Psychopharmacoteratophobia: Excessive fear of malformation associated with prescribing psychotropic drugs during pregnancy: An Indian perspective

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ABSTRACT

“Psychopharmacoteratophobia is the fear or avoidance of prescribing psychotropic medicine to a pregnant woman on a given indication in anticipation of fetal malformation.” It is rooted in the tragedy associated with thalidomide use and is increasing due to the inability to predict accurately, strict legal provision of consumer protection, ethical and legal issues involved, and pitfalls in the available evidence of teratogenicity. In the Indian setting, the physicians face more challenges as the majority of the patients may ask them to decide, what is the best for their health. Most guidelines emphasize more on what not to do than what to do, and the locus of decision is left to the doctor and the patient. In this review, we have focused on relevant issues related to psychopharmacoteratophobia that may be helpful to understand this phenomenon and help to address the deprivation of a mentally ill woman from the required treatment.

KEY WORDS: Causality, drugs, fetal malformation, mental illness, pregnancy, psychotropic drugs, teratogenicity

Introduction

Teratophobia is an excessive fear of giving birth to a malformed child while psychopharmacoteratophobia (psychofarmakoteratofobi) is the trepidation of prescribing psychotropic medicine to pregnant woman on given indication in anticipation of fetus malformation.[1,2] The word has Greek origin and is the combination of four words — πνεύμα (breath, life, soul); pharmakon (drug); τέρας (monster) and φόβος (fear). This phenomenon can be traced back to the thalidomide tragedy that first launched in 1950s for morning sickness and as a sedative during pregnancy. The use of this medication caused phocomelia in about 10,000 newborn and was banned since 1961 in most part of the world.[3]

Five percent of all live births have major congenital anomalies. In only 0.25% of all births, the major congenital anomalies can be attributed to medication.¹,³ Benzodiazepine is the commonly used psychotropic drug (85% of all psychotropic) during pregnancy.⁴ In comparison to the general population, the teratogenic event increase is by 0.2% with benzodiazepine, 1–3% with antidepressant, 0.5% with lithium, up to 5% with carbamazepine, and up to 10% with valproate.⁵–⁷ Prevalence of malformation in India is about 2%,[¹²,¹³]

Approximately, half a million women become pregnant each day, and up to 35% of them use a psychotropic medication at least once before delivery.¹⁴ 15–20% of pregnant women suffer from mental illness, of which 86% remained untreated, and psychopharmacoteratophobia is one reason for the deprivation from treatment.¹⁶–¹⁹

Most of the published reports are case reports, case series, prospective or comparative cohort studies, case-control studies, prescription database studies, and national birth registries done in Western countries. Except for case reports, there is no comprehensive study from India about psychotropic
Factors Contributing to Psychopharmacoteratophobia

In India, paternalistic model of doctor-patient relationship is prevalent, and patients expect and request the doctor to decide the best treatment. The most common but difficult question, a pregnant patient with mental illness asked, is whether she should continue the medication. In the absence of an accurately predictable test, answering such question is constrained by clinical, legal, ethical, and psychosocial issues.

Clinical Issues

Impact of psychotropic medication in pregnancy outcome

Psychotropic medications that are commonly reported with teratogenic effect are:
- Benzodiazepines may increase the incidence (<1%) of cleft lip or palate, infantile hypotonia, and neonatal abstinence syndrome
- Selective serotonin/norepinephrine reuptake inhibitors and tricyclic antidepressants may increase malformation by 1–3% compared to the general population
- Mood stabilizers may increase the malformation from the baseline general population. The increase is <1% for lithium (Ebstein's anomaly), <5% for the carbamazepine (neural tube defects) and lamotrigine (oral clefts), and highest is 5–10% for valproate (neural tube defects)
- Antipsychotic medications may also increase malformation (<1%), particularly second generation antipsychotics
- Currently, there is no effective nonpharmacological intervention except for electroconvulsive therapy that can be used as treatment in severe illness.

Safety issue

Obstetricians have the dual responsibility of safety for mother and fetus. Untreated mental illness poses a problem for both mother and fetus while pharmacotherapy may harm the fetus. If mental illness is untreated, it may affect the health of patients in the form of poor self-care (malnutrition, infection, and poor pregnancy care), self-harm (abdominal injury), impulsive acts (excessive physical activity), self-medication with indigenous method, and substance abuse.

