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Risk Classification Systems for Drug Use During Pregnancy

Are They a Reliable Source of Information?

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Abstract

Background: In several countries, risk classification systems have been set up to summarise the sparse data on drug safety during pregnancy. However, these have resulted in ambiguous statements that are often difficult to interpret and use with accuracy when counselling patients on drug use in pregnancy.

Objectives: The objective of this study was to compare and analyse the consistency between and the criteria for risk classification for medications used during pregnancy included in 3 widely used international risk classification systems. All 3 systems use categories based on risk factors to summarise the degree to which available clinical information has ruled out the risk to unborn offspring, balanced against the drug's potential benefit to the patient.

Methods: Drugs included in the risk classification systems from the US Food and Drug Administration (FDA), the Australian Drug Evaluation Committee (ADEC) and the Swedish Catalogue of Approved Drugs (FASS), were reviewed and compared on basis of the risk factor category to which they had been assigned. Agreement between the systems was calculated as the number of drugs common to all 3 and assigned to the same risk factor category. In addition, evidence on teratogenicity and adverse effects during pregnancy was retrieved using a MEDLINE search (from 1966 up to 1998) for common drugs classified as teratogenic.

Results: Differences in the allocation of drugs to different risk factor categories were found. Risk factor category allocation for 645 drugs classified by the FDA, 446 classified by ADEC and 527 classified by FASS was compared. Only 61 (26%) of the 236 drugs common to all 3 systems were placed in the same risk factor category. Analysis of studies on the safety of common drugs during pregnancy of drugs classified as X by the FDA indicated that the variability in category allocation was not only attributable to the different definitions for the categories, but also depended on how the available scientific literature was handled.

Conclusions: Differences in category allocation for the same drug can be a source of great confusion among users of the classification systems as well as for those who require information regarding risk for drug use during pregnancy, and may limit the usefulness and reliability of risk classification systems.

Background

Since the thalidomide disaster, clinical pharmacologists and teratologists have had a dream: to be able to classify all therapeutic agents according to the risk they pose to fetuses exposed to them during pregnancy. So far, the risks associated with fetal exposure has only been established for a few drugs, and data on the safety of drugs during pregnancy are still incomplete. Methodological and ethical problems make maternal-fetal toxicology an orphan field of research, and consequently information is scarce.[1] Because women of child-bearing age who do not use contraception are usually excluded from clinical trials, little or no data are available on pregnancy outcomes after drug exposures.

Nevertheless, teratologists, gynaecologists and clinical pharmacologists in many countries have set up risk classifications systems based on data from human and animal studies to guide physicians in the interpretation of teratogenic or fetotoxic risks associated with the drugs they prescribe. These systems place drugs in different categories according to risk ranging from class A, for drugs which are considered as safe for use during pregnancy, to class X, for drugs considered to increase the risk of major malformation if taken during pregnancy. Thus, a category (e.g. A, B, C, D, or X) can be used to indicate the degree of safety and risk associated with the use of a particular drug therapy during pregnancy.[2]

The first classification system based on clinical and animal data for risks associated with drug use during pregnancy was implemented in Sweden in 1978.[3] The Swedish Catalogue of Approved Drugs (FASS) contains information on possible risks arising from the use of individual drugs during pregnancy and lactation. This system comprises 4 separate categories (A, B, C, D): A signifies the safest drugs; B is divided into 3 subgroups (B1, B2, B3); and C and D categories are used for drugs which may have different risks for the fetus depending on the evidence on which the risk is based.

The US Food and Drug Administration (FDA) introduced its own system in 1979, also using the letters A to D and adding an X category for drugs demonstrated to be teratogenic.[4] The Australian Drug Evaluation Committee (ADEC) classification was developed in 1989 as an extrapolation from both the previous systems: it uses subcategories B1, B2, B3 and the X category.[5] Since these risk classification systems are the main – and often sole – sources of information for physicians, gynaecologists, teratogenic information services and lay people regarding drug use during pregnancy, their reliability needs to be carefully evaluated.

The definitions of the different risk categories for these 3 classification systems are reported in table I.

Recently, the American Society of Teratology questioned the usefulness of the FDA classification of drugs for determining teratogenic risk in pregnancy.[6] However, no formal comparative and qualitative analysis of the FDA and other classification systems has yet been made.

The aim of this study was to compare the 3 systems on the basis of their allocation of different drugs to the different risk categories and to test the consistency between and the reliability of the systems.

