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Pharmacovigilance in pregnancy: adverse drug reactions associated with fetal disorders

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Abstract

Objective: To provide the first update on drug safety profiles and adverse drug reactions (ADRs) associated with fetal disorders from the Swiss national ADR database.
Methods: We conducted a retrospective study using data from 202 pharmacovigilance reports on drug-associated fetal disorders from the Swiss national ADR database from 1990 to 2009. Evaluated aspects included administrative information on the report, drug exposure, and disorders.
Results: The ADR reporting frequency on the topic of fetal disorders has increased during the last 20 years, from only 1 report in 1991 to a maximum of 31 reports in 2008. Nervous system drugs were the most frequently reported drug group (40.2%) above all antidepressants and antiepileptics. The highest level of overall drug intake could be observed for the 1st trimester (85.4%), especially for the first 6 weeks of pregnancy. The most frequently reported types of fetal disorders were malformations (68.8%), especially those of the musculoskeletal and circulatory systems. A positive association was discovered between antiepileptics and malformations in general and in particular of the circulatory system and the eye, ear, face, and neck.
Conclusions: The results suggest that the nervous system drug group bears an especially high risk for malformations. The most commonly identified drug exposures can help focus pharmacoepidemiologic efforts in drug-induced birth defects.

Keywords: Drug use; fetal disorders; pharmacovigilance; pregnancy; safety; teratovigilance.

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Introduction

Despite lingering safety questions, pregnant women may intentionally or inadvertently be exposed to various prescription drugs for pregnancy and non-pregnancy indications. Current utilization studies that ascertain the most commonly used drugs in pregnancy are important for establishing priorities in birth-defects research with major public health implications [11].

Studies conducted among pregnant women in the USA and in some European countries show exposure to high rates of prescription medications, including exposure to medications with known teratogenic potential [1, 2, 7, 10, 16]. Engeland et al. [7] found that among more than 100,000 pregnant women in Norway in 2004–2006, approximately 57% received a prescription medication. Studies from France and Germany showed an even higher rate of more than 85% [6, 15].

However, at the time of marketing, there exist little data on the safety of a drug used in pregnancy and adverse drug reactions (ADRs) on the fetus. Initial data on a drug's safety profile concerning its use during pregnancy are provided prior to marketing by reproductive toxicity studies in animals. Such studies are quite reliable for the detection of a drug's teratogenic potential because only few drugs that did not show a teratogenic effect in animals are later found to be teratogenic in humans. However, because of differences in the species' pharmacokinetic profiles, findings about toxic doses in animals can only limitedly be extrapolated to humans. Furthermore, clinical trials in drug development generally exclude pregnant women for ethical reasons.

These factors increase the importance of ongoing risk assessment in the postmarketing phase. In fact, postmarketing observational studies have revealed associations between many commonly used drugs and various birth defects [3, 4, 26].

The aim of this study was to provide the first update on the existing postmarketing pharmacovigilance data on drug-associated fetal disorders from the Swiss national ADR database.

Materials and methods

Data source

The Swiss national ADR database, called VigiFlow, contains ADR reports from the entirety of Switzerland's approximately 7 million inhabitants. It is held by the national pharmacovigilance center run by the Swiss Agency for Therapeutic Products (Swissmedic), which is the central supervisory authority for therapeutic products in Switzerland. Swissmedic is a public service organization of the federal government and has its headquarters in Berne. Most of the reports are spontaneous (97%); others are sourcing from clinical studies. Reports on observed ADRs are sent by health-care professionals to one of the regional pharmacovigilance centers (RPVCs) located in Zurich, Basel, Berne, Lausanne, Geneva, and Lugano. The RPVCs register, classify, and evaluate the reports and enter them directly into VigiFlow. Moreover, reports on ADRs are collected by the pharmaceutical companies and sent directly to Swissmedic, which enters the incoming reports into VigiFlow. Every report entering VigiFlow is evaluated by a clinical reviewer and checked for quality and completeness. Swissmedic is closely involved in the World Health Organization (WHO) program for drug monitoring and its classification system. For the classification of ADR reports, several international standards, documents, and guidelines are used [5, 13, 21–23] (Table 1). All ADR reports in VigiFlow are directly submitted to WHO's ADR database in Uppsala, Sweden (VigiBase). VigiFlow is compatible with the International Conference on Harmonisation Guideline E2B and complies with international standards [25]. It contains administrative and identification information (e.g., ID number, primary source and sender, and seriousness) as well as information on the case report (patient characteristics and information on suspected and concomitant drugs and ADRs).

