

Review

Risk and Benefit of Drug Use During PregnancyFerenc Bánhid¹, R.Brian Lowry² and Andrew E. Czeizel³

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Environmental teratogenic factors (e.g. alcohol) are preventable. We focus our analysis on human teratogenic drugs which are not used frequently during pregnancy. The previous human teratogenic studies had serious methodological problems, e.g. the first trimester concept is outdated because environmental teratogens cannot induce congenital abnormalities in the first month of gestation. In addition, teratogens usually cause specific congenital abnormalities or syndromes. Finally, the importance of chemical structures, administrative routes and reasons for treatment at the evaluation of medicinal products was not considered. On the other hand, in the so-called case-control epidemiological studies in general recall bias was not limited. These biases explain that the teratogenic risk of drugs is exaggerated, while the benefit of medicine use during pregnancy is underestimated. Thus, a better balance is needed between the risk and benefit of drug treatments during pregnancy. Of course, we have to do our best to reduce the risk of teratogenic drugs as much as possible, however, it is worth stressing the preventive effect of drugs for maternal diseases (e.g. diabetes mellitus and hyperthermia) related congenital abnormalities.

Key words: human teratogenic drugs, congenital abnormalities, critical period, recall bias, congenital abnormality, preventive effect of drugs.

1. Introduction

Among environmental factors, dangerous lifestyle seems to be the greatest hazard for the development of the fetus due to the common practice of consuming alcohol and smoking tobacco. Alcohol may cause fetal alcohol syndrome or at least fetal alcohol effects [1,2]. It is preventable by abstinence during pregnancy but often unavoidable because approximately 50% of pregnancies are unplanned and hence alcohol consumption occurs before a woman knows that she is pregnant. Recently the teratogenic potential of smoking has been shown in some congenital abnormalities (CAs), particularly terminal transverse type of limb deficiencies [3] and Poland sequence [4], while the gene-environmental interaction was shown in the origin of orofacial clefts [5]. The role of teratogenic effect of environmental pollutants such as methyl mercury [6] was also reported but we cannot estimate the magnitude of this problem. The primary prevention of infectious diseases by vaccination is extremely important particularly in the prevention of CA-syndromes caused by rubella and varicella viruses. Here we focus on teratogenic medication and their prevention.

2. Human teratogenic drugs

In Hungary 92% of pregnant women used medicinal products and the mean number of drugs and pregnancy supplements per pregnant women was 3.4 between 1980 and 1996. About 70% pregnant women were treated with drugs during pregnancy [7]. These figures are in agreement with a recent publication [8].

Experts in many countries have set up risk classification systems based on data from human and animal studies to help physicians interpret the risk associated with drugs during pregnancy. The most well-known classification was introduced by the US Food and Drug Administration (FDA) in 1979, using the letters A, B,

C, D and X for five categories [9]. The definition of category A means no risk, and any risk is unlikely in category B. There is no appropriate data for drugs in category C. The definition of category D is as follows: "There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk" (e.g. in a life-threatening situation). Finally, drugs with classification X are "Contraindicated in women who are or may be pregnant". We do not like this classification system, because all oral contraceptives and female sex hormones (both estrogens and progestins) were classified as X though we have no evidence of a teratogenic effect. It is another matter that these hormones are not indicated during pregnancy. We only found an association between very high doses of oestrogens and unimelic terminal transverse type of limb deficiency when oestrogens were used to induce illegal abortion [10]. This general teratogenic risk for limb deficiency was about 1% instead of the usual 0.05%. On the other hand teratogenic and fetotoxic effects are confused though they have different time factors and consequences. Finally some other drugs were classified as X without any evidence for teratogenic risk (e.g. clomiphene) or with much debated findings (e.g. benzodiazepine such as flurazepam, quazepam, temazepam and triazolam). This problem is more serious in the groups of drugs with classification D because many drugs were classified without any data and were based only on the general similarity of the chemical structure. However, mild differences in the chemical structure can change the teratogenic potential, for example the teratogenic oxytetracyclines and non-teratogenic doxycycline within the group of tetracyclines. At present the population-based Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) [11] contains the largest national case-control data set in the world where the teratogenicity of about a