Consequences of psychiatric illness on outcome of pregnancy

Untreated mental illness in pregnant women may adversely affect the outcome of pregnancy depending upon the diagnosis, severity, and patients’ physical health status. Anxiety disorders have been associated with fetal distress, spontaneous abortion or preterm delivery or prolong the labor, assisted (forceps) delivery, decrease developmental scores, and slow mental development. Similarly, major depression and bipolar disorder are associated with decreased fetal growth/low birth weight, postnatal complications, increased crying, and more admission to neonatal intensive care units. Schizophrenia has also been linked to decreased fetal growth/low birth weight at birth, placental abnormalities, antenatal hemorrhage, postnatal death, and congenital cardiovascular malformations.

Legal Issues

Indian Consumer Protection Act, 1986

Patients are protected by the Consumer Protection Act. The applicable clauses of this act are: (1) An unfair trade practice or
a restrictive trade practice that has been adopted by any trader or service provider; (2) the services hired or availed of or agreed to be hired or availed of by him, suffer from deficiency in any respect; and (3) services which are hazardous or likely to be hazardous to life and safety of the public when used are being offered by the service provider, which such person could have known with due diligence to be injurious to life and safety.\[25\]

**Medical negligence**

Any untoward event in pregnancy in patients with mental illness with or without treatment may be stretched to medical negligence. Medical negligence comprises of: (1) The defendant owes a duty of care to the plaintiff; (2) the defendant has breached this duty of care; and (3) the plaintiff has suffered an injury due to this breach.\[26\]

**The Medical Termination of Pregnancy Act, 1971**

During treatment with psychotropic medication in pregnancy, before considering for termination of pregnancy, it is necessary to ascertain that condition falls under required conditions specified in the act, that is: (1) The continuance of the pregnancy would involve a risk to the life of the pregnant woman or of grave injury to her physical or mental health. (2) There is a substantial risk, which if the child were born, it would suffer from such physical or mental abnormalities so as to be seriously handicapped.\[27\]

**Mental Health Act, 1987 and Protection of Human Rights Act, 1993, Mental Health Care Bill, 2013**

Involuntary treatment, competency to take a decision about treatment, and freedom to live her life as she wants are important issues encountered.\[28,29\]

**The Guardians and Wards Act, 1890**

When pregnancy takes place before the legal age of marriage.\[30\]

**The Pre-Natal Diagnostic Technique, 1994**

When medication may affect gender-specific deformity e.g. genital deformity or malformations.\[31\]

**Ethical Issues**

The most common ethical dilemmas that a clinician or obstetrician's may face are: (1) Conflict between the interest of the mother and fetus; (2) autonomy of patient decision when decision making is compromised; (3) during the decision making limited information can be provided (due to lack of adequate data) and there is ambiguity of absolute risk; (4) coercion by family members; and (5) conflicts between patient and spouse or significant others.

**Psychosocial Issues**

The common issues encountered in Indian setting are: (1) Stigma - related to mental illness, birth of a female child or birth defect; (2) loss of support - loss of emotional and family support from husband and in-laws, physical and psychological abuse, and increased family burden; and (3) Cultural disadvantages - lower status of women and belief that mental illness is punishment of God or evil makes them vulnerable for termination of pregnancy and discrimination, etc.

According to Indian culture, all individuals are indebted to three things: (1) The God (dev rin), (2) ancestors (pitriri rin), (3) the teachers (risci rin), and raising of a normal child is the dharma (sacred duty). One’s own child can relieve the parents from these debts or bondages. A son can directly prevent parents from entering into a specific kind of hell (called pum). Such values are strongly transmitted to next generations by cultural practices that are organized both before and after the infants’ births. Traditionally, the children are the backbone of parents, who support them whole life.\[32\]

**Theoretical Issues**

Most guidelines leave the final decision to patient and physician. According to Food and Drug Administration (USA), most of the psychotropic drugs fall under Category C (to be used after assessment of risk and benefit). In an Indian setting, in the face of ambiguous evidence and guidelines, obstetricians face difficulty when most Indian patients request the doctors to decide the best treatment for them.

