www.tufsteam.com
Innovations in STEAM: Research & Education
ISSN (print): 3105-7071; ISSN (online): 3105-708X
Volume 2; Issue 1; Article No. 24020104
https://doi.org/10.63793/ISRE/0014

REVIEW ARTICLE

A Review of the Teratogenic Effects of Drugs and Environmental Toxins

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METADATA

Paper history
Received: 20 August 2023
Revised: 19 November 2023
Accepted: 02 February 2024
Published online: 17 May 2024

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Keywords
Teratogenesis
Immunotoxicant
Fetus
Embryo
Maternal

Citation
Noor Ul Ain, Shafqat S, Fatima T, Noor M, Sajjad F, Nazim S, Nawaz Z, Ashfaq W, Haider L, Khan A, Arshad M (2024) A review of the teratogenic effects of drugs and environmental toxins. *Innovations in STEAM: Research & Education* 2: 24020104.
https://doi.org/10.63793/ISRE/0014

ABSTRACT

Background: Teratogenesis is the formation of an abnormal or deformed body. It is a process of inducing birth defects in fetus. Birth defects include brain injury, heart abnormalities, kidney defects or defects in spinal cord. It occurs if teratogenic agents (chemical agents, metal, pharmacological agents or environmental toxins) being exposed to fetus during an organogenesis period of 3–8 weeks. Presently the prevalence of teratogenic effect varies according to specific drug, genetic basis, population etc.
Objective: The purpose of this review is to understand the mechanism behind the teratogenic effects, risk factors and to control their exposure to pregnant women.
Methodology: The information for this article was collected from different sources including Elsevier, Springer, Taylor & Francis, Google Scholar, Web of Science, Scopus, HEC Digital Library and other online sources.
Results: Various drugs have been reported to cause teratogenicity to the fetus. These include thalidomide, isotrinitoin, phenytoin and valporic acid, alcohol etc., which adversely affect fetus organ development and tissue formation by impeding cell division, which is necessary for blastocyte formation and organ development. Moreover, environmental toxins including heavy metals (e.g., mercury, lead, and cadmium) act as carcinogen, immunotoxicant, cause malformations and even death in embryos and fetuses. The mechanism behind the teratogenic effects includes folate antagonism, endocrine disturbance, oxidative pressure, vascular disturbance and specific receptor and enzyme mediated teratogenesis. The factors that increase the risk for teratogenic effects include poor maternal nutrition, maternal age (>35) and maternal health conditions. It also includes discontinuation of medications related to acute or chronic conditions.
Conclusion: Preventive measures should be taken to avoid teratogenic effects as the period of the first trimester is most important for the organ development of fetus. Hence, it is necessary to avoid the exposure of teratogens. Taking herbal therapy, neuropathic therapy and acupuncture therapy play a great role in promoting good maternal health and prevent adverse teratogenic effects.

INTRODUCTION

Teratogenicity, also known as reproductive and developmental toxicity, has emerged as a vital component of toxicology overall. Each substance possesses a distinct toxicological profile and a specific mechanism of teratogenicity (Dron 2016; Melo *et al.* 2021). The investigation of teratogenicity is crucial for comprehending the potential dangers linked to various substances and agents (Valladares and Rasmussen 2022). This understanding is essential for averting birth defects and promoting the health and welfare of future generations (Ananya 2016).

While the use of prescription medications is prevalent during pregnancy, the teratogenic risks to humans remain unclear for over 90% of drug treatments that have been authorized in the USA in recent decades. A specific birth defect can originate from various mechanisms and multiple encounters, including those from medicines. A particular

pathogenic mechanism may lead to different results influenced by factors like the embryonic age at exposure, the length of time and amount of encounter, and inherited predisposition (Tona *et al.* 2022). Teratology has operated as a descriptive science centered on identifying birth defects via clinical or laboratory techniques (Lupo *et al.* 2024). Commonly used animal testing systems have demonstrated varying degrees of success in recognizing chemical teratogens.

With the rise of epigenetic research concerning developmental processes, it is now feasible to prevent certain birth and developmental abnormalities through dietary and behavioral modifications. Nonetheless, the prevention of birth defects stemming from genetic origins through gene editing has become a reality, provoking ethical dilemmas (Stump *et al.* 2012).

