Teratogenesis

Healthcare

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Abstract

The world today is experiencing a period of rapid technological versatile. Unfortunately, this development has its negative consequences. Dumping in atmosphere of chemical waste, except to other effects, not pass without consequences on human health and in particular in the period in which it is being formed and developed a future individual, i.e. during pregnancy. It is known that the first quarter of this period is sensitive, because it is precisely this period in which take originated all the structures of the developing organism. Fall into contact with substances assigned in this period, resulting in serious consequences in the future of the individual to be born. In some cases turns out that the substances are considered as medications may have teratogenic effects. Some are known, and are removed from use, some are under study, but may have also some widely used and that can be such.

Purpose

The purpose of this study is just be able to turn in the spotlight the importance of this issue, to promote the deepening of studies on teratogenic problems, to enable us if not to avoid, to reduce these effects.

Method of study

The study is with the descriptive character. Attempts to explain the structural and functional defects that can be seen to the birth, as a result of contact that may have mother, with different substances in different periods of pregnancy. The term comes from the Greek (Teratos = monster)

Divided into two groups:

1-Morfogenetics defects (true teratogenesis)
2-Natural and compartmental defects in the absence of obvious anatomical alterations (Neuro-comportamental teratogenesis).

The appearance of one or another manifestation depends on the type of substance, the sensitivity of species and / or specific individual, by way of making (dose, route, etc.), the stage of fetal development at which exposure verified. Anatomical mechanisms of teratogenesis are still little known, they seem related or interference to the detriment of embryonic cell migration or blood circulation disorders in morphogenetic structures.

A bull directly genomes is negotiable, chromosomal disorders not associated with any specific framework. A clear teratogenesis is noticed by alcohol (fetal alcohol syndrome: growth defect, microcefalia, deformities of the face and limbs, signs of cerebral irritation learning deficit), cocaine (malformations genital and urinary tract and systemic signs of cerebral disorders)), amphetamines LSD. The incidence of malformations in term fetus's results not increased more in subjects with clinical populations with methadone treatment.

According to experimental studies, opioid regulation is responsible for the specific effects on cell growth (further in organs). However, from the clinical point of view, the primary pat genetic mechanism with opioid who exhibit fetal suffer and delay in growth is due to ischemia uterus-placental that appear on maternal abstinence phase (indirect mechanism).

According to the latest epidemiological data, using of marijuana in pregnancy accompanied by increased incidences of infantile non-lymphoblastic acute leukemia, should not be excluded completely the role of co-risk factors, especially native exposure to pesticides.
Patogenetic mechanism may be mutagenic type.

Neuro-comportamental teratogenesis caused by persistence post-natal alteration to the detriment of neuro-psychological functions after stopping exposure to psychoactive substance. This type of teratogenesis can be seen as a special counter-adaptation (neuro adaptation) fixed in the "biological memory" of neural apparatus of the developing individual.

More selective phenomenon would occur only after the introduction of specific structures-sign (equipped with receptors for the substance in question) and before a complete neural system maturity verified functionally indicated.

Presence of neuro-compartmental teratogenesis has been demonstrated in animal models for exposure to many substances, among which benzodiazepines, cocaine, opioids, and other psycho stimulating substances.

For example, benzodiazepines are responsible to a disorder of the response to stress and cocaine from learning disorders observed in experiments in rodents (rats), and opioid are implicated in the way of parental bonding in primates.

The phenomenon of neuro-compartmental teratogenesis so far is difficult to verify in human offspring due to methodological constraints.

For more fine disorders can be seen only after a few years after birth, because it is necessary that any sign functions are expressed in social life to recognize the possible teratogenic effect.

The development toxicology involves pharmacokinetics studies, mechanisms, pathogenesis and the effects of exposure to agents or conditions that lead to an abnormal development (teratogenesis).

