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Long-acting injectable aripiprazole in pregnant women with schizophrenia: a case-series report

Blanca Fernández-Abascal, Maria Recio-Barbero, Margarita Sáenz-Herrero and Rafael Segarra

***Abstract*:** Antipsychotic long-acting formulations (LAI-AP) have emerged as a new therapeutic choice to treat patients presenting a severe mental disorder. Despite that, to date, there is a lack of safety data and studies regarding the use of LAI-AP formulations in pregnant women. Here we present the first six-case series of pregnant women with schizophrenia treated with aripiprazole-LAI reported in the literature. All patients remained psychopathologically stable through pregnancy and the postpartum period, and all of them were in treatment with aripiprazole-LAI. To date, all infants remain healthy with normal developmental milestones, without the presence of congenital malformations or adverse effects. Lack of information on safety data regarding the use of new antipsychotic formulations remains important in treating women with mental illness who desire to become pregnant. Further studies in this clinical population with a larger number of patients included remains necessary.

Keywords: long-acting injectable antipsychotics, pregnancy, schizophrenia, second-generation antipsychotics

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Correspondence to:
Rafael Segarra
Department of Psychiatry, Cruces University Hospital. Plaza de Cruces S/N. Barakaldo, Biscay 48903, Spain;

Biocruces Bizkaia Health Research Institute. Cruces University Hospital, Barakaldo, Spain;

Department of Neurosciences. University of the Basque Country (UPV/EHU), Leioa, Spain;

Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Spain.
rafael.segarraechevarria@osakidetza.eus

Blanca Fernández-Abascal
Department of Psychiatry, Marqués de Valdecilla Hospital, Santander, Cantabria, Spain.

Maria Recio-Barbero
Biocruces Bizkaia Health Research Institute, Cruces University Hospital, Barakaldo, Spain.

Margarita Sáenz-Herrero
Biocruces Bizkaia Health Research Institute, Cruces University Hospital, Barakaldo, Spain;

Department of Psychiatry, Cruces University Hospital, Barakaldo, Spain;

Department of Neurosciences, University of the Basque Country (UPV/EHU), Leioa, Spain;

Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Spain.

Introduction

Schizophrenia is a chronic severe mental disorder usually diagnosed between ages 15 and 35 years, with a second peak of incidence in women after the 40s, affecting a stage of life in which a high number of women become pregnant. Data published in recent years indicate that the fertility rate in women with schizophrenia is growing due to advances in access to Mental Health Community Services and the increasing number of new antipsychotic treatments.[1,2] The release of second-generation antipsychotics (SGAs) in the mid-1990s avoids the "contraceptive effect of well-known typical antipsychotics (FGAs)".[3–5] Among the main benefits described for SGAs is that they do not raise prolactin levels as much as first-generation ones. Finally, once pregnancy is achieved, whether or not to treat the mother throughout gestation with antipsychotic drugs opens another controversial debate.[6] On the one hand, maternal exposure to antipsychotic treatment during pregnancy may affect fetal development while in-utero;[7] on the other hand, not treating the mother would mean an increased risk of clinical decompensation and symptomatic relapse, with the consequent harm to both mother and child.[6,8–11]

It is well known that the first gestational trimester represents one of the most critical periods during pregnancy, as most women probably do not even know they are actually pregnant.[6] Previous reports have described that *in utero* fetal exposure to aripiprazole, olanzapine, and quetiapine has not been associated with an increased risk of major congenital and neurodevelopmental malformations. However, some cases have been reported in patients treated with risperidone and paliperidone.[12] In addition, safety data on ziprasidone and clozapine are limited, and data on other SGAs, such as amisulpride, asenapine, lurasidone, cariprazine, and sertindole are lacking or minimal.

