

Treatment of Mental Disorders in Pregnancy: A Review of Neuroleptics, Antidepressants, and Lithium Carbonate

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PSYCHOTROPIC DRUGS IN PREGNANCY

Pregnancy is frequently complicated by the development or recurrence of a serious mental disorder; neurotic, major affective, and psychotic illnesses have all been observed (1-4). When a major mental disorder arises in a pregnant woman and threatens the health or life of the patient and/or fetus, it should be treated early and aggressively to minimize complications and forestall the advance of the disease. Nonbiologic methods like individual psychotherapy, couples or family therapy, social casework, and hospitalization in a supportive, structured milieu should form the first line of treatment. Electroconvulsive therapy (ECT) may be the treatment of choice for some patients, e.g., a first trimester mother with a life-threatening episode of bipolar illness. If the illness persists in spite of nonbiological interventions, and if the risks of the inadequately treated disease outweigh the risks associated with a potentially useful medication, then a trial of that medication is clearly indicated.

However, the physician's dilemma occurs because although as many as 80 percent of pregnant women take prescribed drugs, and up to 35 percent take a psychoactive drug (5,6), no psychotropic drug has been proven safe for use during pregnancy, and all carry warnings by the FDA (7). Furthermore, in calculating the medication's risks, the physician must rely mostly on animal data and suboptimal human epidemiologic studies. In this review I will first outline the types of risk posed to mother and fetus by drugs in general, with special attention to the features of maternal and fetal physiology which increase those risks. I will then consider the risks and benefits associated with antipsychotics, antidepressants, and lithium, suggesting guidelines for their use in the pregnant patient.

Maternal physiology and risk. For those patients requiring drug treatment, the risks to the mother are similar to the risks posed to the non-pregnant patient, but are compounded by the metabolic, endocrine, renal, and cardiac changes in pregnancy. Delayed gastric emptying and increased intestinal transit time may lead to slower but more complete drug absorption. Plasma volume, total body

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water, and body fat are increased, resulting in a higher volume of distribution and a lower serum concentration for any given dose of drug. This increases the volume of fluid which the kidney must in some cases clear of drug (8). This may or may not be counterbalanced by the steady increase in renal blood flow and glomerular filtration rate which tend to speed the clearance of free drug. Although albumin production is normal or increased, plasma albumin concentration falls and total plasma drug concentration is decreased. If the total circulating albumin is reduced, as by pre-eclampsia or the nephrotic syndrome, binding sites can become saturated and free drug fraction rises (9). The hormonal milieu of pregnancy is thought to increase metabolic activity in the liver (8) and may tend to speed breakdown of some drugs.

Fetal physiology and risk. Further complicating the use of drugs in pregnancy is the presence of an additional but equally complex patient, the fetus. All psychotropic drug classes cross the placenta. Transfer occurs primarily by simple diffusion, dependent upon the chemical properties of the drug (including molecular size, protein-binding affinity, polarity, and lipid solubility), drug concentration, and duration of exposure (10). Non-ionized, low molecular weight, lipid-soluble drugs are well absorbed. Placental metabolism of drugs is probably less active than metabolism within the fetal liver. Intended or unintended drug effects may act to reduce placental blood flow or interfere with active transport and other nutritive functions of the placenta.

Compared to the adult, fetal cardiac output is greater and a higher proportion of blood flow is distributed to the brain. Combined with greater blood-brain permeability this leads to more rapid and more complete drug exposure of the fetal brain (11). Total concentration of plasma protein and protein-binding affinity are less in the fetus than in the mother, leaving more free drug available for tissue penetration and competition with other drugs and endogenous compounds for protein binding (10). Drugs are metabolized chiefly in the fetal liver, where the activity and concentration of certain microsomal enzymes is less than in the adult, prolonging and exaggerating drug effects. Excretion of most drugs, via the placenta and fetal urine, is delayed.

Like the fetus, the neonate has proportionally less total serum protein for binding, less active hepatic degradative enzymes, and lower glomerular filtration rate than the adult (9). The blood-brain barrier is still incomplete and the immature central nervous system (CNS) appears generally more sensitive to drug effects (10). Furthermore, the neonate no longer exists in equilibrium with its mother via the placenta, and a drug concentrated in the fetus shortly before birth may have significantly prolonged postnatal effects.

