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The use of prescription drugs during pregnancy: What are the "teratogens" that should always be avoided?

(This article is the English translation of a large summary of the previous article in Spanish)

María Luisa Martínez-Frías

Profa. Dpto. de Farmacología, Facultad de Medicina, Universidad Complutense de Madrid.
Directora del Centro de Investigación de Anomalías Congénitas (CIAC), y del ECEMC. Instituto de Salud Carlos III, Ministerio de Economía y Competitividad.
IP del Grupo U724 del CIBER de Enfermedades Raras (CIBERER)

Correspondence to: mlmartinez.frias@isciii.es

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HISTORICAL INTRODUCTION

Even with the huge progress in the knowledge of drug treatment during pregnancy, medical professionals are still concerned when faced with a pregnant woman needing medication. A concern that is also common in the pregnant women themselves and the family and friends that surround them. This may be because the risk assessment of prescribing drugs during pregnancy has been transformed into a complex multidisciplinary process, which has made obsolete the information about potential teratogenic risk offered by teratogenic drug classifications, such as the FDA and others[1-4]. This complexity goes beyond the required knowledge of medical doctors of many specialties who treat pregnant women. In addition, because new technologies have elongated the reproductive age of women, resulting in older mothers and an increase of chronic disease during pregnancy, doctors with other specialties are also treating pregnant women. Therefore, due to the lack of such **current knowledge** on teratogens and the complexity involved in teratogenic evaluation, the belief remains that **pregnant women should not use medication:** two aspects that cause the physicians fear and insecurity when faced with a pregnant woman who requires treatment. This situation also poses a risk for pregnant women, which may be equivalent to (or higher than) the risk of exposure to real teratogens. Hence, at present, I believe that this lack of information and its consequences are the "teratogen" which should **always** be avoided, leading to the title of this article.

Here, we include the characteristics and complexity related with the teratogenic evaluation are summarized. In addition, it is included a brief review of the existing systems in developed countries that support health professionals in providing appropriate medication during pregnancy in order not to affect embryonic and fetal development. This support also helps prevent the insecurity that the various health professionals may have when treating and dealing with sick pregnant women, with consequent benefits for her and her baby.

WHY IS IT SO DIFFICULT TO ASSESS THE TERATOGENIC EFFECT?

The identification of drugs (and any other exposure during pregnancy) that causes alterations in human embryonic-fetal development is a very complex process because, as already mentioned, it requires a multidisciplinary approach, including at least knowledge of Embryology, Dysmorphology, Genetics, Teratology and Statistics. However, we can summarize the main difficulties in the following points:

1. **The obvious impossibility in performing human clinical trials to determine the teratogenicity of a drug.** This means that when a new drug is marketed, it is not possible to know if it has a teratogenic effect in humans until this effect is produced. Therefore, it is very important that teratogenic surveillance systems are set up that can identify its effects promptly. This early detection can reduce the number of children who may be affected, and establish standards of safe use. In Spain, the *Spanish Collaborative Study of Congenital Malformations* (ECEMC) has been conducting this multidisciplinary surveillance since it was started in 1976, and the detailed system of this surveillance was published in 2007[5]. Since 1979, ECEMC has also been involved in monitoring at an international level, as a member of the *International Clearinghouse for Birth Defects Surveillance and Research* (ICBDSR)[6], and of the *European Surveillance of Congenital Anomalies* (EUROCAT) since 1980[7].
2. **Simultaneous exposure to other agents which also are teratogenic.** There are many agents that are known to alter human embryonic and fetal development, so these should be considered in conjunction with the risk assessment of drugs during pregnancy (as discussed below). Among them are the following: maternal illness (both chronic and acute), effects of maternal illness (such as high fever),

drugs (including alcohol and tobacco), and different chemical and physical factors (both in the workplace as well as at home).