Materials and Methods

We retrieved all the drugs listed in the American (FDA), Australian (ADEC) and Swedish (FASS) risk classification systems. Drugs classified using the FDA risk classification system were identified using the book *Drugs in Pregnancy and Lactation*.[4] The publication *Medicines in Pregnancy* produced by ADEC[5] was used to identify drugs classified by this system and the publication *Classification of Medical Products for Use During Pregnancy and Lactation*, produced by FASS was used to identify drugs labelled according to the Swedish risk classification.[3] To avoid bias deriving from data of sources with different levels of updating, we used references with the closest time of publication (1994 for the FDA,[4] 1992 for ADEC[5] and 1993 for FASS[3]).

To compare the differences and similarities between the 3 systems we used only drugs that were included in all 3 classification systems. Agreement between the systems was calculated as the number of drugs common to all 3 systems and with the same

Table I. Definitions for the risk categories in the US Food and Drug Administration (FDA),[4] Australian Drug Evaluation Committee (ADEC),[5] and Swedish Catalogue of Approved Drugs (FASS)[3] classification systems

Risk category	FDA classification[4]	ADEC classification[5]	FASS classification[3]
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.	Drugs which have been taken by a large number of pregnant women and women of child-bearing age without an increase in the frequency of malformation or other direct or indirect harmful effects on the fetus having been observed.	Medicinal products which may be assumed to have been used by a large number of pregnant women and women of child-bearing age without any identified disturbance in the reproductive process, e.g. an increased incidence of malformations or other direct or indirect effects on the fetus. This category comprises: drugs that have been available for many years; those that have been used by many pregnant women and women of child-bearing age and; drugs for which satisfactory retrospective studies in pregnant women are considered to have been carried out.
B	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in the later trimesters).	Drugs which have been taken by only a limited number of pregnant women and women of child-bearing age without an increase in frequency of malformation or other direct or indirect harmful effects on the fetus having been observed. As experience of effects of drugs in this category in humans is limited, results of toxicological studies to date (including reproduction studies in animals) are indicated by allocation to one of three subgroups: **B1**: Studies in animals have not shown evidence of an increased occurrence of fetal damage. **B2**: Studies in animals are inadequate and may be lacking, but available data show no evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans. **B3**: Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.	Medicinal products which may be assumed to have been used only by a limited number of pregnant women and women of child-bearing age without any identified disturbance in the reproductive process having been noted so far, e.g. an increased incidence of malformations or other direct or indirect harmful effects on the fetus. As experience of effects of medicinal products in man is limited in this category, results of reproduction toxicity studies in animals are indicated by allocation to one of 3 subgroups B1, B2 or B3 according to the following definitions: **B1**: Reproduction toxicity studies have not given evidence of an increased incidence of fetal damage or other deleterious effects on the reproductive process. **B2**: Reproduction toxicity studies are inadequate or lacking, but available data do not indicate an increased incidence of fetal damage or other deleterious effects on the reproductive process. **B3**: Reproduction toxicity studies in animals have revealed an increased incidence of fetal damage or other deleterious effects on the reproductive process, the significance of which is considered uncertain in humans.
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal, or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.	Medicinal products, which by their pharmacological effects have caused, or must be suspected of causing, disturbances in the reproductive process that may involve risk to the fetus without being directly teratogenic. If experimental studies in animals have indicated an increased occurrence of fetal injuries or other disturbances of the reproductive process of uncertain insignificance in humans, these findings are to be stated for drugs in this category.

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Table I cont.

risk category. Single examples chosen among the common drugs classified as X by the FDA, were analysed and, original studies on their safety during pregnancy were sought. Differences the way the literature available for these drugs was interpreted and evaluated using a MEDLINE search (from 1966 up to December 1998) using the keywords: pregnancy and abnormalities drug-induced as Medical Subject Heading (MeSH) terms (exploded) and the specific drugs as MeSH terms or text words. Risk labels used by the different classification systems were compared with the evidence of risk and safety found with the MEDLINE search.

Results

A total of 1032 drugs were classified by the 3 classification systems: 645 by the FDA, 446 by ADEC, and 527 by FASS. Table II shows the distribution of drugs in the 3 systems according to risk category. Differences in percentages of drugs assigned to different risk factor categories can be partially explained by differences in category definitions. The Australian and Swedish systems use quite similar definitions (table I), except that the Australian system uses a category X, but the FDA is extremely demanding regarding data for drug use during pregnancy and uses the A label only where controlled studies show no risk. The B3 risk factor used by ADEC and FASS, is very similar to FDA risk factor C. However, our analysis did not consider as discrepancies drugs classified as category X by the FDA or ADEC and category D by FASS or category B3 by ADEC or FASS and category C by FDA.