hundred drugs was studied. Our findings do not confirm the teratogenic risk of benzodiazepines such as diazepam [12], chlordiazepoxide [13], nitrazepam, medazepam, tofisopam, aprazolom and clonazepam [14]. The teratogenic effect of diazepam and some other benzodiazepines was not confirmed after self-poisoning (i.e. suicide attempt) with extremely large doses [15,16]. The teratogenic effect of barbitals [17], furosemide [18], aminoglycoside antibiotics [19] and povidone-iodine [20] was also not found. After the negative findings of our studies we cannot accept the risk estimation of the FDA classification system. Similar opinions were stated by other experts as well, therefore two other drug classification systems have been developed in Sweden [21] and Australia [22].

There are about 8,200 medicinal products in the Hungarian market, however, the number of chemical substances, i.e. generic drugs with human teratogenic risk is limited. Table 1 shows drugs with *high and moderate teratogenic risk*. Thalidomide was never marketed in Hungary, however, it is used again in some countries (e.g., Brazil) as an effective drug for leprosy and other diseases. Androgenic hormones are not indicated in the treatment of pregnant women, nevertheless some women used these drugs at the beginning of their unplanned pregnancies due to their body building activity. At present isotretinoin and etretinate are considered the most teratogenic risk used for the treatment of acne and psoriasis in Hungary, therefore an effective campaign was organized to prevent their use during pregnancy. The coumarin derivatives cause the largest clinical problem because pregnant women with a previous thrombosis history frequently need treatment. However, it is possible to change the treatment protocol and use heparin instead of coumarin derivatives in the early pregnancy because the latter drugs are teratogenic in the third and fourth months of gestation. Oxytetracyclines are also teratogenic, but these products are now not on the market. The use of oxytetracyclines was relatively frequent in Hungarian pregnant women, thus we were able to show that Tetran[®] induced - other than staining of deciduous teeth - a characteristic pattern of multiple CA [23]. On the other hand doxycycline is not teratogenic [24]. The use of D-penicillamine (e.g. in Wilson disease) rarely occurs and it may cause cutis laxa, not a severe CA. In addition this CA can be diminished by the parallel use of zinc. Diethylstilbestrol was also withdrawn from the market. The proportion of women treated with drugs with high and moderate teratogenic risk during the study pregnancy was 0.8% and 0.4% in the group of cases with CAs and controls without CAs in the data set of the HCCSCA, 1980-2002, respectively.

The list of drugs with *low and very low teratogenic risk* is longer (Table 2), though the names of drugs with fetotoxic effects, e.g., chlorothiazide, angiotensin-converting enzyme inhibitors, beta-adrenergic blocking agents, reversible goiter inducing potassium iodine, etc, are not mentioned. There is a long list of antineoplastic and anticonvulsant drugs which may be needed in pregnant women with cancer or epilepsy. At present some of them are not on the market, but most drugs in this list have a teratogenic risk between 2 and 5%. Ergotamine and quinine derivatives were used relatively frequent. Among oestrogens and retinol (vitamin A), only high dose treatments are considered. It is worth mentioning that we had three mothers who were treated by 50,000 and one

with 100,000 IU doses of vitamin A daily in the first and second months of gestation, and later they delivered newborn infants without any CAs [25]. Our finding is in agreement with the conclusion of the European Network of the Teratology Information Services, whose data set did not provide evidence for an increased risk of major CAs associated with high vitamin A intake (10,000 IU per day or more) during the organogenetic period of embryo [26].

Here we discuss three problems at the evaluation of human teratogenic risk of drugs.

I. Low scientific quality of previous human teratogenic studies

Unfortunately the scientific quality of most previous studies regarding risk estimation of teratogenic medications was low due to some methodological problems.

