

# Psychotropic Medications in Pregnancy and the Effects in the Fetus and Child

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## Introduction

- A substantial number of women of childbearing age are prescribed psychotropic drugs, and because nearly 50% of pregnancies are unplanned, many women are still taking them upon becoming pregnant.
- Psychotropic drugs are commonly used to treat psychiatric disorders -- antidepressants, benzodiazepines, antipsychotics, antiepileptics, lithium and monoamine oxidase (MAO) inhibitors

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## Introduction

- Evidence-based information from epidemiologic studies indicates that most psychotropic drugs are relatively safe for use during pregnancy.
- There is also an increasingly large body of evidence-based information in the literature indicating that it may be more harmful to both the mother and her baby if she is not treated appropriately when suffering from a severe psychiatric disorder.

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## Introduction

- Therefore, it is important for women with psychiatric disorders and their healthcare providers to have access to evidenced-based information about the safety of these drugs when taken during pregnancy to ensure that women make an informed decision as to whether they should continue with the pharmacotherapy they have been using to treat their condition.

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## Background

- Psychiatric disorders are common among women of childbearing age, and affected women are frequently prescribed psychotropic drugs.
- However, despite the fact that most recent studies have documented the relative safety of these medications during pregnancy, there remains a high level of anxiety regarding their safety among patients and healthcare providers alike.
- For every pregnancy, the baseline risk of a major congenital malformation is 1% to 3% of the population.

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## Classification

### Category A:

- controlled studies in humans have demonstrated no fetal risks e.g. multivitamins

### Category B:

- animal studies indicate no fetal risks but no human data available or adverse effects demonstrated in animals but none in well controlled human studies e.g. penicillin.

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## Classification

### Category C:

- no adequate studies, either animal or human or adverse fetal effects in animal studies but no human data e.g. *codeine, acyclovir*

### Category D:

- There is evidence of fetal risks but benefits outweigh them e.g. *carbamazepine*

### Category X:

- proven fetal risks which clearly outweigh benefits e.g. *isotretinoin*

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## Teratogen

- Word derived from "terato" meaning monster and "gen," to give rise to, so teratogens give rise to monsters (not really).
- Non-genetic factors that interfere with normal embryonic and fetal differentiation and morphogenesis.
- Children who have been exposed to teratogens *in utero* will not pass their defect on to their children.

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## Important factors in Teratogenicity

- **Time.** The gestational age of the fetus at the time of the exposure to the teratogen. Different organs of the body are forming at different times and therefore the sensitivity to the teratogen and the affected organ will vary. There is an "all or none" period in the first two weeks where the fetus is generally not susceptible to teratogens.
- **Dosage.** To how much of the teratogen was the fetus exposed.
- **The genotype of the fetus.** The fetus may be more or less resistant to the teratogen because of inactivation of the teratogen.
- **The genotype of the mother.** Mothers also differ in their ability to detoxify the teratogen.

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## Purpose

- We will examine all of the information in the literature regarding the use of psychotropic drugs during pregnancy to provide you with evidence-based information about the safety of these drugs during pregnancy and help women make an empowered decision regarding pharmacotherapy during pregnancy and guide the treatment of their children.

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## Antidepressants

- Serotonin Reuptake Inhibitors
- Tricyclic Antidepressants
- Others

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## Major Malformations

- To date, none of the antidepressants that have been studied in pregnancy have been found to increase the baseline rate of 1% to 3% for major malformations.
- In addition, a meta-analysis examined almost 1800 women who used the newer antidepressants during pregnancy in 7 prospective, comparative studies and found no increased risk for major malformations.

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## Spontaneous Abortions

- Most studies of antidepressant use during pregnancy report an increased rate of spontaneous abortions in the women exposed to antidepressants.
- The Motherisk Program at The Hospital for Sick Children, Toronto, Canada assessed the rates between women on antidepressants and those not taking the drugs
- No differences were found among antidepressant classes.
- The rate of spontaneous abortion was higher in the exposed group versus the nondepressed, nonexposed group (18% vs 10%).
- However, these results did not reach statistical significance because of the small sample size.

