

# Teratogenicity and teratogenic factors

## Abstract

Teratology is the science that investigates the congenital malformations and their causes. Intrauterine exposure to a toxicant, particularly in early pregnancy, induces embryonic and fetal changes ranging from none up to malformations and stillbirths. The teratogenic agents include some viral, spirochetal and protozoal infections, physical agents as ionizing radiations and excessive heat, pharmacological drugs as thalidomide, excessive vitamin A, corticosteroids, antiepileptic, antimalarial, antileishmaniasis and antihypertensive agents, industrial pollutants as toluene and cadmium, alcohol and smoking abuse, and narcotics. Maternal health problems as diabetes mellitus, multiple sclerosis and rheumatoid arthritis may also add to the etiology list of teratogenesis. The prevalence of the congenital birth defects ranges from 2 to 5% throughout the first year of postnatal life.

**Keywords:** teratogenicity, teratogenic agents, congenital birth defects, rubella, herpes simplex, drugs, pollutants, embryo, syphilis, toxoplasmosis

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**Abbreviations:** AEDs, antiepileptic drugs; ARBDs, alcohol-related birth defects; Cd, cadmium; Dex, dexamethasone; FAS, fetal alcohol syndrome; GA, glatiramer acetate; KT, ketoconazole; MQ, mefloquine; MS, multiple sclerosis; NO, nitrous oxide; NP, nonylphenol; PTH, sodium phenytoin; RA, retinoic acid; RA, rheumatoid arthritis; SM, sulfur mustard; VPA, valproic acid

## Introduction

Teratology is the science of studying and investigating the birth defects and their etiologies. At birth, the incidence of the congenital malformations amounts to 2-3%, however by the elapse of the first neonatal year the incidence rises to about 5%.<sup>1</sup> On exposure to a toxic agent, a developing embryo will exhibit a response that ranges from none to severe (i.e. death or malformation). This response at a given dosage is sometimes defined as teratogenic (or developmental toxic) severity and is dependent on exposure conditions.<sup>2</sup> The factors that induce congenital malformations are termed the "teratogenic factors"; they include infectious, physical, chemical, hormonal, and maternal health factors.

## Teratogenic agents

### Infectious agents

Some infections during pregnancy are teratogenic like viral infections (e.g. rubella, herpes simplex and cytomegalovirus), spirochetal infections (e.g. syphilis), and protozoal infestations (e.g. toxoplasmosis). First trimester maternal influenza exposure is reported to be associated with raised risk of a number of non-chromosomal congenital anomalies including neural tube defects, hydrocephalus, congenital heart anomalies, cleft lip, digestive system abnormalities, and limb defects.<sup>3</sup>

### Physical agents

Radiation is teratogenic and its effect is cumulative. The International Commission of Radiology recommends pregnancy screening- tests (safe and of low cost) to all female patients of child bearing age who will undergo a radiological procedure. The degree

of ionizing radiation needed for these procedures is very close to the threshold for teratogenicity, especially in the first trimester when the signs of pregnancy are not yet manifest.<sup>4</sup> There is a basic assumption that risk prediction for human radiation exposure is proportional to the total radiation dose. However, there is some concern about the feasibility of dose limits for people who may be genetically cancer-prone.<sup>5</sup>

### Chemical agents

Medical prescription and over-the-counter drug use are common and necessary for many pregnant women nowadays. The principal challenge of prescribing physicians is "Will these drugs induce teratogenic effects?" Such a drug-phobia arose after the eruption of thalidomide teratogenicity disaster in 1960s; when the drug was used to relieve morning sickness associated with pregnancy.<sup>6</sup> Most of medication exposures during pregnancy do not carry an increased risk of congenital malformations. Misperceptions of these risks may lead to abrupt discontinuation of therapy and even to termination of an otherwise wanted pregnancy.<sup>7</sup> Maternal depression has a significant effect on the perception of teratogenic risk. It limits the validity of a decision-making process toward pregnancy.<sup>8-12</sup> There is an evidence for the association between health literacy and perception of teratogenic medication risk, beliefs about medications, and adherence or non-adherence to prescribed medicines during pregnancy. It was found that health literacy was significantly associated with maternal health behaviors regarding medication non-adherence. Clinicians should devote some time to inquire into their patients' ability to understand health information, perception and beliefs, in order to promote drug adherence during pregnancy.<sup>13</sup>