Study group

The Swiss national ADR database VigiFlow was searched for all ADR reports from January 1, 1990, until December 31, 2009, categorized in the System Organ Class (SOC) category No. 1500 (fetal disorders) of the WHO-Adverse Reaction Terminology (ART) system. This category consists of predefined terms of abnormal fetal conditions or development occurring during pregnancy or present at birth as well as other negative pregnancy outcomes such as induced abortion. Cases of drug exposure during pregnancy without negative fetal outcome are also included in this category. To restrict the study group to relevant cases of fetal disorders, only reports with sufficient information on at least one negative fetal outcome of the SOC1500 category were included. The exclusion criteria were no information on a negative outcome at all, no negative outcome of the SOC1500 category, or fetal death, intrauterine death, miscarriage, stillbirth, abortion, missed abortion, spontaneous incomplete abortion, or induced abortion as the only reported outcome.

To characterize the study group, the following details from the VigiFlow ADR reports were collected: the report year, the sender, the sender's report number, the report's seriousness (serious, not serious), the reason for seriousness (death, life threatening, hospitalization, disabling, congenital anomaly, other), the number and types of suspected drugs, the active substance with its Anatomical Therapeutic Chemical (ATC) code, the concomitant drugs, the route of administration, the reason for drug intake, the date of drug intake, the date of the last menstrual period, the reported fetal disorders as well as possible neonatal disorders.

Analysis

The gestational age at the time of drug exposure was calculated from the first day of the mother's last menstrual period [weeks post menstruation (p.m.), month or trimester].

Fetal disorders were divided into four subcategories: growth retardation, malformations, chromosomal abnormalities, and other fetal disorders. The subcategory "malformations" was further categorized according to chapter Q of the *International Statistical Classification of Diseases, 10th Revision*, system with respect to the affected organ system.

The reports' quality was assessed by four criteria: ATC code of the suspected drug, route of administration, chronology of drug intake, and listed ADR. A report's quality was categorized as sufficient if all four criteria were provided.

The primary end point was drug exposure (type and number of drugs, gestational age) in relation to observed fetal disorders (focusing on malformations). Secondary end points were parameters characterizing the quality of reports (year, sender).

Statistics

For statistics, the statistical program PASW, version 18, was used. For discrete data, relative frequencies were computed. Continuous parameters were described by mean, standard deviation (SD), median, and interquartile range (IQR). Associations between drugs and disorders were confirmed by the likelihood ratio test and the *t*-test (two-tailed).

Results

The primary search resulted in 1727 cases, of which 1503 cases were ruled out by the exclusion criteria. Of the resulting 224 cases, 16 were excluded as they were incorrectly classified. Another six cases were excluded because they were double reports. The final study group, as defined by the inclusion criteria, therefore included a total of 202 ADR reports from the Swiss national ADR database from January 1, 1990 until

Table 1 Classifications used in VigiFlow.

Reactions/events (ADRs)	WHO-Adverse Reaction Terminology (WHO-ART) [21]
Drugs	WHO-Drug Dictionary (WHO-DD), with information about active ingredients and ATC codes [22]
Medical history/indications	WHO International Classification of Diseases, 10th Revision (WHO-ICD-10) [23]
Seriousness	International assessment criteria, according to ICH E2A and E2D [13]
Causality	WHO classification. Further specification in collaboration with the RPVCs: certain, probable, possible, unlikely, unclassifiable

ADRs=Adverse drug reactions, ATC=Anatomical Therapeutic Chemical, ICH=International Conference on Harmonisation, RPVC=Regional pharmacovigilance center, WHO=World Health Organization.

