Journal of Affective Disorders 238 (2018) 593–596

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Short communication

Aripiprazole and pregnancy: A retrospective, multicentre study

Megan Galbally[a,b,c,*], Jacquie Frayne[c,d], Stuart J Watson[a,b], Martien Snellen[e]

[a] School of Psychology and Exercise Science, Murdoch University, Australia
[b] School of Medicine, University of Notre Dame, Australia
[c] King Edward Memorial Hospital, Australia
[d] School of Medicine, Division of General Practice, The University of Western Australia, Australia
[e] Mercy Hospital for Women, Heidelberg, Australia

ARTICLE INFO

Keywords:
Aripiprazole
Antipsychotics
Pregnancy
Psychosis
Schizophrenia

ABSTRACT

Background: Aripiprazole is a second generation antipsychotic medication that has been a useful addition to the treatment of severe mental illness due to its low metabolic and sedation risk profile. Pregnancy is a time of high risk of metabolic complications such as gestational diabetes and the postpartum period is often a time when sedation can compromise infant care. To date there is limited data in pregnancy on the safety of aripiprazole use. While available data do not suggest an elevated malformation risk in pregnancy, there is less information available on pregnancy and neonatal complications.

Methods: This study presents preliminary data on pregnancy and neonatal complications on 26 women who took aripiprazole in pregnancy. These women attended at antenatal clinics for women with severe mental illness at two hospitals in Australia.

Results: Overall aripiprazole was not associated with an increased risk of gestational diabetes. However, use of aripiprazole in pregnancy was associated with an increased risk of pregnancy hypertension, lower birth weight, shorter gestation at birth and higher rates of admission of the neonate than the expected population rates.

Limitations: These findings need to be replicated in a larger, well-designed study to ensure they do not reflect confounding factors.

Conclusions: Findings demonstrate that aripiprazole is unlikely to pose a metabolic risk in pregnancy but other pregnancy complications including hypertension, need to be examined in further studies.

1. Introduction

The management of severe mental illness in pregnancy such as Schizophrenia and Bipolar Disorder is a challenging area of psychiatric practice where there is a need to consider both maternal and fetal wellbeing in treatment option decision making. The natural course of these disorders during pregnancy make the perinatal period a time of high risk of relapse, with the implication that for many women ceasing treatment is not a viable option if health and wellbeing are to be maintained (Galbally et al., 2017). However, pregnancy related physiological changes and associated metabolic vulnerabilities together with the inevitable fetal medication exposure make the choice of treatment complex in pregnancy.

Contemporary mental health practice has embraced the use of second-generation antipsychotics (SGAs) for first line treatment of severe mental illness, particularly for psychotic disorders. The older SGAs such as risperidone, olanzapine and quetiapine now all have some evidence for the risks and benefits in pregnancy and as such are often the agents used to treat women across the perinatal period. However, each has shown to have limitations when used in the perinatal period. For instance, olanzapine and quetiapine may increase the risk of gestational diabetes (GDM), weight gain and are associated with significant sedation making the postpartum care of their baby challenging (Boden et al., 2012; Gentile, 2004, 2014b; Galbally et al., 2014). Risperidone has been associated with a small increased risk of malformations, including cardiac malformation, following first trimester exposure (Huybrechts et al., 2016). Therefore, for women wanting to avoid excessive weight gain, sedation and are concerned about the potential for a possible malformation risk the current options are limited.

Aripiprazole, a partial agonist of specific dopamine and serotonin receptors, is increasingly being prescribed in general adult mental health. This is particularly in clinical situations where there has not been tolerance or response to other SGAs, there is a need to avoid sedating agents or where there is significant concern about metabolic risk. Unlike many of the other SGAs aripiprazole does not increase metabolic

* Corresponding author at: Murdoch University, 90 South Street, Murdoch, WA 6150, Australia.
E-mail address: m.galbally@murdoch.edu.au (M. Galbally).

https://doi.org/10.1016/j.jad.2018.06.004
Received 29 March 2018; Received in revised form 2 May 2018; Accepted 1 June 2018
Available online 14 June 2018

risk, weight gain and is rarely sedating (L'Italien et al., 2007). In addition, for women planning pregnancy or who become pregnant while on aripiprazole, the question raised is if she is stable on aripiprazole should she remain on this medication? Despite aripiprazole being available since 2002 there is only limited information on the risks and benefits of this treatment in pregnancy (Gentile, 2014a). Most of the information is limited to population based studies examining malformation risk or case studies or small case series (Gentile, 2014b; Huybrechts et al., 2016; Gentile et al., 2011). Frequently missing from these studies is confirmation of timing and dose of exposure, mental health indication, information on confounding factors in pregnancy such as body mass index, smoking and alcohol use and other concomitant exposures (Huybrechts et al., 2016; Bellet et al., 2015). Indeed, in one of the largest studies to date from a French teratogen service there was no information for the majority of subjects on the key pregnancy complications and neonatal outcomes and only one third had information on alcohol exposure. Furthermore, only 21% of the sample took aripiprazole during their pregnancy and most were on multiple psychoactive agents. Therefore, the aim of this study is to report on a case series of women who took aripiprazole in pregnancy where there are robust records of diagnosis, exposures and outcomes in pregnancy recorded to assist in building data on this treatment in pregnancy.