Time factor: first trimester concept is outdated

The first trimester of pregnancy was considered as the critical period of most major CAs. This supposition is unscientific and outdated [27].

At present gestation age is calculated from the first day of the last menstrual period. Thus, "pregnant women" are not pregnant in the first two weeks of their pregnancies. The third week covers the preimplantation period when the zygote goes from the external end of the Fallopian tube to the uterus. The fourth week comprises the implantation period when the blastocyst finds its site in the uterus. However, the zygotes and blastocysts have continuous mitoses producing totipotent stem cells during this period. Serious damage can cause their death, but after limited damage they have a complete recovery. These facts explain the rule of "all-or-nothing effect" or in other words the consequence of these damages have only two outcomes: complete loss of zygotes/blastocysts (which causes only some delay in the seemingly menstrual bleeding) or healthy birth.

In conclusion, human teratogenic drugs cannot induce CA in the first month of gestation because the specific activation of DNA in the stem cells and the so-called differentiation of specific cells, organs and body forms starts on the 29th day of gestation (or on the 15th postconception day). The 29th day of gestation overlaps with the first days of missing menstrual bleeding when women in general can recognize the pregnancy. Thus, it is necessary to know that before the first missed menstrual bleeding, environmental factors cannot induce CAs. The main organ-forming period lasts from the 29th day to the 70th day of gestation. The evaluation of the first trimester is therefore a serious methodological error, only *the second and third months represent the critical period of most major CAs*. On the other hand we know that the critical period of some CAs exceeds the end of third month, e.g., the critical period of posterior cleft palate and hypospadias covers the 12th-14th and 14th-16th weeks of gestation, while the critical period of undescended testis and patent ductus arteriosus is 7 to 9 months and 9 to 10 months, respectively. Thus, the optimal approach is to consider the specific critical period of each CA [7] separately.

Specificity of teratogens

It is not worth studying the total group of CAs because CAs have different etiological backgrounds. Therefore we have to focus our analysis on specific CAs since teratogenic drugs induce *specific CAs* without affecting other CAs and overall rates. Thus, we have to do

our best to develop groups of CAs as homogeneous as possible. In addition the most teratogenic drugs cause *specific CA syndromes* with a characteristic pattern of component CAs. This phenomenon explains the delineation of fetal alcohol, radiation, rubella, hydantoin-phenytoin, warfarin-coumarin, accutane, etc. syndromes. This rule helps us to identify the cause of specific CA-syndrome, e.g., if a case is affected with cleft lip and nail hypoplasia, we can diagnose hydantoin (phenytoin) CA-syndrome in a baby of an epileptic mother who has been treated with this drug.

Another common and serious methodological error occurs when isolated (single) and multiple (syndromic) manifestations of the seemingly same CAs are combined and evaluated together. Most isolated CAs have a complex etiology based on some polygenic predisposition which is triggered by environmental risk factors. The seemingly similar component CAs within multiformed or syndromic cases are caused by chromosomal aberrations, gene mutations or teratogens [28]. We can easily prove the different etiopathogenetic background of isolated and multiple CAs by epidemiological methods. For example, isolated cleft lip has a left sided and male predominance while component cleft lip in syndromic cases has no side predominance and the sex ratio corresponds to the usual population figure [29]. Thus, it is an important rule to evaluate the isolated and multiple manifestations of the same CA separately.

The importance of different chemical structures, administrative routes and reasons for treatment at the teratogenic evaluation of medicinal products was not considered

In general, similar drugs were evaluated together such as penicillins, tetracyclines, cephalosporins (or sometimes as "antibiotics") and sulfonamides in the past. This approach is not correct because each drug within these groups has different chemical structure. As we mentioned previously within the group of tetracyclines, oxytetracyclines [23] were teratogenic while doxycyclines [24] were not teratogenic. At the evaluation of seven orally used sulfonamides, only two showed teratogenic potential, and they induced different CAs [30].