**Teratogenic Risk Factors in Indian Women**

There is a paucity of studies in this area, except for environmental factors such as water pollution, bio-hazards such as Bhopal gas tragedy, etc. Some of the common risk factors are:

- Use of indigenous treatment for physical or mental illness, with uncertain safety and efficacy of treatment during pregnancy
- Delay in treatment-seeking behavior in the face of physical illness, e.g., rubella infection\[31-33\]
- Malnutrition, anemia and other common physical illness, e.g., diabetes, phenylketonuria
- Inadequate health literacy, including reproductive health
- Inadequate preventive care at community level, e.g., water pollution, high level of hazardous metal in drinking water.

**Safety Concerns that May be Associated with Mental Illness During Pregnancy**

Risk factors for suicide includes a family history of suicide attempts, psychiatric disorders requiring hospitalization; a history of suicidal behavior in the past (attempted or aborted suicide/self-injurious behavior), currently a diagnosis of mood disorders, psychotic disorders, alcohol/substance abuse, attention deficits and hyperactive disorder, traumatic brain injury, posttraumatic stress disorder and acute stress reaction, and personality disorders (dramatic, emotional, and erratic cluster). Some symptoms that have been associated with suicidal behavior are anhedonia, impulsivity, hopelessness, anxiety/panic, insomnia, command hallucination, intense feeling of humiliation, shame or despair; and abuse or isolation.\[34\]

Risk factors associated with violence and aggression are characterized by history of childhood/adult abuse (physical or sexual), disorganized behavior or recurrent violent behavior or dissocial behavior; and severe anxiety or agitation or motor restlessness and other severe psychopathologies such as psychotic symptoms (paranoid delusions, command hallucination), poor impulse control, low intelligence, suicidal behavior, absconding or defiant behavior; and severe substance abuse.\[35\]

**Teratogenic Aspect of Psychotropic Medications in Pregnancy**

**Effect of Pregnancy on Psychotropic Drugs**

Medication efficacy may be altered as volume of distribution increases, plasma proteins concentration decreases, hepatic
function is enhanced, and metabolic enzymes are influenced by hormone. Increase in isozyme CYP2A6, 2D6, and 2C9 may decrease the levels of medication such as levels of risperidone, aripiprazole, and loperidone while decreased activity of CYP1A2 and 2C19 may increase the level of clozapine and olanzapine.\[396\]

Criteria to Ascertain Teratogenicity of a Drug

Numerous attempts have been framed to ascertain causality. Teratogenicity is not an idiosyncratic effect and follows some scientific principle (e.g., vulnerable timing of pregnancy, toxicological dose response curve, and specific teratogenic effect not any type of malformation, etc.).\[396\] However, in the court of law, it may not require to determine absolute certainty, but reasonable certainty (more likely than not or more than 50% likelihood) about given child’s abnormality may be sufficient to consider as the cause. Some of the important proposed criteria that have been cited during medico legal trials or during expert witness are:

James Wilson’s criteria

Initially, James Wilson put forward the principles of teratology in 1977 and is well‑accepted even now.\[400–411\] They were: (1) Susceptibility to teratogenesis depends on the genotype of theconceptus, and the manner in which it interacts with environmental factors; (2) susceptibility to teratogenic agents varies with the developmental stage at the time of exposure; (3) teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis); (4) the final manifestations of abnormal development are functional disorder, malformation, growth retardation and death; (5) the access of adverse environmental influences to developing tissues depends on the nature of the influences (agent); and (6) manifestations of deviant development increase in degree as dosage increases from the no‑effect to the totally lethal level.

Sir Austin Bradford Hill modified criteria

In 1965, Sir Austin Bradford Hill proposed criteria for causation in teratology during his address to Royal Society of Medicine.\[414–433\] He proposed that a teratogenic effect should satisfy the following criteria: (1) Degree of association (degree of significant statistical association); (2) consistency of the association (same observation across studies); (3) specificity of the association (whether the specific defect is consistent); (4) appropriate timing (timing of exposure during pregnancy); (5) dose‑response relationship; and (6) biological plausibility.

Breut criteria

In 1995, Brent after extensive review of literature proposed a more comprehensive criteria.\[439, 441\] The criteria were: (1) Strong epidemiological evidence of congenital malformation (or syndrome) in exposed population; (2) incidence of congenital malformations vary with degree of exposure; (3) appropriate animal model demonstrated similar results with equivalent exposures; (4) the appropriate animal model has demonstrated teratogenesis (frequency and severity) to be dose dependent; and (5) the observed teratogenic effect can be explained with the principles of embryology and teratology.

