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Birth weight of infants after maternal exposure to typical and atypical antipsychotics: prospective comparison study†

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Background
The effects of *in utero* exposure to atypical antipsychotics on infant birth weight are unknown.

Aims
To determine whether atypical and typical antipsychotics differ in their effects on birth weight after maternal exposure during pregnancy.

Method
Prospective data on gestational age and birth weight collected by the National Teratology Information Service for infants exposed to typical (*n*=45) and atypical (*n*=25) antipsychotics was compared with data for a reference group of infants (*n*=38).

Results
Infants exposed to atypical antipsychotics had a significantly higher incidence of large for gestational age (LGA) than both comparison groups and a mean birth weight significantly heavier than those exposed to typical antipsychotics. In contrast those exposed to typical antipsychotics had a significantly lower mean birth weight and a higher incidence of small for gestational age infants than the reference group.

Conclusions
In utero exposure to atypical antipsychotic drugs may increase infant birth weight and risk of LGA.

Declaration of interest
J.J.N. has received consultancy fees from Eli Lilly. S.H.T. has undertaken consultancy work for Lundbeck (their product sertindole does not feature in the data-set) and has current (non-psychiatric) research funded by BMS. P.R.M. has received honoraria for speaking engagements from Eli Lilly and Janssen-Cilag, which have been used for educational purposes. R.H.M-W has received honoraria for speaking engagements and attendance at advisory boards for a number of pharmaceutical companies manufacturing antipsychotic drugs, including Janssen-Cilag, AstraZenecca, Eli Lilly and Bristol-Myers Squibb.

Second-generation (atypical) antipsychotics, rather than first-generation (typical) antipsychotics, are used increasingly for first-line treatment for schizophrenia and bipolar disorder. However, atypical antipsychotics have been associated with metabolic disorders such as obesity, diabetes and dyslipidaemia.[1] Little is known of the effects of *in utero* exposure to atypical or typical antipsychotics, although mothers with schizophrenia have been associated with a higher probability of having an infant who is small for gestational age (small for dates, SFD).[2] Whether this lower birth weight is a factor of the maternal medication or illness is unclear. The risks of antipsychotics in pregnancy are an important issue, since schizophrenia and bipolar disorder commonly have an onset in women during the reproductive years. Furthermore, some alternatives to antipsychotic medication require alterations in dosage and careful monitoring owing to altered pharmacokinetics during pregnancy (e.g. lithium),[3] and National Institute of Health and Clinical Excellence (NICE) bipolar and perinatal guidelines have recently advised against the use of valproate in women of child-bearing potential and the preferential use of antipsychotics.[4,5]

Infants born large for gestational age (LGA) are associated with an increased risk of complications to both mother and neonate. Maternal complications of larger birth weights at delivery may include vaginal lacerations,[6] post-partum haemorrhage[7] and a higher probability of emergency Caesarean delivery.[8] In the neonate, risks include birth trauma, shoulder dystocia and foetal hypoxia.[9,10] There are also long-term health implications, since being born LGA, independent of complications in delivery, is also associated with a predisposition for increased body mass index (BMI) and diabetes in later life.[11,12] Predisposing factors for LGA birth include maternal obesity, type I diabetes, gestational diabetes and excessive maternal weight gain.[13–16] All these conditions may be precipitated or exacerbated by use of atypical antipsychotics in non-gravid populations.

Yaeger *et al*[17] highlighted the lack of data on antipsychotic drug usage in pregnancy that can be used to guide clinical decisions. Randomised controlled trial data of drug use in pregnancy will always be rare or non-existent because of ethical constraints.[18] As a result, the best available data in this area tend to come from non-randomised prospective observational studies. Such studies are usually limited in the degree to which confounding variables are controlled for. Nevertheless, they provide an important information source for clinicians in the absence of more controlled studies. To investigate the hypothesis that birth weight would be increased by *in utero* exposure to atypical antipsychotic drugs, we conducted an observational study comparing the birth weights and gestational ages of infants exposed to atypical antipsychotics with a group exposed to typical antipsychotics and a reference group. This is the first such prospective study comparing infants born to mothers exposed to typical and atypical antipsychotics.

Methods

The National Teratology Information Service (NTIS) is funded by the Health Protection Agency to provide telephone and online

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advice to healthcare professionals across the UK on all aspects of toxicity and potential adverse foetal effects of drugs and chemicals in pregnancy. When an enquiry is made to the NTIS, the drug(s) the mother has been exposed to are recorded at the time of enquiry. Cases are subsequently followed-up after the estimated delivery date through use of an anonymised identifier, to collect information from clinicians on the outcomes of pregnancies to inform future enquiries.