PROCESSES OF TERATOGENICITY

Biochemical investigations hold an essential role in the comprehensive strategy for exploring human birth defects. Nevertheless, well-integrated biochemical tests can enhance and question the outcomes from studies reliant on morphological and ultra structural methods (Gomes *et al.* 2021). The theoretical framework of this field remains limited to just a handful of 'rules of thumb' hypotheses. Additional research is necessary to comprehend the biochemical processes that drive teratogenicity. Radiation teratogenesis is an intricate phenomenon. Before reaching the blasto cyst phase, the embryo shows no sensitivity to the teratogenic and growth-inhibiting effects of radiation (Applegate *et al.* 2021). In the initial stages of organogenesis, the embryo becomes susceptible to the growth-inhibiting, teratogenic, and fatal consequences of irradiation. The influence of radiation on the developing embryo is contingent upon both the developmental stage and the radiation dose. There may be shared mechanisms between carcinogenesis and teratogenesis. The intricate mechanisms behind carcinogenesis and teratogenicity remain largely unclear. Nonetheless, some recognized or potential common mechanisms include mutations in genes or chromosomes, disruptions in gene expression, modified membrane characteristics, or changes in intracellular balance.

Teratogens are agents that could lead to physical or functional malformations in a human embryo or fetus following the encounter of the pregnant woman to the agent (Paredes-Páliz *et al.* 2024). Alcohol and cocaine serve as examples of such agents. The effect of the teratogen on the fetus or embryo varies based on factors such as exposure duration, quantity of teratogenic agent, and developmental stage (Mohammadi 2022; Mainprize *et al.* 2023). Vitamin A is an essential dietary nutrient. However, excessive intake of retinoids by expectant mothers can lead to teratogenic outcomes (Saurat and Sorg 2023). The incidence and nature of fetal malformations linked to maternal consumption of both natural and synthetic retinoids have been thoroughly documented. Major congenital malformations are a key contributor to infant illness and death and represent a significant societal and financial burden. Depleted uranium has been associated with teratogenicity, signifying the potential of a substance to induce birth defects. Epidemiological research has examined the possible health impacts of exposure to depleted uranium (Ran *et al.* 2020). Now the agent is recognized as a teratogen if its administration to the pregnant woman leads, either directly or indirectly, to systemic or practical abnormalities in the fertilized conceptus, and trigger abortion of the early embryo, late fetal mortality, congenital anomalies, or inside the uterus growth restriction (Friedmacher and Jesudason 2023).

MECHANISM OF TERATOGENICITY

Teratogenicity involves the stimulation of the transcription of αv and β3 integrin subunit genes by insulin like growth factor I (IGF-I) and fibroblast growth factor 2 (FGF-2) (Fig. 1). The resulting αv-β3 integrin dimer promotes formation of new blood vessels in the developing limb bud, facilitating the outgrowth of the sprout (Tsamantioti and Hashmi 2024). Isotretinoin is a highly effective treatment for acne that works by inducing apoptosis in sebocytes. However, it also has teratogenic effects, leading to birth defects due to its influence on neural crest cells. Furthermore, isotretinoin can cause depression, mucocutaneous side effects, loss of hair, inflammatory bowel disease, muscle pain, and damage to the liver(Draghici *et al.* 2021). The underlying mechanism for these adverse effects is apoptosis, which could be affected by genetic variants (Melnik, 2017). Anticonvulsant medications, utilized to treat epilepsy, also carry teratogenic hazards. Pregnant women affected by epilepsy are at an elevated risk of congenital malformations, miscarriages, and stillbirths (Draghici *et al.* 2021). A 30-year review of medical literature substantiates this heightened risk. Therefore, careful management and consultation with healthcare professionals are crucial for pregnant women with epilepsy.

TERATOGENIC DEFECTS DUE TO DRUGS AND HEAVY METALS

Teratogenic medicinal agents

Some of the possible and reported birth related defects due to medicinal agents are basically the defects relevant to brain injury along with, malformations in the spinal cord, congenital abnormalities, renal fault, GIT problems and all the problems associated with imperforate anus (Shernazarovna, 2024). Many medicinal agents are known to cause congenital defects or birth defects some of them are sodium valproate, alcohol, isotretinoin, aminopterin, cocaine, warfarin, thalidomide, tetracycline, coumarin, buprenorphine, etretinate and phenytoin (Abadie *et al.* 2023), as discussed below.

