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Iffat Ara Zabeen
Department of Pharmacy, Faculty of Life Science, University of Development Alternative, Dhaka, Bangladesh

Md. Mehdi Hasan
1. Department of Pharmacy, Faculty of Life Science, University of Development Alternative, Dhaka, Bangladesh
2. Department of Pharmacy, Faculty of Health Science, Northern University Bangladesh, Dhaka, Bangladesh

Zubaida Khatun
Department of Pharmacy, Faculty of Life Science, University of Development Alternative, Dhaka, Bangladesh

Corresponding Author:
Iffat Ara Zabeen
Department of Pharmacy, Faculty of Life Science, University of Development Alternative, Dhaka, Bangladesh

Comparative study on strategies for the prevention, diagnosis and treatment of birth defects

Iffat Ara Zabeen, Md. Mehdi Hasan and Zubaida Khatun

Abstract
As child mortality rates overall are decreasing, non-communicable conditions, such as genetic disorders, constitute an increasing proportion of child mortality, morbidity and disability. To date, policy and public health programmes have focused on common genetic disorders. Rare single gene disorders are an important source of morbidity and premature mortality for affected families. About 2-3% of all live births suffer from congenital abnormality globally and 70% of those are preventable through community genetics services. The estimated prevalence of congenital abnormalities is about 2-4% in live births along with still born and aborted fetus. As child mortality rates overall are decreasing, non-communicable conditions, such as genetic disorders, constitute an increasing proportion of child mortality, morbidity and disability. To date, policy and public health programmers have focused on common genetic disorders. Rare single gene disorders are an important source of morbidity and premature mortality for affected families. This review will provide a context for the general evaluation of a neonate with congenital anomalies, including adaptation of the most precise terminology, definition of major and minor anomalies, and the determination of whether the anomalies are the result of a sequence, deformation, disruption, or malformation. Practical tools, including a concise family history, nutritional implication, pregnancy history, and the effects of assisted reproductive technologies are also presented.

Keywords: Prevention, diagnosis, and treatment of birth defects

Introduction
The two initial weeks after fertilization, in which the zygote is undergoing mitotic cell division is called the 'all-or-nothing' phase; in case a contact with a teratogenic agent occurs, it can result either in spontaneous abortion or in a normal embryo-fetal development. If teratogenic exposure occurs between the 3rd and 8th week of gestation, a period in which most of the morphological structures develop, it can lead to considerable phenotypical changes in the embryo, such as alterations in the central nervous system, limbs and face. From the 9th week of gestation some organs are still developing, like external genitalia and brain, and exposure to teratogens can culminate in functional abnormalities. However most morphological characteristics are preserved from this phase onward.

A Congenital malformation is a gross structural deformity present at birth. Its incidence is about 2.5% in all the infants born. However, only half of these deformities are apparent at the time of delivery, most of the remaining come to light during the first postnatal year. The term congenital deformity is reserved for a minor congenital disorder such as a deformed finger or ear-lobe. Individuals of a species including human, exhibiting minor deviation from each other are considered normal. Individuals that show gross deviation from the normal due to congenital malformations are known as monsters or terata**.**

Overall child mortality rates have shown large decreases over the past decades, in particular from reductions in deaths from infections, diarrhoea and vaccine-preventable diseases. Consequently, child mortality levels are now very low in many settings and policy attention is shifting to focus on non-communicable conditions, which now make up a larger relative proportion of all under-five deaths. In addition, in the Sustainable Development Goal era, strategies are increasingly seeking to move beyond survival to consider morbidity and disability outcomes, as highlighted in the Global Strategy for Women's, Children's and Adolescent's Health (2016–2030) themes-Survive, Thrive, Transform. In settings with very low levels of communicable disease mortality, genetically determined disorders make up an important proportion of both stillbirths and child mortality, and ongoing disability. Genetically determined disorders can be divided into two broad groups: 'single gene disorders' caused by gene variants with strong effect and 'genetic risk factors'-gene variants with weaker effect

causing disease only when combined with other genetic and/or environmental factors.

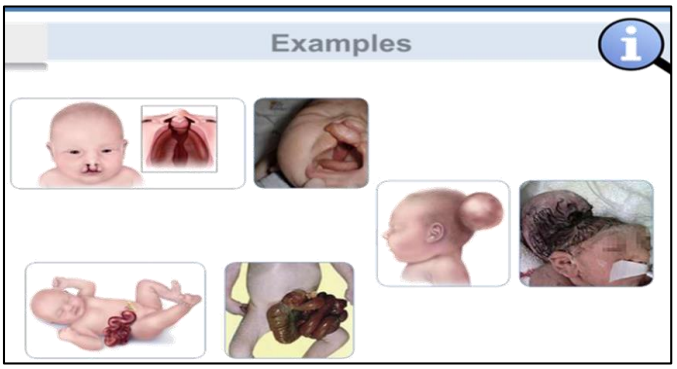

Fig 1: Abnormal genotype or abnormal environmental conditions

Teratogenesis

Abnormal development of a terata is called Teratogenesis and the science of development or formation of terata is called teratology. The development of a normal individual requires both a normal genotype and favorable environment, therefore, teratogenesis can be due to abnormal genotype or abnormal environmental conditions.

