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Research Article

CRITICAL REVIEW ON TERATOGENICITY IN PERSPECTIVE OF ANCIENT AND MODERN TOXICOLOGY

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A B S T R A C T

Teratology is the study of anomalous fetal development. Most of the pregnancies in our country are unplanned. Women, whose pregnancies are unintended and unexpected, are more likely to be exposed to a wide range of potential teratogen which may cause congenital malformation. OurAcharyas strongly suggests that they have got knowledge about the teratogens and what is the outcome of that. So they have also told about the precautions should be taken by pregnant women to avoid these untoward effects. In modern science they also described agents such as Physical, chemicals, environmental etc. that can causes teratological effects. The description of vedic literature about the infection, maternal causes, adverse drug reactions, and other genetic and environmental factors establishing the relationship in between the teratogen and teratogenic changes in the fetus. This concept is explained under different headings like Dushivisha, garavisha, garbhavyapada etc.in various ancient Ayurvedic texts along with different precaution methods and treatment protocol. This is an approach to provide a brief knowledge about ancient and modern teratology and the way to solve this disastrous issue through little efforts

INTRODUCTION

The health of the nation depends on the health of its citizens. Such healthy population makes an important role in the development and progress of country. In Ayurveda, this concept is explained as *Shreyasipraja* (good progeny). As per this concept, the ultimate aim of the conception is to get *Shreyasipraja* (good progeny). Most of the children are born normal; however, there are some children who may have born with some obvious or hidden anomalies. Teratological or congenital anomalies are defined as 'gross structural defects' present at birth. Now a days, advancement in the diagnostic techniques and therapeutic interventions are plays major role in improvement of health of society. But still medical science has failed to keep the incidence of the congenital malformations under control. Throughout the history, the birth of malformed infant features has been well documented and the attitude towards the infants and parents varied according to the cultural state of people and range of admiration to rejection and hostility. Advanced modern medical science even though has extended the life span of the humans, the rate of inborn defects in the newborns is increasing. This is posing a challenge to the aim of a healthy society.The term "teratology" stems from the Greek word "teras" meaning "monster" or marvel; "logos" means "the study of" i.e.

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the study and under-standing of teratogenic agents and their effects on developing organisms. The teratogenicity is the ability to produce birth defects. In human, congenital disorders resulted in about 510000 deaths globally in 2010[1]. About 3% of newborns have a physical anomaly that has cosmetic or functional significance [2]. 20-30% of all infant death is due to genetic disorder[3] and 30-50% of post neonatal death is due to congenital malformation,[4] 11.1% of pediatric admissions are with genetic disorders, 18.5% children are with congenital disorders.[5]

The most common problems among the newborns in human beings is the low birth weight[6] annually about 23.8% of total birth showed the low birth weight,[8] this low birth may be due to the insufficient food intake, stress, use of some drugs and chemicals, exposure to environmental factors etc. during the pregnancy.[9] Some of these drugs, chemicals, environmental and genetic factors fall under the category called teratogens.[10] Teratogens commonly affect the fetus in the organogenesis stage itself.[11] Organogenesis refers to that period of time during development when the organs are being formed. After an egg has been fertilized, damage to any of the organ systems of the body which may ultimately result in some type of birth defect usually strikes during this time frame.[12]

Drugs, chemicals, environmental and genetic factors fall under this category called teratogens. Teratogens commonly affect the fetus in the organogenesis stage itself.[13] Organogenesis refers to that period of time during development when the

organs are being formed. After an egg has been fertilized, damage to any of the organ systems of the body which may ultimately result in some type of birth defect usually strikes during this time frame.

The prevalent health vision of the modern science and its adverse drug reaction has attracted the population worldwide towards the holistic health approach of the Ayurveda, which was visualized thousand years ago. It emphasis strongly on the concept of *Shreyasipraja*.

Objectives

1. To discuss ancient and modern aspect of teratogenicity and its associations with *Garbhavyapada, Garvisha* and*Dushiviasha.*
2. To discuss causative factors like various modern and ayurveda medications, pollution and other environmental factors.
3. To establish preventive protocol as per ayurveda in such teratogenicities

MATERIALS AND METHODS

Literature revived from ancient Ayurveda classical texts and contemporary science.
Information from related websites was searched.

Ancient and modern aspect of teratogenicity

Ancient aspect

In Vedic and other contemporary literature the matter related to the abnormal growth and development in intrauterine life and congenital malformation have limited dealing in comparison to the description present in Ayurvedic literature *Atharva Veda*, *Shatpatha-Brahmana*, *YajnavalkaSmirti, MatsyaPurana* and *Garbhopanisada* has mentioned some quotes regarding this. According to *Garbhopanisada* described about the Psychological state of women. Mental stress during pregnancy leading to congenital abnormalities like blindness, deformed body organs like vertebral column and dwarfism etc. in newborn baby. That type of description has a direct concern with true mental stress (*Garbhopanisada* /3).

The description of *vedic* literature about the infection, maternal causes, mental stress and other genetic and environmental factors establishing the relationship in between the teratogen and teratogenic changes in the fetus. That could be established with the teratological knowledge of the modern medical science. This information suggests the knowledge of teratogenic factor during ancient period was well known.

Acording to description by Acharya*Vagabhatta* about the birth defects, *Doshas* get vitiated and causes defect in the fetus. When *vata*, develops upward movement (which is abnormal) and dries up the channels of rasa in the fetus, the future child will be either a patient of *vataroga* or one born with deficient/poorly developed parts; or it (the foetus) may even remain inside the abdomen for many years[14]. If the pregnant women indulges constantly in foods and activities which cause increase of *Vata*, then *Vata* getting increased abnormally, travels all over her body and also in the uterus, and produces many diseases of *Vata* origin in the child; the child may become inactive, deaf, mute, of nasal speech, stammering, lame, hunch-back, dwarf, of deficient organs (in number) or of extra organs or any other*Vata* diseases [15].

