BSID-III: Bayley Scales of Infant and Toddler Development 3<sup>rd</sup> Ed; ED: Emergency department; FGA: First-generation antipsychotics; LAI: Long-acting injectable; NICU: Neonatal intensive care unit; NR: Not reported; SD: Standard deviation; SGA: Second-generation antipsychotics.

pressure during pregnancy was reported in 5 (6.5%) pregnancies (all were treated with first-generation LAI antipsychotics). One case series[20] reported that pregnant women treated with LAI antipsychotics were more likely to have obstetric complications, including gestational diabetes and pregnancy hypertension, than the general population. They also had elevated rates of psychiatric admission during pregnancy and statutory child protection involvement, while the outcomes were similar for first- and second-generation LAI antipsychotic exposures[20].

### **Pregnancy and delivery outcomes**

Premature rupture of membranes was reported in six pregnancies (7.8%): Four involved the use of first-generation LAI antipsychotics and two the use of second-generation LAI antipsychotics. The use of cesarean section as a delivery method was reported in 24 pregnancies (31.2%): 10 involved first-generation and 14 involved second-generation LAI antipsychotic use. One (1.3%) pregnancy ended in stillbirth, whereas two (2.6%) ended in spontaneous abortion (miscarriage), all of which involved the use of aripiprazole LAI. Preterm birth (< 37 wk) was reported in 11 (14.3%) pregnancies (6 and 5 involved first- and second-generation LAI use, respectively). The reported birth weight of babies ranged from 1800 to 3880 g, while 7 (9.5% of 74 live births) were specified as having a low birth weight (< 2500 g), all of whom were exposed to second-generation LAI antipsychotics (3 to aripiprazole, 2 to risperidone, and 2 to paliperidone). The average Apgar scores at 1, 5, and 10 min were 8.9, 9.7, and 9.8, respectively.

### **Neonatal and developmental outcomes**

Admission to a special-care nursery or neonatal intensive care unit was reported in 21 babies (28.4% of 74 live births); 14 and 7 were exposed to first- and second-generation LAI antipsychotics, respectively. One case series[20] reported that pregnant women treated with LAI antipsychotics were more likely to have special care nursery admissions for their babies than the general population, while outcomes were similar for first- and second-generation LAI antipsychotic exposure[20].

Of the five babies who were exposed to fluphenazine LAI, one was born preterm in the 36<sup>th</sup> week with a normal karyotype but with multiple congenital anomalies (*e.g.*, bilateral cleft lip and palate, imperforate anus, and rectourethral fistula) requiring surgical interventions[36], while two experienced neurological manifestations at 3[37] and 4 wk[38] after

delivery, but afterwards were doing well on follow-up. Neurological manifestations included possible minor extrapyramidal manifestations or withdrawal symptoms, which responded well to diphenhydramine, and this baby was apparently well developed at the 24-month follow-up[37], while the other baby developed symptoms consistent with withdrawal effects (*e.g.*, excessive irritability, choreiform and dystonic movements, jittery behavior, and hypertonicity), which persisted for 9 months and required treatment with diphenhydramine[38]. The baby did not show any abnormalities at the 15-month follow-up[38].

Of the two babies exposed to haloperidol LAI, one[39] developed possible tardive dyskinesia or withdrawal dyskinesia 8 days after birth, which continued until the 14<sup>th</sup> day of life and was successfully treated with clonazepam.

No significant anomalies or problems were reported in the 14 babies exposed to zuclopenthixol LAI[20,40]. Brain ultrasound revealed clinically insignificant periventricular hyperechogenicity in only one baby, but she was normally developed at the 3.5-year follow-up[40].

Of the nine babies exposed to flupentixol LAI, patent ductus arteriosus was reported only in one baby who was managed conservatively[20].

Of the 23 babies born alive who were exposed to aripiprazole LAI, one[21] experienced postural plagiocephaly and hypertonia during the first 6 wk of life that resolved with physiotherapy (he developed normally during the 3-year follow-up), one[21] remained in the incubator for 1 month due to prematurity (but developed normally during the 2-year follow-up), and one[33] was born preterm with Down's syndrome, developed fetal hydrops complicated by septic shock and massive anuria, and died within 10 d (but this syndrome cannot be considered a drug-induced malformation).

