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ORIGINAL ARTICLE

Prescribing during pregnancy and lactation with reference to the Swedish classification system

A population-based study among Danish women

CHARLOTTE OLESEN[1], HENRIK TOFT SØRENSEN[2], LOLKJE DE JONG-VAN DEN BERG[3], JØRN OLSEN[1], FLEMMING HALD STEFFENSEN[4] AND THE EUROMAP GROUP*

From the [1]Danish Epidemiology Science Centre, Department of Epidemiology and Social Medicine, University of Aarhus, the [2]Department of Internal Medicine V, Aarhus University Hospital, the [3]Department of Social Pharmacy and Pharmacoepidemiology, Groninger Utrecht Institute for Drug Exploration (GUIDE), University of Groningen and the [4]Department of Medicine M, Aalborg Hospital, Aalborg, Denmark

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Aim. To assess the current prescribing pattern for 15,756 primiparae before, during, and after their pregnancies with reference to fetal and neonatal risk.
Method. A prescription database study with linkage to The Danish Medical Birth Registry from 1991 to 1996. The drug subsidy system in Danish retail pharmacies, made it possible to identify prescriptions by individual use. All 34,334 prescriptions were set against the Swedish classification of risk of drug use in pregnancy and lactation.
Results. During pregnancy, safe (group A), potentially harmful (group B3, C, and D), and non-classifiable drugs accounted for 40.9%, 26.6% and 28.7% respectively. The proportion of women who redeemed drugs was 29.2%, 8.6%, 18.7% and 0.9% from drug groups A, B, C and D respectively. The proportion of prescriptions from high risk groups declined during the course of pregnancy. Postpartum, safe drugs (group I and II), drugs with possible harmful neonatal effects (group III), and non-classifiable drugs accounted for 43.5%, 4.8%, and 35.8% of the prescriptions, respectively.
Conclusion. According to the Swedish classification system, we found that during pregnancy and lactation a high proportion of Danish women were exposed to one or more drugs in high risk groups; furthermore, knowledge regarding their safety for the fetus and neonate was limited for a large proportion of the prescriptions. Current evidence about long-term effects of prenatal exposure stresses the need for long-term follow-up of health and development among exposed children.

Key words: drugs; lactation; medication; pregnancy; risk classification

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Drugs exposure during pregnancy have been a cause for anxiety since the thalidomide disaster (1) but, more than four decades later, fewer than 30 drugs have proved to be teratogenic in humans (2). Exposure before conception, or during the first trimester of pregnancy, has been of particular concern regarding malformations. However, drugs may exert their effects upon the fetus at other times during pregnancy; for example the use of ACE inhibitors during the second or third trimesters may be fetotoxic, causing prolonged fetal

**EUROMAP: Project steering*: Jørn Olsen (coordinator) and Henrik Toft Sørensen (manager). *Project management*: Henrik Toft Sørensen, Jørn Olsen, Andrew Czeicel, Gunnar Lauge Nielsen, Lolkje De Jong, Lorentz Irgens, Ulf Bergman. *Other members*: Charlotte Olesen, Flemming Hald Steffensen, Lars Pedersen,Rolv T. Lie, Corrine de Vries and Patrick Leurquin.

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hypotension, renal tubular dysplasia, growth retardation and fetal death (3). Furthermore, manifestations of intrauterine exposure to environmental agents may be unexpected and delayed. Thus phenobarbital exposure during early development may have long-term harmful effects on cognitive performance (4), fetuses exposed to diethylstilbestrol have an increased risk of adenocarcinoma of the vagina in late childhood (2,5), and calcium supplementation during pregnancy is associated with lower systolic blood pressure in the offspring (6). Furthermore, human milk may be contaminated by drugs or environmental toxic agents, which may affect the health and development of the growing child (7). The possible long-term consequences of intrauterine exposure to drugs emphasize the importance of focusing on drug exposure before, during, and after pregnancy.

Evaluation of possible teratogenic properties of a specific drug is usually based on animal studies, since observations of a large number of human pregnancies over many years may be needed in order to reach definite conclusion. Toxicology studies in animals are required today for all new products; however, results from animal studies have limited predictive value for humans.