The risks to the fetus include teratogenic effects, long-term neurobehavioral effects, and direct toxic effects. A teratogenic effect may be immediate or delayed; it may consist of abortion, malformation, altered fetal growth, functional deficit, carcinogenesis, or mutagenesis. Psychotropic drugs can also produce long-term functional effects which are not accompanied by gross structural malformations and which may not be measureable or manifest for

years after birth. Since the pioneering studies of Werboff and colleagues established the field of behavioral teratology (12,13), numerous subsequent animal studies have shown that prenatal exposure to a variety of psychoactive drugs can disturb nerve cell proliferation and differentiation (14), neurotransmitter concentrations (15), and behavioral development and performance (16,17). Such psychoteratogenicity may be expressed as disturbed psychomotor activity, faulty adaptation to the extra-uterine environment, abnormal learning or problem-solving capacity, or other more subtle cognitive deficits and mood disturbances.

In humans, alcohol, opiates, and diphenylhydantoin are already well-established psychoteratogens, capable of producing disturbances of arousal and motor coordination as well as specific learning disabilities and mental retardation (18-20).

Functional behavioral or psychological effects may occur at drug doses lower than those required to produce structural defects (21), or they may arise when exposure occurs after the period of organogenesis but during the latter half of pregnancy or early postnatal life when CNS development and maturation is still ongoing. Effects may even be so subtle as to be manifest only if the post-natal environment is enriched or impoverished (22) making routine detection difficult. Even drugs which induce only transient early behavioral changes may lead to permanent behavioral consequences through disturbance of early environmental, including mother-infant, interactions. Neonatal depression (23), hyperactivity, and irritability, as well as mood or behavior disturbances may all interfere with the early mother-infant relationship.

Relatively little attention has been given to studying the long-term neurobehavioral and psychological effects in humans of pre-natal exposure to the antipsychotics, antidepressants, and lithium. The few follow-up studies available will be discussed under the drug classes to which they apply, but the clinician should be aware that our knowledge in this area is inadequate and the implications for exposed offspring are potentially grave. Not only is caution in prescribing advised, but long-term, systematic follow-up of the children is crucial.

Direct toxic effects on the fetus and neonate include the potentially reversible, dose-related effects which may be exaggerated by the immature fetal and neonatal metabolism. Drugs administered at or near term may concentrate in the fetus, and after delivery, when clearance depends upon immature neonatal mechanisms, drug effects may be prolonged. Chronic prenatal administration may lead to fetal dependence and ultimately neonatal withdrawal symptoms when drug exposure ceases at birth.

Methodological difficulties. The calculation of a specific risk and summation of a total risk to the patient and her fetus is a difficult, if not impossible, task. For ethical reasons, randomized prospective clinical trials of psychotropic drug effects on pregnant women have not and should not be performed. Animal

studies can be carefully controlled and may suggest a potential risk, but species differences can be profound and extrapolation from animal studies is always tentative.

To date, all human studies on the effects of psychotropic drugs in pregnancy suffer from poor control of potentially confounding variables such as maternal age, gravidity, and parity, as well as history of miscarriages, still births, and prior malformed infants. Maternal nutrition, alcohol use, cigarette use, and over-the-counter and prescription drug use all need to be carefully controlled or at least matched. The dose of drug, duration of exposure, and timing of exposure are critical variables, exemplified by thalidomide's ability to produce limb defects only between the 42nd and 48th days of gestation (24). Thus a study which combines all first trimester drug exposures may miss a subtle effect produced only during a brief gestational "window." The mother's illness and the indication for drug use is another often neglected variable. Many of the studies on phenothiazine effects were carried out on patients with nausea and vomiting rather than a mental disorder. These doses were lower, and duration of treatment shorter, than those relevant to treatment at mental illness. Finally, the length and thoroughness of follow-up is generally inadequate. As Edlund and Craig (25) have shown, the cumulative incidence of congenital anomalies increases with increasing length of follow-up. Therefore, if we hope to detect subtle or delayed neurobehavioral effects in children exposed prenatally to psychotropic drugs, our observations must be both extensive, in terms of neurobehavioral assessment techniques, and extended, ideally into adulthood.