Regarding one of the most common medical complications related to pregnancy, gestational mellitus diabetes (GMD) has been associated with the development of preeclampsia, hypertension, neonatal hypoglycemia, cesarean delivery, type 2 diabetes mellitus (DM-2), macrosomia, or hyperbilirubinemia, among others.[13–17] There are inconclusive data addressing the relationship between exposure to antipsychotics during pregnancy and the development of GDM. Despite that, some experts have proposed that the use of certain antipsychotics during pregnancy may be associated with development of GDM. This association is mediated by the well-known metabolic adverse effects of SGAs, especially those related to the use of clozapine, olanzapine, or quetiapine.[18–21] Alternatively, aripiprazole might be used owing to its efficacy, and relatively favorable side-effects profile.[12]

Furthermore, it remains controversial and unclear whether the increased risk of preterm birth and low birth weight is related to the effect of antipsychotic treatment.[6,13–15,22] This relationship appears to be mediated by several risk factors, including the psychosis itself and other sociodemographic and clinical variables. Among these, smoking status, substance use, nutritional deficiencies, obesity, and domestic violence are considered.[23–28]

In summary, one of the major problems for physicians in prescribing antipsychotics in pregnant women is the lack of scientific evidence regarding safety and clinical use guidelines in this population. More specifically, if we consider the use of long-acting antipsychotics (LAI-APs) in pregnant women, a very limited number of cases have been reported in the literature. As a result, psychiatrists should consider a risk–benefit approach for those pregnant patients when prescribing antipsychotic treatment,[12] always attending to adequate informed consent.

Despite the efficacy and favorable side-effect profile of aripiprazole,[12] only a few studies examining the oral formulation of aripiprazole in pregnant women with schizophrenia have been published, with no studies or case-reports using aripiprazole-LAI. Trying to provide additional evidence, we present the real-world clinical experience of the first six case-series reported in the literature of pregnant women with a diagnosis of schizophrenia who have been exposed to aripiprazole long-acting treatment during their pregnancies.

Methods

We describe six clinical cases of pregnant women being attended and followed-up at Marqués de Valdecilla University Hospital (Santander, Spain) and Cruces University Hospital (Bilbao, Spain). All of them meet the DSM-5 schizophrenia criteria after structured clinical interview for DSM-5 (SCID) evaluation and were on treatment with aripiprazole-LAI throughout pregnancy. Patients' clinical data about pregnancy status and other relevant clinical variables such as illness-related information, medications, laboratory, and ultrasound procedures were collected. Written informed consent was obtained from all participants for the publication of their clinical data.

Results

Case series

Case 1. Case 1 is a 39-year-old woman with a history of paranoid schizophrenia diagnosed at the age of 24 years. The patient does not present comorbid substance use, other medical conditions, or previous family psychiatric history. It is noted in her electronic medical health records that her father has DM-2. She has been on aripiprazole-LAI (400 mg/28 days) since 2014, and two and a half years later she declared her desire to become pregnant. At the time pregnancy was confirmed, she had been treated with aripiprazole-LAI for 32 months. Considering the psychopathological state of the patient and her desire to become pregnant, a risk/benefit approach of treatment discontinuance was discussed. Finally, the patient decided to continue, reducing the aripiprazole-LAI dose up to 300 mg/28 days. Throughout pregnancy, the patient remained psychopathologically stable, and treatment adherence was maintained. The patient was followed-up by an obstetrician, endocrinologist, and prenatal service. Prenatal screening test results were negative, and the ultrasound controls were normal. Oral glucose tolerance test was performed at week 18 (+6 days) with a diagnosis of GMD; the patient received nutritional counseling, was instructed in self-monitoring of blood glucose, and was encouraged to exercise with proper compliance.

Pregnancy evolved normally and resulted in an uncomplicated delivery of a healthy boy at week 38 + 5. Anthropometric measurements of the newborn are presented in Table 1. The patient decided to breastfeed the child. During the first 6 weeks of follow-up in the pediatric department,

Table 1. Clinical characteristics of six case-reports of pregnant women with schizophrenia treated with aripiprazole-LAI and their offspring.