Our studies showed the importance of interaction of different drugs. We were not able to find a clinically important teratogenic effect after the use of oral metronidazole [31] and the topical miconazole treatment resulted in an obvious negative finding [32]. Nevertheless, the vaginal use of the combination of these two drugs increased the risk for poly/syndactyly six fold [33].

Our analyses also demonstrated that it is necessary to differentiate the administrative route of drugs and their teratogenic potential. We should therefore evaluate the use of the same drugs (e.g., corticosteroids and antifungal agents) according to oral, parenteral, topical (skin, vaginal, eye and ear) and inhaled aerosol treatments separately.

Finally it is necessary to differentiate drugs and pregnancy supplements within medicinal products. Drugs are used for the *treatment* of maternal diseases and pregnancy complications during pregnancy while pregnancy supplements such as folic acid, other vitamins [34], iron, calcium, multivitamins, etc are given to *prevent* pregnancy complications and unsuccessful pregnancy outcomes particularly CAs. These opposite effects of medicinal products have to be considered when evaluating the drugs.

II. Recall bias

The birth of an infant with a CA is a serious traumatic event for most mothers, who therefore try to find a causal explanation such as drug use during pregnancy, something that does not occur after the birth of a healthy infant. Thus the mothers of babies affected with CAs are continually thinking of possible dangerous environmental factors and when asked about the history of their pregnancy, give a long list of supposed agents. On the other hand the mothers of healthy babies are thinking of the present and future of their babies and are likely to forget events during the pregnancy. Retrospective (i.e., after the birth) maternal self-reported information therefore is different in the groups of case and control mothers and this recall bias can mimic an increased risk of drugs in the CA-groups up to an odds ratio of 1.9 (35). Thus a higher risk of less than 1.9 should be interpreted cautiously. In addition, it is possible to reduce recall bias.

Firstly, we evaluate 25 CA-groups and we expect a higher occurrence of one or some CA-groups after the use of the given drug due to the specificity of teratogens. Recall bias may act for all CAs similarly.

Secondly, the use of the drug under study is evaluated during the critical period of CA formation, in general the second and third months of gestation. We may suppose that the teratogenic effect of the drug is shown only during this period because we expect an underreporting of exposure in both the critical and non-critical periods of CA formation in the mothers of healthy babies, i.e., in the population control group.

Thirdly, an independent and prospective source of drug exposure data, e.g., the medically recorded data in the prenatal logbook may serve as a gold standard. Our validation study, however, showed that a small group of pregnant women (2.4%) did not use prescribed and medically recorded drugs or they shortened the duration of treatment due to the supposed teratogenic risk [36]. Another independent and prospective source of drug exposure can be found in pharmacy records [37].

Fourthly, it is worth using a patient control group including mothers of cases with other CAs. In our HCCSCA system, cases with Down syndrome are used as patient controls [11] because the cause of this numerical chromosomal aberration (trisomy 21) is not connected with the teratogenic effect of agents during pregnancy, and particularly in the critical period of most CA formation, i.e., during the second and third months of gestation.

Fifthly, "true" teratogens such as rubella virus, radiation, alcohol, hydantoin-phenytoin, warfarin-coumarin, accutane, etc., cause multiple CA with a characteristic pattern of CAs. Thus multiformed cases need a special and detailed analysis [28] because these data are not distorted by recall bias. Another group of teratogens plays a role as trigger factors in the origin of isolated CAs based on polygenic-environmental interaction, i.e. multifactorial etiology.

III. Teratogenic risk of drugs is exaggerated.

The exaggeration of drug teratogenicity can be explained by several factors.

1. At present the average number of children per family in Hungary is about 1.3 compared to 11 in the 19th century. In the past, the social role of females was the "reproduction" of human beings. Now they take part in the social "production" outside their homes similar to

males but they have to fulfill their traditional role of reproduction as well. A malformed or disabled child curtails their social activity hence the emphasis on having a healthy baby.