ANTIPSYCHOTIC DRUGS

Indications. The antipsychotic drugs have repeatedly been shown effective in the treatment of acute psychotic episodes occurring in schizophrenic, affective, and a variety of other mental disorders (26). They have been used effectively to treat psychotic symptoms in pregnant women as well.

Adverse Effects on Mother. Sedation, postural hypotension, anticholinergic and extrapyramidal symptoms may occur. Anticholinergic effects on the bowel may worsen the constipation which is common in pregnancy. Likewise the sedative effect may compound the pregnant woman's fatigue. Most important, however, is the potential effect on maternal blood pressure, and the potential compromise of placental blood flow should always be kept in mind. The risk of tardive dyskinesia of course always pertains.

Teratogenic Effects. Phenothiazines and thioxanthenes have been shown to pass the placental barrier (27,28) and phenothiazines have been measured in various concentrations in fetal brain and liver.

Most reviews of the use of chlorpromazine, haloperidol, or perphenazine in human pregnancy find no statistically significant increase in the incidence of major congenital structural malformations in exposed offspring (29-36). In a

prospective survey of 12,764 pregnant women, Rumeau-Rouquette and associates (37) found a statistically significant increase in the number of infants born with major malformations when exposed prenatally to phenothiazines with a three-carbon aliphatic side chain (chlorpromazine, methotrimeprazine, trimeprazine, and oxomemazine). Compared to non-exposed controls, a similar increase was not observed with promethazine or the piperazine and piperidine antipsychotics. Of the implicated drugs, only chlorpromazine is used as an antipsychotic in the United States, and although this study might provide reason for avoiding chlorpromazine, many confounding factors among those women were not considered. Probably the best controlled study to date is the one by Milkovich and van den Berg (38). Among 20,504 pregnant women followed prospectively, 19,952 were treated for nausea and vomiting during their first trimester, mostly with phenothiazines and especially prochlorperazine. Maternal age, type of drug, and gestational age at exposure were controlled. They found no increase in the rates of severe congenital anomaly and perinatal death for the exposed group compared to controls. However, no doses were recorded and compliance was not assessed. When used as antiemetics, the phenothiazines are likely to be used intermittently and in lower doses than those needed for the treatment of psychosis.

Long-Term Neurobehavioral Effects. Animal studies have found that prenatal exposure to antipsychotic drugs can affect vasculogenesis (39), neurogenesis (40, 41), central catecholamine levels (15), and dopamine receptor function (42). Some animal studies report persistent abnormalities of learning behavior (16, 43,44) while others do not (45).

Data on long-term behavioral consequences in humans is scarce. After several case reports of persistent neurobehavioral abnormalities in infants of mothers treated with phenothiazines (46), Desmond and associates (47) reported on 19 infants born to mothers on phenothiazines. Agitation and hypertonicity persisted for several months after birth. Many of these infants were also exposed to alcohol and barbiturates in utero, however, and the effect could not be attributed to a single drug. Stone (36) found no difference in IQ scores at four years of age between 151 children exposed to phenothiazines in utero and controls who were not exposed. Kris (48) followed 52 children exposed to low doses (50–150 mg/day) of chlorpromazine prenatally, and found no behavioral or intellectual abnormalities. However, these represent small samples of children, generally exposed to low doses of antipsychotic medication at variable times in gestation; better controlled, more rigorous follow-up studies are needed.

Direct toxic effects on the fetus and neonate. Direct toxic effects of antipsychotic drugs which have been observed in newborns include motor restlessness, abnormal movements, hypertonia, and tremor (46,49–51). Functional bowel obstruction and neonatal jaundice have also been described (52). In vitro studies have raised the possibility of toxic effects on chromosomes (53), lymphocytes (54), and the fetal retina (55).

Recommendations. For the woman with a chronic psychotic disorder or at risk for an acute psychotic episode during pregnancy, early comprehensive obstetrical and psychiatric management and social support should be instituted. Crisis intervention techniques are useful at the first sign of deterioration. If the patient is unstable, hospitalization and use of a therapeutic milieu should be tried first.