*Vata*represent cell division, *Vatika* declaration may lead to anaphase lag. The common error of cell division during meiosis leads to abnormal chromosomal numbers ex. Non disjunction, anaphase lag. *Vatika* vitiation may leads to *Heenanga* and *Adhikanga*, which can be considered either with visible congenital anomalies likes Polydactyl or absence of visible body part. *Sushruta* grouped blindness, lame, deafness etc. under congenital abnormalities due to vitiation of *Vata* disorders. Exposure to mutagens leads to mutations and occurs through errors in DNA replication and repair. Such DNA replication can be considered as *Vatika* vitiation which in turn leads to congenital anomalies.

Maharsi Kashyap has indicated the adverse effect of the smoking of the mother during her prenatal period. In his opinion such activities are likely to produce congenital abnormalities blindness, sickness, discoloration of the new born baby and even *Garbhapata* or abortion.[16]

In ayurveda, *dooshivisha* is the unique concept which was explained under heading *Vishchikitsa.* It is defined as when the poison after treating it is not completely excreted from the body and remains in the body in little amount then when it get exposed to the *dusitadesha* (polluted environment), *dusitakala* (rainy season), *dusitaanna* (spoiled food) and does the *diwaswapna* (day sleep) then the symptoms will be produced called as *dooshivisha*. And other concept called *Garavisha* (artificial poison) is the combination of different parts of body, excreta of different animals, incompatible drugs, chemicals, ashes, and poisonous substances act as low potent poison and some types of teratogen fall under the category of *Garavisha* (artificial poison), and when these artificial poisons get accumulated in the body and produces the condition called *garavishajanyadooshivisha* (low potent poison. In *dooshivisha* the symptoms will be facial paralysis, anorexia, emaciation of the person, loss of sperm and ovum, vomiting, fainting, slurred speech etc.[17]

Visha (poison) which is devoid of two or three *gunas* (properties) out of classical ten properties attains a latent or hidden stage in the body called *dooshivisha* (Latent poison). This low potency of the poison usually won't cause sudden death because of the enveloping *(avarana)* action by *Kapha*, this low potency poisons is retained in the body for long period without producing any grave or fatal symptoms.[18]The conceptual thoughts about *dooshivisha*is that all *vishas* (poisons) being not completely eliminated from the body or partially detoxified due to incomplete metabolism lose its original *gunas* (properties) and gets converted in to low potency due to exposure to heat, flame, fire, sunlight etc or naturally less potent poison after entering the body without elimination due to some conjugation and after a secondary cause causes several diseases, depends where the poison deposited. Poisoning in the body currently happens in the condition that is due to poisonous bites inanimate poison exposure-*viruddhahara* and *ahitaahara*-fast foods and cola beverages like colas-alcohol, tobacco etc. Drugs like quinine, NSAIDs, steroids etc. Pesticides, Metals, Minerals, pollutants etc. Drugs using for long period for Blood pressure, Diabetes mellitus, Despirine, ARTs, Phenobarbitone.[19] with these types of poisoning which currently occurs and accumulates in the body slowly and act as cumulative poison and considered as *Doosivisha*. In *dooshivisha* all the *rasadidhatudusti* takes place and will lead to the *shukra* (sperm or *ojus* or *saptadhatu*)*kshaya. T*here will be denaturing of the *shukra*

(*stree and pumshukra*) and there will be *pratilomadhatukshaya*. *Agnimandya* is one of the symptom of *dooshivisha*, further leads to the *dhatuagnimandya* then all the nourishment of *dhatus* will be lost so there will be effect as mutagenic and even effect of this dooshivisha over the pregnant woman lead to the even *dushana*(destruction) of the fetus,[20] so it can be considered as Teratogenicity

Congenital birth defects induced by maternal exposure to various exogenous agents during pregnancy are preventable, if these agents are identified and avoided. In Ayurveda there are various precautions described in pregnant lady to avoid any malformation or defect in progeny. According to Ayurveda, a pregnant lady should take precautions and exposure to *GarbhopaghatakaraBhavas* (hazardous effects causing factors) should be avoided for any abnormality in fetuses.[21]

Modern Aspect

Until the early 1940‟s, it was assumed that congenital defects were caused primarily by hereditary factors. With the discovery of Gregg 1941 that German measles affecting a pregnant woman during early pregnancy caused abnormalities in the embryo like congenital cataract, it become evident that congenital malformation in human could also be caused by environmental factors.[22]

Along with this new awareness of the in utero vulnerability of the developing mammilian embryo came the development and refinement of *the six principles Ofteratology* which are still applied today. These principles of teratology were put forth by Jim Wilson in 1959 and in his monograph "*Environment and Birth Defects*." These principles guide the study and understanding of teratogenic agents and their effects on developing organisms:

1. Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with adverse environmental factors.
2. Susceptibility to teratogenesis varies with the developmental stage at the time of exposure to an adverse influence. There are critical periods of susceptibility to agents and organ systems affected by these agents.
3. Teratogenic agents act in specific ways on developing cells and tissues to initiate sequences of abnormal developmental events.
4. The access of adverse influences to developing tissues depends on the nature of the influence. Several factors affect the ability of a teratogen to contact a developing conceptus, such as the nature of the agent itself, route and degree of maternal exposure, rate of placental transfer and systemic absorption, and composition of the maternal and embryonic/fetal genotypes.
5. There are four manifestations of deviant development (Death, Malformation, Growth Retardation and Functional Defect).
6. Manifestations of deviant development increase in frequency and degree as dosage increases from the "No Observable Adverse Effect Level" (NOAEL) to a dose producing 100% lethality (LD100).