Placental transporter proteins are involved in the pharmacokinetics of drugs and have an effect on drug level and fetal drug exposure. There is an association between P-glycoprotein polymorphisms and the risk of fetal birth defects induced by medications during pregnancy.<sup>14</sup> Six underlying teratogenic mechanisms are stated to be associated with medication- use. They include folate antagonism, neural crest cell disruption, endocrine disruption, oxidative stress, vascular disruption and specific receptor- or enzyme-mediated teratogenesis.<sup>15</sup> There is a great evidence that individual susceptibility to teratogenic drugs varies

from one individual to another, even following identical exposures. One of the factors that may explain these individual-related variations is the genetic makeup in the pharmacokinetics and pharmacodynamics of the respective drugs.<sup>16,17</sup>

Antiepileptic drugs (AEDs) are frequently used to treat epilepsy, headaches, and psychiatric disorders in women of childbearing age. In many instances, clinicians are obliged to stop these drugs or switch to another category of medications. Discontinuation of AEDs during pregnancy is not advised due to the risk of seizures that may be fatal to both mother and fetus.<sup>18</sup> The teratogenic potential of an AED is determined by both chemical attributes of the drug molecule and genetic attributes of the host. Hepatic mixed oxidase system and other systems like epoxide hydrolase, glutathione reductase, and superoxide dismutase as well as toxin-scavengers are important modifiers that lower the teratogenic risk of the drug.<sup>19,20</sup>

In utero exposure to some AEDs can lead to significant cognitive and behavioral teratogenic risks for the fetal outcome. Valproate obviously induces impaired cognitive development and increased risk rate of autism incidence. Exposure to other AEDs as carbamazepine, lamotrigine, levetiracetam, or phenytoin mono therapy is mentioned to be associated with more favorable cognitive and behavioral fetal outcomes than valproate.<sup>21-23</sup> All old-generation AEDs are considered as teratogenic. In Germany, one out of 200 pregnant women (0.5%) receives AEDs for epilepsy. Consequently, the risk of major congenital malformations during the first trimester is two to three times the rate reported in the general population (2-3%).<sup>24</sup> Several studies reported the teratogenic effects of sodium phenytoin (PTH) to include toe and finger, renal, and facial malformations as well as neural tube closure- defects. Administered of PTH in a strict concentration regimen produced a lower rate of neural tube closure- defects than previously reported.<sup>25</sup> Valproic acid (VPA) is an anticonvulsant and mood-stabilizer used to treat epilepsy, bipolar disorder and migraine. It is known to induce teratogenicity in the form of neural tube anomalies in humans.<sup>26</sup> The teratogenic effects of VPA could involve altered micro RNAs expression.<sup>27,28</sup> Various forms of VPA, and more importantly, newer generation of AEDs like lamotrigine, topiramate, and gabapentin show signals for either congenital jaw or oral malformation.<sup>29</sup>

About half a century ago, thalidomide was widely prescribed to pregnant women as a sedative and anti-nauseant but it proved to be teratogenic, causing multiple birth defects particularly limb malformations. Thalidomide is still used as a powerful treatment of leprosy and multiple myeloma. However, its clinical use remains limited due to its teratogenic properties.<sup>30,31</sup> The mechanisms underlying the teratogenic effects of thalidomide are uncertain. Anti-angiogenic but not anti-inflammatory metabolites/analogues of thalidomide were observed to induce chick embryo- limb defects.<sup>32</sup>

Sulfur Mustard (SM) was used as a chemical poisonous agent, in the World War I and Iraq-Iran war in early 1980s'. It has local and systemic effects that depend on environmental conditions, exposed organs, and extent and duration of exposure. It is a strong alkylating agent with known mutagenic, carcinogenic effects. Craniofacial and septal defects as well as limb malformations were the most common types of birth defects related to SM. These malformations have been postulated to be due to an uncontrolled migration of neural crest cells.<sup>33</sup>