Shepard criteria

Shepard published a catalogue of teratogenic agent in 2001, and proposed a comprehensive criteria.\[444–449\] He offered the following criteria: (1) Proven exposure to agent at critical time in prenatal development; (2) consistent findings of two or more epidemiologic studies of high quality: (a) Control of confounding factors, (b) sufficient numbers, (c) exclusion of positive and negative bias factors, (d) prospective studies, if possible, and (e) relative risk of six or more; (3) careful delineation of the clinical cases; (4) rare environmental exposure associated with rare defect; (5) teratogenicity in experimental animals is important, but not essential; and (6) the association should make biologic sense.

Principles of Determining Teratogenic Causality in Litigation

It is very difficult to ascertain the cause‑effect relationship when inadequate information is available, and level of exposure is uncertain. However, in litigation, common principles employed\[441] to ascertain causality are: (1) Based on scientific evidence; (2) biologically plausible; (3) evidence of exposure; (4) protective level of exposure can be considered causative if evidence exist; (5) causal relationship of an outcome is agent and outcome‑specific; (6) conclusions are based on human data; and (7) single case report is not sufficient to conclude as established causal relationship.

Factors that May Increase the Teratogenic Effect of a Psychotropic Medication

Drug profiles that may enhance the teratogenic effects of a medicine are:\[459\] (a) Chemical and pharmacological properties of the drug (less plasma binding, high placental crossing, the active metabolite, inhibition of folate metabolism, etc.), (b) potency and dose reaching the fetus (low potency, high quantity drug reaching to fetus), and (c) duration of exposure (longer duration of exposure particularly during the first trimester). Patient characteristics that may be associated with increased teratogenic incidence are: (a) Co‑morbid physical illness (e.g., endocrinal or metabolic); (b) individual susceptibility (family history of malformation; patient having malformation; medication for the comorbidity; repeated infection; immune‑compromised status; and medical illness such as obesity, diabetes mellitus, hypothyroidism, hyperthyroidism, hyperparathyroidism,cretinism, and iodine and folate deficiency). During pregnancy, teratogenic susceptibility also depends upon: (a) The critical stage at the time of administration (first trimester); (b) high placental permeability to the medication used; (c) Increased medication dose exposed to the fetus; (d) disposition within the conceptus; and (e) susceptibility of the fetus. Possible environmental factors associated with teratogenicity during pregnancy are frequent intake of fast food, synthetic additive in food, and pollution or contamination of air or water.

Pathophysiology of Teratogenicity

Medication may affect the fetus by direct metabolic or indirect toxic effect mediated by anti‑metabolites, anti‑vitamins, disruption of placental permeability, and alteration of endocrinial function.\[453\] The drug may directly affect fetoplacental unit leading to placental spasm, changes in the volume of amniotic fluid, alteration in fetal or maternal blood flow, or alteration in the transfer of nutrients.\[469\] The drug may also impair the maternal absorption of nutrients; induce metabolic changes such as hyperglycemia, endocrinal alteration, cardiovascular
changes such as hypotension or hypertension. At cellular level, psychotropic drugs may result in mutation and cell division abnormality; disturbance in structure (composition of nucleic acid) or function of cells (biosynthesis, enzyme system) or enzyme system or cell interaction; inadequate energy supply for embryo (vascular disruption); and changes in membrane characteristics (specific receptor- or enzyme-mediated teratogenesis), oxidative stress, endocrine disruption, and fluid and electrolyte balance.

**Outcome of Teratogenic Effect of Psychotropic Medication**

The teratogenic effect of psychotropic medicine may result into variable outcomes such as major malformation (first trimester exposure); miscarriage (spontaneous abortion) or still birth; toxic or withdrawal effects to neonate (third trimester exposure); and long-term neurobehavioural difficulty and growth retardation.

**Food and Drug Administration (USA) Classification of Teratogenic Risk of Psychotropic Medication**

None of the psychotropic medication falls under Category A (no risk in pregnancy). Antipsychotic clozapine and antidepressant buspirone, mirtazapine, venlafaxine, mianserin, reboxetine and bupropion, and zolpidem are listed under Category B (no risk in animal study, but inadequate study in human). Most psychotropic medications fall under Category C (adverse effect on animal study and inadequate study in human). High-risk medications that are listed under Category D (evidence of the human fetal risk present) are carbamazepine, lithium, valproic acid, paroxetine, alprazolam, chloridiazepoxide, clonazepam, clorazepate, diazepam, lorazepam, and oxazepam.