Any drug or chemical given to the mother will cross the placenta to some extent unless it is destroyed or altered during placental passage or its molecular size or lipid solubility limits transplacental transfer. The onset of this placental transfer starts at the fifth embryonic week to seventh gestational week. For drugs or chemicals with low molecular weight, the transplacental passage to fetus is based on the concentration gradient.

***Teratogenic Exposures*:** There are many factors, which are responsible for the teratogenic changes. They are teratogenic agents, drugs dosage to embryo or fetus and period of pregnancy.

***Agent*:** Teratogenicity also depends upon the nature of the chemical, physical or infectious agent, inherent developmental toxicity, and the capacity to produce other kinds of toxicity in the mother

***Dosage to embryo or fetus*:** Teratogenicity may occur due to single, repeated, or chronic exposure, duration of exposure. Other factor also influences the teratogenicity such as maternal dose, maternal route of exposure, maternal absorption, maternal metabolism and clearance as well as, placental transfer

***Period of pregnancy*:** Exposure of specific teratogen during First, second or third trimester may lead to development of congenital anomalies. In other words, specific congenital anomalies may be result of teratogenic drug exposure between conception and onset of embryogenesis, during Organogenesis and Fetal period

***Other factors*:** are Genetic susceptibility of mother**,** Genetic susceptibility of the fetus**,** other concurrent exposures**,** maternal illness or other condition associated with exposure**,** Availability of tests to quantify the magnitude of maternal exposure

Modern Drugs and Their Teratogenic Effects

Role of chemical agents and drugs in production of anamolies is difficult to assess.. Now a days most studies done are retrospective by relying on mothers memory. Thus very few drugs have been positively identified as being teratogenic.

The few drugs have been tested for teratogenecity in controlled clinical trials and are categorized according to their risk factors into 5 categories by FDA [23].

Antibacterial Drugs		
Drug	**Adverse effect**	**Category**
Aminoglycosides	Ototoxicity(damage to fetal labyrinth), resulting in deaf-ness Gray baby syndrome	D
Chloramphenicol	In women or fetuses with G6PD deficiency, hemolysis	C
Fluoroquinolones	Possibly arthralgia; theoretically, musculoskeletal defects (e.g. impaired bone growth), but no proof of this effect.	C
Nitrofurantion	In women or fetuses with G6PD deficiency, hemolysis	B
Primaquine	In women or fetuses with G6PD deficiency, hemolysis	C
Streptomycin	**Ototoxicity**	D
Sulfonamides (except sulfasa-lazine, Which has minimal fetal risk)	When the drugs are given after about 34 week gestation, neonatal jaundice and, with-out treatment**, kernicterus** in women or fetuses with G6PD deficiency, hemolysis	C
Tetracycline	Showed **bone** growth, enamel hypoplasia, permanent yellowing of **teeth**, and increased susceptibility to cavities in offspring Occasionally, liver failure in pregnant women	D
Trimethoprim	Increased risk of neural tube defect due to folate antago-nism	C

Anticoagulants		
Drug	**Adverse effect**	**Category**
Low molecular weight heparin	Thrombocytopenia and maternal bleeding	B
Unfractionated heparin	Thrombocytopenia and maternal bleeding When warfarin is given during first trimester, fetal warfarin syndrome (e.g. nasal hypoplasia, bone stippling, bilateral optic atrophy,various degrees of intellectual disability)	C
Warfarin	When the drug is given during the 2nd and 3rd trimester, optic atrophy, cataracts, intellectual disability, microcephaly, micropthalmia and fetal & maternal hemorrhage	X

Anticonvulsants		
Drug	**Adverse effect**	**Category**
	Hemorrhagic disease of new-born.	
Carbamazepine	Some risk of congenital mal-formations including **neural tube defects**	D
Lamotrigine	No appreciable increased risk with dosage upto 600 mg/day	C
Levetiracetam	Minor skeletal malformations in animal studies, but no appre-ciable increased risk in hu-mans.	C
Phenobarbital	Hemorrhagic disease of new-born , some risk of congenital malformations	D
Phenytoin	Congenital malformations(e.g. cleft lip, GU defects such as a narrowed or an incompletely formed urethra, cardiovascular defects) Craniofacial defects, Nail and digital hypoplasia, growth abnormalities, mental deficiency- The above pattern is known as "fetal hydantoin syndrome"	D
Trimethadione	High risk of Congenital malformations(e.g. cleft palate, cardiac, craniofacial, hand and abdominal defects) and risk of spontaneous abortion Always contraindicated during pregnancy	D
Valproate	Major congenital malformations (e.g. **neural tube defects** such as meningomyelocele, cardiac, craniofacial, and limb defects)	D
	Antihistamine/anticholinergic	
Drug	Adverse effect	Category
Meclizine	Teratogenic in rodents, but no proof of this effect in humans	B

