TECHNICAL COMMENTARY

Parenthood

Introduction

People with schizophrenia have reduced fertility rates (number of offspring) compared to general population rates. There is interest in determining how genetic factors predisposing people to schizophrenia are maintained in the face of these reduced fertility rates and this could be explained by increased fertility rates in unaffected relatives.

Antipsychotic use in pregnant women requires careful consideration of the mother's risk of illness relapse, against the risk of harm or complications for the developing infant if medication is to be continued. However, there is currently very little evidence regarding the use of antipsychotics for schizophrenia during pregnancy and the postpartum period.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found two systematic reviews that met inclusion criteria[3, 4].

- Moderate to high quality evidence finds people with schizophrenia, particularly men, have significantly fewer offspring than people without schizophrenia. Siblings of people with schizophrenia, particularly brothers, also have fewer offspring.

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Parenthood

- Moderate quality evidence finds a small increased risk of heart defect or lower birth weight in infants, and a small increased risk of preterm delivery, but not stillbirth, with exposure to antipsychotics in utero.
- Low quality evidence is unsure about the risk of termination or spontaneous abortion, and size and malformation in infants, after exposure to antipsychotics in utero.

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Bundy H, Stahl D, MacCabe JH

A systematic review and meta-analysis of the fertility of patients with schizophrenia and their unaffected relatives

Acta Psychiatrica Scandinavica 2011; 123: 9-106

View review abstract online

Comparison	**Fertility rates in people with schizophrenia compared to their relatives or people without schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests people with schizophrenia, particularly men, had significantly fewer offspring than people without schizophrenia. Siblings of people with schizophrenia, particularly brothers, had a trend effect of fewer offspring than people without schizophrenia.**
People with schizophrenia had significantly fewer offspring; 6 studies, N = 16,849, fertility ratio = 0.39, 95%CI 0.35 to 0.44, $p < 0.05$, $I^2 = 83.4\%$, $p = 0.000$ *Males with schizophrenia had significantly fewer offspring than females with schizophrenia;* 4 studies, N = 11,809, fertility ratio = 0.54, 95%CI 0.50 to 0.57, $p < 0.05$, $I^2 = 0\%$, $p = 0.414$ *Siblings of people with schizophrenia had a trend effect of fewer offspring;* 5 studies, N = 16,713, fertility ratio = 0.96, 95%CI 0.93 to 1.00, $p = 0.05$, $I^2 = 99.9\%$, $p < 0.0001$ *Male siblings of people with schizophrenia had significantly fewer offspring than female siblings of people with schizophrenia;* 5 studies, N = 16,713, fertility ratio = 0.81, 95%CI 0.71 to 0.92, $p < 0.05$, $I^2 = 80.9\%$, $p < 0.0001$ *There were no differences in fertility between parents of people with schizophrenia and controls;* 3 studies, N = 5,524, fertility ratio = 1.17, 95%CI 0.94 to 1.46, $p > 0.05$, $I^2 = 99.2\%$, $p = 0.000$	
Consistency in results‡	Inconsistent, apart from males vs. females with schizophrenia.
Precision in results§	Precise
Directness of results‖	Direct

Coughlin CG, Blackwell KA, Bartley C, Hay M, Yonkers KA, Bloch MH

Obstetric and neonatal outcomes after antipsychotic medication exposure

in pregnancy **Obstetrics and gynecology 2015: 125; 1224-35** View review abstract online	
Comparison	**Adverse effects of antipsychotic use during pregnancy vs. no antipsychotic use during pregnancy.** **Authors report that the studies did not routinely adjust for potential confounding factors, such as other medications.**
Summary of evidence	**Moderate quality evidence (large samples, consistent, imprecise, direct, possible confounding factors) suggests a small increased risk of heart defect or lower birth weight in infants, and a small increased risk of preterm delivery, but not stillbirth, with exposure to antipsychotics (first or second generation).** **Low quality evidence (inconsistent, imprecise, direct, possible confounding factors) is unsure about risk of termination or spontaneous abortion, and size and malformation in infants with exposure to antipsychotics.**
Prenatal factors	
Elective termination *A large, significant effect of increased risk of elective termination in women on antipsychotics;* 4 cohort studies, N = 3,788, OR = 5.98, 95%CI 2.94 to 12.14, $p < 0.001$, $I^2 = 73\%$, $p = 0.01$ Spontaneous abortion *No significant difference between groups;* 4 cohort studies, N = 3,788, OR = 1.05, 95%CI 0.61 to 1.81, $p = 0.86$, $I^2 = 70\%$, $p = 0.02$	
Perinatal factors	
Preterm delivery *A small, significant effect of increased risk of preterm delivery in women on antipsychotics;* 7 cohort studies, N = 1,534,350, OR = 1.86, 95%CI 1.45 to 2.39, $p < 0.00001$, $I^2 = 46\%$, $p = 0.08$ Stillbirth *No significant differences between groups;* 3 cohort studies, N = 1,018,795, OR = 1.18, 95%CI 0.88 to 1.57, $p = 0.27$, $I^2 = 0\%$, $p = 0.47$	
Postnatal factors	

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Small for gestational age at birth

A small, significant effect of increased risk of being small for gestational age at birth in infants exposed to antipsychotics;

4 cohort studies, N = 1,578,906, OR = 2.44, 95%CI 1.22 to 4.86, $p = 0.01$, $I^2 = 81\%$, $p = 0.001$

Large for gestational age at birth;

No significant differences between groups;

4 cohort studies, N = 1,578,906, OR = 2.50, 95%CI 0.77 to 8.16, $p = 0.13$, $I^2 = 91\%$, $p < 0.001$

Low birth weight

A small, significant effect of lower birth weight in infants exposed to antipsychotics;

3 cohort studies, N = 358,677, WMD = -0.57.89g, 95%CI -103.69 to -12.10, $p = 0.01$, $I^2 = 0\%$, $p = 0.37$

Any malformation

A small, significant increased risk of any major malformation in infants exposed to antipsychotics;

7 cohort studies, N = 1,640,660, OR = 2.12, 95%CI 1.25 to 3.57, $p = 0.005$, $I^2 = 84\%$, $p < 0.001$

Meta-regression demonstrated a significant association between increased study quality and increased effect size.

Heart defect

A small, significant increased risk of any heart defect in infants exposed to antipsychotics;

4 cohort studies, N = 1,628,021, OR = 2.09, 95%CI 1.50 to 2.91, $p < 0.001$, $I^2 = 0\%$, $p = 0.48$

Authors report no differences in results according to first vs, second generation antipsychotics.

Consistency in results‡	Consistent for heart defect, low birth weight, stillbirth, and preterm delivery. Inconsistent for elective termination, spontaneous abortion, gestational age, and any malformation.
Precision in results§	Imprecise
Directness of results‖	Direct

Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), vs. = versus, WMD = weighted mean difference

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[5].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[5].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[6]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship

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between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[5];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[7].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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