In China, *Lignosus rhinocerus* (Tiger Milk mushroom) is an

expensive traditional medicine used to treat liver cancer, chronic hepatitis and gastric ulcers. In Malaysia, it is the most popular medicinal mushroom used by the indigenous communities to alleviate fever, cough, asthma, cancer, food poisoning and as a general tonic. This mushroom is cultivated in South China, Thailand, Malaysia, Indonesia, Philippines and Papua New Guinea. The sclerotium of the mushroom is the active part with medicinal value. In rat, tested different oral concentration of this sclerotial powder did not show any genotoxicity as previously thought.<sup>34</sup>

Retinoic acid (RA) or retinol is the active metabolite of vitamin A and is responsible for all of the bioactivity associated with this vitamin. It plays essential signaling roles in mammalian embryogenesis. It has long been recognized that overexposure to vitamin A or RA induces widespread teratogenesis in rodents and humans.<sup>35</sup> The RA catabolic CYP26 enzymes prevent the teratogenic consequences caused by uncontrolled distribution of RA particularly on the RA-sensitive tissues like the limbs and the testis.<sup>36</sup>

Isotretinoin is a very effective oral medicine for the treatment of severe acne. It is the most widely prescribed teratogenic drug in the USA and Canada. Due to its adverse effect and the necessity for its long term use, most patients show noncompliance and some refuse to take the drug.<sup>37</sup>

Mefloquine (MQ) is a potent effective antimalarial drug against *Plasmodium Falciparum*. It is safe during the second and third trimesters. In early gestation in Wistar rats, MQ induced minimal extension of lateral brain ventricles and renal pelvis together with delayed ossification in the fetuses. Prenatal exposure to MQ in early pregnancy is considered neither embryo lethal nor teratogenic.<sup>38</sup>

Miltefosine a drug used in the treatment of visceral leishmaniasis but its use is hampered by its potential teratogenicity. The duration of adequate post-treatment contraception in females after cessation of a potentially teratogenic drug therapy is a subject of much debate. For the 28day miltefosine regimen, post-treatment contraception may be extended to 4months although shorter regimens of 2months may be adequate.<sup>39</sup>

A study in the USA quantified the benefits (life expectancy gains) and risks (efavirenz-related teratogenicity) associated with using efavirenz in HIV-infected women of childbearing age. It was found that the use of non-efavirenz-based initial antiretroviral therapy may reduce life expectancy gains from antiretroviral treatment, and may also prevent teratogenic events.<sup>40</sup>

Ritodrine is a drug used to stop premature labor, it has been already removed from the US market. Nifedipine (Adalat) is used to manage angina, hypertension, Raynaud's phenomenon and premature labor. Each of these two tocolytics was experimentally used to assess its teratogenic potential in the frog embryo. Nifedipine was determined to be more toxic and teratogenic than ritodrine. However, ritodrine+nifedipine combination had reduced the toxic and teratogenic effects of nifedipine alone on embryos.<sup>41</sup>

Environmental teratogenic pollutants lead to severe birth defects but the underlying biological mechanisms of these developmental abnormalities remain unclear. A link has been discovered between an environmental stress response pathway and key developmental genes during craniofacial development in mice.<sup>42</sup> Toluene is an organic solvent necessary for industry. Many women of childbearing age are increasingly exposed to toluene in occupational settings

(i.e. long-term, low-concentration exposures) or through inhalation abuse (e.g. episodic, binge exposures to high concentrations). Abuse toluene exposure is mentioned to be more teratogenic, than regular occupational exposure, on fetal development.<sup>43</sup>

Cadmium (Cd) is a heavy metal pollutant and teratogen. Cd-mediated teratogenicity, in a chick embryo, had occurred because of impaired endogenous nitrous oxide (NO), increased oxidative stress, and activated apoptotic pathways. Further addition of exogenous NO had abolished these Cd-mediated effects and protected the developing embryo.<sup>44</sup> The toxicity of the pollutant Nonylphenol (NP), on the common South American toad *Rhinella arenarum*, was reported to be stage- (embryos or larvae) and time- (acute, short-term chronic or long-term chronic) dependent. This experimental work highlighted the relevance of extending the exposure time and of considering the most sensitive stage is essential to perform the bioassays for chemical teratogenic agents.<sup>45</sup>