Antihypertensives		
Drug	**Adverse effect**	**Category**
ACE inhibitors (oral ACE inhibitors and angiotensin II receptor blockers for hypertension	When drugs are given during 2nd &3rd trimester, fetal hypocalvaria and hypo perfusion (which can cause **renal defects**), renal failure, and the oligohydramnios sequence (oligohydroamnios, craniofacial deformities, limb contractures, and hypoplastic lung development)	D
β-blockers	Fetal bradycardia, hypoglycemia and possible fetal growth restriction	C
ca- channel blockers	When drugs are given during the 1st trimester, possibly phalangeal deformities During 2nd & 3rd trimester fetal growth restriction.	C
Thiazide diuretics	Prevention of normal maternal volume expansions, reducing placental perfusion and contributing to fetal growth restriction , neonatal hyponatremia, hypokalemia and thrombocytopenia	D

Antineoplastics		
Drug	**Adverse effect**	**Category**
Actinomycin	Teratogenic in animals, but no proof of this effect in humans	D
Busulfan, cyclophosphamide Chlorambucil Mercaptopurine Methotrexate	Congenital malformations (e.g. fetal growth restriction, mandibular hypoplasia, cleft pal-ate, cranial dysostosis, spinal defects, ear defects, clubfoot)	D
Colchicine	Possibly congenital malformations and sperm abnormalities	D
Doxorubicin	Teratogenic in animals potential for dose dependent cardiac dysfunction	D
Vinblastin Vincristine	Teratogenic in animals, but no proof of this effect in humans	D

Anxiolytics		
Drug	**Adverse effect**	**Category**
Baenzodiazepines	When given late in pregnancy, respiratory depression or a neonatal withdrawal syndrome that can cause irritability, tremors and hyperreflexia	C
	Hypoglycemic (oral)	
Drug	Adverse effect	Category
Chlorpropamide Glyburide	Neonatal hypoglycemia	B
Metformin	Neonatal hypoglycemia	D
Tolbutamide	Neonatal hypoglycemia	D
	Lithium	
Drug	Adverse effect	Category
Lithium	Ebstein'sanamoly (1/5000), Possibly teratogenic neonatal lethargy, hypotonia, poor feeding, hypothyroidism, goiter andnephrogenic diabetes insipidus.	C
	Opoids	
Codeine,Meperidine	In neonates of women addicted to opioids, withdrawal symptoms possibly occurring 6h to 8 days after birth	C
Morphine	With high dose given in the hour before delivery, possibly neonatal CNS depression and bradycardia	X
	Retinoids	
Isotretinoin	High teratogenic risk (e.g. multiple congenital malformations), spontaneous abortion and intellectual disability. Reduced and abnormal ear development, flat nasal bridge, cleft palate, hydrocephaly, neural tube defect, heart abnormalities	X

NSAIDs		
Drug	**Adverse effect**	**Category**
Aspirin and other salicylates	Fetal kernicterus (with high doses possibly 1st trimester)	D
Non-salicilate NSAIDs	Spontaneous abortions, delayed onset of labor, premature closing of the fetal ductusarteriosus, jaundice, occasionally maternal (intrapartum and postpartum) hemorrhage, necrotizing enterocolitis and oligohydramnios With low doses (81 mg) of aspirin , no significant teratogenic risk	D For some drugs if given after 30 week
Danazol	Same as those for salicylates NSAIDs, Contraindicated in 3rd trimester	X

Sex hormones		
Drug	**Adverse effect**	**Category**
Synthetic progestins(but now low doses used in oral contraceptives)	When given during first 14 week masculinization of female fetus's genitals (e.g. pseudo-hermaphroditism), sometimes require surgery to correct. Same as those for danazol	X
Thyroid drugs		
Methimazole	Fetal goiter and neonatal scalp defects(alpasia cutis)	D
Propyl-thiouracil	Fetal goiter and maternal hepatotoxicity and agranulocytosis	D
Radioactive iodine (131I)	Destruction of the fetal thyroid gland or when the drug is given near end of 1st trimester, severe fetal hyperthyroidism	D
Saturated solution of K iodide	Large fetal goiter, which may obstruct breathing in neonates	D
Triiodothyronine	Fetal goiter	D

Vaccines		
Drug	**Adverse effect**	**Category**
Live-virus vaccines such as those for measles, mumps, rubella, polio, chickenpox and yellow fever	With rubella and varicella vaccines, potential infection of the placenta and developing fetus With other vaccines potential but unknown risks	B
Others		
Corticosteroids	When these drugs are used during first trimester, possibly orofacialcelefts	B
Hydroxychloroquine	No increased risk at usual doses.	C
Loratadine	Possible hypospadias	B
Ondansetron	No significant teratogenic risk	B
Pseudoephedrine	Plasantal vasoconstriction and possible risk of gastroschisis	C
Vitamin K	In women or fetuses with G6PD deficiency hemolysis	C

FDA pregnancy category

A: Adequate well controlled studies in pregnant women fail to demonstrate risk to the fetus in any or all trimesters.

B: Animal studies do not indicate risk to fetus; however there are no adequate well controlled studies in pregnant women. Or animal studies have shown adverse effect on fetus but adequate well controlled studies in pregnant women have failed to demonstrate a risk to the fetus.

C: Animal studies have shown that drugs exert teratogenic effects and there are no adequate well controlled studies in human or no studies are available in either animals or human.

D: Positive evidence of human fetal risk exists, but benefits in certain situations e.g. life threatening situation or serious disease may make use of drug acceptable de-spite its risks.

X: Studies in human and animals have demonstrated fetal abnormalities or there is positive evidence of human risk. These are contraindicated in pregnant women.

