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REGULAR ARTICLE

Infant neurodevelopment following *in utero* exposure to antidepressant medication

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ABSTRACT

Aim: To examine the impact of pregnancy exposure to antidepressants on infant neurodevelopment.

Methods: A prospective, longitudinal study in which antidepressant-exposed (n = 35) and nonexposed (n = 23) infants were administered the Bayley Scales of Infant Development (BSID–III) at 18 months, which measures neurodevelopment across five domains. Data on obstetric and perinatal complications, maternal IQ, presence of mood disorder in pregnancy and up to and including 18 months, and psychosocial status were also collected.

Results: Almost 90% of infants were exposed throughout the second and third trimesters to therapeutic antidepressant doses. Bivariate analysis showed no difference between exposed and unexposed infants in any of the neurodevelopmental outcomes. Maternal depression around birth or up to time of developmental testing was not associated with neurodevelopmental outcomes.

Conclusion: Our results suggest that pregnancy antidepressant exposure (mostly serotonin reuptake inhibitors) is not associated with poorer cognitive, motor or language development outcomes in infants at 18 months. This information supports earlier studies and adds into the available data used by clinicians and mothers making key decisions around the use of antidepressants in pregnancy. However, given the small sample size, and some degree of heterogeneity in terms of antidepressant exposure, these results need to be treated with caution.

INTRODUCTION

Around 7.2% of pregnant women are affected by a major depression many of whom would benefit from an antidepressant (1). Studies suggest that up to 50% pregnant women cease antidepressant use without consulting a medical practitioner (2), placing them at increased risk of relapse (3). Thus, almost 70% of women ceasing antidepressant preconception relapsed in pregnancy versus 26% in the medicated, depressed comparison group (3). High relapse rates may be associated with indirect risk to the foetus by suicidal behaviour, poor self-care, inadequate nutrition and poor antenatal clinic attendance, with a consequent lack of foetal monitoring (4). Previous maternal death reports have shown that 'psychiatric-related deaths' are among the leading causes of maternal death with almost two-thirds of these occurring in pregnancy (5) and the majority being associated with severe, and often untreated, depressive illness (6).

Another aspect of untreated maternal mental illness in pregnancy is the possible direct effect of maternal illness *per se* upon the pregnancy and foetus. These include increased obstetric complications such as prematurity, low birthweight (7) and adverse impact on neurodevelopmental (cognitive, motor, emotional and behavioural) outcomes (8).

Up to 8% of women will be prescribed a selective serotonin reuptake inhibitor (SSRI) or an SNRI (e.g. Efexor) in pregnancy (9) with a trend towards increased

Key notes

- A controlled, prospective trial examining pregnancy SSRI exposure on neurodevelopmental outcomes at 18 months.
- There was no effect of SSRI exposure (majority of infants exposed in at least the second and third trimesters) on any Bailey's neurodevelopmental outcomes (cognition, language and motor development).
- Our findings confirm earlier studies, but given the small sample size (SSRI exposed = 35; controls = 23), they need to be treated with caution.

prescribing in the last 10 years. Foetal antidepressant exposure is substantial as antidepressants cross the placental barrier at significant, albeit at differing, concentrations (10).

In spite of greatly varying methodologies among studies, overall, the lack of reported impact of SSRIs and other antidepressants on neurodevelopmental outcomes is encouraging [see review (11)]. So far, the main finding is that antidepressant exposure is associated with poorer motor outcomes (11–15). The current paper explores the impact of SSRI pregnancy exposure on infant cognitive and motor development in the second year of life.

PATIENTS AND METHODS

Patients

This longitudinal cohort study recruited pregnant women or early postpartum women (Group 1) who had been on an antidepressant for at least 1 month during pregnancy for treatment of depression or an anxiety disorder (n = 35). Women who were recruited to the control group (Group 2) had no history of mood disorders and were not using antidepressant medication or any other psychotropic medication (n = 23) during pregnancy. A power analysis was not undertaken because recruitment was opportunistic and recruitment capacity was limited. Women were excluded from the study if they satisfied any of the following conditions: significant current alcohol or illicit drug use; diagnosed as suffering from any other mental disorders; taking the psychotropic medication for a condition other than depression or anxiety disorders as defined above; and significant obstetric history (e.g. hypertension or diabetes) unless these medical problems were well controlled.