2. Materials and measures

2.1. Measures

Data were collected at two sites, Mercy Hospital for Women in Victoria and King Edward Memorial Hospital in Western Australia both in Australia. These hospitals are tertiary maternity hospitals with antenatal clinics for women with severe mental illness. The authors extracted the data from hospital medical records. This study had ethics approvals from Human Research Ethics Committee at both hospitals.

2.2. Demographics

Demographic data included maternal age and BMI at the first antenatal appointment. Maternal BMI score was used to produce a binary variable, where BMI < 25 was coded as 0 (Healthy Weight) and BMI ≥ 25 was coded 1 (Overweight or Obese). Women's current smoking status (0 = Non-smoker, 1 = Smoker), alcohol consumption (0 = No, 1 = Yes) and current substance abuse status (0 = No, 1 = Yes) was also extracted.

2.3. Maternal mental health

Severe mental illness (SMI) was coded on the primary mental health diagnosis recorded in the patients' files. Both clinics have experienced perinatal psychiatrists who assign diagnoses following a comprehensive assessment. Women were assigned to one of three diagnostic groups: psychotic disorders (including schizophrenia, schizoaffective and related psychotic disorders), bipolar disorder, and non-psychotic SMIs. Non-Psychotic SMIs include major depressive disorder, obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, anorexia and bulimia nervosa.

2.4. Obstetric and neonatal complications

Pregnancy complications including GDM was coded from the hospital records as no GDM (coded 0) and GDM (coded 1). GDM in both centres is diagnosed at 28 weeks gestation using the full 75 g two-hour glucose tolerance test (GTT). Pregnancy Hypertension included all those women with elevated blood pressure in pregnancy including pregnancy-induced hypertension and pre-eclampsia, following the definitions outlined by the Society of Obstetric Medicine of Australia and New Zealand (Lowe et al., 2014). Delivery mode included normal vaginal delivery, assisted delivery and Cesarean, which differentiated between emergency and elective Cesarean. Neonatal outcomes included gestational age measured in weeks, infant birth weight in grams, birth weight percentiles by gestational age (Dobbins et al., 2012), infant height and head circumference in centimetres and the 5-min Apgar score (<7 = *Abnormally Low*, ≥7 = *Normal*). In addition, admission for care to either a Special Care Nursery or Neonatal Intensive Care Unit was also extracted.

2.5. Aripiprazole

The duration and dose of exposure to aripiprazole was extracted from across pregnancy and recorded as exposure and dose in 1st and 3rd trimester. The number and type of additional psychotropic medications were also collected. There were 12 on two medications (one additional to aripiprazole) and 3 on 3 psychotropic medications and 3 on 4 psychotropic medications. The majority were also on an antidepressant; in addition, there were other antipsychotics, mood stabilisers and benzodiazepines.

2.6. Statistical analyses

Descriptive statistics are presented as either frequencies (i.e., *n* and *%*) or measures of central tendency (*M, SD* or *Mdn, IQR*). Where inferential comparisons are made, the Fisher's Exact test was used to compare differences amongst frequencies, and the analyses of variance (ANOVA) test to compare groups on measures of central tendency. Where variances were significantly heterogeneous, group difference was determined using the more robust *Welch's F* test. Inferential comparison of birth weight percentile by gestational age was conducted using a Mann-Whitney U test. Comparisons of sample rates with Australian population rates (Hilder et al., 2012) were conducted using Goodness of Fit χ^2 with Fisher's Exact test. Significance was assessed when $p < .05$.

3. Results

There were 26 women identified across the two hospitals who took aripiprazole in pregnancy. Of these 26 women, 12 remained on this medication for the duration of their pregnancy. Table 1 reports the maternal age, diagnosis, BMI and smoking, alcohol and illicit substance use for the total sample, and those who ceased and those who continued aripiprazole. There were no significant differences between the groups on any of the demographic variables. The majority who took

Table 1
Demographic statistics of pregnancy women on aripiprazole (*N* = 26; mercy *n* = 9, KEMH *n* = 17).

Maternal age	Ceased aripiprazole during pregnancy (*n* = 14)		Continued aripiprazole during pregnancy (*n* = 12)		Total sample	
	M	*SD*	*M*	*SD*	*M*	*SD*
	28.5	4.74	29.42	7.1	28.92	5.84
	n	*%*	*n*	*%*	*n*	*%*
SMI diagnosis						
Psychotic disorders	10	71.4	9	75	19	73.1
Bipolar disorder	4	28.6	2	16.7	6	23.1
Non-psychotic SMI	0	0	1	8.3	1	3.8
Body mass index ≥25	11	78.6	9	75	20	76.9
Smoking	7	50	5	41.7	12	46.2
Alcohol use	2	14.3	4	33.3	6	23.1
Illicit drug use	2	14.3	1	8.3	3	11.5