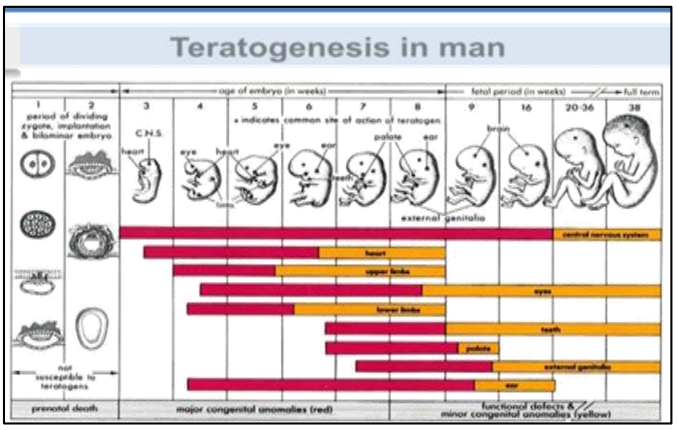

Fig 2: Teratogenesis in man

Teratology

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% [1]. 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 [2]. The factors that induce congenital malformations are termed the "teratogenic factors"; they include infectious, physical, chemical, hormonal, and maternal health factors.

Teratogenic agents

Infectious agent

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 [3].

Chemical agent

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 [6]. 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.

Physical agent

Radiation is teratogenic and its effect is cumulative. The International Commission of Radiology recommends pregnancy 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 [7]. 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 [8]. 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 [8].

Fig 3: Fetal Alcohol Syndrome

Maternal nicotine consumption isteratogenic 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 [54].

Thalidomide-induced teratogenesis

History and thalidomide embryopathy

Thalidomide was released in the late 1950's as a nonaddic-tive, nonbarbiturate sedative by the German pharmaceutical company, Chemie-Grunenthal. Thalidomide was very effective

and quickly discovered to also be an effective anti-emetic and used to treat morning sickness in pregnant women. Thalidomide was marketed and distributed in 46 countries around the world using different names. For example, the drug was known as Distaval in the UK and Australia, but was called Softenon in Europe and Contergan in. Thalidomide became one of the world's largest selling drugs, and was marketed heavily and advertised as completely safe right up until it was eventually banned in Novem-ber, 1961. Indeed, sample packets of the drug were given out to physicians to distribute freely to patients suffering from morning sickness. Precisely how many women were given the drug will never be known.

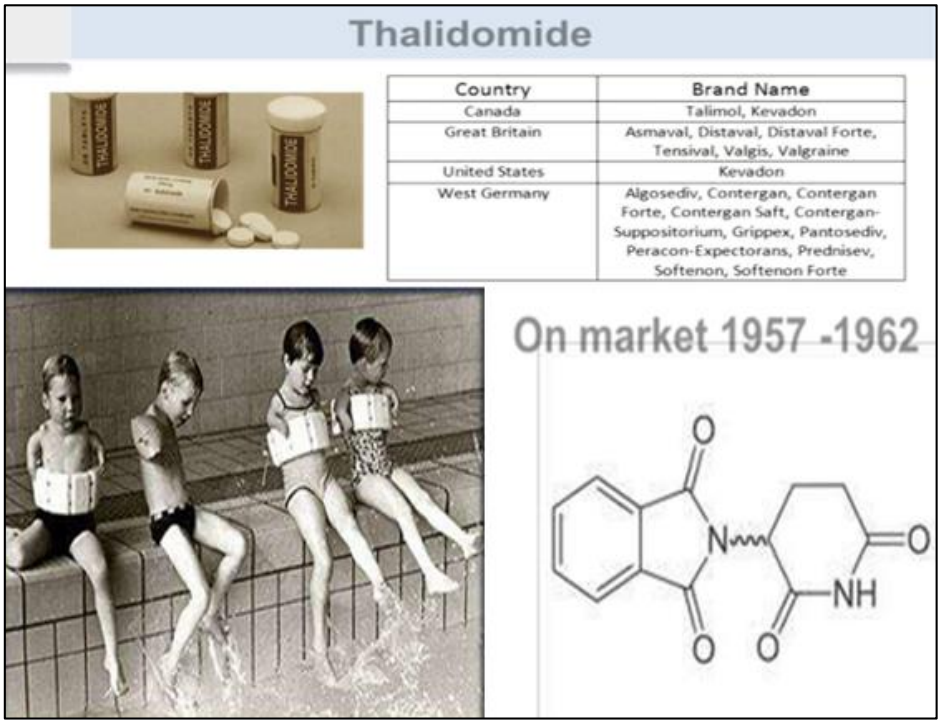

Fig 4: Thalidomide

Soon after thalidomide's release, reports surfaced of patients developing peripheral neuropathy after taking the drug. Reports of occurrences of severe birth defects affect-ing multiple body systems were also coming to light, that initially were not linked to, or were denied to be due to thalidomide. It was not until 1961 that thalidomide was confirmed by two independent clinicians, Lenz in Germany and McBride in Australia, to be the cause of the largest man-made medical disaster in history with huge numbers (over 10,000) of severe birth defects in children. In addition, there were reports of increased miscarriage rates during this period.