Medicated women were recruited by authors Austin & Kennedy between 2007 and 2010 either from the perinatal mental health clinic at the Royal Hospital for Women (RHW) in Sydney, Australia or through 'MotherSafe', a drug advisory service that offers counselling to women concerned with medication exposure during pregnancy or breastfeeding. Controls were recruited through the antenatal clinics at the RHW and an early postnatal mother's group. Mothers and infants were followed up by paediatricians Oei and Mishra who oversaw the Bailey's assessments. Bailey assessments were carried out by our research psychologists (and co-authors) Karatas & Christl.

Measures

Demographic and clinical information

Information on age, marital status, obstetric history, educational level, cigarette, alcohol and recreational drug use during pregnancy, and perinatal outcomes was collected.

Medication calendar was used to collect information from women in Group 1 regarding the name and dosage of the antidepressant use for each month of pregnancy. Clinical validation of compliance with medication was not possible as women were recruited from across Sydney and thus could not be systematically followed up at our clinic.

Edinburgh Postnatal Depression Scale (EPDS) (16) is a 10-item self-report scale identified the rate and intensity of depressive symptoms present in the previous 7 days.

National Adult Reading Test (NART) (17) is a widely accepted tool used for estimating intelligence in neuropsychological research.

The MINI-Plus (version 5.0.0) is a structured, diagnostic interview for mental health disorders (18). The MINI-Plus was used to examine current and past episodes of the full spectrum of depression-, mania- and anxiety-related mental health disorders.

The Bayley Scales of Infant and Toddler Development (Third Edition) (BSID-III) (19) is a standardized instrument designed to measure the developmental functioning of infants and toddlers (age 16 days–42 months 15 days) across five domains: cognitive, receptive language, expressive language, gross motor and fine motor development. The test scale scores are age standardized using a normative sample of 1700 children in the United States. According to its technical manual, the Bayley-III scales have good validity, reliability and internal consistency (19). Assessors were blinded to exposure status.

Data analysis

Our outcome variables were the BSID-III scaled scores for cognition, receptive language, expressive language, fine motor and gross motor development. Data were explored initially with descriptive statistics and graphs. Normality of outcome variables was checked. All outcome variables were continuous.

The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

RESULTS

A total of 102 women were recruited to the study. Of these women, 17 were excluded for the following reasons: history of mental health condition in controls (n = 6), premature delivery (n = 7), stillbirth (n = 1), miscarriage (n = 1), twin pregnancy (n = 1) and one woman moved too far away for follow-up. A further 27 women were lost to follow-up (not contactable at the 18 month follow-up time point or no longer willing to participate). There were no significant differences between the women who dropped out and those who completed the study on the following parameters: number of women in the medicated or control group (p = 0.81), maternal age (p = 0.43), maternal level of education (p = 0.22), baseline depression scores (EPDS, p = 0.73), baseline NART scores (p = 0.41) and neonatal outcomes: gestation (p = 0.48) and birthweight (p = 0.31).

Sample characteristics

The final sample was made up of 58 women, 35 with antidepressant use during pregnancy and 23 controls. Table 1 lists demographic, neonatal and maternal characteristics. The MINI diagnosis showed that there were no

