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Drugs and their potential teratogenic effect: A literature review

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Abstract

When addressing the etymological meaning, the word teratogenesis denotes gross or "monstrous" malformations, it is currently accepted that teratogenesis is related to any defect or alteration of embryo-fetal development, whether at the functional or structural level. In general, for gross structural defects to occur, the noxa or offending substance must act on a specific period of embryonic development, which is usually at the end of the second week from conception and up to approximately 8 weeks after conception. During this critical period, organs are forming, and teratogens can produce malformations that are usually apparent at birth.

Keywords: Pregnancy; Drug use; Teratogenic effects

1. Introduction

Contemporary medicine should be based on relevant studies that allow the health professional to have empirical and experimental knowledge of cases, in order to have a better diagnosis of their patients. In the case of pregnant women, detailed information is a priority at the time of consultation to determine possible risks to

the embryo in its early stages and to avoid complications or malformations of the pregnant woman, including inquiring about possible genetic factors of the mother and her close relatives, which is why, in this scientific article, we will review issues concerning the teratogenic effect of some drugs during pregnancy, especially those that are administered in the embryogenic stage, in which they can bring more serious repercussions in the product. Recent research carried out in animals and humans has shown that certain teratogenic drugs when administered to pregnant mothers, such as thalidomide, produce serious malformations in the fertilization and embryonic stages. (1) For this reason, this study seeks to provide the health professional with a broader knowledge of the subject and to illustrate the management and treatment of cases of certain gynecological pathologies and the contraindications contained in these drugs for the follow-up of the product.

2. Epidemiology

Congenital anomalies in humans may result from genetic, environmental or unknown causes. About 25% are undoubtedly genetic in origin; drug exposure accounts for only 2 to 3% of congenital anomalies. Approximately 65% of anomalies are of unknown etiology, but most are believed to be combinations of genetic and environmental factors.

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The incidence of severe malformations in the general population is 2 to 3%. (2) A severe malformation is defined as one that is incompatible with survival, such as anencephaly; one that requires major surgery for correction, such as cleft palate or congenital heart disease; or one that results in severe dysfunction, such as mental disability. If minor malformations, such as preauricular papillomas or supernumerary digits, are also taken into account, the rate can be as high as 7- 10%. The risk of malformation after drug exposure should be compared to this baseline rate. Animal studies can be used to estimate the human risk for about 24% of drugs (3).

The spontaneous frequency of serious birth defects is in the order of 2-3%; they cause approximately 20% of infant mortality. However, teratogens would explain only 10% of malformations, i.e., 0.2 to 0.3% of all births.

3. Ranking

Due to the teratogenic risks, different drug distributions have been proposed. In 1979, FOOD and the FDA established a way to categorize them. The first goal was to reduce the prescription of these drugs during pregnancy. It is believed that it was not the first, nor will it be the best, but so far it is the most recognized and common in the market (4).

More than 30 years ago, Sweden classified these drugs into 6 classes, in Germany into 11 groups, in Australia 7, which have been widely accepted, but there are also classifications by importance or by frequency of teratogenicity.

However, the FDA has some limitations that have been questioned, such as giving a risk degradation from A to X or having drugs that have the same categories when the risk is different, so the route of administration or the time of exposure must be taken into account.

For any method, it is difficult due to the lack of information certifying good quality, therefore, drugs should be classified taking into account animal studies, case reports or retrospective epidemiological studies. It is also necessary to evaluate the period of development, the dose, the duration of treatment, the underlying disease, the effect of other drugs, the individual susceptibility of the mother and the fetus. When comparing three of these drug classification systems such as the FDA, the Australian Drug Evaluation Committee (ADEC) and the Swedish Catalogue of Approved Drugs, there was only 26% agreement. For all these reasons, there are authors who are announcing changes in the way of evaluating and reporting the teratogenic risk considerations of a drug (5).

4. Isotretinoin

Isotretinoin is a major human teratogen. This drug is also marketed for the treatment of cystic acne and, unfortunately, has been taken by women who were not planning a pregnancy (6). Long-acting reversible contraception, such as an intrauterine device (IUD), or an etonogestrel implant is recommended. Isotretinoin is classified as contraindicated in pregnancy (FDA category X), with appropriate warnings that a negative pregnancy test is required before treatment.

Of the 154 human pregnancies exposed, 21 cases of congenital anomalies, 12 spontaneous abortions, 95 planned abortions and 26 normal infants were reported in women taking isotretinoin during early pregnancy.

5. Mycophenolate mofetil

This drug has a moderate teratogenic risk, including defects such as cardiac anomalies, facial dysmorphia, cleft lip or cleft palate, microtia or anotia. There are too few cases to conclude the causal relationship of the drug in the malformations (6).

6. Methotrexate

There is little evidence demonstrating teratogenicity for this drug, as it is a folic acid antagonist.