2. The positive findings of animal investigations are frequently extrapolated for the human fetus contrary to the well-known species specificity.

3. The previous teratologic studies had several methodological weaknesses and recall bias which are summarized above and which resulted in false positive findings.

4. The editors of scientific periodicals have an aversion to publishing papers with negative results, but are happy to publish selected case reports and the positive findings of animal and human epidemiological studies. This publication bias distorts the thinking of experts as well as the general population.

5. The false balance of risk and benefit of drug use during pregnancy is seriously augmented by the defensive policy of pharmaceutical companies and regulatory agencies which are gradually labeling most drugs with the recommendations to avoid their use during pregnancy, at least in "the first trimester".

6. This unbalanced opinion is amplified by a self defensive attitude of some doctors and is partly understandable. They may not be well informed and may exaggerate the risk by relying on manufacturers drug pamphlets. They may also be thinking about possible law suits and are therefore over cautious forgetting that the chance of any pregnancy ending with a baby who has a major CA is approximately 3%.

The exaggeration of teratogenic risk of medicinal products causes several hazards.

First, many pregnant women do not get the necessary drug treatment and it results in serious consequences both for the mothers and their fetuses. If influenza [38] and other acute infectious diseases of respiratory system [39] with high fever in early pregnancy are not treated by appropriate methods including drugs, therefore the teratogenic effect of hyperthermia can induce hyperthermic embryopathy (Table 3), among others, neural-tube defects. In Hungary, about 40 % of pregnant women have some sexually transmitted infections and/or diseases in their genital organs [40]. Most medical doctors do not dare to treat them, therefore the ascending infections are followed by preterm birth and serious intrauterine infection of the fetus. Our study showed that the fetuses of inappropriately or untreated asthmatic pregnant women have a higher risk for intrauterine growth retardation [41].

Second, many planned and wanted pregnancies are terminated due to the anxiety and fear created by the notion that nearly all drugs cause CAs [42]. Recently the number of induced abortions before the 12th week of gestation is about 60,000 per year in Hungary and about 3,000 are terminated due to a medical indication connected to drug use during pregnancy. However, our analysis showed that the great majority of these pregnancy terminations had unfounded medical indications [43].

Third, pregnant women using necessary drug treatments may suffer permanent psychological stress and may be seriously depressed until the end of the pregnancy [44].

Fortunately the scientifically proved human teratogenic drugs are not used frequently in pregnant

women (Table 1 and 2). The total proportion of CAs induced by drugs is less than 1 % in the database of the HCCSCA, if we calculate 65.27 per 1,000 total rate of CAs in Hungary [45].

3. Benefit of medicine use during pregnancy is underestimated

Maternal drug use during pregnancy may pose a teratogenic risk for the embryo. However, the recommendation to avoid all drugs during early pregnancy [42] is unrealistic and may be dangerous. About 8% of pregnant women need permanent drug treatment due to their chronic diseases such as epilepsy, diabetes mellitus, bronchial asthma, hypertension, thyroid disorders, migraine, and severe depression [40]. More pregnant women require transient drug treatment because of influenza, acute infectious diseases of respiratory system and urogenital organs, the latter mainly due to sexually transmitted infections. In addition, headache, nervousness, constipation and other common complaints may also need drug treatments. Finally there are many pregnancy complications such as nausea and vomiting, threatened abortion, preterm delivery, toxemia and anemia which may also require drug treatments.

The benefits of medicine use during pregnancy are not restricted to the recovery of maternal health but also result in some advantages for the fetus as well, because the maternal well-being is important for the optimal development of the fetus. Poorly controlled diabetes mellitus, particularly type 1 is teratogenic. However, the appropriate management of diabetic pregnant women can prevent diabetic embryopathy [46]. In addition the effective treatment of infectious diseases of genital organs can significantly reduce the prevalence of preterm birth and its related effects, among others, undescended testis [47]. Finally the periconceptual folic acid or folic acid-containing multivitamin supplementation can prevent most neural-tube defects [48] and a considerable number of CAs in the cardiovascular system, urinary tract and limb deficiencies [49-51].