Table 1 Characteristics of study and control sample

Maternal characteristics	Medicated (n = 35) Mean (SD)	Control (n = 23) Mean (SD)	t	p
Age	34.9 (3.4)	32.7 (3.0)	−2.5	0.02
EPDS at baseline	7.4 (5.5)	3.5 (3.1)	−3.1	0.004
EPDS 13 & above	n = 4	n = 0		
EPDS at follow-up	6.2 (4.9)	3.8 (4.2)	−1.9	0.06
EPDS 13 & above	n = 3	n = 1		
NART score	112.2 (6.5)	111.9 (6.5)	−0.15	0.88
Alcoholic drinks per month during pregnancy	3.0 (6.3)	2.4 (6.9)	−0.36	0.72
	n (%)	n (%)	χ^2	p
Type of delivery				
NVD	23 (68)	16 (70)	0.76	0.68
Caesarean	7 (21)	3 (13)		
Emergency caesarean	4 (12)	4 (17)		
Depression at baseline (MINI)				
Current	2 (5.7)	0 (0)	1.36	0.24
Past (lifetime)	28 (80)	0 (0)	35.57	<0.001
Depression at follow-up (MINI)				
Current (@BSID-III assessments)	1 (3)	0 (0)	0.64	0.43
Since birth	8 (26)	0 (0)	6.12	0.01
Partner status				
Not partnered	2 (6)	0 (0)	1.36	0.24
Partnered	33 (94)	23 (100)		
Maternal education				
No university	9 (26)	5 (22)	0.12	0.73
University/postgraduate	26 (74)	18 (78)		
Paternal education				
No university	8 (28)	11 (50)	2.7	0.10
University/postgraduate	21 (72)	11 (50)		
Infant characteristics	**n (%)**	**n (%)**	χ^2	**p**
Gender				
Female	19 (54)	14 (61)	0.25	0.62
Male	16 (46)	9 (39)		
Apgar at 1 min				
0–7	7 (21)	4 (18)	0.05	0.78
8 or higher	27 (79)	18 (82)		
Apgar at 5 min				
0–7	4 (12)	0 (0)	2.79	0.09
8 or higher	30 (88)	22 (100)		
	Mean (SD)	Mean (SD)	t	p
Gestation (weeks)	39.3 (1.1)	39.7 (1.5)	0.93	0.36
Weight (g)	3586 (543)	3585 (583)	−0.004	0.99
Length (cm)	52.0 (2.7)	52.0 (2.7)	0.10	0.92
Head circumference (cm)	34.5 (1.6)	35.0 (1.4)	1.01	0.29
Infant age at follow-up (months)	19.1 (1.61)	18.9 (1.46)	−0.47	0.64

EPDS, Edinburgh Postnatal Depression Scale; NART, National Adult Reading Test; MINI, Mini international neuropsychiatric interview; BSID, Bayley Scales of Infant Development; NVD, normal vaginal delivery.

Missing values: maternal age: 1; EPDS at follow-up: 1; Alcohol per week: 1; Type of delivery: 1; Depression since birth: 7; Current depression at follow-up: 6; paternal education: 7; Apgar 1 min: 2; Apgar 5 min: 2; gestation: 8; weight: 6; length: 7; and head circumference: 9.

women in the control group who reported symptoms that would warrant a clinical diagnosis of depression in the past or a current diagnosis (previous 2 weeks, Table 1).There were a number of significant differences between the medicated and control group mothers. Medicated women were older (t = −2.5; p = 0.02);their baseline EPDS scores (t = −3.1; p = 0.004) were significantly higher than those of the control group; the majority had a past diagnosis of depression (80%), and 23% of the medicated group had experienced a major depression in the 18 months since

Table 2 Medications and the mean and range dosages at each trimester

Medication (n = 35)	1st trimester Mean mg (min–max) dose	2nd trimester Mean mg (min–max) dose	3rd trimester Mean mg (min–max) dose
Sertraline (n = 11)	57.5 (0–150)	60 (0–150)	62.5 (25–150)
Fluoxetine (n = 6)	24 (0–40)	25 (20–40)	25 (20–40)
Citalopram (n = 5)	18 (0–40)	22 (10–40)	18 (10–20)
Escitalopram (n = 2)	5 (0–10)	5 (0–10)	5 (0–10)
Venlafaxine (n = 4)	150 (150–150)	168.7 (75–300)	178.4 (113.5–300)
Paroxetine (n = 1)	20 (20–20)	20 (20–20)	20 (20–20)
Fluvoxamine (n = 1)	100 (100–100)	100 (100–100)	100 (100–100)
Dothiepin (n = 5)	20 (0–75)	35 (0–75)	70 (25–100)

Table 3 Performance and difference on Bayley Scales of Infant Development III (scaled scores) between SSRI exposed and control infants

Bayley scales	Medicated (n = 35) Mean (SD)	Control (n = 23) Mean (SD)	z	p
Cognitive	11.1 (2.1)	12.6 (2.6)	−1.86	0.06
Motor				
Fine motor	12.1 (2.4)	11.8 (2.0)	−0.85	0.40
Gross motor	9.2 (2.6)	9.1 (2.0)	−0.38	0.71
	Mean (SD)	**Mean (SD)**	**t**	**p**
Communication				
Receptive	9.5 (2.5)	10.0 (2.1)	0.81	0.42
Expressive	9.2 (2.7)	9.7 (2.3)	0.75	0.46

birth, compared with none in the control group (p = 0.01). Although the intention was to follow-up participants at 18 months after birth, infants' age at assessment ranged from 17 to 24 months with a mean age of 19 months. There was no significant difference in age at follow-up between the exposed (mean age: 19.1 months) and nonexposed control infant groups (mean age: 18.8 months; t = −0.60; p = 0.55). Scaled scores from the BSID-III have been used in all analyses, which are adjusted for infant age thus allowing for comparison of scores across age groups.