Thalidomide was subsequently withdrawn from the UK in Nov 1961 [9]and by 1962 from most of the world. As a result, the incidence and occurrence of these severe birth defects was then not seen Whether this disaster could have been prevented remains unclear.

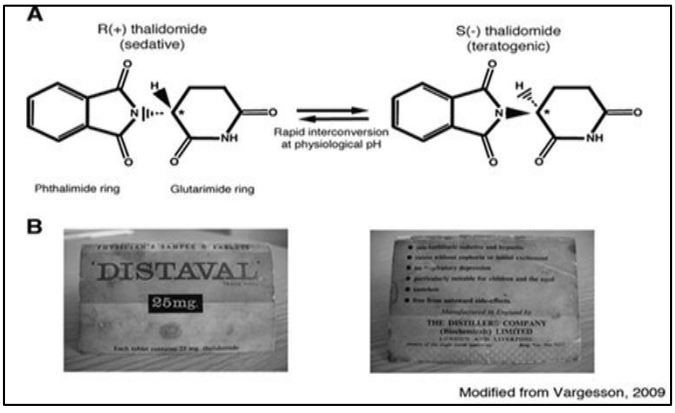

Fig 5: Structure of thalidomide enantiomers and packaging.

A: Thalidomide is a stereo-isomer and can exist in two enantiomeric states, depending on the state of the chiral carbon (see asterisk) allowing each form to have slightly different structural moieties. Both enantiomers, R and S, can rapidly interconvert (race-mize) in body fluids and tissues [10] and form equal concentrations of each form. B: Thalidomide was sold/distributed as a racemic mix of both enantiomers and called "Distaval" in the UK. These images are from an actual packet of "Distaval," which was a Physician's Sample and given to women in early pregnancy.

Thalidomide-induced damage can phenocopy some other human conditions

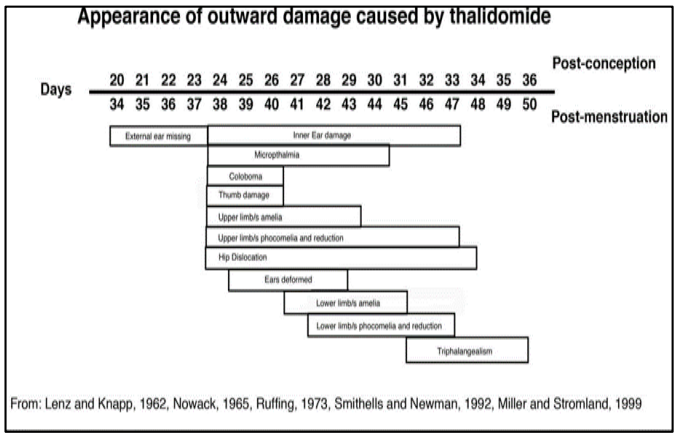

Fig 6: Time sensitive window of thalidomide embryopathy or the "critical period." Chart indicating when the major outward appearing damage occurred in the embryo following thalidomide exposure.

Thalidomide is antiangiogenic

Thalidomide was demonstrated in a landmark study to inhibit angiogenic vascularization of rodent corneas induced by fibroblast growth factor (GF) protein. This discovery led to the suggestion that tha-lidomide might cause its teratogenic damage by targeting embryonic blood vessels.

Angiogenesis is Essential for Embryogenesis

Blood vessels are essential for normal embryonic develop-ment. Blood vessels supply oxygen and nutrients to grow-ing tissues and remove unwanted waste products. During embryogenesis, vessels form first by vasculogenesis and are then modified into the complex vascular tree required for embryonic and fetal growth and throughout adult life by angiogenesis. Angiogenesis [11] is where the primitive vessels formed by vasculogenesis are elabo-rated upon where endothelial cells in the existing vessels proliferate and migrate to avascular areas in response to signals, including hypoxia or vascular endothelial growth factor. Once a new vessel tube has been made, the vascular tube recruits vascular smooth muscle cells, which stabilize the vessel. The smooth muscle coating is lost to allow endothelial cells to proliferate and migrate into new regions if signaled to do so.

Angiogenesis is essential for embryogenesis

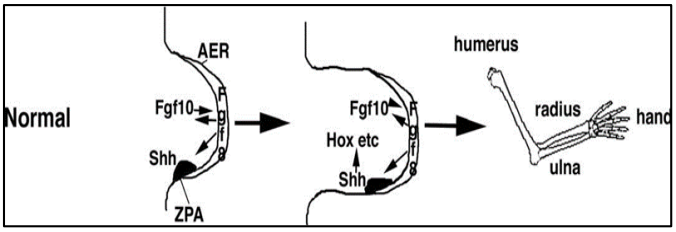

Fig 7: Embryonic limb development.

