Review: women with schizophrenia have poorer pregnancy outcomes than other women, but it is unclear whether antipsychotic medications affect their infants

Patton SW, Misiri S, Corral MR et al. ***Antipsychotic medication during pregnancy and lactation in women with schizophrenia: evaluating the risk.*** *Can J Psych 2003, Dec;47:959–65.*

QUESTION: Does exposing infants to antipsychotic medication during pregnancy and lactation increase the risk of teratogenic, neonatal, and long-term neurobehavioural effects? Are schizophrenia symptoms altered by pregnancy and lactation, and vice versa?

Source of funding: not specified.

For correspondence: S Patton, British Columbia Women's Hospital, Reproductive Mental Health Program, Vancouver, Canada.

Design
Systematic review.

Data sources
The authors searched Medline to December 2001 and the reference lists of identified articles.

Study selection
Studies of any design were eligible if they examined the extent to which antipsychotic medication exposure during pregnancy or lactation contributes to poor obstetrical outcomes in women with schizophrenia or poor developmental outcomes in their babies.

Data extraction
The authors did not provide detailed inclusion or exclusion criteria, nor did they describe how data were extracted for the review.

Main results
Few prospective studies were identified. There is inconsistent reporting about medication dosage and duration for infants exposed to antipsychotic medication during pregnancy and medication levels in breast milk and in infant blood and urine. Most studies include little detail about possible confounding factors, such as the mother's use of drugs or alcohol during pregnancy and lactation.

Women with schizophrenia have a greater risk of poor obstetrical outcomes, including preterm delivery, low birth weight, and babies small for their gestational age. Exposure to typical antipsychotics (phenothiazines) during weeks 4-10 gestation may increase the risk of congenital malformations. There is a lack of data about the effects of exposing developing infants to atypical antipsychotics. There is also little evidence about whether changes associated with pregnancy and lactation alter schizophrenia symptoms.

Conclusions
Women with schizophrenia have a greater risk of adverse pregnancy outcomes compared with other women. The relative risk of using antipsychotic medications during pregnancy and lactation remains uncertain. There is no clear evidence that antipsychotic drugs are associated with major malformations. The authors suggest that further research is needed so that clinicians can limit treatment to situations in which the risk of untreated maternal illness outweighs the risk of exposing a developing infant to medications. The authors recommend against breastfeeding while a woman is receiving antipsychotics.

COMMENTARY

For the most part, this timely review addresses the authors' objectives. The findings suggest that women with schizophrenia have increased risks during pregnancy that other women do not have, including preterm deliveries, other obstetrical complications and increased possibility of a psychotic breakdown during pregnancy or the post-partum period. With increased use of atypical antipsychotics, which are less likely to cause hyperprolactinemia induced infertility, more women with schizophrenia are likely to become pregnant, especially with unplanned pregnancies. The available evidence suggests that these drugs are relatively safe to use during pregnancy and lactation.

The main problem with this review is that the authors' conclusions somewhat contradict their findings, specifically regarding the safety of typical antipsychotic drugs during pregnancy and lactation. The authors do not present compelling evidence that these drugs are harmful in pregnancy or lactation, and even caution about abruptly discontinuing them. These drugs have been on the market for more than forty years. There is no convincing evidence that any of them increase the baseline rate for major malformations or other long term neuro-developmental problems.[1,2] The amount of drugs excreted in breastmilk is also minimal. There have been only occasional reports of sedation in exposed babies.[3]

Patton *et el* used limited search terms. For example, the key word "phenothiazines" was absent, resulting in the omission of two important papers. If included, these may have altered the conclusions of the review and implications for clinical practice. One of the omitted papers was the largest study from the Collaborative Perinatal Project, involving 1309 children exposed to phenothiazines during pregnancy. This study found no adverse effects on physical or mental development.[4] The other omitted study was a review of phenothiazines used for nausea and vomiting in pregnancy. Here again, there was no increased risk of birth defects.[5]

The authors suggest that antipsychotic medications should be avoided in the first trimester if possible. This may be difficult, as more than 50% of pregnancies are unplanned in the general population, and probably an even higher proportion in people with schizophrenia. It is therefore likely that many women with schizophrenia will be on medication when they become pregnant, exposing the fetus during the first trimester.