	Mother 1		Mother 2		Mother 3		Mother 4		Mother 5		Mother 6	
Maternal and pregnancy outcomes												
Year of delivery	2016		2017		2019		2018		2019		2019	
Age (years)	35		29		35		31		38		30	
Psychiatric diagnosis	Schizophrenia		Schizophrenia Schizotypal personality disorder		Schizophrenia		Schizophrenia		Schizophrenia		Schizophrenia	
Psychiatric admission	2		2		0		0		1		1	
Previous AP treatment	ziprasidone, risperidone LAI, paliperidone palmitate LAI, fluphenazine decanoate depot		paliperidone palmitate LAI, olanzapine		olanzapine		aripiprazole		paliperidone palmitate LAI		aripiprazole	
Parity	Primiparous		Primiparous		Primiparous		Primiparous		Multiparous		Multiparous	
Aripiprazole-LAI therapy duration before pregnancy (months)	32		19		60		36		6		12	
Aripiprazole-LAI exposure	All pregnancy		All pregnancy		All pregnancy		All pregnancy		All pregnancy		Until 1st trimester (400 mg/28 days)	
Aripiprazole-LAI dosage (mg/day)	- 400 mg/ 28 days wk 0–8. - 300 mg/28 days wk 8-delivery		- 400 mg/28 days wk 0–20. - 300 mg/28 days wk 20-delivery		- 400 mg/28 days wk 0–5. - 300 mg/28 days wk 5-delivery		- 160 mg/28 days wk 0-delivery		- 300 mg/28 days wk 0-delivery		- 400 MG/28 days wk 0–8	
BMI	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
	29.75	28.41	25.62	24.26	32.71	38.73	23.38	24.84	24.06	26.5	25.5	27.7
Weight (g)	80	76.4	69.7	66	87	95	69	73.3	77	85	72	78.2
Weight gain in pregnancy—Kg	–3.6		–3.7		8		4.3		8		6.2	

(Continued)

Table 1. (Continued)

	Mother 1	Mother 2	Mother 3	Mother 4	Mother 5	Mother 6
Gestational diabetes	Yes	No	Yes	No	No	No
GA partum (weeks)	38 + 5	31 + 5	39 + 6	39 + 5	39	40
Type of delivery	Eutocic, term birth.	Eutocic, preterm birth	Eutocic, term birth	Eutocic, term birth	Eutocic, term birth	Eutocic, term birth
Neonatal outcomes						
Infant sex	Female	Female	Male	Male	Male	Male
Weight (g) (%tile)	3300 (p50–75)	1800 (p75–90)	3140 (p50)	3102 (p50)	2940 (p50)	3400 (p70)
Length (cm) (%tile)	49 (p25–50)	44 (p75–90)	50 (p50)	53 (p75)	48.5 (p50)	53 (p75)
Cranial perimeter (cm) (%tile)	34.5 (p50–75)	30 (p50–75)	36 (p50–75)	35.8 (p50–75)	33.1 (p25–50)	36.2 (p50–75)
Apgar score 1/5 min	9/10	10/10	9/10	10/10	8/10	9/10
Breastfeeding	Yes	No	No	No	No	No
Developmental abnormalities	No	No	No	No	No	No
Status last observation	At 3 years: weight: 12.5 kg (p25–50); height: 92 cm (p50). Normal development	At 2 years: weight: 12.5 kg (p75–90), height: 85 cm (p50); Normal development	At 2 months: weight: 4.870 gr(p70); height: 57 cm (p 25–50.) Normal development	At 2 years: weight: 13.4 Kg (p75); height: 89 cm (p75). Normal development	At 1 year: weight: 10.3 Kg (p50); height: 74.3 cm (p50). Normal development	At 1.5 years: weight: 11.9 kg (p75–90); height: 89 cm (p75) Normal development

AP, Antipsychotic; GA Partum, Gestational Age at Partum; LAI, Long-acting injectable; p, percentile; wk, weeks

postural plagiocephaly and hypertonia were noted, that finally were resolved with physiotherapy. Locomotor development was described as normal, with sedestation achieved at 6 months. The child was socialized at nursery school at the age of 6 months. He developed normally during a 3-year follow-up (Table 1). To date, the patient continues attending follow-up visits to the Psychiatry Service with proper compliance with aripiprazole-LAI (300 mg/28 days) and psychopathological and functional stability.