In humans the upper limbs form around a day earlier (day 26) than the lower limbs (day 27). The limb bud consists of two key signaling centers. The apical ectodermal ridge (AER), a thickened epithelium lining the distal tip of the bud and separating the dorsal from ventral surface; and the zone of polarizing activity (ZPA) in the posterior-distal mesenhcyme. The AER expresses which signals to the mesenchyme to induce Fgf10 and to the ZPA to induce and maintain Shh, which itself feeds back to maintain [12-15]. This feedback loop maintains cell proliferation and limb outgrowth and induces other genes, for example the Hox genes, which establish the pattern of the limb elements, humerus, radius, ulna, and handplate, as well as the soft tissues. The limbs grow out from specific regions of the flank of the embryo and as the limb grows out the limb is patterned proximally to distal, that is, humerus/femur are laid down before the radius, ulna/fibular, tibia, and then the handplate/footplate.

vessels are rapidly changing throughout embryogenesis and organogenesis to accommodate the changes and growth of the embryo.

Blood vessels are essential for normal embryonic devel-opment, and vessel loss or disruption can unsurprisingly result in death or birth defect.

Angiogenesis is targated by thalidomide in embryotic Development and in Adults

Thalidomide has multiple actions in the adult body and causes a variety and range of damage in the embryo. To determine how and which of its activities actually cause teratogenesis, stable, structural analogs of thalidomide were screened to determine their function, confirm which aspect of thalidomide action, antiangiogenesis or antiin-flammation, results in teratogenesis, and study the result-ing damage to gain insights into how the drug causes birth defect.

Why are some vessels targated while others are apparently unharmed

Blood vessels undergoing angiogenesis lose their vascular smooth muscle coats to allow endothelial cells to proliferate and migrate to form new tubes. Vessels with smooth muscle coats are quiescent and not undergoing angiogenesis. Using *in-vitro* rat and mouse aortic ring culture assays, CPS49 was dem-onstrated to destroy vessels without smooth muscle, but blood vessels possessing smooth muscle coats were pro-tected. This indicates that newly formed and forming blood vessels without smooth muscle coats could be susceptible to thalidomide. In the chicken embryo at the time the drugs are applied to the embryo,

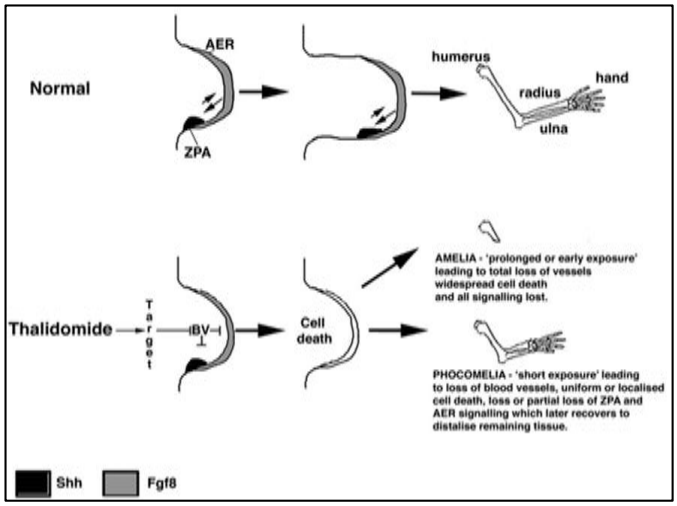

Fig 8: How does thalidomide induce Phocomelia?

Molecular targets of thalidomide

Much is known about thalidomide's mechanism of action underlying its anti-inflammatory and anti-myeloma activ-ities in human adults, than its teratogenic activities. Thali-domide inhibits TNF-a expression rapidly, vital for the inflammatory response. However, new targets have been identified and linked to thalidomide teratogenesis, though how these targets cause the embryonic damage still remains unclear.

Tubulin: An analog of thalidomide, 5HPP-33, can bind tubulin, which was demonstrated through crystal structure binding assays. Tubulin is part of the cyto-skeleton, and,is required in cell proliferation, which is essential for angiogenesis and formation of new vessels in the embryo. This study demonstrated that tubulin is bound by the 5HPP-33 thalidomide analog and cytos-keletal dynamics are altered preventing cell division. In the time-sensitive window many organs/tissues are under-going growth and maturation and could be affected in this manner, either directly or through loss of vessels, resulting in hypoxia and cell death. This work supports that of other studies which showed disruption of actin cytoskeleton [16].