Considering only the drugs common to all 3 systems (tables III and IV), we notice that the Australian and the Swedish systems are quite similar in terms of drug distribution between categories but differ considerably from the FDA category allocation. Only 61 (26%) of the 236 drugs common to all 3 systems are assigned to the same risk category (3 assigned to category A, 13 to B, 30 to C and 15 to D). Of the 236 drugs common to all 3 classification systems, only 6 are assigned to risk category A (i.e. safe for use during pregnancy) by the FDA.

Table I. Contd.

Risk category	FDA classification[4]	ADEC classification[5]	FASS classification[3]
D	There is positive evidence of human fetal risk, but the benefits from the use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).	Drugs which have caused an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.	Medicinal products which have caused an increased incidence of fetal malformations or other permanent damage in humans, or which, on the basis of e.g. reproduction toxicity studies, must be suspected of doing so. This category comprises drugs with primary teratogenic effects that may directly or indirectly have a harmful effect on the fetus.
X	Studies in animals or humans have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.	Drugs that have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.	

Despite the more restrictive requirements of the FDA system, retinol (vitamin A), classified as safe for use in pregnancy by the FDA, is considered potentially teratogenic (category D) by ADEC and FASS. This may be attributable to the fact that risk factors in these 2 systems are based only on data related to the drug and not to dose. However, even though the teratogenicity of retinol is well established in animals, it has not been conclusively established in humans.[7,8] Other FDA category A drugs such as nicotinic acid and calcitriol are considered categories B2 or B1, respectively, by ADEC and FASS.

In general the FDA classification system is more restrictive about assigning drugs to categories A or B, although for 21 drugs the Swedish and Australian systems used a more severe risk factor. For example, several nonsteroidal anti-inflammatory drugs (ketoprofen, naproxen, sulindac, piroxicam, ibuprofen, etc.) are considered category B drugs by the FDA but category C by ADEC and FASS. Category C is the one that contains the most drugs in all 3 systems, but only 30 of these are common to all 3 systems. The 16 and 22 drugs considered safe during pregnancy (category A) according to the ADEC and FASS systems, respectively, are considered potentially feto- or embryo-toxic (category C) using the FDA classification [e.g. ephedrine, methyldopa, theophylline, bromocriptine, salbutamol (albuterol), etc.]. A few drugs classified as category C by the FDA, such as aminoglycosides (gentamicin, amikacin), dacarbazide and tobramycin, are classified as potentially teratogenic (category D) by the Australian and Swedish systems.

Eight of the drugs found in all 3 classification are labelled with an X risk factor (teratogenic) by the FDA. Of these, 3 are classified as safe (B or A) by ADEC or FASS. Oral contraceptives, estradiol and clomifene, for instance, are not identified as major teratogenic agents by the Australian and Swedish classification systems, in disagreement with the FDA. Triazolam is another drug classified as teratogenic in the FDA system, but assigned to category C in the ADEC and FASS systems.

Table II. Drugs classified by the US Food and Drug Administration (FDA),[4] Australian Drug Evaluation Committee (ADEC),[5] and Swedish Catalogue of Approved Drugs (FASS)[3] classification systems according to risk category

Risk category[a]	Number of drugs (%)		
	FDA classification	ADEC classification	FASS classification
A	27 (4)	122 (27)	114 (22)
B	148 (23)		
B1		33 (8)	59 (11)
B2		84 (19)	64 (12)
B3		51 (11)	60 (12)
C	291 (45)	106 (24)	160 (30)
D	143 (22)	45 (10)	70 (13)
X	36 (6)	5 (1)	
Total	**645**	**446**	**527**

a Definitions of the different risk categories are provided in table I.

Several drugs have different risk factors in all 3 systems. Metoclopramide is classified as category B by the FDA, category A by ADEC and category C by FASS; chloroquine and hydroxychloroquine are assigned to category C by the FDA, but to category D by ADEC and category B3 by FASS; salbutamol and isoniazide are considered category C by the FDA, but category A by ADEC and FASS; griseofulvin, phenylephrine, phenylpropanolam there is disagreement in category assignment between the 3 systems.