Includes:
-Structural malformations
- Delay in growth
-Functional damage
-Death of the body
Studies show such a high percentage
-Loss after implantation 35%
-Major defects in the birth 4% at the moment of birth and 6-7% in the first year
- Small defects at birth 14%
-Low weight at birth 7%
-Infant mortality rate (per year) 1.4%
-Abnormal neurological functions 16-17%
Less than half of all pregnancy's born normal and healthy children.
Causes a dramatic such evidence is not all known but the most popular are:
-Genetic causes 15-25%
-Native causes 4%
-Maternal infections 3%
-Deformities 1-2%
-Chemical agents and environmental factors <1%
-Unknown etiology 65%

Were tested over 3000 chemicals of which only 35% of them or other conditions are clearly consistent with prenatal development disorders. Among them are:

TALIDOMIDI

In 1960 was evidenced in Germany increased neonate with rare malformations of the limbs.
Was present Amelia (total absence of limbs) or Different grade focomelia (abbreviation of limb bone length)? In general more affected upper limb. Co-associated with:
-Cardiac malformations
-Ocular, intestinal and renal anomalies
-Malformations of the external ear

In Obstetric Clinic of Hamburg percentage of Amelia and Focomelia present at birth was:

-40-59 years no case
-1959 1 case
-1960 30 cases
-1961 134 cases

In 1961 it was discovered to thalidomide responsible agent.
Drug was introduced into circulation in 1956 as a sedative / hypnotic, used to improve nausea and vomiting during pregnancy. In toxicological tests, in therapeutic doses, had not shown effects on people and adult animals.

Thalidomide was removed from circulation by the end of 1961. Numerous studies made to understand the mechanism gave no result, although it is finally noticed that inhibits the formation of blood vessels (angiogenesis in rabbit).

DIETILSTILBESTROLI

Is an Estrogen non steroid?
Usage matter in the first quarter of pregnancy causes in a greater incidence of female newborns adenocarcinoma with clear cells of the vagina at the age of 15-22 years, which normally is rare before age 30 years.
Men entail increased incidences of installments of epididimis, hypertrophic testis, lowering the volume and quality of semen.

ETHANOL

Fetal alcohol syndrome (SFA) includes disorders cranial-facial, intrauterine growth delay and post-natal, delay in psychomotor and intellectual development.
Q.I. medium is 68.
The emergence of syndrome u vu re only we children born from mothers that abusing with alcohol and incidence in Alcoholics is around 2.5%.
It is also confirmed that the level of making ethanol to cause SFA is about 100 g / day.
Exposure in uterus is associated with a wide spectrum of effects, including malformations typical SFA and moderate forms of neurological and behavioral disorders, known as fetal alcohol effects (EFA).
It is not well known what are the reasons, but it is frequent presence of an increase in cell death in sensitive cell population.

COCAINE

Blocks nerve transmission by blocking Na+ channels and absorption of catecholamine's and 5-hidroksitriptamines.

Effects in the fetus:

-Placental rupture

-Premature birth

-Microcefalia

-Decreased birth weight

-Neonatal neurological syndrome:

-Sleep disorder

-Tremor

-Malnutrition

-Irritability

-Sudden death

Has been seen congenital malformations of the uro-genital tract

RETINOIDI

it is known that for 40 years that increased vitamin A (retinol) induces malformations of the face, limbs, heart, CNS and skeleton.

Based Drugs retinoid (13-cis-retinoic acid) are used against acne.

VALPROIC ACID

Drug against convulsions. Is the cause of neural tube malformations (spine bifida)?

BENDECTINA

Benedictine (dozilamina and pyridoxine), used to alleviate nausea is not toxic for human development. A case of a child born with a unilateral reduction in the length of the wing led to the prohibition of the production of this drug in 1983.

Critical periods of risk

Development is characterized by changes in size, biochemical and physiological, in form and function. It is directed by a number of factors that regulate genetic promoted transcription, first among which is the native cultural heritage present in the egg before fertilization. One by one these factors activate regulatory genes in the embryonic genome and sequential genetic activation continues during development. Due to the rapid changes that occur during development, changing the nature of the target embryo / fetus.