Teratogenicity Due To Ayurvedic Drugs

Some of Ayurvedic medications also shows the teratogenic effects like a study done on Shivalingi (*Bryonia Laciniosa*), Majuphal (*Quercus infectoria*) shown that some of the preparations contain hormones (testosterone) and natural steroids. The scientific validity of such measures is however unknown. Sex selection drugs are consumed between 6-8 weeks of pregnancy – the most critical period of fetal development during which fetal sexual differentiation occurs under influence of both genetic and hormonal factors. Any exposure of the fetus to steroids and particularly hormones can have deleterious impact on sexual differentiation and probably on the behavior of the individual. The amount of different constituents that the fetus is exposed to is still unknown. Exposure of a female fetus to testosterone during this phase can lead to masculinization of genitalia. In fact, androgenic stimulation at any time during fetal life can cause clitoral hypertrophy.[24][25]

Traditional Ayurvedic drugs can have adverse effects on pregnancy.

Following factors can be attributed for development of teratogenicity

1. Phytochemical and pharmacological properties and many documented ADR of drugs which also include acute and chronic toxicities
2. Adulteration of drugs, adulteration of declared ingredients intentionally or by accident by toxic drugs and undeclared medicines
3. Microbial contamination like Staphylococcus aureus, e coli, salmonella, shigellaetc
4. Contamination by toxic metals (lead, mercury, cadmium, arsenic), radioactive materials and pesticide
5. Adulteration by synthetic drugs e.g. with steroids, anti-inflammatory drugs etc

The ADR for Ayurvedic drugs searched from the available literature from authentic indexed journals, websites and sources books, following drugs may leads to teratogenicity [26]

Vacha (Acorus Calamus): In view of toxic property of beta asaron associated with calamus. It should be avoided in pregnancy because it has emmenagogue and genotoxicactivity.

Kitamaari (Aristolochia spp/ A. Indica/ A. Bracteata): It is emmenogogueabortifacient, antifertility effect, passage of Aristolochic acid into human breast milk has been reported recent studies in Rodent suggest that it may cause carcinogenic effects. It also shows genitotoxic and mutagenic effects.

Daruharidra (Berberis aristata): Berberin containing plants are contraindicated during pregnancy. Higher doses may interfere with Vitamin B metabolism. Decoction 50-100 ml, berberincauses a strong contraction of the isolated pregnant mouse uterus, it is the mitochondrial mutagen in yeast.

parnyayavani (Borage officinalis): because of hepatotoxic and hepatocarcinogenicpyrrolizidine alkaloid. Content though in small quantity, it is contraindicated in pregnancy. It also shows mutagenic effects.

Genda (Callendula officinalis)**:** Contraindicated in pregnancy. It has spermatocyte, anblastocite and aborting agent.

Swarnapatri(Cassia angustifolia): It is contraindicated in pregnancy and while nursing not to be used in children under 12 years of age prolonged use cause loss of electrolyte, potassium resulting in Albiminurea and haematuria. Not for use while nursing *Sennaalexandrina* is part of the formation to be used for constipation, this stimulant laxative is the most commonly used anthranoid laxative. In the case of pregnant women. The use of laxative containing anthraquinones is potentially dangerous, because the ingredients can induce uterine contractions, increase blood flow to uterus and its attachments, increasing the fetal loss and may pass into breast milk cause unwanted effects such as spasms in the infant to be avoided especially in the first trimester.

Karpur (Cinnamomum camphora/ Camphor): Animal studies shows that experienced varied degrees of bleeding and significant structural changes in the uterus, shown to cross placenta, nursing mother also also should avoid camphor.

***Guggul (Commiphora mukul)*:** Oleo gum resin is reported to enhance the menstrual discharge and hence should not be used in pregnancy.

***Vidang (Embelia basal)*:** The aqueous extract of the drug acts as an long acting contraceptive by inhibing endometrial alkaline phosphatase and hence preventing implantation of fertilized ovum.

***Nilgiri (Eucalyptus Globulas)*:** It should not use internally in pregnancy. A study in rat shows eucalyptol is able to penetrate the placental tissue and reches in concentration in fetal blood adequate for stimulating hepatic enzyme activity.

***Gandpuro (Gaultheria procumbens*/ Oil of wintergreen):** Salicylate content (teratogenic and embryocidal in various species of animals). Since salicylates are distributed into breast milk, oil of wintergreen shold be avoided by pregnant and nursing women.

Tulasi (Ocimumbasilicum Sweet Basil): Contains about 0.5% essential oil with up to 85% estragole. Because of high estragole content in the essential oil, the herb should not be taken during pregnancy, because a mutagenic effect in vitro and a carcinogenic effect in animal experiments have been demonstrated for estragole, oil of basil should also not be demonstrated for estragole oil of basil should also not be administrated while nursing.

***Chitrak (Plumbago zeylanica)*:** It is contraindicated during pregnancy. It's root powder produced antifertility activity in albino rats (oestrogenic anti gonadotrophic and antiovulatory activities)

***Eranda (Ricans communis)*:** Castor oil should not be taken during pregnancy as it can cause uterine contraction. Seed can contain poisonous principle ricin and enzyme lipase. Long term use of oil can cause a reduction of absorption of nutrients.