Table V shows the list of common drugs classified as category X by the FDA. Many of these are commonly used drugs, such as oral contraceptives and benzodiazepines, which may be the subject of enquiries about risk and safety during pregnancy. In some cases, depending on the risk classification system used, the answer will be different. Table V also provides an updated summary of the scientific evidence regarding risk and safety during pregnancy retrieved using the MEDLINE search. For some drugs, the risk during pregnancy is probably based on animal studies and case reports. Even though there is no conclusive evidence of teratogenicity or adverse reactions after use during pregnancy of estradiol, oral contraceptives, clomifene and triazolam, these drugs are assigned to category X by the FDA but to categories B and C by ADEC and FASS, respectively.

Table III. Drugs common to the US Food and Drug Administration (FDA),[4] Australian Drug Evaluation Committee (ADEC),[5] and Swedish Catalogue of Approved Drugs (FASS)[3] classification systems according to risk category

Risk category[a]	Number of drugs (%)		
	FDA classification	ADEC classification	FASS classification
A	6 (3)	50 (21)	59 (25)
B	62 (26)		
B1		18 (8)	19 (8)
B2		31 (13)	26 (11)
B3		22 (9)	20 (8)
C	115 (49)	84 (36)	85 (36)
D	45 (19)	29 (12)	27 (11)
X	8 (3)	2 (1)	
Total	236	**236**	**236**

a Definitions of the different risk categories are provided in table I.

Discussion

The use of drugs during pregnancy is a very complicated issue. The misunderstanding about teratogenic risk may lead to anxiety or termination of otherwise wanted pregnancies.[1] The aim of the risk classification systems should be to guide physicians in the interpretation of this risk. Although the American Society of Teratology has proposed that the FDA abandon the current classification system in favour of more meaningful evidence-based narrative statements,[6] some authors have concluded that classification of teratogenic risk for the prescribing physician is still the most efficient approach for establishing the risk and safety of drug use during pregnancy.[2]

This study is the first to attempt a quantitative and qualitative comparative analysis of the different risk classification systems for drug use during pregnancy. Since the FDA risk classification system reserves category A only for drugs where controlled studies have shown no risk, the FDA system would permit only a few drug options in terms of safety for the fetus exposed during pregnancy.[2] Thus, while 26% of the drugs in Sweden are classified as category A, only 0.7% of the drugs marketed in the US are in FDA category A.[2] The Swedish and Australian systems assign the safest risk factor category to all drugs where reliable clinical data indicate no evidence of disturbance of the reproductive process. Even though the main differences between systems seem to be mostly due to

Table IV. Examples of drugs or drug classes according to the risk category assigned by the US Food and Drug Administration (FDA),[4] Australian Drug Evaluation Committee (ADEC),[5] and Swedish Catalogue of Approved Drugs (FASS)[3] classification systems[a]

Risk category[b]	FDA classification	ADEC classification	FASS classification
A	Retinol (vitamin A), nicotinic acid, calcitriol	Ephedrine, methyldopa, theophylline, bromocriptine, salbutamol (albuterol), isoniazide, metoclopramide	Ephedrine, methyldopa, theophylline, bromocriptine, salbutamol, isoniazide, phenylephrine, phenylpropanolamine, spironolactone
B	NSAIDs, metoclopramide	Nicotinic acid (B1), calcitriol (B1), phenylephrine (B2), phenylpropanolamine (B2), griseofulvin (B3), spironolactone (B3)	Nicotinic acid (B2), calcitriol (B2), chloroquine (B3), hydroxychloroquine (B3), meprobamate (B3)
C	Ephedrine, methyldopa, theophylline, bromocriptine, salbutamol, aminoglycosides, dacarbazide, tobramycin, chloroquine, hydroxychloroquine, isoniazide, griseofulvin, phenylephrine, phenylpropanolamine	NSAIDs, meprobamate	NSAIDs, metoclopramide
D	Meprobamate, spironolactone	Retinol, aminoglycosides, dacarbazide, tobramycin, chloroquine, hydroxychloroquine	Retinol, aminoglycosides, dacarbazide, tobramycin, griseofulvin

a Examples of category X drugs are shown in table IV.

b Definitions of the different risk categories are provided in table I.

NSAIDs = nonsteroidal anti-inflammatory drugs.