If psychotic symptoms severe enough to threaten the life or health of the woman or her fetus persist in spite of aggressive nonbiologic treatment, the use of an antipsychotic drug is indicated, but delay is recommended through the first trimester if at all feasible. Obtain informed consent from the patient and her spouse if possible. In choosing a drug, consider the patient's prior drug response and tolerance of side effects, or that of family members if applicable. Use the side effect profile of the antipsychotic drug to optimize treatment of the patient's symptoms. If she is profoundly agitated and sleepless, choose a low potency drug like thioridazine or chlorpromazine, but beware of hypotensive effects. Otherwise, a high potency agent like haloperidol or fluphenazine is generally preferred. Give a low initial test dose and increase cautiously until the minimum effective dose is reached.

The treatment goal is sufficient control of symptoms to ensure the safety of the woman and her fetus to term; it is not necessary or advisable to strive for complete eradication of symptoms. Anticholinergic medications may be used if necessary for treatment of extrapyramidal symptoms, but these medications also have potential for toxic effects on the fetus. Avoid the use of other medications.

There is considerable evidence that maintenance use of antipsychotic medications after remission of the acute phase helps prevent relapse, but maintenance drug treatment should be based on the severity of symptoms, the chronicity of the illness, and the availability of social support systems. Consider the natural history of the individual patient's illness, and reduce or discontinue the medication if at all possible.

ANTIDEPRESSANTS

Indications. Heterocyclic antidepressants are generally the treatment of first choice for major depression and the depressed phase of bipolar disorder. They have also found therapeutic usefulness in dysthymic disorders, atypical depressions, personality disorders with depressed mood, panic and phobic disorders, obsessive-compulsive disorders, chronic pain syndromes, and depression in schizophrenia and schizo-affective disorders (26,56). They may be indicated in pregnancy when the mother's depression is severe enough to threaten the life and health of herself and her fetus. This includes suicidal intent, vegetative and nutritional disturbance, or severely impaired functioning and judgement not responsive to nonbiological interventions including hospitalization.

Adverse effects on the mother. These include anticholinergic effects (dry mouth, decreased GI motility, mydriasis, cycloplegia, urinary hesitancy or

retention, tachycardia, and delirium), orthostatic hypotension and sedation. Imipramine and other tertiary amines more commonly cause hypotension and should generally be avoided in favor of less hypotensive drugs.

Teratogenic effects. Imipramine and desipramine have been shown to cross the placenta in animals and humans (57,58). In at least one animal study imipramine and desipramine were found to cross the placenta and to potentiate the pressor response to norepinephrine, while amitriptyline and protriptyline did not. Van Petten (58) noted that even closely related compounds can show differences in penetration of the placenta and subsequent pharmacologic effects on the fetus. Demonstration of such differences in human pregnancies in the future could facilitate the choice of the antidepressant safest for the fetus.

Sporadic case reports suggesting a possible association between maternal imipramine or amitriptyline use and fetal limb reduction deformities have appeared in the literature (59,60). One retrospective case control study of 2,784 cases of birth defects was inconclusive (61), while other small cohort studies (62-65) found no causal relationship between maternal imipramine or amitriptyline intake and congenital anomalies in the offspring.

Long-term neurobehavioral effects. Animal studies have clearly demonstrated that prenatal exposure to tricyclic antidepressants, in therapeutic doses, can produce behavioral and neurochemical disturbances lasting well past termination of drug exposure and into adulthood. Rats exposed prenatally to imipramine show decreased hypothalamic dopamine levels and decreased cortical beta adrenergic receptors (66), delayed reflex development and decreased exploratory responses (67), and reduced physiological and behavioral responsiveness as adults (68). Similar results have been obtained after prenatal clomipramine exposure (69). Early neonatal treatment of rats with a monoamine oxidase inhibitor has resulted in nerve cell changes and decreased concentrations of norepinephrine and dopamine in the hypothalamus, reduced learning capacity, and diminished emotional reactivity in later life (70-72). Neurobehavioral follow-up studies in humans have not been done.

Recommendations. Antidepressants should be reserved for the pregnant woman whose depression is severe enough to threaten the life and health of herself and her fetus, and which is unresponsive to nonbiologic interventions. Reactive depressions or biological depressions that are less severe should be treated with psychotherapy alone or in a therapeutic milieu. A careful history, especially of cardiac diseases, review of systems, physical examination and EKG should precede the initiation of treatment. Inquire about a prior response to a specific antidepressant or to ECT.