Data requested include gestational age and weight at birth. The extent of data collection is limited to that which the clinician is able to provide when contacted by the NTIS. The NTIS have previously published on the safety of other agents in pregnancy from cases in the UK and through collaboration with other national information services.[19–22] A search was conducted of the NTIS database between January 1995 and July 2006 for prospective cases (i.e. enquiry made prior to birth) involving maternal antipsychotic exposure.

For a reference group, the database was searched for a list of drugs compiled by the NTIS considered to be non-teratogenic and with no associated foetal or adult weight side-effects. These drugs were predominantly antihistamines, antibiotics, laxatives, β_2-agonist inhalants, astringents, proton pump inhibitors and antimalarials. All cases of exposure to monotherapy with these agents were extracted for use as a reference group.

Inclusion and exclusion criteria

Only babies born after full-term (37 weeks gestation) deliveries to mothers exposed to antipsychotics in therapeutic doses or one of the reference medications were included in the analyses. Postdate deliveries (gestational age >42 weeks) were excluded. For the antipsychotic groups, cases of monotherapy with a single antipsychotic and antipsychotic exposure with more than a single therapeutic agent (including over-the-counter medicine) were included. Medications given in multiple drug exposures were not necessarily given concurrently but there was exposure to more than one drug during the pregnancy. However, cases where exposure occurred to both a typical and atypical antipsychotic were not included. Exclusion criteria were if the infant displayed congenital malformations, maternal diabetes was recorded or if there was missing birth weight, gestational age or gender data.

Analyses

The numbers of LGA and SFD infants were compared between groups (maternal exposure to atypical or typical antipsychotics and the reference group). Large for gestational age was defined as a birth weight above the 90th percentile for gestational age. In contrast, SFD was defined as a birth weight under the 10th percentile for that gestational age. Mean birth weight and gestational age were compared between exposure groups. Gender-specific comparisons of mean gestational age and mean birth weight were also performed.

In addition to analysis of the entire data-set, an analysis was conducted that excluded cases where concomitant exposure to potentially weight-altering medications (excluding antipsychotics) had occurred. Whether a drug was associated with weight gain or loss was judged on a case-by-case basis by an independent specialist with no knowledge of the patients or the antipsychotic that was taken.

Categorical outcomes (LGA, SFD, prematurity, postdatism) were compared using chi-squared analysis or Fisher exact test. Continuous data (birth weight and gestational age) were compared between groups using one-way analysis of variance followed by *post hoc* least significance difference analyses when data were normally distributed. Where data were not normally distributed, the Kruskal–Wallis test was used followed by independent sample Mann–Whitney U-tests. Normality of distribution was examined using the Kolmogorov–Smirnov test. SPSS version 12 for Windows was used for all statistical analysis. All tests were two-tailed.

Results

An initial sample of 86 live births following maternal antipsychotic exposure met inclusion criteria. Of this sample, 56 were exposed to typical antipsychotics and 30 to atypical antipsychotics. Nine infants exposed to typical (16%) and 5 exposed to atypical (17%) antipsychotics were excluded owing to premature birth, and 2 infants exposed to typical antipsychotics (4%) were excluded for postdatism. There were no significant differences in the number of premature ($P>0.5$) or postdate ($P>0.5$) deliveries after exposure to typical or atypical antipsychotics. In the reference group, 1 premature (2%) and 2 postdate (5%) deliveries were excluded from an initial set of 41 live births. There were significantly more premature births in the typical antipsychotic group than in the reference group ($P<0.05$) but there was no difference in postdate deliveries ($P>0.5$) or between the atypical antipsychotic and reference groups. No infants were excluded because of maternal diabetes.

Of the remaining sample, 45 (53% males) were exposed to typical antipsychotics (10 monotherapy), 25 (24% males) to atypical antipsychotics (10 monotherapy) and 38 (38% males) to reference agents. The distribution of cases for each antipsychotic drug can be seen in Table 1. Mean maternal age was not significantly different between the typical (31 years, s.d.=6), atypical (31 years, s.d.=5) and reference (31 years, s.d.=5) exposure groups ($P>0.5$). Mean number of previous children was also comparable between the typical (1 child, s.d.=1), atypical (1 child, s.d.=1) and reference (2 children, s.d.=2) exposure groups ($P>0.5$). Three infants in the atypical antipsychotic exposure (12%), four in the typical antipsychotic exposure (9%) and one in the reference group (3%) displayed mild transient neonatal problems (e.g. jaundice). These were within expected incidences and there were no significant differences between groups in the rates of these problems. Gestational age was not normally distributed in all samples so non-parametric tests were used. A main effect of type of exposure was observed for gestational age in the overall analysis ($\chi=7.53$, d.f.=2, $P<0.05$).