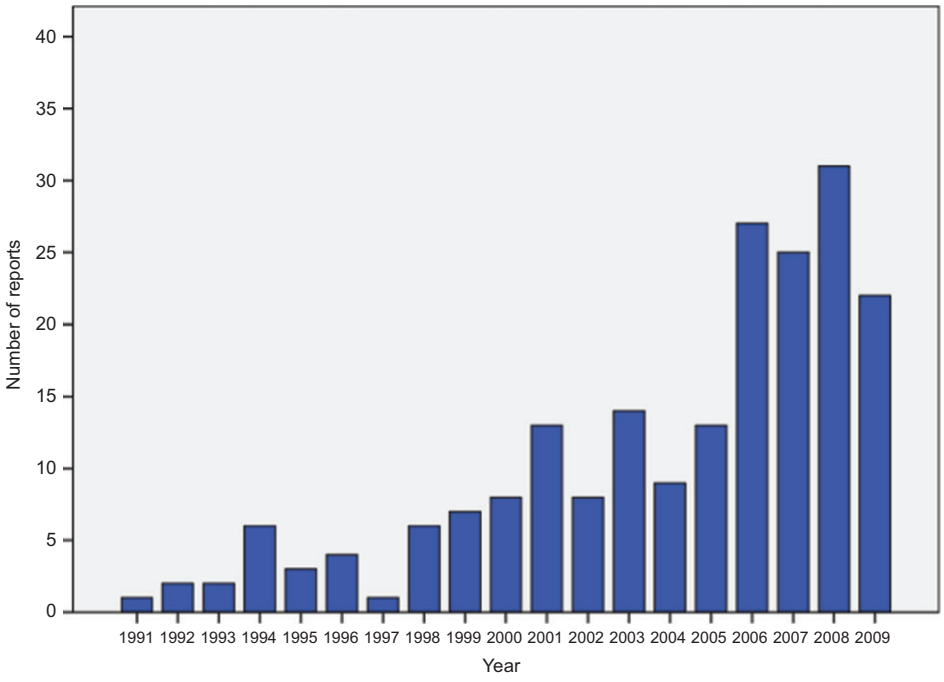

Figure 1 Frequency of reports (n) per year in the study group.

December 31, 2009, with sufficient information on at least one negative fetal outcome of the SOC1500 category.

Reports about fetal disorders have increased considerably during the last 20 years (Figure 1). Starting from 1991 with only one case, the number of reported cases significantly increased in 2006, reaching a maximum in 2008 with 31 reports about fetal disorders. The overall reporting frequency in VigiFlow shows that in the general population also, the number of ADR reports sent per year has increased during the last 20 years (Figure 2).

Most ADR reports were sent by the Swiss Teratogen Information Service (38.6%) followed by the RPVCs (37.6%) and the pharmaceutical companies (21.8%); other senders played only a minimal role (2.0%) (Figure 3).

Sufficient quality (as defined above) was provided for 315 of the reported drugs (87.3%). The most frequent reason for insufficient quality was the missing chronology of drug intake (6.4%) followed by the missing route of administration (3.6%). Within the study group, 78.7% of the reports were classified as "serious" and 21.3% as "not serious". The most frequent special reasons for a report to be classified as serious were "congenital anomaly" (28.3%) and "death" (16.4%).

Drug exposure

A total of 361 suspected drugs were reported in the study group. Most women reported only one suspected drug (58.9%). Two drugs were taken by 22.3% of the women, three drugs were taken by 10.4% of the women, and four or more drugs were taken by 8.5% of the women. The maximum number of suspected drugs reported in a case was nine (mean: 1.79; SD: 1.31; median: 1.00; IQR: 1).

Drugs acting on the nervous system (anatomical main group N) were most frequently reported, whereas drugs from

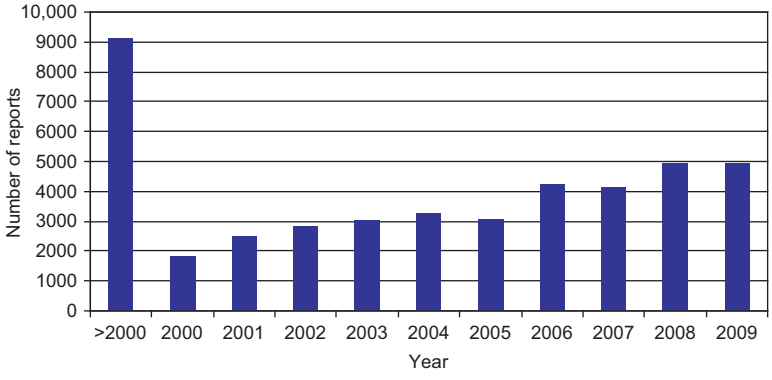

Figure 2 Overall frequency of reports (n) per year in VigiFlow.