Case 2. Case 2 is a 32-year-old woman whose first contact with mental health services was at the age of 23, being 2 years later diagnosed with schizophrenia and schizotypal personality disorder. Her psychiatric family history includes a deceased poly-drug addict father. She was a regular hashish and cocaine user until the end of the first trimester and smoking 6–9 cigarettes/day throughout pregnancy. The biological father of the newborn presented a diagnosis of psychosis.

After testing different antipsychotics, aripiprazole-LAI 400 mg/28 days was first introduced in 2015. One year later, she was notified in the fifth month of pregnancy of her status. When pregnancy was confirmed, she had been under treatment with aripiprazole-LAI for 19 months. From the Gynecology-Obstetric Service, ultrasound control was performed, presenting normal placenta anterior and normal amniotic fluid without structural anomalies. Considering the advanced state of gestation and the patient's desire to continue with the pregnancy, a benefit/risk approach of treatment discontinuation was explained. Finally, the patient decided to carry on with the pregnancy, reducing the dose of aripiprazole-LAI to 300 mg/28 days. Adherence was maintained throughout the pregnancy with psychopathological stability and good adherence to both treatment and follow-up visits to psychiatry and obstetric-gynecology departments.

At the 32nd week, she was admitted to the Emergency Department for spontaneous delivery, and a right medial episiotomy was performed. Anthropometric measurements of the newborn are presented in Table 1. The newborn was transferred to the Neonatal Service, where she remained for 1 month in an incubator due to prematurity. No congenital malformations were observed at delivery or during the postpartum period. Breastfeeding was not performed. At discharge from the Neonatal Service, the newborn presented weight of 2885 grams, and was 46 cm in length. Neonatal, Cardiology, Otorhinolaryngology, and Neuropediatric Services performed periodic controls on the girl, discounting the presence of any organic pathology. Psychomotor development was evaluated as normal, achieving sedestation at 6 months and wandering freely at 13 months. She was socialized from 3 months in Nursery Care. At the 2-year routine evaluation she remains in good health (Table 1). The mother presented a clinical worsening 3 months after delivery, so required an increase in aripiprazole-LAI dose from 300 mg to 400 mg/28 days. At the time of this communication, the patient remains psychopathologically stable and without disruptive behaviors.

Case 3. Case 3 is a 36-year-old woman diagnosed at age 23 years with paranoid schizophrenia. Medical family history includes a paternal grandmother with a medical diagnose of DM-2. The patient presented chronic untreated cutaneous lupus and type I obesity. A smoker of 6–9 cigarettes per day, she finally quit smoking when pregnancy was confirmed. Since 2014 she was on treatment with aripiprazole-LAI 400 mg/28 days, remaining stable and asymptomatic. After 5 years of treatment with aripiprazole-LAI, the patient reported she was pregnant. Considering her clinical condition and her desire to maintain the pregnancy, the benefits/risks of discontinuing antipsychotic treatment were explained. Finally, the patient decided to continue with treatment, reducing the dose to 300 mg/28 days, which was maintained throughout the pregnancy with psychopathological stability and proper treatment adherence.

Follow-up was carried out by the Gynecology-Obstetric, Rheumatology, and Endocrinology Services, performing diagnostic tests with the low risk of chromosomal abnormalities, normal fortnightly ultrasound controls, and diagnosis of GMD at week 25 (+2 days) that was managed with healthy hygienic-dietary habits and daily glucose monitoring.

Pregnancy evolved normally and resulted in the delivery of a healthy boy at week 40. Anthropometric measurements of the newborn are presented in Table 1. The patient decided to feed the child with artificial lactation. No congenital malformations were observed at birth, and the postpartum period proceeded without relevant events. The newborn was kept in the neonatology unit during the mother's admission for study due to a cutaneous lupus history. The controls performed by neonatology

and cardiology during this period were normal, except for autoantibodies Anti-SSa and Anti-SSb positive. He developed normally during a 1-month follow-up (Table 1). The patient attended the follow-up visit with Psychiatry Service 3 weeks after partum to be administered aripiprazole-LAI, being psychopathological stable. Despite that, due to the mother's fear and stress of a possible relapse and clinical consensus, it was decided to adjust the dose to 400 mg/28 days.