In general, avoid the tertiary amines (imipramine, amitriptyline) because of their increased hypotensive effects. A reasonable choice for cardiac safety is trazodone if sedation is desired, desipramine if it is not. These drugs have relatively low anti-cholinergic effects as well. Begin with a low dose and increase slowly, using plasma drug levels and clinical response to achieve the minimal dose effective in relieving the major depressive symptoms. Monitor pulse,

orthostatic blood pressure changes, and EKG if any abnormality is found on the baseline EKG. Give the entire daily dose at bedtime if daytime sedation is to be avoided or nighttime sedation desired. Divide or reduce the dose if the patient develops hypotension, hypertension, arrhythmias, fainting, or heart failure. Persistent adverse cardiovascular effects may necessitate stopping the drug.

Avoid co-administration of other drugs, over-the-counter or prescription, especially those that affect the cardiovascular system. If at all possible, avoid the use of antidepressants during the first trimester, and attempt to reduce or discontinue the medication before term. There is a particularly high risk of depression in the post-partum period, when resumption of medication and avoidance of breastfeeding may be indicated.

LITHIUM

Indications. Lithium is the drug of choice for prophylaxis against bipolar affective episodes of the manic type. It also carries FDA approval for use in acute manic episodes and in prophylaxis against the depressive phase of bipolar disorder (73). It may also be useful in acute depression for patients who are unresponsive to other somatic treatments, as prophylaxis against recurrence of schizoaffective illness, in disorders of impulse control and episodic violence, and possibly in some alcoholics.

Approximately one-half of patients with bipolar disorder are women, and the first manic episode typically occurs before age 30, well within the limits of a woman's reproductive life. Women may first manifest the disorder during a pregnancy, and may have up to 50 percent risk of developing a post-partum psychosis which can appear from days to weeks following the birth (2). Practitioners in both obstetrics and in general psychiatry will undoubtedly encounter pregnant patients with bipolar disorder.

Adverse effects on mother. Lithium presents the same spectrum of side effects and adverse reactions for pregnant women as for others (endocrine, renal, gastro-intestinal, neurologic), but physiological changes in pregnancy may increase the relative risk. Progressively increasing lithium clearance by the kidney may require increasing lithium dose to maintain a therapeutic serum concentration. The precipitous fall in glomerular filtration rate and lithium clearance after delivery may leave the patient toxic (74). The use of thiazide diuretics or sodium restriction to treat hypertension or edema of pregnancy may change the fluid and electrolyte balance and quickly lead to maternal and fetal lithium toxicity (75).

Teratogenic effects. Lithium freely crosses the placenta, and the concentration in cord blood equals that of maternal serum (76).

Lithium has repeatedly been shown to be teratogenic in pre-mammalian species, causing abnormal tissue differentiation, disorganized CNS development, and head and neck anomalies (77). Studies in non-human mammals are contradictory; one showing lithium to be teratogenic (78), while others do not

(77). One study showed an adverse effect on human chromosomes in vitro but lithium levels used were in the toxic range.

In order to assess the possible teratogenic effect of lithium in humans, the International Register of Lithium Babies was begun in 1968. Although the incidence of malformations in babies of untreated mothers with affective disorders is unknown, and although a study of this design cannot produce a true incidence of malformations, pathologic trends may be revealed (79). Consecutive reports from 1971 to 1975 revealed increasing likelihood that lithium exerts a teratogenic effect in humans, especially on the developing cardiovascular system (80-82). As of 1980, 225 babies exposed to lithium in the first trimester of pregnancy had been reported to the register, 25 of whom were born with congenital malformations. Besides one baby with intracerebral toxoplasmosis, two with Down's syndrome, and seven stillborn; 18 of the 25 babies with congenital malformations had involvement of the heart and great vessels, six of them the exceedingly rare Ebstein's anomaly (comprising defects of the tricuspid valve, atrial septum, and right ventricle). Lithium is therefore generally felt likely to be teratogenic with respect to the cardiovascular system when administered in the first trimester (83,84).