Independent sample Mann–Whitney tests revealed that infants exposed to typical antipsychotics had a significantly shorter gestational age than infants exposed to reference agents (median=273 and 280 days respectively; $P<0.01$). Gender-specific comparisons demonstrated that this effect was statistically significant for males ($P<0.01$) but not females. These differences remained when mothers exposed to weight-altering medications were excluded. There was no significant difference in gestational age between the atypical antipsychotic exposure group and the typical antipsychotic or reference group.

Birth-weight data were normally distributed in all samples for analysis. A main effect of type of exposure was observed for birth weight in the overall analysis ($F=3.58$, d.f.=2, $P<0.05$). This effect remained if pregnancies exposed to other potentially weight-altering medications were excluded from analysis. *Post hoc* (least significance difference) analysis revealed that infants exposed to typical antipsychotics weighed significantly less than infants in both the atypical antipsychotic ($P<0.05$) and reference groups ($P<0.05$). Gender-specific comparisons demonstrated that this

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Table 1 Number of mothers using each antipsychotic drug, including and excluding cases of polytherapy with a potentially weight-altering medication

Antipsychotic	Including polytherapy *n*	Excluding polytherapy *n*[a]
Typical	45	22
Chlorpromazine	4	3
Chlorpromazine/haloperidol	1	1
Flupentixol	8	8
Flupentixol/haloperidol	1	1
Flupentixol/trifluoperazine/zuclopenthixol	1	–
Haloperidol	3	–
Pimozide	1	1
Promazine	1	–
Sulpiride	6	4
Sulpiride/trifluoperazine	1	–
Thioridazine	10	1
Thioridazine/trifluoperazine	1	–
Thioridazine/zuclopenthixol	1	–
Trifluoperazine		–
Atypical	25	3
Amisulpiride	1	15
Clozapine	3	3
Olanzapine	13	9
Quetiapine	3	2
Quetiapine/risperidone	1	–
Risperidone	4	1

a. Cases excluded were mothers treated with a selective serotonin reuptake inhibitor, amitriptyline, lithium and venlafaxine.

was because female infants exposed to typical antipsychotics weighed significantly less than infants in both the atypical antipsychotic ($P<0.05$) and reference ($P<0.05$) groups. When mothers exposed to potentially weight-altering medications were excluded all significant differences remained apart from that between the typical antipsychotic and reference group (Table 2).

Large for gestational age

There were significantly more LGA infants in the atypical antipsychotic exposure group (5/25; 20%) than in both the typical antipsychotic exposure group (1/45; 2%; $P<0.05$) and the reference group (1/38; 3%; $P<0.05$), even after mothers exposed to concomitant potential weight-altering medication were excluded. For this latter analysis, the proportion of LGA infants was 4/15 (27%) in the atypical antipsychotic group and 0/22 in the typical antipsychotic group ($P<0.05$). Three of the five LGA infants in the atypical antipsychotic group were above the 98th percentile for their gestational age compared with none in the other two groups. Medications taken by mothers of LGA infants are reported in Table 3.

Small for date

There was no significant difference in the number of SFD infants between the atypical antipsychotic group (2/25; 8%) and the typical antipsychotic group (7/45; 16%; $P>0.1$) or reference group (0/38; $P>0.5$), even after mothers exposed to concomitant potential weight-altering medication were excluded. In contrast, there were significantly more SFD infants in the typical antipsychotic group than in the reference group ($P<0.05$). However, with the exclusion of mothers exposed to potential weight-altering medication this difference was no longer significant with the proportion of SFD infants in the typical antipsychotic group changing to 2/22 (9%). Of the SFD infants with typical antipsychotic exposure, one was below the 2nd percentile compared with none of the SFD infants in the atypical antipsychotic or reference groups. Medication exposure for the SFD infants is reported in Table 3.