One baby exposed to olanzapine LAI developed normally during the 3-year follow-up[42].

Of the 14 babies exposed to paliperidone LAI, one[34] experienced transient tachypnea that was managed with nasal continuous positive airway pressure (he developed normally during the 12-month follow-up), while another[46] was born with a minor correctable congenital anomaly, bilateral talipes equinovarus, which was managed conservatively (he was otherwise normal and the early postnatal course was uncomplicated). The average maternal plasma concentration of paliperidone in the latter case[46] was 13.8 ng/mL (15 h before delivery, 12.7 ng/mL; 9 h before delivery, 15.0 ng/mL), while the umbilical vein concentration was approximately half of the average maternal concentration (7.3 ng/mL), implying appreciable fetal exposure to the drug. However, it was also noted that the relationship between the baby's bilateral talipes equinovarus and paliperidone exposure is uncertain, considering that antipsychotic drug exposure in pregnancy has not been previously recognized as an association[46].

Of the six babies exposed to risperidone LAI, one[20] had undescended testes and was managed conservatively, while another[47] had intrauterine growth restriction and was born healthy but preterm with bilateral supernumerary nubs/digits on his hands that were removed after birth (this anomaly was a paternal family trait). This child met developmental milestones at 16 months[47].

### Ongoing clinical studies

We identified only one currently recruiting study ("Long-acting Injectable Antipsychotics for Mental Ill-Health in Pregnancy and Postpartum" - NCT05766007) that specifically aims to assess safety and clinical outcomes of LAI antipsychotic use during pregnancy and postpartum[50]. This study also aims to determine the magnitude of changes in pharmacokinetics during pregnancy, assess the extent of fetal exposure at delivery, describe breastmilk pharmacokinetics of selected LAI antipsychotics, the extent of breastfed infant exposure, and the sources of variability in maternal and fetal/breastfed infant LAI antipsychotic exposure[50]. The study population includes pregnant and postpartum women aged at least 18 years receiving maintenance doses of LAI antipsychotics (risperidone, paliperidone palmitate, fluphenazine decanoate, flupentixol decanoate, and zuclopenthixol decanoate)[50]. This observational prospective cohort study is being conducted in Nigeria and is sponsored by the University of Liverpool[50]. The study started on August 01, 2023 and is estimated to be completed in August 2025[50]. The estimated number of participants enrolled is 125[50]. We also found three currently recruiting studies that aim to evaluate outcomes of antipsychotic treatment during pregnancy, but these are not restricted to LAI antipsychotic use: "Maternal And Infant Antipsychotic Study" (NCT06049953)[51] being conducted in the United States since 2023, "National Pregnancy Registry for Psychiatric Medications" (NCT01246765)[52] being conducted in the United States since 2008, and "The National Register of Antipsychotic Medication in Pregnancy" (NCT00686946)[53] being conducted in Australia since 2005.

## DISCUSSION

The currently available research on the use of LAI antipsychotics during pregnancy consists only of case reports and series, which are small and not generalizable. It is difficult to adequately interpret the data from these publications because many of the women who were evaluated had concurrent prescriptions for LAI and oral antipsychotics or other medications at some point throughout their pregnancy, and no control group was available for comparison. However, most of the women included in our review (about 64%) either had satisfactory control of the symptoms or no information about relapse, while about 12% had developed gestational diabetes mellitus (mostly on second-generation LAI antipsychotics). It is also important to note that a minority of cases reported adverse outcomes, such as stillbirth, spontaneous abortion, preterm birth, low birth weight, congenital anomalies, and neurological manifestations in newborns. Stillbirth and spontaneous abortion were reported only during the use of aripiprazole LAI, whereas low birth weight was reported only in newborns exposed to second-generation LAI antipsychotics. Preterm birth was reported with both first- and second-generation LAI antipsychotics. Neurological manifestations in newborns, including possible minor extrapyramidal manifestations, withdrawal symptoms, tardive dyskinesia, and withdrawal dyskinesia, were