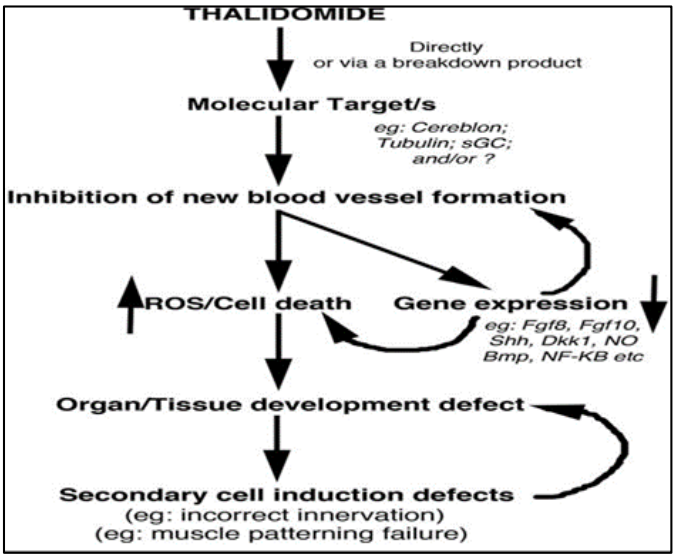

Fig 9: Framework of thalidomide induced embryonic damage.

This frame-work incorporates the majority of the previously proposed models/hypotheses to attempt to provide an explanation for thalidomide embryopathy. Thalido-mide and/or a breakdown product after binding a molecular target acts nega-tively on smooth muscle negative blood vessels, likely affecting the actin cytoskeleton of the endothelial cells, and preventing their proliferation and migration into avascular regions, causing oxidative stress, cell death, and gene expression loss, resulting in tissue damage. In rapidly developing tissues and organs, such as the limbs and internal organs, this would be devastating, causing tissue loss or tissue function loss, preventing growth. The damaged or missing tissues would then also fail to properly recruit and pattern proper chrondrogenesis, nerve innervation, muscle patterning, etc., exacerbating the condition and damage.

Biomolecular Mechanisms in Teratogenesis

The most common mechanisms of action of terato-gens are hyperacetylation, cholesterol imbalance, alteration of folate metabolism [17-20] and folate antagonism, retinoic acid imbalance, endocrine disruption, vascular disruption and oxidative stress.

Conceptus development stage

Organisms present distinct sensitivity to external agents according to their gestational age. A conceptus is a fertilized egg cell until the 3rd week of gestation. The period from the 3rd to the 8th week it is called embryonic phase, and from the 9th week onward the fetal phase.

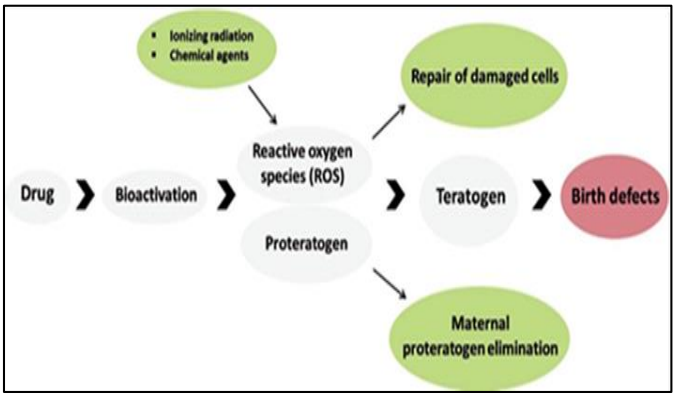

Fig 10.1: - Teratogenesis pathways due to oxidative stress

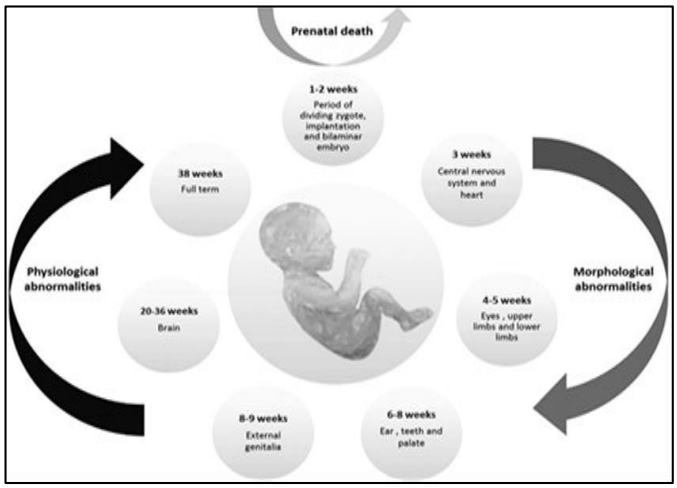

Fig 10.2: Critical stages of human embryological development

The two initial weeks after fertilization, in which the zygote is undergoing mitotic cell division is called the 'all-or-nothing' phase; in case a contact with a teratogenic agent occurs, it can result either in spontaneous abortion or in a normal embryo-fetal development. If teratogenic expo-sure occurs between the 3rd and 8th week of gestation, a pe-riod in which most of the morphological structures develop, it can lead to considerable phenotypical changes in the em-bryo, such as alterations in the central nervous system, limbs and face. From the 9th week of gestation some organs are still developing, like external genitalia and brain, and exposure to teratogens can culminate in functional abnor-malities. However most morphological characteristics are preserved from this phase onward.