Long-term neurobehavioral effects. A study of behavioral effects on rats exposed to lithium in utero showed a significant decrease in performance on a T-maze and changes in avoidance behavior (85), but animal studies may not reflect the effects on humans. A case report exists of developmental motor delay persisting at one year of age in a human infant found to be lithium toxic at birth, but it is not clear whether the motor delay was due to high lithium levels at birth or due to cerebral hypoxia associated with lithium-induced cardiac hypofunction (86). A follow-up study of 60 lithium children not malformed at birth did not reveal any significantly increased frequency of physical or mental anomalies in the lithium children as compared to sibling controls (87), but conclusions were based only on mothers' subjective assessments, not actual examination or neurobehavioral testing.

Direct toxic effects on the fetus and neonate. Several authors have reported neonatal toxicity in the offspring of mothers on toxic or even therapeutic doses of lithium at the time of delivery (75,88,89). Findings in the neonate include: cyanosis, muscle flaccidity and hypotonia, poor suck and grasp reflexes, absent Moro reflex, and lethargy which may take up to 10 days to resolve. Other adverse effects reported in the neonate include atrial flutter (90), functional tricuspid regurgitation and congestive heart failure (91), reversible inhibition of fetal thyroid (92), and nephrogenic diabetes insipidus which persisted for two months after birth (93).

Recommendations. Lithium should be used in pregnant women only for unequivocal indications, and only after careful consideration of all potential risks and benefits. Women with a history of bipolar disorder have a high risk of developing a manic episode off lithium, as studies have shown that 70 percent of patients will have at least one relapse within a year of discontinuing lithium

versus 20 percent of those who are maintained on lithium. A pregnant woman in an acute manic phase can do serious harm to herself and her fetus. On the other hand, use of lithium carries multiple potential serious risks to both mother and child as outlined above.

Women on lithium should be urged to avoid pregnancy and to maintain effective contraception. One who plans to become pregnant or who inadvertently becomes pregnant should be withdrawn from lithium prophylaxis during the first trimester unless there is convincing evidence that doing so would endanger the woman or her fetus. The decision to institute, continue, or discontinue lithium administration in a woman for whom pregnancy is a fact or a possibility should be made with the collaboration and informed participation of both the patient and her mate.

If a pregnant woman develops an acute manic episode, hospitalization with a structured, supportive milieu and regular individual psychotherapy would be indicated first. Judging by currently available evidence, antipsychotic drugs are probably safer than lithium in the first trimester, and more rapidly effective for acute manic symptoms. Choose a low-dose, high-potency agent at the lowest dose effective in alleviating dangerous symptoms.

If it is believed safest for the woman and her fetus to institute lithium treatment after the first third or half of pregnancy, use the minimum dose necessary to achieve the desired therapeutic or prophylactic effect, achieving a serum level of 0.7 to 1.2 mEq/L in most cases. A single lithium dose should not exceed 300 mg, given as often as necessary to achieve the target serum concentration. This avoids "pulses" of lithium which may be more harmful to the fetus than a steady serum concentration. Serum lithium levels should be closely monitored, as often as weekly towards the end of pregnancy and even more frequently in the days before term. Monitor thyroid status during pregnancy and use thyroid supplement as needed to protect mother and fetus against goiter formation. Sodium-depleting diuretics should not be used; sodium-restricted diets should be used only with great caution. Reduce the daily lithium dose by 50 percent in the last week of gestation and stop completely at the onset of labor. Reinstitution of lithium at pre-pregnancy dosage (or 50 percent of the term dosage if no pre-pregnancy dose was established) as soon after delivery as fluid homeostasis is re-established, usually three days.

In conclusion, it is not infrequent that a pregnant woman will develop psychotic or affective symptoms severe enough to threaten the life or health of herself and her fetus. Early and aggressive nonbiologic therapies, including hospitalization and supportive milieu treatment, should be instituted first. If the patient's symptoms persist, the use of an antipsychotic, antidepressant, or antimanic medication should be considered. The decision rests upon a calculation and balancing of the risks associated with the untreated illness, and the risks associated with the drug. This paper has attempted to review the data available on the risks of these drugs to the pregnant woman and her fetus, for it is this data upon which current clinical decisions must be made. I have also

attempted to stress the limitations involved in most of the studies to date, and to suggest the development of more carefully controlled, more extensively followed-up studies in the future.

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