reported only for first-generation LAI (fluphenazine and haloperidol). Multiple congenital anomalies, such as bilateral cleft lip and palate, imperforate anus, and rectourethral fistula requiring surgical intervention, were reported in only one baby exposed to fluphenazine LAI. Other reported congenital anomalies were mostly managed conservatively. Only one neonate born preterm and exposed to aripiprazole LAI died 10 d after birth. However, the baby was born with Down's syndrome, which cannot be considered a drug-induced malformation, and developed fetal hydrops, septic shock, and anuria. In addition, no negative long-term developmental outcomes following exposure to LAI antipsychotics during pregnancy were reported.

As previously noted, in terms of the use of LAI formulations in pregnancy as compared to that of oral formulations, there are currently no data in the literature that can be generalized; therefore, whether the risks of LAI antipsychotic use are the same, or more or less concerning, or if there are completely different risks involved compared to those of oral antipsychotics remains unclear[19,32]. However, more constant plasma drug levels associated with the use of LAI formulations may reduce fetal exposure to the highly fluctuating plasma drug levels associated with the use of oral formulations[32,54]. One case series[20] found that pregnant women treated with LAI antipsychotics were more likely to have obstetric complications and special care nursery admission for their babies compared to the general population, and outcomes were similar between first- and second-generation LAI antipsychotic exposure. Determining whether the outcomes are due to illness or medication factors (class of medication or long-acting formulations) remains an ongoing problem in this area[20]. In addition, some studies on the use of oral antipsychotics during pregnancy indicate a possible increased risk for complications like gestational diabetes[55-59], preterm birth[56,60-62], congenital malformations[63-65], withdrawal symptoms[66], and neonatal hospitalization[66-69]. Nevertheless, many of these findings have not been consistent across studies[60,62,70-75]. Furthermore, these studies are inherently confounded by indications as most have examined the use of medications during pregnancy[19,76]. It is also difficult to distinguish the effects of maternal illness from those of antipsychotic medications because there is documented evidence that the offspring of women with psychotic illness are highly likely to be at an increased risk of adverse outcomes due to higher rates of smoking, alcohol consumption, illicit substance use, maternal obesity, and reduced serum folate levels related to low dietary vitamin intake [77-80].

Another interesting observation in our review was that stillbirth and spontaneous abortion were only reported with the use of aripiprazole LAI. However, no causal relationship between these adverse pregnancy outcomes and the use of aripiprazole LAI could be established based on these data. One large nationwide cohort study found that women exposed to oral antipsychotics during pregnancy had a 34% higher risk of spontaneous abortion than unexposed women; however, the risk was similar to that in women exposed before (but not during) pregnancy[81]. In addition, the risk did not increase in exposed pregnancies compared with unexposed pregnancies in the same women[81]. Risk estimates were also rather similar for several types of antipsychotic medications, but the confidence intervals were wide, and the numbers were too small to perform adjusted analyses for most drugs[81]. Previous smaller studies did not find an increased risk of spontaneous abortion after prenatal exposure to atypical antipsychotics[82,83], therefore, the authors suggested that the overall higher risk of spontaneous abortion initially observed could be due to factors related to the underlying disease rather than antipsychotic medications[81]. In contrast, in the same study, the risk of stillbirth was twofold higher in pregnancies exposed to antipsychotics; however, owing to the small number of cases, they could not simultaneously adjust for multiple confounders[81]. A previous study found that the number of stillbirths was within the reference range (0 in 561 pregnant women exposed to second-generation antipsychotics and 2 in 284 pregnant women exposed to first-generation antipsychotics)[82].

Although most of the women included in our review (approximately 64%) either had satisfactory control of symptoms or no information about relapse, one case series[20] reported that pregnant women treated with LAI antipsychotics had elevated rates of psychiatric admissions during pregnancy and statutory child protection involvement, suggesting potential destabilization in the mental state associated with pregnancy or compounding psychosocial comorbidities[20].