Previously we mentioned that less than 1 % of CAs may be caused by human teratogenic drugs. The number of CAs induced by human teratogenic drugs is about 6 per 1,000 on the basis of Table 1 and 2 (Table 3). Of course, we have to do our best to limit this risk. However, there is another aspect of CA prevention which is connected with drug use. High fever (at least 38.9°C) due to influenza [38] and acute respiratory diseases [39] during the second and third months of gestation occurs in about 4% of pregnant women in Hungary. Offspring of these pregnant women have a higher risk for neural-tube defects, cleft lip with or without cleft palate, posterior cleft palate and some other CAs. The total number of CAs which may be associated with hyperthermia is 8.7 per 1,000 and these CAs can be prevented by effective antifever therapy, including drugs (Table 3). Thus our estimation shows that CA-preventive effect of only antifever drugs may exceed the CA risk caused by all human teratogenic drugs.

Thus, a better balance is needed between the risk and benefit of drug treatments during pregnancy.

4. General conclusions

1. The use of teratogenic drugs should be avoided during pregnancy in less severe (non life-threatening) diseases such as acne and psoriasis.

2. It is necessary to select non-teratogenic drugs instead of teratogenic drugs during pregnancy if possible and not harmful for pregnant women. The best example for this strategy is to replace coumarin derivative with heparin in early pregnancy.

3. The necessary use of teratogenic drugs may have to be continued in severe maternal diseases such as epilepsy and cancer if the discontinuation of treatment causes worsening of the disease and pregnant women agree with it.

4. Teratogenic drugs cannot cause CAs if the exposure is in the first month of gestation and in general after the third month of pregnancy. However, the fetotoxic effect of some drugs should be considered in the second part of pregnancy.

5. Recent effective ultrasound scanning can detect major fetal defects about the 18th-20th week of gestation with a high degree of efficacy. Thus we have a chance to evaluate the risk after the inadvertent or necessary use of teratogenic drugs during pregnancy. If serious fetal defects are detected, the couple can then be given information to help them decide whether to terminate their pregnancy or not.

6. The use of non-teratogenic drugs may prevent the teratogenic effect of maternal diseases such as diabetes mellitus, influenza, and other acute infectious diseases with high fever and this preventable part of CAs exceeds the proportion of CAs caused by teratogenic drugs.

7. The periconceptional folic acid-containing multivitamin supplementation can prevent the major proportion of neural-tube defects and a considerable portion of cardiovascular, urinary tract CAs and limb deficiencies. According to the estimation of the WHO expert committee about one-third of major CAs are preventable by this new primary preventive method. Folic acid alone will also significantly reduce the first occurrence and recurrence of neural-tube defects. [52]

Conflict of interest

None declared.

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Tables

Table 1. Drugs with high and moderate teratogenic risk, their FDA categories and cardinal congenital abnormalities (CAs) and the number of their use in the mothers of cases with CA and controls without CAs in the HCCSCA, 1980-2002

Chemical substance (generic name)	Trade names	FDA risk categories (%)	CAs	Cases (N=29,922)	Controls (N=52,299)
<i>High risk (more than 25%)</i>					
Thalidomide	Contergan	* 75	Phocomelia, CAs of external ear, Facial hemangioma	0	0
<i>Moderate risk (10-25%)</i>					
Androgenic hormones		40	Masculinized external genitalia in girls		
Danazol	Danaval	X		0	0
Methyltestosterone	Ambosex	X		2	0
Nandrolone	Nerobolil	X		6	10
Isotretinoin	Accutane	X 25	Microtia	1	1
	Roaccutan		Cardiac CAs		
Etretinate	Tigason	X 25	Small ear	0	0
	Neotigason		Adactyly Cardiac CAs		
Coumarin derivative	Warfarin, Dicumarol, Syncumar	D 25	Nasal hypoplasia-depressed nasal bridge	6	8
Oxytetracycline	Tetramycin, Tetran, Chlomocycline	D 20	Staining of deci-duous teeth	206	199
D-penicillamine	Duprenil, Byanodine	D 15	Cutis laxa	2	3
Diethylstilbestrol	Stilbestrol, Syntestrin	X 15	Clitoromegaly, Hypotrophic testis	11	8
Total No.				234	229
%				0.8	0.4