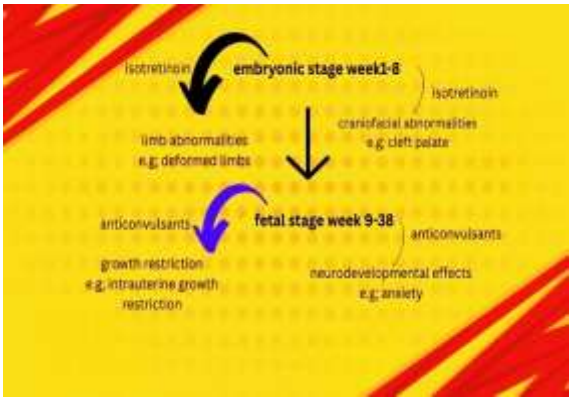

Fig. 1: Mechanism of teratogenicity

Drugs use in pregnancy at any time during pregnancy can affect the fetus and cause numerous diseases in fetus and embryo. If the pregnant women suffering from acute or chronic condition and take medication so discontinue the medication which is against the chronic condition so, it prevents the fetus from abnormalities. Does not use the over-the-counter drugs during pregnancy take multivitamins and folic acid during pregnancy because these prevent the adverse pregnancy outcome. For the pregnant women medication always chooses from pool of effective drugs so that prevent the congenital development disorders (El Shamy and Tamizian 2018). Avoid the use of Drugs like anti- epileptic, ACE inhibitors, Antibiotic, thalidomide, and NSAIDs cause the structural and functional defects in fetus. For the protection of fetus use effective strategies like patient education and use safer therapeutic alternatives (Sun *et al.* 2022). Provide the patient counselling about the medication which are harmful during pregnancy. Develop and implement the risk management program so effective outcome achieve (Griffin *et al.* 2018; Khadivzadeh *et al.* 2023).

Isotretinoin: The intake of isotretinoin by pregnant lady increases the risk of teratogenic malformations or deformities by 25% (Brzezinski *et al.* 2022). Buildup of CSF in brain abnormally a condition also known as hydrocephalus, microcephaly, a structural defect in head of ana infant, cerebellar hypoplasia, depressed nasal bridge, microtia or absence of outer ears, cleft palate, aortic arch defects, heart anomalies (ventricular septal defect, atrial septal defect, tetralogy of Fallot), and hypoplastic adrenal cortex included in the defects. Furthermore, there is an increase in unplanned abortions. Isotretinoin (analogue of retinoic acid) is a dermatologically active compound reported to cause malformations in fetus when mother is on the intake of it. In first trimester if the pregnancy its oral use is strictly prohibited (Altıntaş Aykan and Ergün 2020).

Etretinate: Etretinate and its active metabolite acitretin can cause teratogenicity. Parturiency should not be planned in the course of the treatment and even after 2 years of treatment termination (Jeong *et al.* 2022). The most important and functional knowledge is given by reports in females who were vulnerable to either retinoid before or during pregnancy (Menezes and Almeida 2024). This information shows an increased risk of spontaneous abortion or congenital mutation when the drug is taken during the first trimester of gestation(Jeong *et al.* 2022). After treatment has stopped, the risk is considered to be low since the number of problems seems not to surpass those noticed in a widespread inhabitant. Teratogenicity is the possible side effect of oral retinoid therapy and the risk with etretinate is particularly high because of its ability to store in fat and continues release after discontinuing the treatment embryonic malformation was observed in a pregnancy occurred almost a year after the last dose of the drug (Jeong *et al.* 2022). Moreover, Etretinate can result in skeletal, cardiovascular, and central nervous system malformations, just like its congener isotretinoin. Etretinate, in contrast to isotretinoin, tied to lipoproteins and remain longer in the bloodstream even for years after treatment (Sarkar and Meena 2023).

Thalidomide: The crucial phase was not more than 14 days after gestation, and the delicate period for the occurrence of human thalidomide birth defects was 23 to 28 days post conception(Sarkar and Meena, 2023). Throughout this time, before birth encounters give rise to about 20% of births to result in newborns with defects, the most usual of which were limb deformities ranging from tetra-amelia or phocomelia of the upper and lower limbs to triphalangeal thumb, seldomly with preaxial polydactyl of six or seven toes of each foot. In over 10,000 children, thalidomide caused severe birth defects between 1957 and 1962. Any tissue or organ of fetus could be affected by thalidomide. Due to the extensive mengle and circumstances that thalidomide exposure can result in, the damage is commonly referred to as thalidomide embryopathy or thalidomide syndrome (Vargesson 2019). Damage to limbs is one of the most ordinary features. phocomelia remains the most obvious limb defect produced by thalidomide. The legs can also reveal thalidomide-induced problems. Phocomelia or Amelia are seen, as well as shortening in the long bone. Nevertheless, the malformations of the lower limbs are seen infrequently as those of the upper limbs. Damage to the face is another key symbol of thalidomide embryopathy. At birth the existence of hemangioma, that is also known as a "storkmark". The facial asymmetry and facial palsy because of the feeble facial muscles and facial nerve damage is a hallmark of thalidomide teratogenicity (Yamanaka *et al.* 2021). Cases report that about 20% birth anamolies was caused by prenatal exposure to it. The frequent of which were limb deformities including phocomelia of the upper and lower limbs to triphalangeal thumb, sometimes accompanied by thumb duplication also known as preaxial polydactyly in which a baby has six or seven toes each foot (Anonymous 2018). Moreover it may cause anamolies of limbs, urinary tract, facial weak matches, esophageal and duodenal atresia, cardiac defects and a condition in which kidneys fail to develop (Vianna *et al.* 2017).