Gametogenesis → formation process of haploid embryonic stem cells (egg and sperm).

Such gametes to join in the process of fertilization to form the zygote diploid or monocelular embryo, the process of "imprinting" happens during Gametogenesis, giving some alleles a different exponents, dependent on the fact of being the mother or father.

Exposure to a toxic substance as:
-Ethylene oxide
-Etilmetan sulfur
-Etilnitrosurea
-Trietilenmelamina

During a short period (about 6 h) after fertilization causes malformed fetuses: The cause is not known. After fertilization, the embryo down in the fallopian tube and placed in the uterine wall. Pre-implantation period is characterized by an increase in the number of cells derived from a series of rapid cell division with a modest increase in size. In this way are formed blastocoels.
This stage, called blast cist, and is formed by about a thousand cells. Only three cells are designed to give embryo origin, others will to form extraembrional membranes and support structure (egg .trophoblasts and placenta). During pre-implantation exposure (to DDT, nicotine) causes deficits organic / cerebral, death of the embryo, but no malformations. In contrast, metilnitrosamina causes neural tube defects and palatoskisis. Of course are all toxic substances that interfere with DNA synthesis, with rapid mitosis. After implantation, the embryo moves towards grastrulation stage, process of formation of the three primary cell lines: the ectoderm, mesoderm and endoderm.
During this period, the embryo is completely vulnerable to teratogenesis. Many substances cause ocular, cerebral and facial malformations.
These malformations are indicators of damage to anterior neural plate, from which the ectoderm formation determines the appearance of organ formation.
This is the period of increased risk to the abnormality and duration (in humans) from the 3rd until the 8th week of pregnancy. In this period are noted effects of retinoic acid.
Conclusion of organogenesis gives start fetal period (56°-58° day of pregnancy), which is characterized by tissue differentiation, growth and functional maturation. The formation of organs is not yet complete, but all organs are present and easily distinguished. Damaging effects during fetal been to the detriment of growth and functional maturation;
Abnormality of the CNS
Abnormality of the reproductive system
Behavioral deficit mental and motor
Fertility reduction
Major structural alterations during this period are called deformities (variations of normal structures).
For example, the extremities may be blocked; umbilical cordon torsion or vascular disorders can be observed with loss of tissue structures.

Dose-response concept and one threshold
Major effects of prenatal exposure are:
Embryonic mortality
Malformations

Delay in growth

Problems associated with these events are visible even though it may not be related to each other. On the other side, is not distinct threshold, even if a point mutation can be induced by a single blow or from a molecule to be exploded a cascade adverse effects.

MECHANISMS AND PATOGENESIS

Cell death plays a critical role in normal morphogenesis. Apoptosis is necessary for the formation of the fingers and on the appropriate link to the CNS and distal structures.
There is a delicate balance between cell proliferation, cell differentiation and apoptosis in embryo and any type of event (egg DNA damage) may upset the cell cycle.

LINKS BETWEEN MATERNAL CONDITIONS AND DEVELOPMENT

Maternal factors

Genetic →genotype
Disease → HTA, diabetes, infections
Nutritional → deficit protein, vitamins, minerals
Stress

Placental toxicity

Toxicity versus placenta can compromise its functionality, especially the ability to produce hormones for the maintenance of pregnancy and the ability to metabolized ksenobiotiks.
Many substances are toxic to the placenta;
Cd, As, Hg, smoke tobacco, ethanol, cocaine, salicilates.
Cd interferes in Zn transfer through the placenta.

Conclusions

1. An agent that causes adverse effects on the development of experimental animals shows a sufficient risk to humans following exposure during development.
2. 4 manifestations of toxicity for development (death, structural abnormalities, growth disorders, functional deficits) should be taken into consideration;
3. Type the developing effects observed in experimental animals is not necessarily the same as those shown in humans.
4. Species suitable to be used for human risk measurement, when the data are available (in the absence of appropriate species with sensitive.
5. In general has reached a threshold dose-response curve for agents that cause development toxicity.

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