Many drugs has abortifacent, antifertility, teratogenic, mutagenic, genotoxic, carcinogenic effects. Some interfere in metabolism, some causes allergy and other ADR which further leads to intake of other conventional drugs which can be further harmful. Adulteration and substitution can also be one of the cause of ADR during pregnancy by traditional drug because of unknown pharmacological action and toxicity exerted. For example, substitution of *Cinnamomumzeylanicum* with *Cinnamomum cassia* causes ADR as *Cinnamomumzeylanicum* only contains low level of coumarin while Cinnamomum cassia contains large amount of coumarin which leads to severe liver damage and jaundice

Metallic Drugs and Metallic Contaminants Affecting The Pregnant Mother

All the forms of mercury are teratogenic in animal tests cases of human fetal poisoning have mostly been traced to mercury vapours and organic mercurial, especially methyl mercury. Arsenic cross the placental barrier and acute placental barrier and acute maternal arsenic poisoning has been incriminated neonatal death inorganic arsenic compound are established carcinogens in men. Lead as a contaminant can also cause toxicity lead is clearly teratogenic in labouratory animals in man reproductive system appears to be very sensitive to chronic lead exposer cognitive developmental deficits have been observed in infants born with cord blood lead levels > 0.5 micromol/lit can affects fetus all stages. Exposer to low levels of lead, before the birth of baby, it thought to affects the developing child. Exposer limit for lead are set lower for women of child bearing age in order to protect the fetus from the injury in the weeks before a pregnancy is confirmed. Exposer of Antimony, Arsenic, lead and mercury can cause birth defect. Arsenic, cadmium, lead, mercury can cause growth retardation. Cadmium and lead can cause functional defect. Antimony, arsenic, cadmium, lead, manganese and mercury can cause breast milk contamination.[27][28][29]

Cigarette Smoking and Nicotine

Smoking of cigarettes during pregnancy and nursing causes leads to considerable health damage in the fetus and infant during the initial growth phase. A smoking mother puts her child at considerable risk, not only of higher incidence of spontaneous abortion, premature ablation placentae and reduced weight at birth but also deformities like cheilognathopalatoschisis, deformed extremities, polycystic kidneys, aorto-pulmonary septal defects, gastroschisis, skull deformation, etc. Development of Down syndrome is the subject of some controversy. These types of damage can caused by the hypoxia followed by carboxyhaemoglobinemia occurring during smoking and are also observed in carbon monoxide poisoning that also result in deformities. Numerous infants die during first months of life of the so called sudden infant death syndrome (SIDS), which can also be caused by maternal smoking and passive smoking. The contribution of nicotine to such damage is still unclear, especially animal trial data is available. The applicability to of which to human being is questionable. It can be said that studies to date have revealed no deformities can have been confirmed as having been caused by nicotine. Cardiopulmonary disturbance resulting from changes in regulation of dopaminergic receptors are under discussion, but have not yet reached the status of a pathogenic principle. On the whole, all child health complicationsarising during pregnancy can be attributed almost exclusively to tobacco combustion products including the CO formed. Passage of nicotine into human milk have been confirmed in nursing smokers: passive smoking by mother and child also raises nicotine and cotinine levels in the milk and in the infant[30]. A nicotine stimulate acetylcholine receptors, it is believed that this may disrupt the maturation of developing brain.

Alcohol Induced Teratogenicity

The alcohol induced teratogenicity grouped into 4 categories: Central nervous system dysfunction, growth deficiencies, a characteristic cluster of facial abnormalities, and variable major and minor malformations. To make diagnosis of fullblown fetal alcohol syndrome (FAS), abnormalities of all above four categories must be present. Along the continnum toward normal are infants with variable combinations of FAS anomalies. One of the most common and serious defect associated with ethanol teratogenicity is mental retardation. At birth infant with FAS are deficient for both length and weight, usually at or below the 3rd percentile or for both parameters. Growth and mental deficiency are seen in many conditions, but the rather striking facial appearance of children with FAS secures the diagnosis. The characteristic face of small children

with FAS secures the diagnosis. The characteristic face in small children include short palpebral fissures, short upturned nose, hypoplastic maxilla, and thinned upper vermilion. A table lists the variety of malformations that may found in other organ system in patients with FAS. The likelihood miscarriage increases directly with alcohol consumption. Risk of abortion is twice as high in women consuming 1 ounce of absolute alcohol (AA) as infrequently as twice in week. On average, infant born to women who smoke during pregnancy are 200 gm lighter than babies born to comparable to women who do not smoke. The finding of antepartum bleeding of unknown cause has constantly been found more often in smokers compared with non-smokers. Sudden infant death syndrome has been found to be closely associated wiyh both the frequency and level of maternal smoking during pregnancy [31].

Environmental factors associated with teratogenicity

Environmental toxins can causes teratogenic effect like structural abnormalities. Altered growth, functional deficiencies, congenital neoplasia or even death of the fetus. Some of these factors are Polychlorinated biphenyls, organochlorine pesticides, perfluorinated compounds, phenols, polybrominateddiphenyl ethers, phthalates, polycyclic aromatic hydrocarbons, perchlorates, PBDEs, etc.Exposer to environmental toxins such as lead, tobacco smoke, and DDT have been linked with an increase in risk of spontaneous abortion, low birth weight, or preterm birth[32]

Many of autism are related to particular geographic area, implying that something in environment is complementing an at risk genotype to cause autism in vulnerable individuals. Elemental mercury or methyl mercury are the forms of mercury that leads to mercury poisoning in the pregnancy. Methyl mercury is the worldwide contaminant of sea food and freash water fish is known to produce adverse nervous system effects, especially during brain development leading to learning disabilities. [33] One well documented case of widespread mercury ingestion and subsequent fetal development complication took place in 1950 in Minamata Bay, Japan where the villagers who consumes the mercury-laden meat began meat experiencing negative effects from ingesting the toxins; however the mercury especially impacted women and their fetus, resulting in high rate of miscarriage. Surviving infants exposed to mercury in-utero has extremely high rate of physical and mental handicaps. [34] Mercury exposer in pregnancy can also cause limb defect.Adverse effects of lead exposer leads to miscarriage, low birth weight, neurological delays, anemia, encephalopathy, paralysis, blindness. [35] Several studies shows that even low maternal exposer to lead produce intellectual and Behavioral deficit in children.