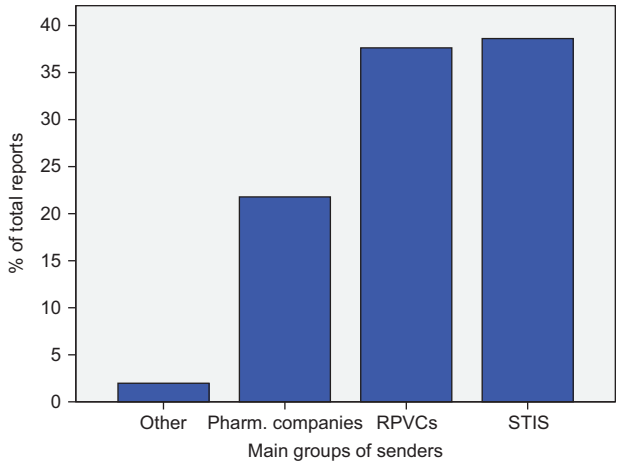

Figure 3 Frequency of reports (%) according to the sender. STIS=Swiss Teratogen Information Service, RPVC=Regional pharmacovigilance center.

other anatomical main groups did not differ significantly from each other in frequency (Table 2). The six most frequently reported therapeutic subgroups were psychoanaleptics (N06, 13%), psycholeptics (N05, 12.5%), antiepileptics (N03, 8.6%), antivirals for systemic use (J05, 5.5%), antiacne preparations (D10, 5%), and antibacterials for systemic use (J01, 4.7%). From the pharmacological subgroups, antidepressants (N06A, 12.5%), antiepileptics (N03A, 8.6%), anxiolytics (N05B, 6.1%), direct-acting antivirals (J05A, 5.5%), antipsychotics (N05A, 5.3%), and antiacne preparations for topical use (D10A, 3.9%) were most frequently reported. The three most frequently reported chemical subgroups were from the nervous system: selective serotonin reuptake inhibitors (SSRIs) (N06AB, 6.9%), benzodiazepines (N05BA, 6.1%), and antidepressants excluding SSRIs (N06AX, 4.7%).

The drug intake per trimester could be assessed for 329 of the reported 361 drugs; 25.8% were taken in all three trimesters. Most drugs were consumed in the 1st trimester (85.4%), followed by the 2nd trimester (44.1%) and the 3rd trimester (36.5%). The drug intake per week of pregnancy could be assessed for 284 drugs. It shows a high intake in the 1st trimester, mainly during the first 6 weeks p.m. (range: 57.7%–67.6%). In week 7, the drug intake was 50.0% and decreased further afterwards (Figure 4).

Disorders

Among fetal disorders, malformations were most frequently reported (68.8%) followed by growth retardation (18.3%) and other fetal disorders (17.8%). Chromosomal abnormalities were reported in 6.9% of the cases (Figure 5). In cases of malformation, the most frequently afflicted organ system was the musculoskeletal system (35.3%), followed by the circulatory system (25.2%). Malformations of the eye, ear, face, and neck (15.1%), malformations of the urinary system (13.7%), of the nervous system (12.9%), of genital organs (7.9%), as well as "other malformations" (7.9%), cleft lips and cleft palates (7.2%), and malformations of the digestive system (6.5%) were reported less often (Figure 6).

Statistically significant associations between drugs and disorders were confirmed for antibacterials for systemic use (J01) and chromosomal abnormalities and fetal death, respectively, as well as for antiepileptics (N03) and malformations (in general and particularly of the circulatory system and the eye, ear, face, and neck) and neonatal disorders, respectively (Table 3).

Discussion

The first study about ADR reports in Switzerland focusing on the WHO-ART SOC category No. 1500 (fetal disorders) includes all reports of the existing (since 1990) Swiss national ADR database.

Table 2 Frequency of anatomical main groups.