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## Long-term Neurodevelopmental Adverse Outcomes

- A concern is the possibility of adverse neurodevelopmental sequelae with exposure to these medications *in utero*.
- One study evaluated the effects of fluoxetine and tricyclic antidepressants (TCAs), for temperament, mood arousability, activity level, distractibility, and, most importantly, global IQ and language development in children exposed to these meds during the first trimester of pregnancy.
- Assessment of language development and IQ occurred between 16 and 86 months postnatal age.
- No significant differences between the groups were detected in any of the parameters examined.

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## Long-term Neurodevelopmental Adverse Outcomes

- A second long-term neurodevelopmental follow-up, examined the offspring of women exposed to TCAs and fluoxetine throughout gestation and compared them with those of 36 non-teratogen exposed women with respect to language development, global IQ, and temperament between 15 and 71 months postnatal age.
- The analysis was adjusted for the effects of duration and severity of maternal depression, duration of pharmacologic treatment, number of depression episodes after delivery, maternal IQ, socioeconomic status, cigarette smoking, and alcohol use.
- No association between gestational use of TCAs or fluoxetine and language development, global IQ, or temperament was observed.
- By contrast, global IQ was negatively associated with duration of depression, and language development was negatively correlated with the number of postnatal depressive episodes, suggesting that the children of depressed mothers have decreased global IQ and language development in comparison to the children prenatally euthymic women.

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## Poor Neonatal Adaptation

- Reports describing poor neonatal adaptation in some babies and documenting increased admission to the neonatal intensive care unit (NICU) in neonates exposed to antidepressants during the last trimester of pregnancy.
- Clinical manifestation of poor neonatal adaptation has included such symptoms as jitteriness, tachycardia, hypothermia, vomiting, hypoglycemia, irritability, constant crying, increased tonus, eating/sleeping difficulties, convulsions, and respiratory distress;
- Symptoms are usually transient and self-limiting.
- Unfortunately, because of the lack of epidemiologic studies, there is no definitive prevalence as to how often this actually occurs.
- However, after examining all of the reports, it seems that this pattern of symptoms may occur in up to 30% of all babies who have been exposed to selective serotonin reuptake inhibitors during late pregnancy.

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## Untreated Depression During Pregnancy

- Untreated depression during pregnancy appears to carry substantial perinatal risks, which include suicidal ideation; increased risk for miscarriages, hypertension, preeclampsia, and lower birth weight; and, importantly, an increased risk for postpartum depression.
- The Committee on Research on Psychiatric Treatments of the American Psychiatric Association identified treatment of major depression during pregnancy as a priority area in clinical management.
- A position paper was published on the risk-benefit decision making for treatment of depression during pregnancy.
- There is no evidence to implicate antidepressants as causing harm to an unborn baby and that a pregnant women should be treated so long as the benefits and possible risks are well explained to her.

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## Benzodiazepines

- The safety of their use during pregnancy remains controversial because there have been conflicting results regarding their teratogenicity, with some studies citing an increased risk and others not.
- There is insufficient evidence to prove that benzodiazepines are human teratogens, but there may be a higher chance (2-fold difference) in the incidence of cleft lip and palate.

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### Benzodiazepines

- Babies of mothers should be watched carefully after birth for signs of abrupt discontinuation syndrome, which may include sedation, hypotonia, reluctance to suck, apnea, cyanosis, and impaired metabolic responses to cold stress. However, these effects are self-limiting.
- There have been no reports of long-term adverse effects on the IQ or neurodevelopment in children born to mothers taking benzodiazepines during pregnancy

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### Antipsychotics

- Typical [e.g. haloperidol (Haldol®)]
  - have been on the market for more than 40 years, and there is no evidence that, when used during pregnancy, they increase the rates of major malformations.
- Atypical (e.g. quetiapine (Seroquel®))
  - Little information available
  - Possibility of low birth weights and higher rates of spontaneous abortions (not statistically significant due to low sample size)

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## Antipsychotics

- No long-term neuropsychological effects have been seen in children exposed as a fetus.
- Possible Neonatal Effects
  - Infants who have been exposed to neuroleptics throughout pregnancy should be watched carefully after birth for any signs of extrapyramidal symptoms.
  - A woman requiring antipsychotic medication during pregnancy should not change her treatment if she is well controlled, as it is important for her child that she be a well-functioning individual who can adequately interact with and take care of her baby.

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## Anticonvulsants

- The commonly used older anticonvulsants (phenytoin, carbamazepine) used to treat epilepsy are established human teratogens.
- Some of the newer agents may be considered safe while others (lamotrigine) have been shown to have an increase in major malformations.