*not approved in USA, therefore thalidomide was not classified

Table 2. Drugs with low (less than 10%) and very low (less than 3 %) teratogenic risk used in Hungary and the number of cases and controls in the HCSCA, 1980-2002

Chemical substances (generic name)	Trade names	FDA category	Cases (N=29922)	Controls (N=52599)
<i>Antineoplastic drugs</i>				
Azathioprine	Imuran	D	2	2
Cyclophosphamide	Cytoxan	D	2	0
Chlorambucil	Leukeran	D	0	1
Mannomustine	Degranol	D	0	5
Melphalan	Alkeran	D	0	1
Mercaptopurine	Leupurin	D	0	1
Methotrexate	Methotrexat	D	1	0
Mitobronitol	Myelobromol	D	6	19
Ritrosulfane	Lycurim	D	0	2
Vincristine	Vincristin	D	2	0
Subtotal			13	31

<i>Anticonvulsant drugs</i>				
Clonazepam	Antelepsin	C	6	5
	Clonazepamum			
	Rivotril			
Carbamazepine	Azepal	B	47	41
	Neurotop			
	Stazepine			
	Tegretol			
	Temporal			
	Timonl			
Ethosuximide	Suxilep	C	4	3
Lamotrigine	Lamictal	C	10	1
Mephenytoin	Sacerno	C	8	5
Morsuximide	Perlepsin	*	4	4
Oxcarbazepine	Trileptal	D	1	0
Phenacemide	Neophedan	*	3	2
Phenytoin	Epanutin	D	35	39
	Diphedan			
Primidone	Mysoline	D	25	13
	Sertan			
Sultiame	Ospolot	D	12	2
Trimethadione	Ptimal	D	4	1
Valproic acid	Convulex	D	41	15
	Depakine			
	Everiden			
	Orfiril			
Subtotal			200	131
<i>Others</i>				
Ergotamine	Ergam	D	37	64
	Kefalgin			
	Neo-Gynofort			
	Secadol			
Oestrogens very high dose	Akrofolin	D	20 (40)	8 (43)
	Hogival			
	Limovan			
	Limovanil			
	Ovestin			
	Strytanon			
Methimazole (thiamazole)	Metothyryn	D	10	1
Misoprostol	Cytotex	X	0	1
Lithium	Litium karbonat	D	10	16
Quinine	Chinidinum	D	40	85
	Chinacisal			
	Diapulmon			
Retinol very large dose	Vitamin A	A (X)	0 (39)	4 (95)
Total No.			340	341
%			1.1	0.6

*not approved in USA, therefore was not classified

Table 3. Comparative analysis of CAs induced by human teratogenic drugs and maternal hyperthermia due to influenza and acute infectious diseases of respiratory system

Human teratogenic drugs		Entire pregnancy	Maternal hyperthermia due to influenza and acute infectious respiratory diseases	
Cases	Controls		Cases	Controls
1.9%	1.1%		14.5%	13.4%
OR with 95% CI 1.79 (1.59 - 2.01)			OR with 95% CI 1.09 (1.04 - 1.15)	
1.4%	0.8%	Second and third months	4.5%	3.7%
OR with 95% CI 1.74 (1.52 - 2.00)		No. of CAs per 1000 informative offspring due to teratogenic factors under study	OR with 95% CI 1.25 (1.15 - 1.36)	
6.0 (4.2 - 8.0)			8.7 (5.3 - 12.5)	