3. **The genetic background of humans.** This determines the susceptibility of each person in their response (resistant or susceptible) to various disease processes, or to develop adverse effects following the exposure to various environmental agents, including drugs. An example is the great variability in adverse effects that different people may suffer after taking the same drug, and the susceptibility to develop cancer as a result of exposure to certain substances, such as lung cancer from exposure to tobacco.
4. **In each human pregnancy, there exists a risk for birth defects called the population, or baseline, risk.** The probability is estimated to be between 3-6% in each pregnancy that the child will be born with defects of any kind (physical, sensory, mental, functional…), a risk that varies for each type of defect, and which reflects the average susceptibility of the population. This ranges from individuals who are genetically resistant, followed by those with less resistance, to those who are susceptible.
5. **No environmental factor affects 100% of exposed individuals.** As indicated in the previous point, there is no exposure whatsoever (including drugs) that can be considered 100% safe or 100% harmful for all individuals in the population, including pregnant women and the embryo/fetus. In fact, the existing evidence on teratogens show that even those involving higher risks (such as thalidomide and synthetic retinoids)[8-11] affect 25-30% of infants who were exposed prenatally. This data indicates that 70-75% of pregnancies exposed to these teratogens resulted in the birth of unaffected children, which may lead one to consider that this teratogenic risk is not actually that high. However, these risk values are in fact very large; indeed, a 2% risk is already considered significant. To contextualize the magnitude of that risk value, let us compare it to a well known example: all women over 35 are considered to have a higher risk of having a child with Down syndrome (DS, trisomy 21), which increases with maternal age. However, in women of 35 years the risk has a value of 0.28%, whereas in women of 42 years the risk is 1.7-2%. These increases in risk (which are much smaller than the risks associated with the two mentioned teratogen drugs) are considered important enough, that prenatal diagnostic programs specific to women aged 35/37 years and above have been put in place in most developed countries.
6. **The lack of cause-effect specificity.** That is, one birth defect (whether physical, mental, sensory or functional) can be produced by a variety of genetic and environmental causes. For example, the malformations caused by prenatal exposure to thalidomide are identical to those seen in many genetic syndromes (i.e. Roberts, thrombocytopenia absent radius (TAR), DK-phocomelia, hypoglossia-hypodactyly, Holt-Oram, Okihiro, Brachmann-de Lange, and others)[8]. But conversely, the same agent (either genetic or environmental) produces different types of malformations in different people, for example thalidomide, isotretinoin and all known teratogens give rise to a variation of expression in different patients. This also occurs in genetic anomalies, in that the same gene can lead to various clinical pictures or syndromes, such as the gene *FGFR3* (fibroblast growth factor receptor 3), in which mutations cause different clinical syndromes such as achondroplasia, hypochondroplasia, thanatophoric dysplasia I and II and Crouzon, among others[12-15]. Therefore, to attribute congenital defects to a drug, first it is necessary to disregard other environmental and genetic causes (including genetic syndromes).
7. **The identification of human teratogens is a difficult process that requires complex statistical studies.** This complexity stems from the six previous points, starting because clinical trials cannot be carried out, the existence of the baseline, or population risk, and the lack of cause-effect specificity. Thus, to identify if a drug (or other environmental agent), is a human teratogen, it is necessary to

show that the frequency of the defect (or defects) is significantly higher in children of women exposed to the drug, than the frequency of the defect in the offspring of a similar group of mothers not exposed to the drug. Although this analysis is complex, the basic essence of the risk quantification can be understood by simplifying it using the following theoretical example:

- The aim is to analyze whether treatment with drug **A** during the early months of pregnancy is associated with the occurrence of tetralogy of Fallot in children. Under this hypothesis, we assessed the newborns of 10,000 mothers exposed to the drug during the first six months of gestation, and observed that 12 mothers had a child affected by that heart condition. On the other hand, in a similar group of 10,000 mothers **NOT** exposed to drug **A,** 2 of them had a child with tetralogy of Fallot. Dividing these two results: 12 affected children among the exposed mothers, by 2 affected in the unexposed mothers, results in a value of 6. The value obtained indicates that the frequency of affected children among exposed mothers is **6 times higher** than that of the group of unexposed mothers (as the population risk). If the drug were not associated with tetralogy of Fallot, the frequency would not be expected to be more than two affected children among those born to exposed mothers. Therefore, the conclusion of this analysis is that, if a pregnant woman takes drug **A** during the first months of gestation, she multiplies (increases) her baseline risk (which in our example is 2/10,000) of having a child with tetralogy of Fallot by approximately 6.

DIFFICULTY OF THE TERATOLOGICAL EVALUATION AT THE CLINICAL SETTING

Bearing in mind the previous information, when a woman has undergone treatment in the early months of pregnancy, or when a pregnant woman needs treatment, the evaluation of the potential effects needs to include other data. These include various agents or factors that may also be human teratogens and, in many cases, could entail a greater risk than the pharmacological treatment. This information, which can be different for each mother, should include the patient history, including the following information:

— The exact gestational age at which treatment began and ended, and the dosage,
— The reason for which the treatment was prescribed,
— If other medication has been used, including non-prescription drugs (eg, analgesics, inhalants for colds...etc), doses and why they were used,
— If they have a chronic illness, its treatment and control,
— If they follow a well balanced diet,
— If they smoke and/or drink alcohol and/or consume drugs, specifying the doses, frequency and during what times of the pregnancy,
— If they take any herbal products [16],
— Occupational exposures for both the woman and her partner from three months before pregnancy,
— Family history of birth defects.

