**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-

1-Use of indigenous treatment for physical or mental illness, with uncertain safety and efficacy of treatment during pregnancy.

2-Delay in treatment seeking behavior in the face of physical illness e.g. rubella infection33,34,35.

3-Malnutrition, anemia and other common physical illness e.g. diabetes, phenylketonuria.

4-Indequate health literacy, including reproductive health.

5-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, post traumatic stress disorder and acute stress reaction, personality disorders (dramatic, emotional, and erratic cluster). Some symptoms that have been associated with suicidal behaviour are anhedonia, impulsivity, hopelessness, anxiety/panic, insomnia, command hallucination, intense feeling of humiliation, shame or despair, abuse or isolation36.

Risk factors associated with violence and aggression are characterized by history of childhood/ adult abuse (physical or sexual), history of disorganized behavior or recurrent violent behavior or dissocial behavior, history of severe anxiety or agitation or motor restlessness, other severe psychopathology such as psychotic symptoms ( paranoid delusions, command hallucination), poor impulse control, low intelligence, suicidal behavior, absconding or defiant behavior, severe substance abuse37.

**Teratogenic aspect of psychotropic medications in pregnancy**

**A-Effect of pregnancy on psychotropic drugs**

Medication efficacy may be altered as volume of distribution increases, plasma proteins concentration decreases, hepatic function are enhanced, and metabolic enzymes are influenced by hormone. Increase in isozyme CYP2A6, 2D6 and 2C9 may decrease the level of medication such as levels of risperidone, aripiprazole, and iloperidone while decreased activity of CYP1A2 and 2C19 may increase the level of clozapine and olanzapine38.

**B-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, specific teratogenic effect not any type of malformation etc.) 39. 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 has been cited during medico legal trials or during expert witness are-

1-James Wilsons Criteria: Initially, James Wilson put forward the principles of teratology in 1977, and is well accepted even now40,41 .They were: 1) Susceptibility to teratogenesis depends on the genotype of the conceptus, 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); 6) Manifestations of deviant development increase in degree as dosage increases from the no-effect to the totally lethal level.

2-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 Medicine41,42,43 . 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; 6) Biological plausibility.

3- Brent criteria: In 1995 Brent, after extensive review of literature, proposed a more comprehensive criteria44,41 . 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; 5) The observed teratogenic effect can be explained with the principles of embryology & teratology.

4- Shepard criteria: Shepard published a catalogue of teratogenic agent in 2001, and proposed a comprehensive criteria45, 41. 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; 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 exposure is uncertain. However, in litigation common principles employed41 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; 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 profile that may enhance the teratogenic effects of a medicine are46 - 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 foetus (low potency, high quantity drug reaching to foetus), 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; medical illness such as obesity, diabetes mellitus, hypothyroidism, hyperthyroidism, hyperparathyroidism, cretinism and iodine & 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 foetus; d) Disposition within the conceptus; and e) Susceptibility of the foetus. 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 endocrinal function46. The drug may directly affect fetoplacental unit leading to placental spasm, changes in the volume of amniotic fluid, alteration in foetal or maternal blood flow, or alteration in the transfer of nutrients47. The drug may also impair the maternal absorption of nutrients; induce metabolic changes such as hyperglycaemia, endocrinal alteration, cardiovascular changes such as hypotension or hypertension47. 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); changes in membrane characteristics (specific receptor- or enzyme-mediated teratogenesis), oxidative stress, endocrine disruption and fluid and electrolyte balance48,49.

**Outcome of teratogenic effect of psychotropic medication**

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

**Food and Drug Administration (U.S.) 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 & 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 foetal risk present) are carbamazepine, lithium, valproic acid, paroxetine, alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, lorazepam, 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 (hCH) ( low total free beta-hCG and higher total hCG) and low levels of α feto protein, unconjugated estriol (uE3), dimeric inhibin-A and pregnancy associated plasma protein A (PAPP-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**

**1-General treatment principle**

a) In general, maternal safety is considered first. If pregnancy can cause life threatening risk to the mother, then termination of pregnancy should be considered.

b) When a mother wants to continue a pregnancy at her own risk –regular safety monitoring of the mother and the foetus is needed. Investigate for foetal teratogenic effect and on presence, consider for the termination of pregnancy if foetus is unlikely to survive.

c) 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.

d) 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, paediatrician and psychiatrist).

**2-Prescribing a psychotropic medication in Indian setting**

a-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 paediatrician. Obtain written consent before starting a medication.

b-Medication- 1- Establish a clear indication. 2- Select a drug (prefer monotherapy): a) Lowest known risk or prior exposure in previous pregnancy, b) Available reproductive safety data, c) Known effectiveness, d) Higher protein binding, e) High potency, f) Short period of exposure (e.g.during peak of the symptoms) or intermittent dosing, f) Lowest effective dose and smaller multiple divided doses, and h) Optimise if necessary rather than switching or combining.

c- 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, non-pharmacological option.

d-Safety monitoring- close monitoring of foetus (appropriate foetal screening and monitoring) and mother (severity of illness, level of personal social and occupational impairment).

e- Good practice- Be familiar with risks of medication, risks of maternal illness and treatment guidelines. Adequately document, appropriately communicate & collaborate with patient and if required, refer to a specialist.