Air Pollution

It can negatively effect on pregnancy and causes higher rates of preterm births, growth retardation, and heart and lung problems in infants. Compounds like CO, SO2 and NO2
All causes potential serious damage when inhaled by pregnant women. Low birth weight, preterm birth, intrauterine growth retardation, and congenital abnormalities are associated with fetal exposed to air pollution.[36] Partical pollutant ranging from PM 10 to PM 2.5 which can easily enters into lungs. They leads to unhealthy outcomes for fetal development such as poor and slow fetal growth increase in fetal morbidity and mortality.[37]

Pesticides

Studies shown that pesticides particularly fungicides, have shown up in analysis of infant's cord blood, proving that such toxins are indeed transferred into the baby's body. Overall the two pesticides most frequently detected in cord blood are diethyltoluamide (a commonly used repellent) and vinclozolin (a fungicide) [38]. Contamination of pesticide occurs at many times from merely engaging in everyday activities such as walking down a pathways near a contaminated are or eating food that not be washed properly.

Benzene

Benzene exposer in mother has been linked with the fetal brain damage especially neural tube defect especially neural tube defect. Women with occupational benzene exposer have been shown to have an increased rate on miscarriage. Ambiant ozone have been negetivlyassociated with the sperm concentration in man, chemicals associated with sperm concentration in man, chemicals associated with UOG operations (e.g., benzene, toluene, formaldehyde, ethylene glycol, and ozone) have been associated with negative impact on semen quality, particularly sperm count[39].

Categories of teratogenic effects

General effects**:** Alterations of morphogenesis**,** Alterations of CNS function**,** other functional impairments**,** Death of the conceptus, embryo, or fetus**,** Prenatal-onset growth deficiency**,** Carcinogenesis

Specific effects**:** It includesrecognizable syndrome and other distinctive features

Magnitude of risk**:** are absolute (death) and relative

Prenatal diagnosis**:** Prenatal diagnosis of suspected /expected congenital anomalies can be made by detailed ultrasound examination, Amniocentesis or other invasive method, availability, reliability and utility

Prevention

Ayurveda has great approach to avoid these uncertain events. The foremost approach is *NidanaParivarjana*i.e., avoid the causative factors. For this purpose to avoid the drugs and environmental toxicants that causes teratogenicity is most important during pregnancy. Avoiding the paint supplies such as stained glass materials, oil paints and ceramic glazes, and instead using water colour or acrylic paints and glazes. Check the quality of the tap water or bottled water and changing water drinking habits if necessary. To decrease exposer to pesticides, washing all the products throughoutly, peeling the skin from fruit and vegetables or buying organic products if possible. Second is fulfilling desires and treatment of illness through safe drugs and mild therapies. There are certain drugs mentioned by *Kashyapa* which can be used in pregnant women during acute illness that are listed below [40]

Jwara (Fever)	
Vataja	Vidharigandha, Kalari, Gandharvhasth,Madhuk, Bhadrdaru, Erand, Varun, Brahti(Both), Panchmool(Both),Rasna .
Pittaja	Sariva, Pyasya, Kshirkakoli, Mridvika, Madhuka, Nilotpla, Pippli, Maricha, Ushira, Lodhra, Laja, Root of Nala, Vanjula, Gundra, Saha, Sahdeva, MarkaaPatali,Jambu, Amra, Utpal, Chandan, Pad-ma, Manjishta, Yava , Honey .
Kaphaja	Rasna, Bhadrdaru, Chandan, Vasa, Amrita.
Kapha-Pittaja	Shriparnika, Amrita, Yashtimadhuka.
VātaKaphaja	Vrihtpanchmool, Rasna.
Vāta-Pittaja	Vidarigandha.
Fever of wine addict	Soup of Hrenu, Mudga, Cuccu, Karkati with Sour Article

Atisara (Diarrhea)	
Associated with Kapha and Ama	Kutaja, Musta, Patha, Subha, Ajmoda, Sarala, Ativisha.
Associated with Pitta and Ama	Pātha, Chandna, Kutj, Ativisha fruit.
Associated with Vata and Ama	Hingu, Rocksalt, Naga, Brahti(Both), fruit of Kutaj, Pipplimool, Ativisha.
Associated with Tridosh and Ama	Brahtyadi Group.
Kaphaja	Ambasthadi Group with Honey, Kutaj, Dhatki, Maricha, Lodhra, Katvanga, Devdaru with Honey. Kesar of Nalina with rice water.
Pittaja	Nyogrodha decoction with honey, Kana, flowered Dhatki, Madhuka, pulp of Bilva, Padma, Samanga, Kernel of mango, Madhuka, Padamkesara, Lodhra, Mochrasa mixed with honey.
Vātaja	KhuddakaPanchmool excluded Eranda with Kala, Katvang, Levigated Padma, Samanga, Kernel of mango, Brahti, pulp of Bilva, Pippli, Dhatki, Padma, Samanga, Mochrasa, Matsyandika, Indradhanya. LevigatedMusta, unripe fruit of Bilva, Ananta and Madhuka, mixed with Ghrita.
Diarrhea	Pippli, Dhatki, Lodhra, Samanga, Padmkesra, Padma, Mochrasa, Dirghavranta and Kesara.
Diarrhea with blood	Bana Root, Trapusi seed, Padma, Smanga, Madhuka, Chandana, Padamkesra. Black Tila, Yashtimadhu, Utpala, Mochrasa, Lodhra, Kamal, Pyasya, Chandna, Lodhra, Padmkesra,Madhuka.
Dysentery	Bark of Kashmari, root of Syama, Kirattikta, Lodhra, Yashtimadhu, Mollasses. Kapitha, Masa, Komalamoca, Pippli, Sringbera.