With this information it is possible to make an overall and individualized assessment of the potential risk **attributable** to the drug, or the absence of that drug risk. It can be determined if, being a risk-associated drug, it was used outside the period in which it is known to produce a teratogenic effect. Also, if there is a risk attributable to **any other** agents to which the pregnant woman was exposed, or any genetic-risk factors in their family. Therefore, this assessment will be different for each woman, even for the same medication, depending on at what point of the pregnancy the exposure(s) occurred, and their personal characteristics (commented above). With all this information in hand, it is possible to:

a. Decide the treatment to be prescribed to the pregnant woman, and importantly, if other treatments are being used, the appraisal of potential interactions. In this regard it should be remembered that, whenever possible, mono-therapy should be followed, as some drug interactions and high doses increase the teratogenic risk.

b. Evaluate the potential teratogenic risk of the treatment the pregnant woman is currently using.

c. Always bear in mind when prescribing medication to women of childbearing age, that she may be pregnant of only a few days, so the weeks of amenorrhea and negative pregnancy tests are not always reliable.

Finally, it is necessary to explain that obtaining all the data mentioned above is not only absolutely necessary to make a proper assessment, but also for the information that is necessary to be given to the prospective parents, as well as to prevent other conflicts:

a. Because if these other concomitant factors are not evaluated and the information given to the pregnant women (or the couple or both) is limited to the drug being considered as "not risk-associated" for the embryo-fetus, this could have serious consequences if the child is born with defects.

b. Because, in such a situation where the child has defects, it is likely that the woman and her family will blame the medical treatment. Even if subsequently it may be recognized that these defects are related to any of the other factors to which the mother was exposed (and were not considered in the assessment of the risk), it will not be easy to convince the parents (and perhaps the judge) that the treatment prescribed by the doctor did not cause the defects in the child.

SUPPORT SYSTEMS FOR HEALTHCARE PROFESSIONALS WHO HAVE TO PRESCRIBE MEDICATION DURING PREGNANCY

Taking all of the above into account and with the current state of knowledge, it is necessary to have alternative systems to the standard classification of drugs, that provide support for physicians in their evaluation of the maternal benefit-fetal risk, to select the appropriate treatment in each pregnant woman. These systems are called the Teratology Information Services (TIS), which currently exist in all developed countries (and some developing), and are attended by experts in carrying out that evaluation. In addition, the already-existing TIS have formed networks between themselves to enable a quick consultation, and exchange of knowledge about exposures to rare factors, newly marketed drugs, and medication whose use in pregnant patients is rare, as well as other types of exposures such as different chemicals. In the United States and Canada, the network of these services is called the *Organization of Teratology Information Specialists* (OTIS)[17], and that of Europe (which also includes Argentina, Australia and Brazil) is called the *European Network of Teratology Information Services* (ENTIS)[18], of which ECEMC was one of the groups that organized this network in 1991.

The operation of these TIS is similar and based on a telephone consultation, which has the advantage that the doctor can use the service from their clinic before prescribing medication, or to assess a treatment that the patient is following. However, these TIS differ slightly from each other, primarily in the target users, and the type of documentation that they offer to complement the information provided by telephone. Some basically only take calls from women, while others also attend (or only attend) clinicians. Some of these services, after the telephone consultation, send a report on the drug that has been inquired about. The ECEMC group provides two different TIS, one for healthcare professionals and the other aimed for the general public.

The first service attends doctors, midwives, nurses and pharmacists and is called the **Spanish Telephone Information Service for Teratogens** (**SITTE**, using the Spanish abbreviation). Although the information offered to healthcare professionals focuses

primarily on drug treatments before and during pregnancy (which is the main motive for calls from this group), any other pregnancy-related exposures are also evaluated, such as maternal infections/disease, exposure to X-ray, immunizations, lifestyles, parental occupational exposures, and many others. In each consultation, before offering advice on a particular treatment, all the important information mentioned previously in this article is collected. Thus, the expert attending the call is not only informed about the treatment that is the motive for the call, but also about other risks that the woman may have, and can assess the kind of objective information that should be given to the couple. Moreover, at the end of the call a technical report is offered, by post or email, which is an up-to-date summary of the potential adverse effects, if any, of the requested pharmacologic treatment, along with any other risk factors identified to which the woman or partner have been exposed. Alongside the report are included some of our "PROPOSITUS: ECEMC Fact Sheets"[19-23] on medications or other exposures, which are related to the topic of the query.