This drug has characteristics similar to a human teratogen and makes it a folic acid antagonist. Cases have been reported, in which three women who had received this drug in the first three months of pregnancy, the infants presented multiple congenital anomalies, such as cranial anomalies and limb malformations.(7)

On the other hand, eight cases were also reported of women who received treatment with this drug inadvertently, after having been erroneously diagnosed with ectopic pregnancy, resulting in three patients miscarrying spontaneously and

three deciding to abort, two infants presented serious malformations. Another case report shows that children up to two years old under normal conditions,

whose mothers were treated with low-dose oral methotrexate (7.5 mg/week) combined with other drugs after the first months of pregnancy for rheumatoid disease, five full-term infants were normal and three of these mothers experienced spontaneous abortions. (8)

7. Methylprednisolone

Forty patients with hyperemesis who were admitted to the hospital were randomized to receive oral methylprednisolone or oral promethazine, and methylprednisolone was more effective. In a larger study in which all patients received promethazine and metoclopramide, methylprednisolone did not reduce the need for rehospitalization. Methylprednisolone should be used only after 10 weeks of pregnancy because of the potential risk of cleft lip and/or cleft palate.(9)

8. Sulfamethoxazole with trimethoprim

Trimethoprim is often given with sulfonamide to treat urinary tract infections. However, an unpublished study of 2,296 Michigan Medicaid recipients noted an increased risk of cardiovascular abnormalities after first trimester exposure. Contraindicated before 12 wk and after 28 wk (3 trimester) in adverse effects we found Hemolysis in the presence of glucose 6-phosphate dehydrogenase deficiency. Teratogenic in animals (Trimethoprim). Its use in pregnancy is restricted to severe cases because it interferes with folic acid metabolism. Its use in the 3rd trimester may favor kernicterus in the NB because sulfas compete with bilirubin for plasma albumin. There are publications that relate sulfas to different congenital malformations (cleft lip, persistent ducts, adrenal hypoplasia and others), although their use in ulcerative colitis or Crohn's disease has not been related to adverse neonatal effects (10). (10)

9. Metronidazole

Metronidazole is a synthetic antibacterial and antiparasitic agent that is classified within the class of nitroimidazoles, today in the treatment of a variety of infections caused by different types of organisms. The mechanism of action as an antibiotic and antiparasitic MTZ is relatively inactive until it is metabolized within susceptible organisms; it is activated when it is reduced, postulating that its mechanism of action is through the elimination of the reducing potential of anaerobic and microaerophilic microorganisms. This occurs through the action of electron transporting proteins such as pyruvate: ferredoxin oxidoreductase or flavodoxin located inside the parasite/bacteria, which carry out the reduction of the nitro group of MTZ resulting in the formation of N-(2-hydroxyethyl) oxalic acid and acetamide. MTZ damages cells by forming adducts with proteins and nucleic acids.(11)

Given the ease with which MTZ crosses the placental barrier, this drug has a teratogenic and embryotoxic potential in mice, rats and rabbits. In humans, it has been shown that at therapeutic doses of MTZ, this drug does not apparently present any serious teratogenic hazard. However, treatment with MTZ is not recommended during the first trimester of pregnancy.

10. Lindane

Research groups have studied the effects on human health of lindane and other organochlorine contaminants present in waste, in particular their relationship with breast cancer, urogenital tract malformations in children exposed in utero and also with male fertility problems (12).

The effects, included in a United Nations report, reflect liver, immune system, reproductive, adverse developmental effects (growth or reduced testosterone levels) or genotoxicity (DNA damage). In addition, the International Agency for Research on Cancer (IARC) has classified alpha, beta and gamma HCH as possible carcinogens to humans (13).

11. Codeine

It is a drug considered safe during pregnancy. Due to some reports of association with malformations, its use should be avoided during the first trimester (14). In

the Collaborative Perinatal Project, no increase in the relative risk of malformations was observed in 563 codeine users. In a recent study, maternal treatment with opioid analgesics was associated with an increased risk of cardiac anomalies, spina bifida, and gastroschisis. Codeine can cause addiction and withdrawal symptoms in the newborn if overused in the perinatal period.

12. Bisphosphonates

The bisphosphonate drug class represents a group of drugs used to treat a variety of bone disorders, such as osteoporosis and Paget's disease, and to control excess calcium in the blood in the setting of cancer or following the administration of chemotherapy. A published clinical case review for the bisphosphonate class of drugs - comprising alendronate, ibandronate, risedronate, etidronate, pamidronate, tiludronate and zoledronic acid - in both short- and long-term use showed no serious fetal or neonatal adverse effects. Marginal decreases in gestational age, birth weight, and neonatal anomalies can be attributed to bisphosphonate use. The decision to continue bisphosphonate use during pregnancy is based on the duration and amount of osteopenia or osteoporosis in the patient. Patients should also be counseled about adequate supplemental calcium intake and vitamin D use, which may decrease the risk of bone-related problems. (15)

13. Conclusion

This paper summarizes the harmful effects of the main teratogenic drugs during the embryonic period. Most of the most important malformations are produced during the period from the third to the eighth week of gestation. However, earlier periods are also susceptible. Therefore, it is important to know the effects of these drugs, in order to use them with caution during pregnancy if indicated.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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