Ergotamine: Ergotamine is an alkaloid of ergot present naturally that has ability to contract smooth muscles. Females

who used ergotamine for the cure of migraine in the first trimester of their pregnancies gave birth to babies with neural tube defects (Bérard *et al.* 2021). Ergot toxicity which can result in acute vasospasm does not spare the fetus or mother so it should not be considered without risk. The correlation between low birth weight or premature birth & ergotamine medical care could be attached with ergotamine produced narrowing of vessels in the placenta of expecting women (Aukes *et al.* 2019; Bérard *et al.* 2021). Genitourinary malformations in relation to ergotamine usage were reported rarely but 20% cases of renal agenesia had been reported.

Trimethadioine: About 1/4th of pregnancies results in immediate abortion due to maternal utilization of Trimethadioine. Most of infants have deformities, developmental slow up, and prenatal and postnatal growth insufficiency (Andrews *et al.* 2019). These deformities include brachycephaly with mid facial hypoplasia, broad nasal bridge, V-shaped eyebrows with or without synophrys, arched or cleft palates, and misplaced ears. Tetralogy off a lot and septal defects are common cardiovascular problems. Other frequent conditions include kidney deformities, trachea esophageal abnormalities, hernias, and hypospadias. Mental retardation and mild to moderate speech difficulties has been observed I survive (Tarate *et al.* 2022). During early embryonic stage the administration of drug over the phase of first trimester causes early embryonic organogenesis and caused 80% embryo mortality. Apart from that the very frequent defects involve cleft palate, cardiac defects, urogenital deformities, and skeletal problems. Slow mental and physical growth was observed as well. However, anticonvulsant Trimethadioine is a highly potent inducer of ventricular septation defects and many other congenital defects so its use in pregnancy is highly discouraged (Kaleelullah and Garugula 2021).

Phenytoin: Phenytoin is an anticonvulsant medication that is utilized for curing epilepsy. If consumed by the mother in the first trimester, there are chances for a series of congenital defects known as the fetal hydantoin syndrome. The pattern of abnormalities consists of developmental detain or frank mental inadequacy, dysmorphic craniofacial traits, and hypoplasia of the distal phalanges (Tsamantioti and Hashmi 2024). The existence of vital phenytoin-associated birth defects in little ones relates with an incapability of lymphocytes to remove the drug. There appears to be inheritable vulnerability to phenytoin fetal defect. The chance of growth delays in phenytoin encountered children ranges from 1 percent to 11 percent. Moreover benzodiazepines could cause apnea, hypotonia, hypothermia, and neonatal abstinence syndrome with signs and symptoms of neuromuscular excitability (Ritchie *et al.* 2021). Additionally, if at all possible, it should be discontinued at least two weeks before conception (Cassina *et al.* 2012). The incidence of anomalies, primarily cleft palate, and decrease in maternal plasma folate levels on day 12 of pregnancy. Also it has the ability to bring about embryonic hypoxia mediated via bad effects on the heart of embryo (Marefat and Sadeghi 2020).

Environmental toxins and their effects

Heavy metals are naturally found elements that increased density and can be poisonous even in small amounts. These elements have elevated atomic weight and are at least five times denser than water. Examples include lead, arsenic, mercury, cadmium, silver, copper, iron, chromium and nickel (Cooper *et al.* 1984). These metals can be found in the surroundings naturally, or as a result of industrial countries with more industrial development. Metals such as lead, silver, cadmium and mercury, along with metalloids such as arsenic, are causative agents of reproductive toxicity. The metals released by industries can damage the soil, and because these metals accumulate through the food chain, they eventually pose a significant risk to human health. These metals are found in higher concentrations in plants and aquatic animals than what is considered safe by the World Health Organization (Ashraf *et al.* 2019). Environmental degradation also increases the risk of human exposure to heavy metals, leading to health issues like reproductive problems.