**Screening of the Teratogenic Effect in Patients with Psychotropic Medication During Pregnancy**

All patients receiving psychotropic drugs should be screened for the reported teratogenic effect of the given drug and other malformation. The common method of examination includes: (a) Ultrasonography may be considered for all pregnancies with mental illness and on psychotropic medication to rule out the neural tube defect or any other malformation; (b) amniocentesis may be considered for high-risk patient such as past or family history of malformation or genetic disorder. Some indicators that have been reported are changes in serum human chorionic gonadotropin (hCG) (low total free beta-hCG and higher total hCG) and low levels of α fetoprotein, unconjugated estriol-3, dimeric inhibin-A and pregnancy-associated plasma protein A. (c) Chorionic villi sampling may be considered for family history of known genetic disorder.

**Starting, Maintaining or Discontinuing a Psychotropic Medication During Pregnancy in Indian Setting**

**General Treatment Principle**

- In general, maternal safety is considered first. If pregnancy can cause life-threatening risk to the mother, termination of pregnancy should be considered.
- When a mother wants to continue a pregnancy at her own risk, regular safety monitoring of the mother and the fetus is needed. Investigate for fetal teratogenic effect and on presence, consider for the termination of pregnancy if fetus is unlikely to survive.

- When a mother does not have any safety concern, let the decision to continue the medication be made by the patient alone or with her guardian or joint decision by the physician (panel of physician-obstetrician, pediatrician, and psychiatrist) and the patient.
- When there is an anatomical evidence of defect and the child’s life is compatible to life, explain the outcome of pregnancy and advise to review the continuation of pregnancy, however final decision to be made by the patient alone or with her guardian or joint decision by the patient and the physician (panel of physician-obstetrician, pediatrician, and psychiatrist).

**Prescribing a Psychotropic Medication in Indian Setting**

**Decision-making**

It should be ideally decided by the patient. In India, the patient usually asks their physician to decide for her, and appropriate way could be a joint decision by the patient (with her husband and other family member), obstetrician, psychiatrist, and pediatrician. Obtain written consent before starting a medication.

**Medication**

- Establish a clear indication.
- Select a drug (prefer monotherapy):
  - Lowest known risk or prior exposure in previous pregnancy.
  - Available reproductive safety data.
  - Known effectiveness.
  - Higher protein binding.
  - High potency.
  - Short period of exposure (e.g., during peak of the symptoms) or intermittent dosing.
  - Lowest effective dose and smaller multiple divided doses, and.
- Optimize if necessary rather than switching or combining.
- Provide adequate information - this is most important before starting any medication. Explain about teratogenic potentials in simple terms (e.g., in percentage), efficacy of medication, nonpharmacological option.
- Safety monitoring - close monitoring of fetus (appropriate fetal screening and monitoring) and mother (severity of illness, level of personal social and occupational impairment).
- Good practice - be familiar with risks of medication, risks of maternal illness, and treatment guidelines. Adequate document appropriately communicates and collaborates with the patient referred to a specialist if required.

**Threshold for Initiating or Maintaining on Medication**

There is no general guideline as to when the medication should be started during pregnancy. Establish that severity of illness that requires active supervision or behavior posing/or invariably may lead to a safety issue to the patient or the fetus. A score below 30 on the global assessment of functioning may be considered as a gross threshold when specific assessment cannot be done. Some of the symptom severity indicators are severe insomnia and loss of appetite, being immobile or very...
Choice of Psychotropic Medication During Pregnancy

After extensive review, National Institute for Health and Care Excellence provided with medication with a better safety record as drugs of choice. These medications are:

- Hypnotic and sedative: Zolpidem or promethazine
- Antipsychotics: Chlorpromazine, haloperidol, and trifluoperazine
- Antidepressant: Nor triptyline, am triptyline, imipramine, and fluoxetine
- Mood stabilizers: High potency typical antipsychotics may be considered as a mood stabilizer during pregnancy.

Preventing the Teratogenic Effect of Psychotropic Medication

One-third of major physical anomalies can be prevented (primary prevention). The most advocated measures are folic acid and multivitamin supplementation, use of drug with better safety and prevention of infection, and other physical disorder during pregnancy.

Conclusion

Physicians in India are more likely to face psychopharmacoteratophobia and issues related to this phenomenon are distinct in India. Clear guidelines is required to address this issue for Indian setting.

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