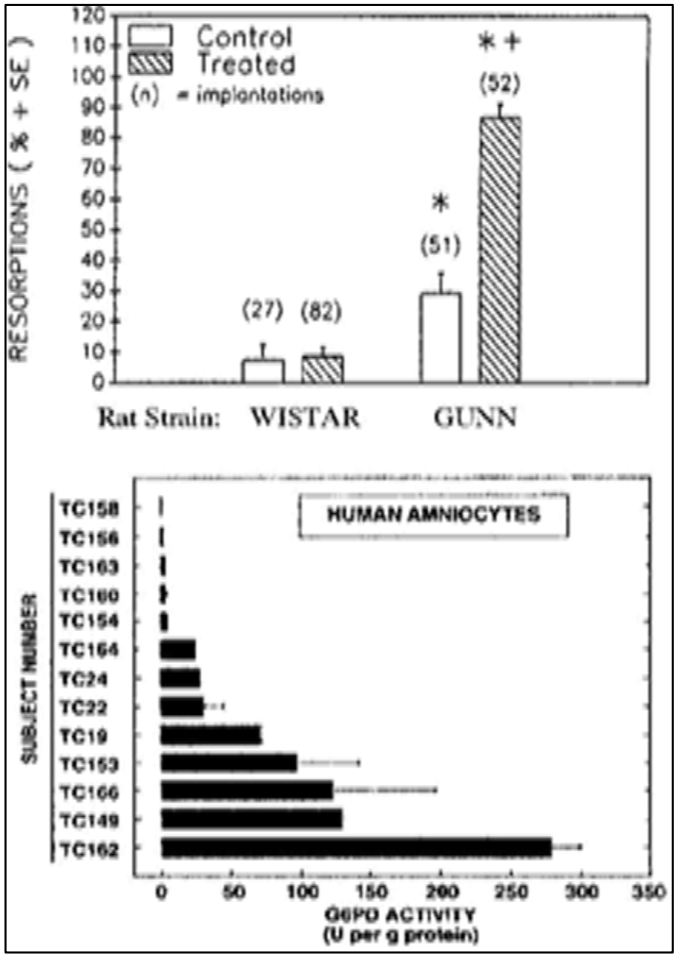

Fig 11: Potential maternal and fetal determinants of risk

Upper panel: effect of a genetic deficiency in maternal glucuronidation on benzo[a]pyr-ene-initiated in utero resorptions (fetal death). Pregnant mutant Gunn rats with a hereditary deficiency in the UDP-glucuronosyltransferase (UGT) 1 family, or the parent Wistar strain with normal UGT activity, were treated with benzo[a]pyrene (25 mg/kg ip) or its corn oil vehicle (control) on gestational day (GD) 10. Dams were killed on GD 20 for examination of the uterus and fetuses. Implantations include resorptions and fetuses delivered alive. Asterisks indicate a difference from Wistar rats with the same treatment, and the plus symbol indicates a difference from the Gunn control group ($P < 0.05$). Lower panel: Interindividual variability in the activity of glucose-6-phosphate dehydrogenase (G6PD) in amniocytes obtained from human subjects. Fetal amniocytes were obtained from term amniotic membranes of volunteer mothers who had (n = 8) or had not (n = 5) taken an anticonvulsant drug throughout pregnancy. Of those women taking anticonvulsants, 4 took phenytoin, 2 took phenobarbital, 1 took carbamazepine and 1 took phenytoin plus primidone. No correlation was apparent between anticonvulsant exposure and G6PD activity. Cells were cultured to confluency, aliquotted and kept frozen until assayed for G6PD activity. For each subject, 4 amniocyte aliquots were homogenized in PBS buffer (pH 7.4), sonicated for 5 min to ensure membrane lysis and analyzed [21] as described elsewhere. All results were standardized with respect to total protein content and reported in International Units (U) per gram (g) of protein (U/g). Values represent the mean T SD.

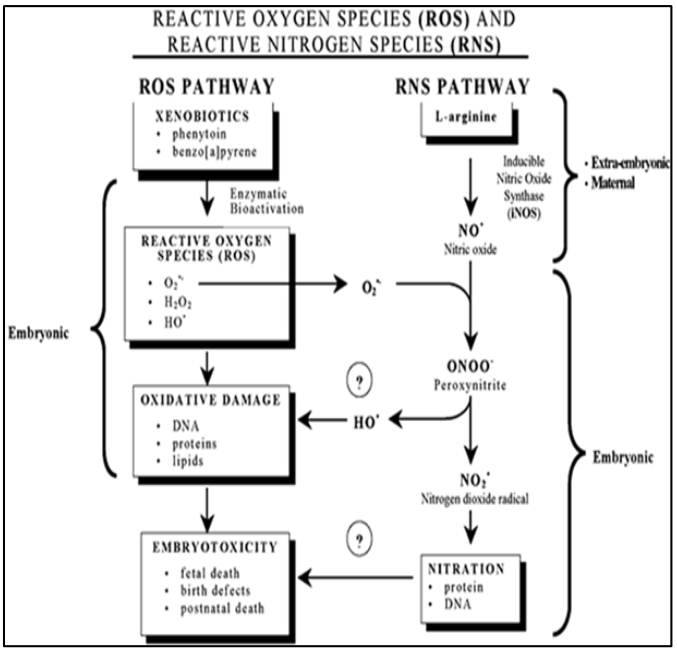

Fig 12: Postulated interactions between the pathways for formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS).