For women on LAI antipsychotic treatment who become pregnant, it can be difficult to decide whether to continue with LAI or to switch to an oral form of the same antipsychotic, particularly considering that the discontinuation of antipsychotics during pregnancy is linked to an increased risk of bipolar and schizophrenia episode recurrence[84]. Each situation needs to be individually weighed on a case-by-case basis, and clinicians should plan, evaluate, and tailor treatment and management strategies during pregnancy, considering the patient's medical history, current treatment, and symptomatology[32]. Further well-designed research (*e.g.*, prospective longitudinal, observational, and database studies) is needed to properly evaluate the risks and benefits of continuing LAI *vs* switching to oral antipsychotics[19,32]. A shared large database, *i.e.*, registers, for monitoring outcomes of mothers and their children over time could make significant progress in this area, and clinicians could incorporate planned longitudinal follow-up following discharge in their clinical practice to systematically collect all clinical variables of newborns exposed to LAI antipsychotics during pregnancy and the postpartum mental health status of women[32]. Our review identified only one ongoing observational prospective cohort clinical study conducted with the specific aim of assessing the safety and clinical outcomes of LAI antipsychotic use during pregnancy[50]. We hope that this study will provide further insights into the risks and benefits of LAI antipsychotic use during pregnancy.

## CONCLUSION

Most of the women included in our review had either satisfactory symptom control or no information about relapse. A minority of the cases reported adverse outcomes, such as stillbirth, spontaneous abortion, preterm birth, low birth weight, congenital anomalies, and neurological manifestations in newborns, and there were no reported negative long-term

developmental outcomes. Further well-designed studies are required to evaluate the risks and benefits of LAI antipsychotic use during pregnancy.

## ARTICLE HIGHLIGHTS

### Research background

Long-acting injectable (LAI) antipsychotics have been widely used to improve adherence and prevent relapse in patients with various severe psychotic disorders, but there is a lack of high-quality data from previous research on the safety of LAI antipsychotics during pregnancy.

### Research motivation

Considering that previous reviews on this topic included only selected cases published before January and March 2021, respectively, and that several case reports/series reporting outcomes of pregnancy in women using LAI antipsychotics were published in the meantime or were published earlier but not included in previous reviews, there is a need for an updated review.

### Research objectives

We aimed to provide an up-to-date summary of the relevant data on maternal, pregnancy, neonatal, and developmental outcomes from available published cases of LAI antipsychotic use in pregnancy.

### Research methods

A literature search was performed through November 11, 2023, using three online databases: PubMed/MEDLINE, Scopus, and Web of Science. Case reports or case series that reported information about the outcomes of pregnancy in women who used LAI antipsychotics at any point in pregnancy, with available full texts, were included. Descriptive statistics, narrative summation, and tabulation of the extracted data were performed.

### Research results

A total of 19 publications satisfied the inclusion criteria: 3 case series, 15 case reports, and 1 conference abstract. They reported the outcomes of LAI antipsychotic use in 74 women and 77 pregnancies. Most of the women (approximately 64%) had either satisfactory control of symptoms or no information about relapse. A minority of cases reported adverse outcomes such as stillbirth, spontaneous abortion, preterm birth, low birth weight, congenital anomalies, and neurological manifestations in newborns. However, there were no reports of negative long-term developmental outcomes.

### Research conclusions

Currently available data seem reassuring, given that most of the women seemed to have satisfactory control of the symptoms and that a minority of the cases reported adverse outcomes.

### Research perspectives

Considering that the currently available research consists only of case reports and series, additional well-designed studies are needed to properly evaluate the risks and benefits of LAI antipsychotic use during pregnancy.

## FOOTNOTES

**Author contributions:** Pejčić AV, Stefanović SM, Milosavljević MN, Janjić VS, Folić MM, Folić ND, and Milosavljević JZ contributed to conception, design, literature search, data analysis, drafting and editing of the manuscript, and approved the final manuscript.

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