Anatomical main groups.		Frequency, n (%)	95% CI	
			Lower	Upper
A	Alimentary tract and metabolism	31 (8.6)	5.5	11.4
B	Blood and blood-forming organs	10 (2.8)	1.1	4.4
C	Cardiovascular system	21 (5.8)	3.6	8.3
D	Dermatologicals	28 (7.8)	5	10.5
G	Genitourinary system and sex hormones	15 (4.2)	2.2	6.4
H	Systemic hormonal preparations (excluding sex hormones and insulins)	10 (2.8)	1.1	4.7
J	Antiinfectives for systemic use	41 (11.4)	8.3	14.7
L	Antineoplastic and immunomodulating agents	24 (6.6)	4.2	9.7
M	Musculoskeletal system	10 (2.8)	1.4	4.7
N	Nervous system	145 (40.2)	35.5	45.2
P	Antiparasitic products, insecticides and repellents	9 (2.5)	1.1	4.2
R	Respiratory system	14 (3.9)	2.2	6.1
V	Various	2 (0.6)	0	1.4
	Unknown	1 (0.3)	0	0.8
Total		361 (100)	100	100

CI=Confidence interval.

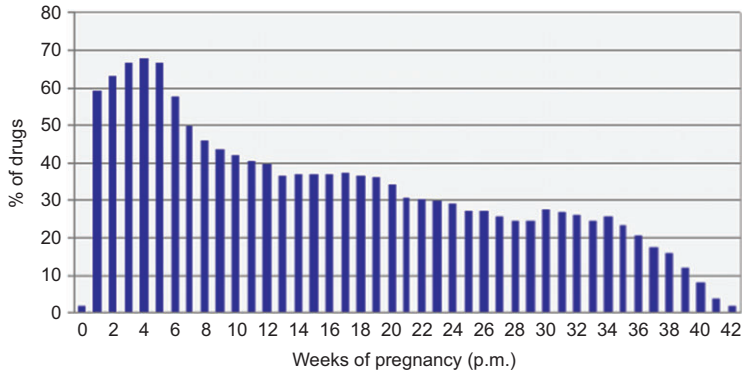

Figure 4 Drug intake per week of gestation.

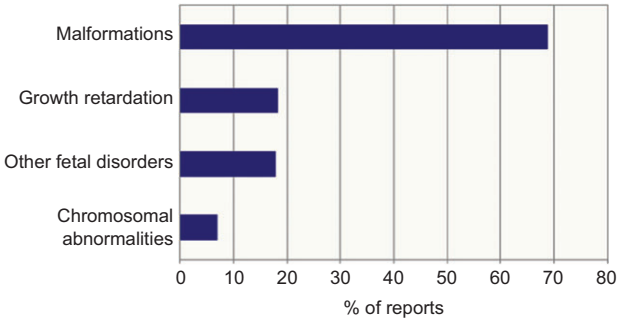

Figure 5 Type of fetal disorder (frequency, %) in reports.

We have been able to show that the number of reports on the topic of fetal disorders has increased considerably. This may be a result of the development and improvement of the reporting system in Switzerland, which is now working much more efficiently than 20 years ago rather than of an increase in the appearance of fetal disorders over the years. This interpretation is supported by the overall reporting frequency in VigiFlow, which shows that not only in the study group but also in general the number of ADR reports sent per year has increased during the last 20 years. Not only the number but also the quality of the reports has increased with the years. For 87% of the reported suspected drugs, the informational content could be classified as sufficient. Information about the time of drug exposure was missing entirely for only 6.4% of the drugs, demonstrating a good overall quality of reports.

In almost 60% of the cases, only one suspected drug was reported. This simplifies the evaluation of the cases regarding the association between drug and ADR. The finding that an association between drugs and fetal disorders was most frequently reported for drugs acting on the nervous system (N) (40.2% of all drugs) has to be interpreted carefully. It does not necessarily mean that these drugs are the most dangerous ones. If these data are compared with the overall reporting frequency in VigiFlow, it becomes obvious that drugs acting on the nervous system (N) are also the most frequently reported anatomical main group throughout the general population. Drugs acting on the nervous system (N) are widely used and, more importantly, are the drug group of primary interest concerning ADRs. These factors should be borne in mind when drawing conclusions from these data.