Among the nitric oxide synthases (NOSs), inducible nitric oxide synthase (iNOS) appears to be expressed during organogenesis only in extra-embryonic (ectoplacental cone) and maternal tissues, producing relatively stable nitric oxide that diffuses into the embryo where it reacts with embryonically generated superoxide anion to produce highly reactive peroxynitrite (see text). The embryopathic roles of the neuronal and endothelial forms of NOS have yet to be shown. Among other reactions, peroxynitrite can initiate oxidative damage to cellular macromolecules, oxidize soluble (e.g. GSH) and protein thiols, cause the nitration of aromatic amino acids (tyrosine, tryptophan, phenylalanine) in proteins and similarly cause the nitration and in some cases deamination of DNA bases (e.g. guanine, adenine), all of which could have embryopathic [22] consequences.

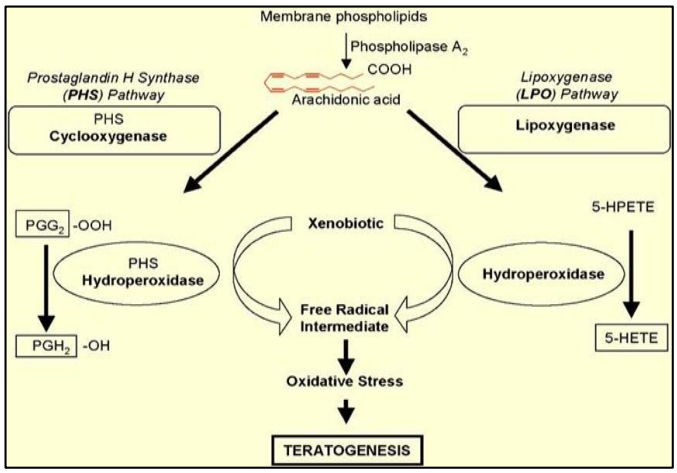

Fig 13: Xenobiotic bioactivation by prostaglandin H synthases (PHSs) and lipoxygenases (LPOs).

List of Teratogenic Drugs Used in Dermatology

1. Acitretin (Soriatane®)
2. Finasteride (Propecia®) *
3. Fluorouracil (Fluoroplex®, Efudex®)
4. Griseofulvin (Grifulvin® V, Fulvicin®, Gris-Peg®, Grisactin®)
5. Goserelin (Zoladex®)
6. Isotretinoin (Accutane)
7. Methotrexate †
8. Podophyllin/podophyllum (Podocon®-25)
9. Stanozolol (Winstrol®)
10. Tazarotene (Tazorac®)
11. Thalidomide (Thalomid®) †

Pregnancy Labeling for Prescription Drugs: Historical Perspective

September 12, 2007 marks the tenth anniversary of a public hearing that was hoped to be the death knell of the pregnancy labeling categories for pharmaceuticals, the A, B, C, D, X system of designations that was put in place by the US Food and Drug Administration (FDA) in 1979 (US FDA, 1979). The replacement of the pregnancy labeling categories had been sought by the Public Affairs Committee of the Teratology Society, and the public hearing that was believed to herald the impending de-mise of the system in 1997 was seen as an important public health advance. On this tenth anniversary, the sys-tem remains in place, although some progress has been made in replacing [23] it. We examine here the history of and rationale behind the effort to change the pregnancy label and the current status of proposed new labeling, and we offer recommendations for the future.

The first public affairs committee position paper

Teratology Society members who counseled patients on drug use during pregnancy did not find the categories to be helpful. In fact, it was the opinion of many clini-cians that the inflexible use of prescribed language in pregnancy categories created patient and physician anxi-ety, which was compounded by the assumption that the categories represented a gradation of risk

[24]. The lack of in-formation about the nature, severity, timing, or treatabil-ity of the putative fetal damage that resulted in a Cate-gory D or X classification was also viewed as a shortcom-ing of the pregnancy categories [25-29].

Table 1: Drugs/Chemical

Agent/Drug/Chemical	Risk	Fetal effects	Fetal risks	Maternal risks
Prescribed or street drugs				
Ethanol	D/X	FAES:IUGR, MR, microcephaly,	40% risk of FAES	–
		characteristic facies, CHD, joint,	6 drinks/day	
		skeletal, dermal		
Cocaine	C/X	IUGR, cerebral infarction, bowel	Fetal death	Abruption placenta
		atresia, heart, limb, facial, GU tract,		
		vascular disruption		
Toluene	X	Toluene embryopathy similar to FAS	Maternal inhalation 10–100	–
			times occupational exposure	

Table 2: Characterization 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
Recognizable syndrome
Other distinctive features
Magnitude of risk
Absolute
Relative
Prenatal diagnosis
Detailed ultrasound examination
Amniocentesis or other invasive method
Availability, Reliability
Utilty