These metals affect female reproduction at every stage, from development to maturation and hormone regulation, and are linked to higher rates of infertility in women (Fig. 2). Long-term exposure may result in serious conditions such as menstrual issues, miscarriages, preterm births, and stillbirths (Agarwal *et al.* 2012). Heavy metals can alter neurotransmitter activity in the CNS and disrupt the normal release of gonadotropin-releasing hormone (GnRH) from the hypothalamus (Gerhard *et al.* 1998). High levels of these toxins in infants are linked to issues such as low birth weight, developmental and behavioral problems, as well as growth restrictions and delays during fetal development (Palmieri *et al.* 2019). One of the factors studied for decreased birth weight is exposure to heavy metals, including cadmium, mercury, lead, arsenic and zinc. These metals are particularly concerning for maternal reproductive health and fetal wellbeing because they can cross the placenta, leading to potential toxicity in the developing fetus (Sabra *et al.* 2017). Three most noxious teratogenicity causing heavy metals are described below.

Mercury (Hg): Hg contamination can happen through food, water, air, or skin contact. It may be the only thing that builds up in the food chain and can effortlessly change into more poisonous organic forms, like methyl mercury (MeHg), dimethyl mercury, and ethyl mercury. The effects of Hg exposure vary widely, depending on factors like the level and duration of exposure, as well as the age and health of the individual (Zulaikhah *et al.* 2020). Hg contamination in the environment is primarily caused by human activities, such as coal burning, mining, cement production, and the chemical industry. Once Hg is released into the environment,

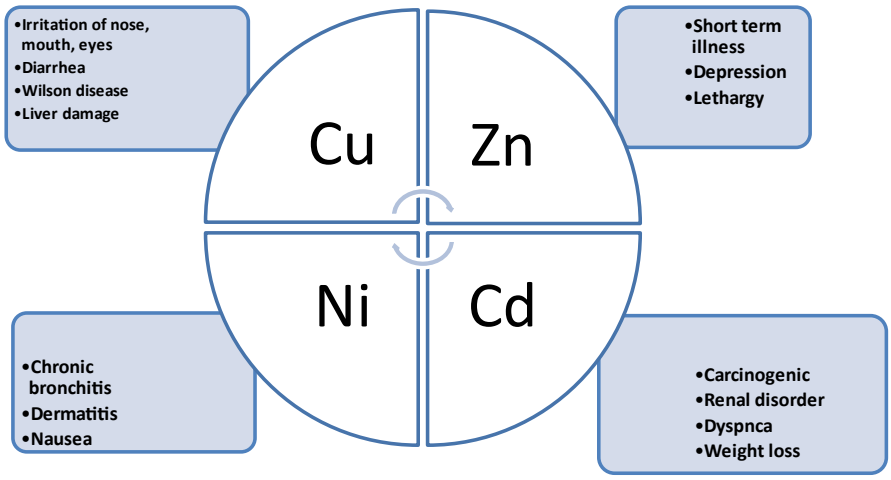

Fig. 2: Heavy metals causing potential toxicity in fetus

groundwater, bacteria and other microorganisms often play a key role in transforming it into MeHg, a more toxic form of Hg. Organic types of Hg are more harmful than their inorganic counterparts (Bjørklund *et al.* 2019). MeHg is fat-soluble, which means it can easily cross the cell membranes. It can pass through the placenta at a rate 10 times higher than other Hg compounds (Dutta 2015). Organic Hg also easily passes into breast milk so the infants who are breastfed are more vulnerable to Hg toxicity. Infants exposed to methylmercury can experience damage to the nervous and immune systems, DNA repair disruptions, destruction of mitochondrial membranes and neurodegenerative diseases.

Cadmium (Cd): It is heavy metal present naturally in our environment. It enters into the human body at workplaces, through nutritional meals, or utilizing contaminated water. It is capable to disrupt body hormonal balance so it disrupts endocrine level (Ali *et al.* 2023). Moreover it alters the natural steroid synthesis process, cause miscarriage, interferes the menstrual cycle and cause birth defects in neonates (Ali *et al.* 2023). It is also examined that Cd interferes with methylation of DNA that affects both mother and fetus (Moynihan *et al.* 2017). It taking notice of action ways of cd includes the mechanism of oxidative stress that induces cell death and cause irreversible harm to mitochondria and endoplasmic reticulum organelles of cell (Jacobo-Estrada *et al.* 2017). Women are more likely to affect by cd instead of men. Cd-induced birth defects include clubfoot, spinal cord defects, lung abnormalities, fluid accumulation in brain.