The other ECEMC TIS is called the **Telephone Information Service for Pregnant Women** (**SITE**, using the Spanish abbreviation), and the operation is the same as that described above. This service addresses the questions of women, and also those of their spouses, or their parents if there are minors involved. The caller is also always offered information on what are the known measures for primary prevention of birth defects, as well as when to begin to apply them to the woman and her partner[24]. The only exception to the questions answered by SITE is technical information related to drug treatments or diseases, which should be requested by the attending physician. In addition, after answering the query, additional information is offered to the caller, which may be: a) to take along to their doctor, b) about certain occupational exposures, to take to their company or occupational health and safety service, c) our "PROPOSITUS" fact-sheets with related information aimed at the general population, and measures to promote primary prevention of congenital defects[24-28].

FINAL COMMENT

In reality, what **CANNOT** be used in pregnant women are medications and dosages that are **not fully indicated**. When there is no clear clinical requirement, even for drugs that are considered suitable during pregnancy, this treatment is **absolutely contraindicated** (remember that not all people have the same genetic susceptibility). In general, and as a rule to follow, **any drug treatment during pregnancy has to control the maternal illness, and should implicate the least possible risk for embryo/fetal development.** In other words, it must be assessed whether the disease may also confer a risk for the embryo/fetus, by the assessment of fetal risk-maternal benefit. In addition, the treatments must be used **at the lowest therapeutic doses.** This last aspect is very important, since the molecular weight of the vast majority of drugs does not exceed 600 Dalton. Therefore, the treatment given, and inevitably received by the embryo/fetus, will be of an adult dosage: a quantity that would never be given to a child. For this reason, any medication of any type whatsoever must always be applied starting with the **minimal dosage** and increasing slowly to achieve the desired therapeutic effect. This should be applied also to drugs that are considered "safe" (although, as said before, there does not exist any exposure that is 100% safe for all individuals in the population). An example is the use of paracetamol, which is used without prescription, sometimes at high doses, without considering that more than 4 or 5g could be hepatotoxic for adults. Finally, it should be mentioned that the risk-benefit assessment should continue throughout the entire pregnancy, not just the first trimester, because some drugs, once past the first trimester, may also affect fetal development and the function of various systems such as the kidneys or nervous system. Therefore, this ought to be applied also to over-the-counter products, some of which should not be used during pregnancy (eg. vasoconstrictors), and others which may be used depending on the time of gestation, such as non-steroidal anti-inflammatories, which from the 28-29th week of gestation can cause premature closure of the ductus arteriosus and fetal death.

With respect to drugs that are **completely contraindicated,** there are not many, and most of them fulfil two important aspects: a) some treat diseases for which alternative therapies exist that do not carry risk for embryonic development, b) others often treat non-serious diseases, which can also usually be handled with symptomatic treatment, and there is no risk to the mother, so they should not be used in pregnancy. On the other hand, if a woman of reproductive age has to be treated only by contraindicated drug during the pregnancy (eg. isotretinoin), there are rules for its correct use that include [11]: initiating treatment on the first day of the period in which there is an abundant shedding of the endometrium, and following two contraceptive methods (or abstinence) during the treatment and, depending on the type of drug used, continuing these measures throughout a post-treatment period, which typically ranges from one to three months depending on the characteristics of the drug.

As mentioned earlier in this article, given the complexity of the teratological evaluation of drugs (and any environmental factor), the existence of a telephone information service for teratogens is invaluable for health professionals, as it offers them the latest knowledge that not only exceeds their specialty, but which is constantly evolving. In addition, the service provides other advantages for the health system, not only the avoidance of potential legal problems, but the promotion of an adequate and safe health practice during pregnancy, to prevent alterations during embryonic development. This also lessens maternal distress, reducing pressure on the health system and resulting in large financial savings, as well as the personal satisfaction of the clinician, and the absence of family suffering.

Arriving at this point, it is difficult to understand why not all health authorities in our country recognize and value the need for these excellent, **worthwhile,** and efficient services offered, as also are the SITE and SITTE.

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