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## Seizures as risk

- Studies do not support common belief that epilepsy *per se* is a teratogenic risk.
- The risk for congenital malformations in the offspring of women with untreated epilepsy was not higher than among nonepileptic controls
- By contrast, the offspring of epileptic women who received antiepileptic drugs had higher incidences of malformation than controls

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## Neonatal Concerns

- If phenobarbital, carbamazepine, or phenytoin is administered, maternal vitamin K supplementation may be given to the mother 4 to 6 weeks before the expected date of delivery and administered immediately after birth to the newborn.
- However, studies to date have not demonstrated a proven benefit in this practice.
- The neonate should be also be assessed carefully for epilepsy and anticonvulsant associated dysmorphism.

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## Anticonvulsants

- Phenylhydantoin®(Dilantin)
  - "fetal hydantoin syndrome":
    - IUGR, mental retardation, digital hypoplasia, craniofacial abnormalities
    - Full syndrome less 10% of children exposed but up to 30% have some manifestations
- Valproic acid:
  - 1% Neural tube defects (spina bifida, meningomyelocele), craniofacial and cardiac abnormalities
- Carbamazepine
  - similar to hydantoin
- Phenobarbital
  - Microcephaly but no growth deficiency; developmental delay 20%. 38% had 3 or > minor malformations.
  - No increase in major malformations.
  - Baby may have withdrawal symptoms/bleeding (needs Vit K).
  - Similar cranial facial defects and nail hypoplasia to others

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## Fetal Hydantoin Syndrome



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## Valproic Acid



Effects of fetal exposure to Valproic Acid (Smith 1982).



Child with lumbosacral meningocele whose mother received valproic acid during pregnancy (Scardin 1995).

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## Long-term Neurodevelopment

- Children exposed in utero to carbamazepine did not differ from their controls in any of the administered neurobehavioral tests with respect to global IQ.
- Children in the phenytoin group scored 10 points lower in the global IQ and a significantly higher number of them scored less than 84.
- Children into adolescence who had been exposed in utero to various antiepileptic drugs (monotherapy and polytherapy) appear to have long-term effects which manifest in EEG patterns, minor neurologic dysfunction, and intellectual performance

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## Lithium

- On the market for many years and is commonly used to treat bipolar disorder
- International Registry of Lithium Exposed Babies
  - number of cases of Ebstein's anomaly far exceeded the spontaneous occurrence in the general population
  - To rule out this specific abnormality, the pregnant woman should undergo adequate screening tests, including detailed ultrasound and fetal echocardiography

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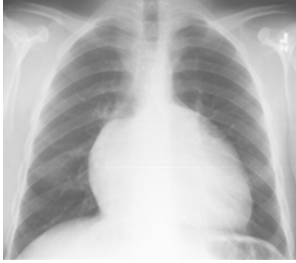
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## Lithium and Ebstein Anomal



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## Lithium

- Lithium is frequently associated with perinatal complications and reversible neonatal toxicity
- Babies present with neurodevelopmental deficits and depressed neurologic status, including hypotonia, respiratory distress syndrome, cyanosis, lethargy, and weak suck and Moro reflexes during the neonatal period.
- Majority of these adverse effects resolved, and most babies made a full recovery.
- The newborn should be monitored carefully for possible
- Lithium toxicity, which can include cyanosis, hypotonia, bradycardia, thyroid depression with goiter, atrial flutter, cardiomegaly, hepatomegaly, and diabetes insipidus.

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## Abrupt Discontinuation of Psychotropic Drugs

- Pregnant women should be very cautious about discontinuing any psychotropic drugs abruptly.
- A study of women taking antidepressants and/or benzodiazepines, all of whom reported abrupt discontinuation of the drug for fear of harming their fetuses, was conducted at The Motherisk Program.
  - In this study, 34/37 women discontinued the drugs abruptly and 3 patients used some form of tapering off.
  - Almost one third of the patients reported suffering from suicidal ideation because of "unbearable" symptoms, 4 of whom required hospitalization.
  - Another woman had a therapeutic abortion because she did not feel that she could go through the pregnancy because of the effects
  - One woman who had abruptly discontinued a large daily dose of a benzodiazepine used alcohol to combat the abrupt discontinuation symptoms
- If there is a safety/risk issue, the medication should be slowly tapered off.

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