Table 2 lists the medication and dosage of antidepressants in the medicated sample. SSRI dosages are at the low-to-mid range of the therapeutic scale and remain constant across pregnancy. A large proportion (74% n = 26) of women used antidepressants throughout the whole pregnancy, while the great majority (about 90%) were on an antidepressant throughout the second and third trimesters. More specifically, one woman used them only in the first and second trimester, and three used them in the third trimester only.

Infant neurodevelopmental outcomes

Group differences in the BSDI-III scores were tested using Mann–Whitney U-test for non-normally distributed cognition, fine motor and gross motor scores and using independent t-tests for the normally distributed language scores. Antidepressant exposed infants did not score significantly different on cognitive, receptive language, expressive language, fine motor and gross motor development than control infants (Table 3), although the control infants did score higher on the composite cognitive scale (11.1 vs. 12.6; p = 0.06). Thus, a further analysis of possible confounders was not conducted.

DISCUSSION

This prospective, observational study shows no significant difference in infant neurodevelopmental outcomes – either motor or cognitive – after in utero exposure to antidepressants, predominantly SSRIs, in contrast to the comparison group. Our findings add to a number of other studies showing a lack of association between in utero exposure to antidepressants and infant *cognitive function*, whether it be in younger infants (12,20–24) or school-aged cohorts (25,26). In addition, it does not support those clinical (12,13,22) and birth-register studies (14,15) suggestive of an association with poorer motor development. Interestingly, other studies have also failed to find an increase in reports of difficult infant temperament (20,26) or a clinically significant increase in behavioural disorders in older cohorts – including internalizing and externalizing disorders (27,28), and autism spectrum disorders (29).

The strengths of the current study include recruitment and follow-up of women on antidepressants by the four clinician researchers (Austin, Kennedy, Mishra, Oei), thus greatly increasing accuracy of medication timing and duration of exposure, baseline depression diagnosis, and rigour of outcome status both maternal and child. Almost 90% of women were on therapeutic doses of antidepressants for at least the second and third trimesters, leading to uniformity of foetal exposure. Compared with some earlier studies, we used the gold standard neurodevelopmental tool – the BSID-III – and our toddlers were at least 17 months old at age of testing. This is an important consideration as the older the child the more accurate and predictive the BSID-III becomes. In addition, unlike most other studies (other than the Nulman studies 2002, 2012), we controlled for the important maternal confounder of verbal IQ (NART), and additionally for measures of socioeconomic status, maternal pregnancy illness and substance use. To our knowledge, this is the only study that examined maternal depression both in terms of symptom score (EPDS) and presence of a clinical episode in pregnancy or in the postnatal period – up to and including the time of infant testing.

While there was no association between EPDS scores (either baseline or follow-up), or a MINI diagnosis of major depression (baseline or since birth), and Bayley scores, we were unable to comment on the role that maternal depression *per se* might have played on infant developmental outcomes. This is because a main limitation of this study is a lack of a comparison group of untreated depressed women, allowing us to measure the potential impact of untreated depression on neurodevelopmental outcomes. Indeed, the largest and most methodologically rigorous study now following up its cohort into junior school age (25) has found that exposure to depression in pregnancy is the significant factor in terms of infant neurodevelopment, not SSRI exposure. Another limitation was the use of convenience samples, which could have introduced a selection bias to the study – however, the two groups were well matched (see Table 1), with the only significant difference between them being maternal age (the medicated sample was about 2 years older). Clinically this would not be expected to impact on infant developmental outcomes.

In conclusion, our findings add to the literature suggesting that pregnancy SSRI exposure does not impact negatively on infant cognitive or motor outcomes. We hope that these findings will assist clinicians and mothers making key decisions around the use of antidepressants in pregnancy. However given the small sample size, some degree of heterogeneity in terms of antidepressant exposure, and a trend for control infants to score higher on the composite cognitive scale (but not the other subscales), these results need to be treated with caution.

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