Parikartika(Anal Fissure)	
Vātaja	Brahti, Bilva, Ananta.
Pittaja	Madhuka, Hamspadi, Vittunika.
Kaphaja	Kantakari, Svadmastra, Asvatha.
Rigidity in Flanks	Salaparni, Prsniparni, Brahti, Kantkari, Bilva, Agnimantha.
Stomatitis	Kaval/Pratisarna of Daruhridra, Lodhra, Ananta,Samanga, Mochrasa with honey.
Rigidity in Flanks	Salaparni, Prsniparni, Brahti, Kantkari, Bilva, Agnimantha
Stomatitis	Kaval/Pratisarna of Daruhridra, Lodhra, Ananta,Samanga, Mochrasa with honey.

Apasmar (Convulsions)	
Vātaja (Apatānaka)	Matulunga juice with Vida and rock salt, Agnimantha, Varuna, meat soup of Lava or partridge soup of Vadul
Pittaja	Meat soup of wild animals sweetened by cooking.
Vāta-Kaphaja	Meat soup of wild with Yavakshara

Chhardi (Vomiting)	
Vātaja	Matulunga, Laja, kernel of Kola, Anjana, Dadima Sara meat soup of Buffalo.
Pittaja	Laja, Chaturjata mixture. Laja meat soup of wild animals sweetened with honey.
Kaphaja	Tender leaves of Amra and Jambu, Mudgasoup.
Oedema	Varsabu, Bhadrdaru, Murva.
Jaundice	Pippli and Ankotha, juice of horse dung, curd of buffalo.

Hrutshula (Cardiac Pain)	
Vātaja	Juice of Matulung with Rocksalt.
Pittaja	Priyanu, Pipppli, Bhadramusta, Harenu, Badra.
Kaphaja	Pippli, Paste of Patra Coca and Priyangu with Matulunga Juice.

Kasa (Cough)	
Vātaja	Kulirangi, Sarata, Bhargi, Pippli with Matulung Juice
Pittaja	Madhulika, Gokshiri, Pippli, Saraka with Draksha and honey.
Kaphaja	Pippli,Triphla, Rasna, Bhadradaru
Kshataj	Madhuka, Sankha, Jiva, Laksha.

Shwasa(Dyspnoea)	
Kaphaja	Body hair of peacock, porcupine, pieces of Pippli, root of Kola.
With Cough and Tamaka	Rasna, Pippli, Draksha with Marica, Haridra, Smanga. Abhaya, Amalki, skin of porcupine, smoke of house, bone of camel. Pippli, Amalki, Musta, Molasses, Haritki.
UrdhvaVata	Bhadradaru, Haritki, Rock Salt, Kushta, Ghrita, Molasses

Hikka(Hiccough)	Pippli, Gairika, Bhargi, Hingu, Karkatki
Loss of Appetite	Pippli, Pipplimool, Musta, Tagra
Retention of Urine	Satavri, root of Darbha, Madhuka, Kshirmorta,Pasanbhedha, Usira, fruit of Kataka
Vataja Disorders	Leaves of Eranda with milk.

DISCUSSION

Although women often state a desire to avoid medications during pregnancy, almost all women will use over the counter drugs. Nearly 2/3 will use prescription and almost half will take herbal remedies. Majority of women uses such medications during the first trimester which is the most critical period in pregnancy. Interaction with prescribed medications can also haves unidentified effects in pregnancy or can cause some serious complications in fetus. The use of herbal medicines does not have strict regulations like contemporary medicines and rising trend in the use of traditional drugs can a matter of concern if unaware to its ADR. Pregnant women should also educate to increase their awareness regarding the effect of medications and the importance of taking guidance from their healthcare providers.Many times combination of medications rather than individual medicine are possibly associated with increased risk of birth defects. The babies safety from exposer of medications used by nursing mother can be estimated by the understanding the characteristics of the drug and timing of exposer. It is the main responsibility of physician to counsel patients with complete, accurate and current information on the risks and benefits of using medications during pregnancy. Caunselling women who have had exposure to drugs about risk of teratogens involves accurately identifying exposure to drugs about risk of teratogens involved accurately identifying exposure and qualifying the magnitude of exposure. This may be straightforward for prescribed drugs but it can be much more difficult with ethanol or other illicit substance or OTC drugs.

In Ayurved various safe medications for disorders during pregnancy are elaborated in very lucid manner these drugs can be taken into consideration. Some disorders where the medications are not explained, in such cases *dosha, dushya, vyadhibala* and *rugnabala* are taken into consideration for determination of proper medicine. While treatment for *Dushivisha* and *Garavisha* also can been used if such disorders. Neural tube defects (NTDs) are most common teratogenic effect contributing to infant mortality and serious disability like anencephaly, spina bifida, encephalocele etc.

which can be avoided by providing folic acid supplement during perinatal period. All women of 14 to 50 years of age who could become pregnant need to eat food that are high in folate and take supplement with 400 mcg (0.4 mg) folic acid every day.

CONCLUSION

As per the descriptions given byAcharyasin our ancient texts strongly suggests that they have got knowledge about the teratogens and what is the outcome of that. So they have also told about the precautions should be taken by pregnant women to avoid these untoward effects. In modern science they also described agents such as Physical, chemicals, environmental etc. that can causes teratogenic effects. The applications of Ayurvedic concept along with modern approach is very useful in preventive for such teratogenic effects in our society and get *Shreyasipraja*(good progeny) which take part in development and progress of country.

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