Ketoconazole (KT), as a potent antimycotic agent, exerts its therapeutic effects through interfering with steroid biosynthesis in the fungal walls. It is reported to be embryotoxic and teratogenic when administered in high doses. Concomitant prednisone supplementation therapy revealed reductions in the incidence of KT-induced cranial and appendicular skeletal anomalies as well as cleft palate in rat.<sup>46</sup>

Prenatal alcohol is considered as a teratogenic agent.<sup>47</sup> Genetic factors seem to influence fetal alcohol spectrum disorders in both humans and animals.<sup>48–50</sup> Micro RNAs and their target genes are involved in the pathogenesis of fetal alcohol syndrome.<sup>51</sup> Some socio-behavioral risk factors (e.g. low socioeconomic status) are permissive for fetal alcohol syndrome (FAS). These permissive factors are related to biological factors (e.g. decreased antioxidant status) which together with alcohol, provoke FAS/ alcohol-related birth defects (ARBDs) in vulnerable foetuses.<sup>52</sup> The high incidence of ocular malformations, produced by oral ethanol intake in mouse model, are excellent utilization clues in experiments involving factors administered to the embryo that might alter ethanol's teratogenicity.<sup>53</sup>

Maternal nicotine consumption is teratogenic leading to increased incidence of attention hyperactivity disorder, major depressive disorder and substance abuse in exposed children and adolescents. Whether these syndromes are caused by nicotine (smoke) exposure itself or by genetic and psychosocial mechanisms is still not completely elucidated.<sup>54</sup> Studies have provided a correlation of teratogenic effects of alcohol and tobacco, and the risk of anorectal atresia. Animal researches have suggested that caffeine may potentiate the teratogenicity of these agents.<sup>55</sup>

Cocaine abuse significantly reduces fetal weight, increases the malformation rate, and augments the stillbirth rate due to abruptio placentae.<sup>56</sup> cocaethylene or ethylbenzoylecgonine is formed in the liver when cocaine and alcohol are simultaneously ingested; each is a potent stimulant and dopamine uptake blocker that is more toxic to myocardial cells than cocaine alone. Good nutrition is very important in preventing congenital anomalies and fetal death.<sup>57</sup>

### Maternal health problems

Maternal diseases as diabetes mellitus are of great concern during pregnancy. Teratogenesis is associated with pre-existing and gestational diabetes. The risk of congenital anomalies increases in the offsprings of obese diabetic women. The use of biguanides may be associated with other adverse perinatal outcomes. The use of other

oral antihyperglycemic agents is not recommended during pregnancy. Healthy diet and regular exercise may help optimize pre-pregnancy weight and reduce the risk of congenital anomalies. Women with diabetes mellitus have to attend pre-conception counseling with a multidisciplinary team, optimize general health and glycemic control, and review the risks of congenital anomalies.<sup>58</sup> Cardiac and neural tube defects are the most common malformations observed in fetuses of pre gestational diabetic mothers.<sup>59</sup>

Pregnant women with multiple sclerosis (MS) should carefully consider the risks and benefits of ongoing therapy for the health of both the mother and the fetus. The immunosuppressant mitoxantrone and fingolimod are teratogenic and should be prescribed only with strict effective contraception. Usage of Glatiramer acetate (GA), interferon beta-1a (IFN $\beta$ -1a), and natalizumab has not shown malformations suggestive of teratogenicity.<sup>60</sup>

For pregnant women suffering from rheumatoid arthritis (RA), the use of immune modulating medications has low risk allowing for optimal outcomes. NSAIDs should be avoided in the third trimester. Corticosteroids in the lowest effective dose could be used throughout pregnancy. Antimalarial agents, sulfasalazine and azathioprine are safe options in this condition. Methotrexate and leflunomide are contraindicated as they are teratogenic.<sup>61</sup>

There is some evidence of a slightly increased risk of congenital malformation in children born to women with asthma, although it is not attributed to asthma drugs. Commonly used asthma medications are generally safe. Moderate teratogenic risk of cromones is reported.<sup>62</sup> Excessive dexamethasone (Dex) administered into pregnant mice during periods of palatal development were found to induce a high incidence of cleft palate. Vitamin B12 is reported to prevent the teratogenic effects of Dex.<sup>63</sup>

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### Conflict of interest

Author declares that there is no conflict of interest.

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