Table V. Drugs common to the US Food and Drug Administration (FDA),[4] Australian Drug Evaluation Committee (ADEC),[5] and Swedish Catalogue of Approved Drugs (FASS)[3] classification systems and classified by FDA as teratogenic (category X), with summary of evidence about safety during pregnancy

Drug	Category for each classification system			Evidence of risk and safety during pregnancy[a]
	FDA	ADEC	FASS	
Estradiol	X	B1	B2	Although animal data on teratogenicity exist,[9] no human data have been found relating to its teratogenicity.[10]
Oral contraceptives	X	B3	B3	Some reports have associated the use of these drugs with several birth defects,[11] in particular with changes in the development of sexual organs.[12] However, 2 meta-analyses show no increase of general or external genital malformations after use of oral contraceptives during the first trimester.[13,14]
Clomifene	X	B3	B3	Despite the paucity of human data, there are no studies showing any increase in the risk of malformations after use of clomifene during pregnancy.[15,16]
Triazolam	X	C	C	No epidemiological studies on the use of this specific drug during pregnancy have been located. However, a meta-analysis shows no increase risk after use of benzodiazepines during the first trimester.[17]
Misoprostol	X	X	C	Case series and case-control studies show an increased risk of Moebius sequence[18,19] after use of the drug as an abortifacient.
Norethisterone	X	D	D	Animal studies have reported teratogenicity.[20] Masculinisation of the female fetus has been associated with the use of this drug during pregnancy.[21,22] (see also oral contraceptives)
Etretinate	X	X	D	This drug is a potent teratogen in animals.[23,24] Case reports and case series associate its use with risk for CNS, craniofacial, cardiovascular and other defects.[23,25-30]
Danazol	X	D	D	Case reports[31,32] and a retrospective study[33] associate exposure to the drug *in utero* with female pseudohermaphroditism.

a MEDLINE search up to December 1998.

the differences in the definition of the safest category (category A),[2,34] this is not enough to explain the inconsistencies seen. The other categories (B, C, D and X) should represent more or less the same indicators establishing the risk levels for pregnancy and the fetus. However, our analysis showed that even the 2 systems with very similar definitions for risk categories have differences in assignment in several cases. These differences may be due not only to the different criteria used for assignment, but may also be due to how the original data source were interpreted. The analysis on single drugs examples shows that the real problem is how accurately original data are translated into risk category assignment.

These 3 systems produce ambiguous statements that may be difficult to interpret and use to guide prescribing and to give advice. In addition, the classification for single drugs is often not updated when new data become available. None of the drugs common to all 3 classification systems and assigned to category X by the FDA changed category assignment in the most recent source of the FDA classification.[35]

The nature of these systems implies a grade of risk, but the classification does not consistently follow this grading.[36] Often drugs usually considered as safe by 2 of the systems (ADEC and FASS) are not classified the same way by the third system (the FDA system). For instance, although 2 meta-analyses found no association between first-trimester exposure to oral contraceptives and malformations in general or external genital malformations in particular,[13,14] the FDA still labels these drugs as teratogenic. Considering that at least half the pregnancies in North America are unplanned,[37] women still using oral contraceptives during the first trimester of pregnancy will be alarmed by the FDA labelling.

Some of the agents listed as category X in FDA system (e.g. clomipramine and triazolam) have

been classified by their manufacturers and not the FDA. The manufacturer used the FDA guidelines but actually assigned the category themselves. This may be considered a limitation of our analysis if we assume that the manufacturer might label a drug as contraindicated in pregnancy for different reasons than those used by the FDA. When the manufacturer is responsible for the classification, it is possible that in some cases legal aspects are considered to be even more important than the medical aspects. However, risk factor categories appear to be an oversimplification and are not really helpful for explaining the risks of drug use during pregnancy to physicians and patients. Furthermore, these systems, as they have been designed, cannot take into account, for the same drug, the different kinds of risks associated to its use during pregnancy. These risks are, for example, teratogenicity (i.e. risk of congenital abnormalities mainly in the critical period of fetal development) versus feto-toxicity (i.e. fetal renal malfunction or intrauterine growth retardation, etc.) or postnatal complications (e.g. hyperbilirubinaemia, etc.). The actual risk depends on the dose used; therefore it would be necessary to differentiate the usual clinical dose and overdosage (e.g. ADEC and FASS classification systems are not dose-related). Finally, the underlying diseases being treated are very important confounders, therefore the indication for drug use should be considered.

Conclusion

In conclusion, the original dream of summarising using a single indicating factor all the variables which make the use of a drug during pregnancy safe or unsafe (dose, period and duration of exposure, co-morbidity, etc.), is still very much a dream, besides – apparently – being a questionable approach because of its limited reliability. Differences in category assignment for the same drug could be a source of great confusion among users and may limit the usefulness of these systems.

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