We feel that a pregnant or lactating woman with schizophrenia should be treated with these drugs if indicated, after being given evidence-based information to assist in her decision making. Withholding the medication could impair the mother's mental health and limit her potential to care for and interact appropriately with her baby.

Andrea Levinson, MD
Resident in Psychiatry
The Motherisk Program
The Hospital for Sick Children
Toronto, Ontario, Canada

1 Arnon J,Shechtman S, Ornoy A. The use of psychiatric drugs in pregnancy and lactation. *Isr J Psychiatry Relat Sci* 2000; **37**: 205–22.
2 Elia J, Katz IR, Simpson GM. Teratogenicity of psychotherapeutic medications. *Psychopharmacol Bull* 1987; **23**: 531–86.
3 Hale Thomas W. *Medications and Mothers Milk (10th ed).* Texas: Pharmasoft Publishing, 2002: 148–341.
4 Slone D, Siskind V, Heinonen OP *et al.* Antenatal exposure to the phenothiazines in relation to congenital malformations perinatal mortality rate, birth weight, and intelligence quotient score. *J Obstet Gynecol* 1977; **128**: 486–8.
5 Mazzotta P, Magee LA. A risk-benefit assessment of pharmacological and nonpharmacological treatments for nausea and vomiting of pregnancy. *Drugs* 2000; **59**: 781–800.

Purpose and procedure

Evidence-Based Mental Health alerts clinicians to important advances in treatment, diagnosis, aetiology, prognosis, continuing education, economic evaluation and qualitative research in mental health. We select and summarise the highest quality original and review articles. Experts in the field comment on the clinical relevance and context of each study.

Our target audience includes psychiatrists, psychologists, nurses, social workers, occupational therapists, pharmacists and other professionals whose work may be enhanced by up to date research. *Evidence-Based Mental Health* is multidisciplinary. It covers studies of adults, children, older adults, people who have developed psychiatric or psychological problems as a result of trauma and people with learning disabilities, head injuries, drug and alcohol problems and personality disorders.

Evidence-Based Mental Health is published quarterly by the BMJ Publishing Group. The Editors are Professor John Geddes at the University of Oxford, Professor Shirley Reynolds at the University of East Anglia, Professor David Streiner at the Baycrest Centre for Geriatric Care and the University of Toronto and Professor Peter Szatmari at McMaster University in Canada. Dr Debbie Singh is the Managing Editor, based at Bazian Ltd, London.

SELECTION PROCEDURE

Evidence-Based Mental Health:

- selects the best original and review articles on the causes, diagnosis, prevention, treatment, clinical course and quality of care in mental health using pre-stated, empirically derived criteria;
- summarises these articles using structured abstracts to describe their questions, methods and results;
- adds brief commentaries by experts to place each study in its clinical context;
- disseminates these summaries to clinicians soon after the publication of the original article.

The following journals are regularly reviewed:

Acta Psychiatrica Scandinavica
Addiction
Age and Ageing
American Journal of Psychiatry
American Journal of Public Health
American PsychologistAnnals of Internal Medicine
Archives of General Psychiatry
Australian and New Zealand Journal of Psychiatry
British Medical Journal
Behaviour Research and Therapy
Behaviour Therapy
British Journal of Clinical Psychology
British Journal of General Practice
British Journal of Psychiatry
Canadian Journal of Psychiatry
Child Development
Clinical Psychology Review
Cochrane Library
Cognitive and Behavioral Practice
Developmental Medicine and Child Neurology
General Hospital Psychiatry
Health Psychology
International Journal of Behavioural Medicine
International Journal of Geriatric Psychiatry
Journal of the American Medical Association (JAMA)
Journal of Abnormal Child Psychology
Journal of Abnormal Psychology
Journal of Affective Disorders
Journal of Autism and Developmental Disorders
Journal of the American Academy of Child and Adolescent Psychiatry
Journal of the American Geriatrics Society
Journal of Child and Adolescent Psychopharmacology
Journal of Child Psychology and Psychiatry and Allied Disciplines
Journal of Clinical and Experimental Neuropsychology
Journal of Clinical Psychiatry
Journal of Clinical Psychopharmacology
Journal of Consulting and Clinical Psychology
Journal of Neurology, Neurosurgery, and Psychiatry
Journal of Neuropsychiatry and Clinical Neurosciences
Journal of Psychosomatic Research
Lancet
New England Journal of Medicine
Psychiatric Services
Psychiatry Interpersonal and Biological Processes
Psychological Bulletin
Psychological Medicine
Psychology and Aging
Psychosomatic Medicine
Schizophrenia Bulletin
Social Science and Medicine
United Kingdom Health Technology Assessment Reports

We also assess journals nominated by our readers.

CRITERIA FOR SELECTING ARTICLES

Articles are considered for inclusion in *Evidence-Based Mental Health* if they are:

- original or review articles
- in English
- about humans
- about topics that are important to clinical practice in the field of mental health
- use analysis techniques consistent with the study design.

Studies of prevention, treatment, quality improvement and continuing education must also:

- randomly allocate participants to comparison groups
- follow up a high proportion of the original participants (eg 80%)
- measure an outcome of known or probable clinical importance

Studies of causation (aetiology) must:

- collect data prospectively if possible

- identify a comparison group(s) for the outcome of interest
- mask outcome observers to exposure (this criterion is assumed to be met if the outcome is objective)
- include data about the relationship between modifiable exposures and clinical outcomes

Studies of diagnosis must:

- include a spectrum of participants, some, but not all of whom have the disorder of interest
- include a diagnostic (gold) standard
- include information about reliability if possible (measure of agreement among observers, for example)
- ensure each participant receives both the new test and some form of the diagnostic standard
- interpret the diagnostic standard and the new test result independently, without knowledge of the other test

Studies of prognosis must:

- include an inception cohort of participants (first onset or assembled at a uniform point in the development of the disease), all initially free of the outcome of interest
- follow up at least 80% of the original participants

Studies of the cost-effectiveness of interventions must:

- compare alternative diagnostic or therapeutic services or quality improvement strategies
- compare activities on the basis of the outcomes produced (effectiveness) and resources consumed (costs)
- include data from real (not hypothetical) participants from studies which meet the quality criteria for other articles described above
- present results in terms of the incremental or additional costs and outcomes of one intervention over another
- include a sensitivity analysis when there is uncertainty in the estimates or imprecision in measurement

In review articles, at least one article included in the review must meet the quality criteria for treatment, diagnosis, prognosis, causation or cost effectiveness studies described above. Review articles must also:

- clearly state the clinical topic
- describe sources and methods
- explicitly state inclusion and exclusion criteria for selecting articles

Qualitative studies must meet the following criteria:

- the content must relate to how people feel or experience situations that relate to mental health care
- data collection methods must be appropriate for qualitative studies. (For example, unstructured interviews, semi-structured interviews, participant observation of people in natural settings, focus groups, review of documents or text).

SUMMARISING MATERIAL

Relevant articles which meet these criteria are summarised using a structured abstract. Articles are reviewed by experts in the field who provide commentaries describing the context of the article, methodological problems that may affect interpretation and recommendations for clinical application. If you are interested in writing an expert commentary, please contact the Managing Editor (Debbie.Singh@Bazian.com). Where possible, the author of the original article is given an opportunity to review the abstract and commentary.

CORRECTION

A commentary by Levinson which appeared in the August issue (*Evid Based Ment Health* 2003;**6**:89) has displayed the author listing incorrectly. The commentary currently shows Andrea Levinson as the sole author. However, the author listing should read as follows: Adrienne Einarson, Kate McKenna, and Andrea Levinson. The journal apologises for this error.