Case 4. Case 4 is a 31-year-old woman diagnosed at 26 years of age with schizophrenia. The patient showed comorbid cannabis use from early adolescence to the previous month before schizophrenia diagnosis, and denied other substance use. She also reported bronchial asthma with occasional treatment with budenoside oral inhalation. Psychiatric family history included a father with paranoid schizophrenia, and she described no other familiar psychiatric history. From October 2014, she was under psychiatric treatment with aripiprazole, first oral 10 mg/day, then in May 2015 with oral 5 mg/day, and since March 2016, she was on aripiprazole-LAI (160 mg/28 days).

Three years later, she declared her desire to become pregnant (no previous children). Considering the psychopathological state of the patient and her desire to become pregnant, a risk/benefit approach of treatment discontinuance was discussed. Finally, according to her psychiatrist's opinion, the patient decided to continue at the same aripiprazole-LAI dose to 160 mg/28 days. It is worth noting that since 2004 Cruces University Hospital has run a First Psychotic Episodes Program (CRUPEP Program), with at least a 5-year follow-up of patients' outcomes and a protocolized strategy of low-dosage antipsychotic monotherapy medication. The equivalent aripiprazole schedule is: 5 mg daily oral/160 mg LAI every 4 weeks; 10 mg daily oral/200 mg LAI every 4 weeks; 15 mg daily oral/300 mg LAI every 4 weeks; 20 mg daily oral/400 mg LAI every 4 weeks; 25 mg daily oral/560 mg LAI every 4 weeks; 30 mg daily oral/700 mg LAI every 4 weeks. This is the main reason for such a low aripiprazole-LAI dosage in this patient. Throughout the pregnancy, the patient remained psychopathologically stable, and treatment adherence was maintained. Regular follow-up visits to Prenatal Consultation were carried out. The pregnancy evolved normally and resulted in the uncomplicated delivery of a healthy boy at week 39 (+5 days). Anthropometric measurements of the newborn are presented in Table 1. The patient decided not to breastfeed the child. During follow-up in the pediatric department, the child's locomotor development was described as expected, with sedestation achieved at 7 months. The child was socialized at nursery school at the age of 9 months. In the 2-year follow-up he remained in good health (Table 1). To this date, the patient continues attending follow-up visits to Psychiatry Service with adequate compliance with aripiprazole-LAI (160 mg/28 days) and psychopathological and functional stability.

Case 5. Case 5 is a 39-year-old woman, diagnosed at the age of 37 with schizophrenia. She had three previous children with her ex-partner. She lived on welfare support from the basic Social Services due to domestic violence history. She presented no medical–surgical history of interest or history of toxic consumption. Although she was Senegal natural-born and all her family lived there with her oldest son, there was no known family psychiatric history. As personal antecedents, she presented a psychiatric admission in March 2017, with a diagnosis of schizophrenia at discharge, and started treatment with LAI Paliperidone 75 mg/4 weeks. In January 2018, it was decided to change to oral aripiprazole 15 mg/day due to secondary side effects (akathisia, rigidity, amenorrhea, and galactorrhea). Due to the good tolerance, in March 2018, aripiprazole-LAI 300 mg/28 days was recommended. In July 2018, she went to medical consultation and reported 2-month amenorrhea. She also reported she had returned to live with her ex-husband.

A pregnancy test was performed and confirmed that she was pregnant. The patient was informed on the situation, and due to her psychopathological stability the benefits/risks of maintaining or withdrawing the medication were considered. Finally, in agreement with the patient, it was decided to maintain antipsychotic treatment, and she was referred for follow-up in at-risk pregnancy consultations. In January 2019, at week 39 of gestation, a healthy male was born. Anthropometric characteristics are presented in Table 1. Breastfeeding was suspended, and oral cabergoline tablets were prescribed to the mother. During follow-up visits to the Pediatric Department, a normal child's psychomotor development was described, with adequate sedestation at 6 months. During the first year of life, the child was under the care of his mother and his siblings. Pediatric evaluations were regular. At 12 months, the baby's health is good (Table 1). The patient regularly attends the consultations, maintains

adequate social and family activity, and has a complete psychopathological stabilization. The patient continues to be supported by social services supervision and maintains a long-term injectable aripiprazole pattern 300 mg/28 days.