The fact that 25% of the drugs were taken during the whole pregnancy indicates a high percentage of long-term therapies during pregnancy. More drugs were taken in the 1st trimester (85.4%) than in the 2nd (44.1%) and the 3rd (36.5%) trimesters. Our data are in contradiction with those of other authors who have found an increase in the number of exposed women and the number of prescribed drugs during pregnancy [6, 14]. One explanation could be that in the other studies only prescribed

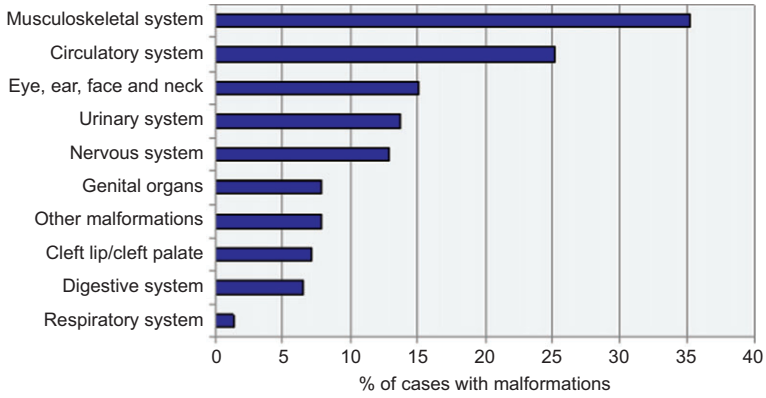

Figure 6 Type of malformations (frequency, %) in the subclass “malformations”.

Table 3 Drugs and corresponding disorders.

	ATC therapeutic subgroups						
	D10	J01	J05	N03	N05	N06	Other drugs
Fetal disorders							
Growth retardation							
Malformations				+			
Eye, ear, face, and neck				+			
Circulatory system				+			
Chromosomal abnormalities		+					
Other fetal disorders							
Fetal death		+					
Neonatal disorders				+			
Other disorders							+

Likelihood ratio test and *t*-test with significance level of 5%+positive association ($P<0.05$).
ATC=Anatomical Therapeutic Chemical, J01=Antibacterials for systemic use, N03=Antiepileptic drugs, "other drugs"=ATC therapeutic subgroups other than D10, J01, J05, N03, N05, and N06.

drugs were assessed while in this study any kind of drug intake (including self-medication and medication errors) was evaluated. Furthermore, in this study only cases with a negative fetal outcome, which occurred more frequently after drug intake in the 1st trimester, were analyzed.

Malformations were the most frequently reported subcategory of fetal disorders. The circulatory and the musculoskeletal systems were the most frequently affected organs, suggesting a higher susceptibility compared with other organ systems. Our data are in line with data from other sources such as from EUROCAT, 2000–2008 [8], or from Sachsen-Anhalt, Germany, 2008 [9].

The association between antiepileptics (N03) and malformations is widely described in the literature, suggesting that antiepileptic drugs (AEDs) (especially valproate but also other AEDs such as phenobarbitone, phenytoin, and carbamazepine) are potentially teratogenic [12, 19, 20] and that the exposure to AEDs is associated with a two- to threefold increased risk for congenital malformations [12, 18, 24]. Data from the North American Antiepileptic Drug Pregnancy Registry 2010 show that valproate is associated with a significantly higher risk (about twice as high) of malformations than other antiepileptics [17, 26]. In our study group, valproate was used in only 15 cases, and we are therefore unable to statistically describe the effect of valproate alone on the frequency or type of malformations. Nevertheless, we have been able to demonstrate that the association between antiepileptics and malformations is focused on the circulatory system, the eye, ear, face, and neck, whereas other authors have earlier described an association between antiepileptics and malformations of the circulatory system only [18–20].

Conclusions

A substantive amount of information on pharmacovigilance has been gained from the Swiss national ADR database's reports associated with fetal disorders.

Our results have demonstrated the important relationship between drugs acting on the nervous system and malformations of the circulatory system as well as the relationship between nervous system drugs and malformations of the eye, ear, and neck. It is hoped that this study will lead to further prospective pharmacoepidemiological and pharmacovigilance studies confirming these results.

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