Exposure to olanzapine or clozapine

There were 16 infants exposed to either olanzapine or clozapine (13% male). It was not deemed suitable to examine other types of atypical antipsychotics as only 9 cases remained. The gestational age of those exposed to olanzapine or clozapine was not significantly different from the typical antipsychotic and reference groups, whereas a main effect of type of exposure was observed for birth weight ($F=3.37$, d.f.=2, $P<0.05$). *Post hoc* (least significance difference) analysis revealed infants exposed to olanzapine or clozapine weighed significantly more than infants in the typical antipsychotic group ($P<0.01$) but not the reference group ($P>0.05$) (Table 3). All differences remained when mothers exposed to potentially weight-altering medication were excluded. Numbers were too small for gender-specific comparisons of gestational age and birth weight. Of the 16 infants exposed to olanzapine or clozapine, 5 were LGA (31%). This was significantly more than in both the typical antipsychotic and reference exposure groups ($P<0.01$ in both comparisons). When mothers exposed to concomitant potential weight-altering medication were excluded, the proportion changed to 4 out of 12 (33%), which remained significantly more than in the typical antipsychotic ($P<0.05$) and reference ($P<0.01$) groups.

Table 2 Comparisons of mean birth weight between groups

Exposure group	Overall *n*	Overall Weight, g Mean (s.d.)	Male *n*	Male Weight, g Mean (s.d.)	Female *n*	Female Weight, g Mean (s.d.)
Including cases with weight-altering concomitants						
Atypical	25	3291 (446)*	6 (24)	3433 (460)	19 (76)	3377 (523)*
Olanzapine/clozapine	16	3500 (500)**				
Typical	45	3158 (440)†	24 (53)	3271 (478)	21 (47)	3029 (361)†
Reference	38	3382 (384)	14 (37)	3492 (387)	24 (63)	3318 (376)
Excluding cases with weight-altering concomitants						
Atypical	15	3473 (490)*	4 (27)	3260 (481)	11 (73)	3551 (492)***
Olanzapine/clozapine	12	3625 (450)**				
Typical	22	3162 (450)	12 (55)	3377 (469)	10 (45)	2905 (261)‡
Reference	38	3382 (384)	14 (35)	3492 (387)	24 (65)	3318 (376)

*$P<0.05$ *v.* typical antipsychotics; **$P<0.01$ *v.* typical antipsychotics; ***$P<0.001$ *v.* typical antipsychotics; †$P<0.05$ *v.* reference agents; ‡$P<0.01$ *v.* reference agents.

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Table 3 Medications taken in cases where infants were large for gestational age and small for gestational age

Exposure group	Case	Medications
Small for gestational age		
Atypical	1	Olanzapine and venlafaxine
	2	Quetiapine and nitrazepam
Typical	1	Flupentixol, trifluoperazine, zuclopenthixol, fluvoxamine, lithium, ferrous sulphate, vitamins and ibuprofen
	2	Sulpiride
	3	Sulpiride
	4	Sulpiride, fluoxetine, clonazepam, zopiclone, atenolol[a]
	5	Thioridazine and paroxetine
	6	Trifluoperazine, amitriptyline and procyclidine
	7	Trifluoperazine, paroxetine, paracetamol and cigarettes
Large for gestational age	1	Clozapine
Atypical	2	Clozapine, zopiclone, omeprazole and ispaghula husk[a]
	3	Olanzapine
	4	Olanzapine[a]
	5	Olanzapine and sodium valproate[a]
Typical	1	Sulpiride, trifluoperazine, paroxetine, carbamazepine, temazepam, procyclidine and amitriptyline
Reference	1	Trimethoprim

a. Infant either under 2nd percentile if small for gestational age or over the 98th percentile if large for gestational age.

Discussion

It needs to be acknowledged at the outset that there are a number of weaknesses with the current data related to the small sample size, selective nature of the cases included and the lack of data relating to potentially confounding variables that might have a significant impact on the findings. Nevertheless, this is the first study to suggest that babies born to mothers taking atypical antipsychotics during pregnancy may be at risk of being large for gestational age. There were significantly more LGA infants among those exposed *in utero* to atypical antipsychotics than among those exposed to either typical antipsychotics or reference agents. The mean birth weight was also found to be significantly greater in the atypical antipsychotic exposure group than the typical antipsychotic exposure group. However, there was no significant difference between the atypical antipsychotic and reference groups. Differences in birth weight were not attributable to differences in gestational age, maternal age or gender between samples. These preliminary findings suggest that the risk of weight gain seen in patients treated with atypical antipsychotics may also occur to infants exposed *in utero*. The differential effect on birth weight of atypical *v*. typical agents was further supported by findings also being present in a sub-population exposed to olanzapine or clozapine, which appear to be the atypical antipsychotics that carry the greatest propensity for metabolic abnormalities.