Case 6. Case 6 is a 30-year older woman, diagnosed at the age of 26 with schizophreniform disorder and presenting with a substance-induced psychotic disorder. In fact, and considering her clinical evolution, she presents a current diagnosis of schizophrenia since December 2017. Psychiatric family history includes father's alcoholism with antecedents of domestic violence. Somatic family history includes a mother with obesity. Personal history of gender violence is registered from her ex-husband, the father of her twins. Sporadic amphetamine use is recorded, being stopped in both pregnancies. Treatment with aripiprazole-LAI (400 mg/28 days) was introduced in her first hospital admission in 2017, with good tolerance. In December 2017 the patient was referred to another facility following a change of address. During this period, the patient remained stable, with good tolerance and adherence to depot formulation. In January 2018, the patient reported to the medical staff that she was pregnant. Pregnancy was finally confirmed, and after the risk–benefit of discontinuing was explained, the patient decided to stop antipsychotic treatment. The patient was exposed to aripiprazole-LAI treatment during all the first trimester of pregnancy. Also, the prescription dose of benzodiazepines was adjusted downwards until they were withdrawn along 4 weeks. To ensure psychopathological stability and to detect warning signs of decompensation, the patient was closely monitored weekly in the CRUPEP Program to alert prodromic symptoms. Follow-up was carried out jointly by the Psychiatry and Gynecology-Obstetrics Services.

All the performed ultrasound presented the absence of abnormalities of malformations. The patient presented subclinical hypothyroidism during pregnancy, treated with levothyroxine 25 mg/day. At week 40, a healthy boy was born. Anthropometric characteristics are presented in Table 1. Breastfeeding was not performed. To date, the child has been followed for 18 months, and no malformation or growth retardation was detected. More detailed clinical characteristics are presented in Table 1. The patient was attended during the follow-up visit in the CRUPEP Program, and 3 months after delivery she was again prescribed aripiprazole-LAI 400 mg/ 28 days due to patient's fear and stress derived of a possible prodromal relapse and by clinical consensus with her psychiatrist.

Discussion

Non-adherence to medication is an inherent characteristic of many chronic diseases. However, there are certain mental illnesses, such as schizophrenia, where it becomes a multidimensional process where several factors such as social isolation, comorbidities, substances use, and low-income family support, among others, are added.[29,30] In fact, treatment satisfaction is positively correlated with treatment adherence, which is likewise associated with perceived effectiveness, side effects, and the type and route of prescribed medication.[31–33] Attending this scenario, LAI-APs ensure treatment adherence and maintain stable plasma levels of the drug, enduring better tolerability and clinical efficacy.[34]

In the case of pregnant women with schizophrenia, being treated with a LAI antipsychotic formulation might assure clinical stability and better functionality, and it would mean greater autonomy, better productivity in activities oriented to self-care during pregnancy, greater quality of life, and adequate care for the mother and the newborn after delivery. The posology comfort of LAI-APs, especially in those life-challenging situations such as pregnancy, also eases the reduction of stressful situations in this group of more vulnerable patient.[35] For all these reasons, the use of LAI-APs formulations should be considered a real treatment option for pregnant women with severe mental disorders who need antipsychotic therapy.

Despite the lack of literature regarding potential effects in the fetus of using LAI antipsychotic formulations during pregnancy, our six-case series allows a specific advance toward understanding how treatments impact pregnant women, avoiding the risk of relapse in mothers in the absence of significant abnormalities or harm to the development of the fetus. In fact, few case reports have been described in the literature regarding the use of atypical LAI-APs while pregnant.[36–38]

None of the newborns included in this report presented congenital malformations that can pose a vital threat to the child or result in developmental problems in milestone achievement. Moreover, in

the six cases described, after they had been treated with aripiprazole-LAI antipsychotic monotherapy, the patients maintained exhaustive monitoring visits, carried out satisfactory self-care during pregnancy, and showed secure attachment to the baby. Our presented case-series highlights that LAI-APs could be a therapeutically safe option for pregnant women and their future newborns.