Lead (Pb): In developed and developing countries, Pb toxicity is becoming a major health problem. It cause immune imbalance, infertility, vitamin D deficiency (Mitra *et al.* 2017). Exposure to this metal causes developmental problems including premature birth and pregnancy loss. When Pb amount increases up to a highly toxic level, it causes abortion. It effects DNA transcription cause damage to cell structure and cell membrane (Collin *et al.* 2022). Along with calcium greater amount of Pb passes from maternal to fetus through placenta and after birth it transfer to baby through breast milk (Yurdakök 2015). In fetus calcium transfer from mother is maintained but 1,25 dihydroxy vitamin D. In last trimester which is the period of development of neuronal structures, brain growth, shoulders heel and synapse formation so calcium transfer increase and as Pb follows calcium to pass to fetus through placenta so Pb quantity increase and cause more birth defects (Rísova 2019).

PREVENTION OF TERATOGENESIS

Avoidance from environmental exposure

Perfluro alkylating Agents are present in industrial and consumer products, which can cause the effect on the immune system and neural defect and fetus growth during pregnancy. Avoidance from the Cd exposure in the course of pregnancy is important because it can result in premature birth and low birth weight. There is a need to minimize exposure to pesticides or organophosphate during pregnancy because it can cause the effect on neural behavior development in fetus. Likewise, exposure to air pollutants during pregnancy can cause developmental disorder in fetus such as impaired lung development, altered immune development and low birth weight (Rani and Dhok 2023). Alcohol consumption during pregnancy leads to fetal suffering from various developmental disorders (Ali *et al.* 2021). Pb exposure during pregnancy be avoided because it causes the abortions and offspring suffering from neuro behavioral development, and reduced fetal growth (Santana *et al.* 2023).

Alternative therapy to prevent teratogenesis

Nutritional therapy: Supplements like folic acid or vitamin B9 play an important role during pregnancy, as they are involved in nucleic acid synthesis and it prevents neural tube defects. Chorine is very essential nutrient it protects from

neutral tube defects during pregnancy (Best *et al.* 2022). Omega-3-fatty acid is involved in fetal brain and retina development. Antioxidants such as vitamin C, E, selenium, zinc and manganese in pregnancy prevent the oxidative stress and reduce miscarriage and preeclampsia (Banović Fuentes *et al.* 2024).

Herbal and traditional therapy: Herbal and traditional therapy play an important role during pregnancy because it reduces nausea, vomiting other GIT (gastrointestinal tract) related problems and infections. Ginger is used as anti-inflammatory, antioxidant and antihypertensive and it prevent nausea and vomiting during pregnancy (Sarecka-Hujar and Szulc-Musioł 2022). Turmeric reduces oxidative stress and inflammation.

Naturopathic therapy: Cholelithiasis of pregnancy is treated with activated charcoal used for detoxification (Smith 2022). Probiotic fermented foods has positive effect on fetal heath development (Maunder *et al.* 2024).

Acupuncture therapy: It plays a significant role during pregnancy because it promotes the normal birth and reduce stress (Lin *et al.* 2022, da Costa *et al.* 2022).

CONCLUSION

Selection of appropriate medications and reduction of environmental toxins represent vital pregnancy concerns because teratogenic risks are high. Medical drug avoidance of isotretinoin as well as thalidomide and warfarin are essential while prevention of developmental disorders in the fetus requires managing environmental contaminants such as Pb, Hg and pesticides. The combination of patient education together with risk control measures alongside folic acid and chorine and antioxidant supplementation reduces the potential negative pregnancy outcomes. The combination of herbal medicine and acupuncture therapy provides support to pregnant patients without creating significant birth defects. Healthcare professionals must employ combined medical and environmental and lifestyle strategies to protect fetal wellbeing. The advancement of maternal care research and policy adjustments will lead to better maternal wellness and decreased teratogenic threats.

AUTHOR CONTRIBUTIONS

Noor Ul Ain: Topic decision in publication, journal approach, publication process, data defining, writing and data collection. Rest of the authors: Data collection, writing of article

CONFLICTS OF INTEREST

The authors affirm that they possess no conflicts of interest.

DATA AVAILABILITY

The data will be made available on a fair request to the corresponding author.

ETHICS APPROVAL

Not applicable

FUNDING SOURCE

This project is not funded by any agency.

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