In contrast, the typical antipsychotic group's significantly higher incidence of SFD infants than the reference group's and its lower mean birth weight than both the reference and atypical antipsychotic groups is consistent with previous findings. This further supports the hypothesis that atypical antipsychotic-induced weight gain *in utero* is attributable to the medication and not a facet of the illnesses being treated with antipsychotic medication. However, there were insufficient data in the NTIS database to allow a comparison of diagnoses of the mothers in the two antipsychotic groups and so this conclusion needs to remain tentative.

An earlier prospective study examined birth weights after maternal exposure to atypical antipsychotics by comparing infants with those of mothers who took a non-teratogenic agent.[23] In contrast to the present study, this found no significant difference in mean birth weight between groups but found a significantly higher rate of SFD infants in the atypical antipsychotic exposure group. However, this earlier study did not exclude infants displaying congenital malformations and neonatal problems which may have been associated with being SFD irrespective of medication. Further, no adjustment for infant gender was made and the ratio of male:female infants was not stated. Effects of gender could have masked effects of differences in mean birth weight.[24] In our study, there was a higher proportion of male infants in the typical antipsychotic group (53% *v*. 37%), which would be expected to bias this group towards being heavier.

Limitations

Our study has a number of limitations. In many cases, the NTIS had not received information on variables that may affect birth weight such as maternal weight, multiparity, and maternal cigarette and alcohol use. Smoking and alcohol misuse are likely to reduce birth weight and to be more prevalent in women with psychiatric disease compared with the reference group. This would tend to mask rather than enhance any weight differences associated with atypical antipsychotic exposure.

However, smoking and alcohol use may contribute to the lower birth weights observed in the typical antipsychotic group. Information regarding exact dosing and trimester of exposure to antipsychotics was often not provided consistently and so no conclusions could be drawn regarding these factors. The small number of infants included in the study means that the proportion of males to females was unequal between exposure groups and there were limited cases of atypical antipsychotic exposure in male infants. Gestational age was significantly higher in the reference group, which may have biased the group towards being heavier although this difference was, at most, a week's gestation.

Care also needs to be exercised in the interpretation of the data owing to the possibility of cohort effects. The data were collected over an 11.5-year period. It might be expected that proportions of typical and atypical exposures varied over this time. Given that there has been an increase in maternal weight over recent years,[25] it is possible that this has contributed to the increased rate of LGA babies found in those exposed to atypical compared with typical antipsychotics. Further, there is a potential issue with the small number of cases meeting our inclusion criteria in the NTIS database (86) over this period of time, which raises questions regarding the nature of these mothers and the clinicians contacting the NTIS. This was an important reason why only prospective data

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were examined. With regard to the issue of power, LGA is defined as being a birth weight above the 10th percentile. For reference, a sample size of 41 would be required for an 80% power of detecting an increase in the LGA rate to 25% with $P<0.05$. However, note that as expected, the rates of LGA births among the babies exposed to typical antipsychotics was lower than 10% and that a sample size of just 26 is required for an 80% power of detecting a difference of LGA from 5% to 20% with $P<0.05$. This study had sample sizes of 25 in the atypical, 45 in the typical and 38 in the reference groups.

Concluding remarks

This study suggests a possible association between *in utero* atypical antipsychotic exposure and increased infant birth weight and LGA births, particularly with use of clozapine and olanzapine. However, this conclusion is tentative pending further, larger studies.

Such studies require a more systematic collection of data from representative cohorts, ideally mothers with severe mental illnesses on no medication and those on antipsychotic monotherapy. Data collection needs to include more information than currently available regarding the dose of drug used, the timing of exposure during pregnancy and maternal diagnosis, as well as information regarding potential confounders, including maternal smoking status, alcohol usage, weight and physical health. The effects of potential increases in birth weight in babies exposed *in utero* to atypical antipsychotics on the longer-term health of the offspring are currently unknown and further studies are needed to explore these issues. The available data are insufficient to justify wholesale changes in prescribing recommendations[5] but do point to the need for careful monitoring of foetal growth in pregnant women prescribed atypical antipsychotics. Although there are risks associated with an infant being born SFD, switching a mother from a typical antipsychotic to an atypical with the sole intention of increasing the baby's birth weight is not clinically justified because of the lack of an understanding of the long-term consequences of *in utero* exposure to an atypical plus the risks of destabilising the mother's illness by switching treatments.

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