Considering the clinical cases, at the time pregnancy was reported, most women were being treated with aripiprazole-LAI 400 mg/28 days dose (Table 1). It was decided by clinical consensus to decrease the dose of aripiprazole-LAI to 300 mg/28 days (as described in cases 1, 2, 3, and 5). The main reason to reduce the antipsychotic dose was the consolidated clinical stability that patients presented. These results are in line with clinical trials evaluating the efficacy of aripiprazole-LAI, showing that 300 mg/28 days is the minimum effective dose.[39] At this point, it is worth repeating that the Cruces University Hospital has, since 2004, developed a First Psychotic Episodes Program (CRUPEP Program), with at least a 5-year follow-up of patient outcomes and a protocolized and successful strategy of low-dosage antipsychotic monotherapy medication. The treatment rationale for aripiprazole schedule is: 5 mg daily oral/160 mg LAI every 4 weeks; 10 mg daily oral/200 mg LAI every 4 weeks; 15 mg daily oral/300 mg LAI every 4 weeks; 20 mg daily oral/400 mg LAI every 4 weeks; 25 mg daily oral/560 mg LAI every 4 weeks; 30 mg daily oral/700 mg LAI every 4 weeks. This is the main reason for the low aripiprazole-LAI dosage in patient 4. Despite the fact there is evidence of a decline in the plasma levels of antipsychotic from the first to third trimester of pregnancy, and that an increase of antipsychotic dose is partially recommended to ensure psychopathological stability,[40] a close follow-up in the CRUPEP Unit at Cruces University Hospital with a reduction of the antipsychotic dose was agreed with the patient in order to avoid the occurrence of potential adverse effects.

Exceptionally, one woman (case 6) decided to interrupt the treatment (400 mg/28 days), by her own decision, at the end of the first trimester, restarting LAI-AP treatment after childbirth. We have included this patient in the case-series due to the impact of antipsychotic treatment during the first trimester. To ensure psychopathological stability and detect warning signs of decompensation, the patient was closely monitored weekly in the CRUPEP Program at Cruces University Hospital, looking for prodromic alert symptoms. Furthermore, from a pharmacokinetic point of view, after a single dosage of a LAI formulation, relapse prevention derived for antipsychotic plasma levels enough to block up to 60% D2 receptors remains active for several weeks (up to 24 weeks if we use paliperidone LAI monthly).[41,42]

All patients were closely monitored by multidisciplinary clinical staff to detect the presence of risk signs or complications (psychiatry, obstetric-gynecology, endocrinology, and rheumatology). Pregnancies proceeded without significant malformations or obstetric complications. As described above, two patients presented GDM and weight gain (cases 1 and 3), in which psychoeducation and healthy lifestyle habits were introduced. In cases of women presenting GDM, previous first or second-degree family history of DM-2 was described, and both were overweight or presented pre-gestational obesity (Table 1). As a result, those related factors may favor the appearance of GDM.[43,44]

In addition to these previously mentioned risk factors, the impact of the mental illness itself should be considered. A recent review and meta-analysis have shown that patients with bipolar disorder and schizophrenia present double the risk of developing DM-2.[45] Atypical antipsychotics appear to be related to several metabolic side effects; nevertheless, some studies suggest that aripiprazole presents a better metabolic profile, with a lower risk for weight gain, dyslipidemia, and diabetes compared with other SGAs.[21,39,46–49] Therefore, aripiprazole could be a suitable antipsychotic for this profile of patients.

Concerning late pregnancy and delivery, it should be noted that having schizophrenia and the exposure to SGAs itself may be related to a slight increase in the risk of preterm birth and low birth weight.[6] In the case-series presented in this article, all pregnancies (except for case 2) occurred in a standardized and uneventful way: full-term births, healthy newborns with average weights, and proper psychomotor developments. As previously mentioned, case 2 presented preterm delivery with a low birth weight newborn that required special care in an incubator. Finally, the child was closely monitored by Pediatric Service, with no abnormalities found so far. One of the possible explanations for the prematurity in case 2 could be related to certain psychosocial factors in the mother that may have influenced the pregnancy (substance use,

reduced self-care, low socioeconomic level).[12,16,21] The mother also had a smoking habit, which is described as a risk factor for preterm birth and low birth weight.[22]