**3-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 behaviour posing / or invariably may lead to a safety issue to the patient or the foetus. A score below 30 on the global assessment of functioning (GAF) 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 hyperactive, impaired judgment, severe impairment in personal care, patient requiring active supervision for daily routine, inability to follow the recommendation by an obstetrician or any risk that poses threat to the safety of self or to the growing foetus. In other words, without treatment there is a high chance of poor outcome of pregnancy and safety issues may invariably arise. Other factors that are often considered before prescribing psychotropic are: imminent safety issue (suicidality, harm to others), poor support system, severe relapse in the past, causing safety issues, a malformation in children or first degree relative, history of substance use during illness, mental illness during a past pregnancy and more than 12 weeks gestation50.

**4-Dilemma for asymptomatic patient on medication, but at risk of relapse during pregnancy**

Most guidelines are in opinion that if the patient is asymptomatic, reduce the dose and high teratogenic medicine should be switched to a less teratogenic medication. In general, folate supplement should be given. In depression and anxiety disorder, single antidepressant may be continued at the lowest effective, dose except for paroxetine and venlafaxine. Benzodiazepine can be used intermittently, or on requirement basis. Patient with schizophrenia should continue their typical antipsychotic, atypical antipsychotic may be changed to typical antipsychotics, and if the patient has a poor response to typical then reduce to lowest effective dose of atypical antipsychotics. Do not give depot antipsychotics. Anticholinergic should not be used routinely. Valproate, carbamazepine, lithium and lamotrigine should not be used, unless there is no alternative. Antipsychotics can be an alternative option to mood stabilizers in the management of bipolar disorder during pregnancy. If clinician / obstetrician has decided to stop the medication, it should not be abrupt. There is no clear guideline regarding the discontinuation of psychotropic medication, and general term such as gradual tapering has been used in literature. Usually discontinuation of a psychotropic medication depends on many factors such as duration of illness, duration of remission, diagnosis, possibility of withdrawal symptoms, psychosocial issues, etc. Attempt has been made as to how a psychotropic medication may be discontinued51,52,in such situation an appropriate approach may be-

1-If the patient is asymptomatic for more than six months and on single medication-If the medication is a high potency then quarter dose reduction weekly with continuous observation of symptoms of relapse.

2-If the patient is asymptomatic for more than six months and on single medication-If medication is lower potency than half dose reduction weekly with continuous observation of symptoms of relapse.

3-If the patient is asymptomatic for more than six months and on single medication-If medication is more than one, both high potency and low potency, then simultaneous quarter dose reduction for high potency and half dose reduction for low potency medication every week with continuous observation of symptoms of relapse.

4-If the patient is asymptomatic for less than six months and on single medication-If the medication is a higher potency then 20% dose reduction weekly with continuous observation of symptoms of relapse.

**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 dugs of choice53. These medications are-

1-Hypnotic and sedative: zolpidem or promethazine.

2-Antipsychotics: chlorpromazine, haloperidol and trifluoperazine.

3-Antidepressant: nortriptyline, amitriptyline, imipramine, fluoxetine.

4-Mood stabilizers: High potency typical antipsychotics may be considered as a mood stabilizer during pregnancy.

**Preventing the teratogenic effect of psychotropic medication**

According to the estimation of the WHO expert committee, at least one-third of major physical anomalies can be prevented (primary prevention)54. 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 pregnancy53,54,55,56,57.

In conclusion, physicians in India are more likely to face psychopharmacoteratophobia and issues related to this phenomena is distinct in India. Clear guideline is required to address this issue for Indian setting.

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**Reference**

34. Acs N, Bánhidy F, Puhó E, Czeizel AE. Maternal influenza during pregnancy and risk of congenital abnormalities in offspring. Birth Defects Res A Clin Mol Teratol 2005; 73 (12):989-96.

35.Acs N, Bánhidy F, Puhó EH, Czeizel AE. Acute respiratory infections during pregnancy and congenital abnormalities: a population-based case-control study. Congenit Anom (Kyoto) 2006;46(2):86-96.

36.Jacobs DG. Suicide assessment, five-step evaluation and triage. In: Best Practices Registry (BPR) for suicide prevention. SPRC (Suicide Prevention Resource Center) Web site http://www.sprc.org/library/safetpcktcrdedc.pdf Accessed December 22, 2014.

37.Dubin WR, Jagarlamudi K. Safety in the evaluation of potentially violent patients. Psy Times 2010:1-4.

38.Robakis T, Williams KE.Atypical antipsychotics during Pregnancy: Make decisions based on available evidence, individualized risk/benefit analysis. Current Psychiatry2013;12 (7):12-18.

39.Brent RL. Bendectin: review of the medical literature of a comprehensively studied human nonteratogen and the most prevalent tortogenlitigen. Reprod Toxicol 1995; 9:337–49.

40.Wilson JG. Current status of teratology. General principles and mechanisms derived from animal studies. In: Wilson JG, Fraser FC, editors. Handbook of teratology. General principles and etiology. New York: Plenum Press. 1977 ; 1: 47–74.

41.Scialli AR. Causation in teratology-related litigation. Birth Defects Res A Clin Mol Teratol 2005;73(6):421-3.

42.Hill AB. The Environment and Disease: Association or Causation?, Proc R Soc Med 1965; 58:295-300.