Table 3: Characterization of teratogenic exposures*

Agent
Nature of the chemical, physical or infectious agent Inherent developmental toxicity
Capacity to produce other kinds of toxicity in the mother Dosage to embryo or fetus
Single, repeated, or chronic exposure Duration of exposure
Maternal dose
Maternal route of exposure Maternal absorption
Maternal metabolism and clearance Placental transfer
Period of pregnancy
Between conception and onset of embryogenesis Embryogenesis
Fetal period Other factors
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

Primary prevention of congenital anomalies

Purpose of the recommendations

Most congenital anomalies are rare and form an important group of Rare Diseases, for which EU Member States are developing National Plans. Primary prevention of congenital anomalies was identified as an important action in the field of Rare Diseases in the Communication from the Commission to the European Parliament, the Council, the European economic and social committee and the committee of the regions of 11th November 2008. However, it has not been included in the Council Recommendation on an action in the field of rare diseases of 8th June 2009. This document aims at providing an outline of evidence-based policy actions for primary prevention of congenital anomalies. It does not seek to recommend specific policy options, rather to indicate the areas that Member States could target in their strategies for Primary Prevention of congenital anomalies. EUROPLAN [1] will support and facilitate Member States to incorporate the recommendations specified here in their National Plans, and will facilitate exchange of experience among Member States, in collaboration with EUROCAT [2].

The scope of policy actions needed for primary prevention of congenital anomalies

In the field of medicinal drugs

- to advise women taking
- medication to seek medical advice before trying to get pregnant [4];
- to ensure that guidelines are, or are going to be, made available for physicians regarding risk-benefit balance for use of medications in pregnancy, particularly those medications used for treating chronic diseases [5];
- to provide a teratogen information service where specialized advice can be sought by women and professionals [6];
- to conduct postmarketing pharmacovigilance to detect any risk of congenital anomalies associated with use of medications, with the support of population-based congenital anomaly registries [7].

In the field of food/nutrition and lifestyle

- to improve folate status through periconceptional supplementation with folic acid, promotion of the consumption of foods rich in natural folates, and the appropriate use of fortified foods [8].
- to prevent overweight/obesity and underweight [9, 11];
- to promote effective information on diet and nutrition in women at childbearing age, minimizing the risks of deficiency and/or overdosing of vitamins and essential trace elements(12);further to the implementation of EU food safety strategies, to prevent food contamination by recognized developmental toxicants [13];
- to reduce active and passive smoking [14];
- to promote alcohol avoidance in women who are pregnant or wishing to get pregnant [15, 18].
- to pay special attention to diet and lifestyles in communities with low socio-economic status or of recent immigrants.

In the field of health services

- to make available preconceptional care including genetic testing and counselling for families at risk [19];

- to ensure that women with diabetes, epilepsy and other chronic diseases receive preconceptional care in order to minimize the risk of congenital anomalies [20];
- to ensure evidence based vaccination policies to ensure women are protected against infectious diseases associated with congenital anomalies and avoid contraindicated vaccinations during pregnancy [21];
- to include in school educational programs the awareness that congenital anomalies may be caused very early in pregnancy, often before the pregnancy is confirmed, and hence healthy practices should start preconceptionally;
- to include consideration of specific pregnancy-related actions in public health action plans on all the major health determinants.

In the field of environmental pollution including the workplace

- Further to the implementation of EU policies on high-concern chemicals, to ensure both regulatory actions and risk.
- communication towards citizens in order to minimize exposure to pollutants identified as teratogens [22];
- to ensure a suitable surveillance system where environmental risks can be identified through the integration of congenital anomaly registers with developments in biomonitoring [23];
- to minimize exposure of pregnant workers in their workplace to risk factors for congenital anomalies (chemical, physical and biological) [24].

Types of primary preventive actions and their effectiveness

A number of types of primary preventive action can be identified:

1. Advice to future parents by health professionals during individual preconceptional and early pregnancy consultations, tailored for high and "low" (average population) risk couples.
2. Health education campaigns targeted to potential future parents.
3. EU-based and/or national regulatory actions which affect risk factors at source such as medicines, chemicals, infectious agents, foods, tobacco and alcohol and other recreational drugs.
4. Surveillance, research and evaluation generating evidence for the initiation or updating of primary preventive measures. This includes also the establishment of expert committees to review evidence.

The effectiveness of targeted actions towards primary prevention of congenital anomalies is expected to be markedly improved by

- an integrated primary prevention plan involving all relevant health professionals, thus avoiding isolated and/or uncoordinated actions/recommendations;
- Implementation and refinement of EU food and environmental control programs providing special attention to congenital anomaly risk factors;
- proper evaluation and integration of new scientific knowledge into public health actions;
- ensuring preconception health
- care in local public
- health programs [25, 29], while recognizing that many pregnancies are unplanned;
- availability of epidemiological surveillance data from population-based congenital anomaly registers, to monitor the effectiveness of services and interventions to build a sound evidence base for policy development planning and action;
- to ensure sustainability through national and international funding.

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