Focusing on breastfeeding, only one of the patients presented in our case-reports decided to breastfeed her child after having the risks/benefits explained (see Table 1). No breastfeeding issues were described, nor was there any impact on feeding and sleeping patterns or tendency to daytime sleepiness in babies. Information on the use of antipsychotics during breastfeeding is very scarce, and it is based mainly on the collection of single case-reports.[12,50] Aripiprazole is known to be present in human breast milk at a relatively low level, and published cases do not reflect adverse reactions in infants.[12,51]

All newborns were closely monitored and followed during the neonatal period by the Pediatric Service, which performed exhaustive follow-ups of physical or motor, cognitive, and social development areas.[52] From the psychomotor development point of view, all children presented normal development except for case 1, in which a psychomotor problem appeared; this was finally resolved with physiotherapy. On a cognitive and social level, all children presented a normal development up to the time of this report.

Regarding the clinical stability of the included cases, all patients continued maintenance treatment with aripiprazole-LAI following delivery and remained stable and asymptomatic at doses of 300 mg/28 days, except for cases 3, 4, and 6. It is well known that after delivery there is a sudden drop in estrogen levels that increases the mother's vulnerability, especially increased by sleep deprivation and other psychosocial stressors such as essential newborn care. Therefore, the perinatal period is a period of high risk of instability for mothers, with particular relevance for those with severe mental disorders.[53] Consequently, treatment adherence is essential during this period, along with close monitoring of the psychopathological state. As stated above, in case 4, the patient was treated with a maintenance aripiprazole-LAI 160 mg/28 days dose through pregnancy and postpartum, while in cases 3 and 6, patients required a dose optimization at 400 mg/28 days[53] at 3 months postpartum due to slight prodromal clinical worsening. This clinical worsening was apparently related to the patients' greater vulnerability to stress and poor social and family support environment.[54,55] Finally, after a dose increase, a good clinical response was observed, and the patients are currently stable. Therefore, in all clinical cases presented in this article, no acute decompensations occurred in the preconception period, during pregnancy, or in the immediate postpartum period.

Among the main factors that may have influenced symptom stability and relapse prevention would be: (a) good coordination between Psychiatric and Obstetric-Gynecology-Pediatric Services, offering close care in the mental health and prenatal areas, and (b) adherence to antipsychotic pharmacological treatment. These results might be related to the efficacy and tolerance of aripiprazole and dosage convenience through monthly administration of LAI-Aps.[34,35] Once again, it is important to highlight the psychopathological stability of all these cases, despite some of them being patients with more than 10 years of illness evolution who had required previous hospital admissions with the consequent deterioration that this would imply.

Limitations

It is necessary to consider that despite the favorable results with regard to pregnancy development and neonatal outcomes, there are certain limitations in our study. First, although we have presented a series of six cases of pregnant women with schizophrenia who are being treated with aripiprazole-LAI, the results are limited to generalization due to the small sample size. Despite that, real-world naturalistic studies provide further advantages compared with classical randomized clinical trials (where selection bias and increased treatment adherence have been pointed out).[56] Furthermore, it is necessary to consider that some of the women included in the present case-series were closely followed in a FEP Unit, where close follow-up visits are made with a low-dose rationale of antipsychotics, ensuring treatment adherence and psychopathological stability.

Conclusion

According to the evidence presented, further research on the use of long-acting antipsychotics in pregnant women is needed. The favorable results in this case-series suggest that despite the lack of evidence on reproductive safety and treatment with aripiprazole-LAI during pregnancy, this therapeutic option should be considered in pregnant women with schizophrenia. Besides, to prevent the risk of psychosis recurrence during

pregnancy, the use of this formulation in pregnant women with schizophrenia offers several advantages, including the avoidance of impaired functioning of both mother and child and the absence of neurodevelopmental abnormalities or malformations in children. Further studies in this population with a larger number of patients will be necessary to corroborate this data.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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ORCID iDs

Maria Recio-Barbero https://orcid.org/0000-0003-1783-5453

Rafael Segarra https://orcid.org/0000-0002-2033-8151

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