Despite the difficulties in evaluating potential risks to the fetus and newborn child, different classification systems place drugs in risk groups regarding their known or unknown effects on the fetus. The Food and Drug Administration (FDA) in 1979 presented a system based on the degree to which available clinical information indicates risk to the fetus (8). Only 55% of the drugs in the Danish prescription database could be assigned to FDA pregnancy categories. The objective of the Swedish Classification System, which uses risk categories for drugs used during pregnancy and lactation (9), is to refer all approved medicinal products to one of four risk categories. No assessment of potential long-term consequences is included in the classification system.

The aim of this study was to examine the pattern of prescribing for Danish women before, during, and after pregnancy, with respect to fetal and neonatal risk. The study was based on a population-based prescription database, in which prescriptions are set against the Swedish Classification system for drug use during pregnancy and lactation (9).

Materials and methods

The population-based Pharmacoepidemiological Prescription Database of the County of North Jutland, Denmark (10), was used to identify all redeemed prescriptions in the County from 1 January 1991 until 31 December 1996. The county has 490,000 inhabitants, constituting approximately 10% of the total Danish population. All pharmacies in the county are equipped with computerized accounting systems transferring data to the Danish National Health Service. The Danish National Health Service provides tax-supported health care for the entire population by providing free access to general practitioners, hospitals, and public clinics. The health insurance program also refunds part of the costs of most prescribed drugs. The information that is transferred to the Pharmacoepidemiological Prescription Database from the pharmacies includes the customer's personal identification number (which incorporates date of birth) and the type of drug prescribed according to the Anatomical Therapeutical Chemical (ATC) classification system (11). Use of the 10-digit personal identification number, which is assigned by the Central Population Register, to all citizens shortly after birth ensured a complete prescription history for each participant.

The Danish Medical Birth Registry includes all births since 1973 with information about the child′s date of birth, gestational age, outcome of pregnancy and malformations. The data in this registry are obtained from official reports completed by the midwives in attendance at all deliveries.

Linking these registries by using the personal identification number provided the information needed to characterize each individual pregnant woman in the analysis using the following variables: age, child's date of birth, duration and outcome of pregnancy, number of prescriptions and for each prescription the ATC code and date of redeeming.

According to the Swedish classification system (9) ATC codes in the database were set against the risk groups A, B1, B2, B3, C, D, I, II, III, IVa and IVb (Table I). The Swedish classification system is based on clinical and/or animal data, and consists of four separate groups; the classification with respect risk groups during lactation is based only on human data. For detailed description, see Appendix A.

ATC codes that were not listed in the Swedish classification were set against the Food and Drug Administration's classification system of drugs with respect to their known or suspected risks in pregnancy (8); this was done in order to describe risk for as many prescriptions as possible.

Analysis

The analyses were based on prescriptions redeemed by primiparae who gave birth in the County of North Jutland during the study period.

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Table I. Risk groups in pregnancy and lactation. The Swedish classification system for drug use in pregnancy and lactation (9)

Pregnancy	
Group A	Reliable clinical data indicate no evidence of disturbance of the reproductive process.
Group B	Data from pregnant women are insufficient; classification based on animal data (by allocation to three subgroups B:1, B:2, and B:3).
Group C	Drugs which may involve risk to the fetus without being directly teratogenic.
Group D	Data indicate increased incidence of malformations in man.
Lactation	
Group I	The drug is not excreted into breast milk.
Group II	The drug is excreted into breast milk but is not likely to influence the child when therapeutic doses are used.
Group III	The drug is excreted into breast milk in such quantities that there is a risk of influence on the child when therapeutic doses are used.
Group IV	It is unknown if the drug is excreted into breast milk, or available information is insufficient for assessment of the risk to the child.

Women who had given birth to twins or triplets were excluded (n=320) because they are often cared for at hospitals. Prescribed drugs, which were not refunded (mainly oral contraceptives, major tranquillizers and some benzodiazepines), and over the counter drugs, which included iron, vitamin supplements and many analgesics, are not in the database. Until April 1996 prescriptions for children were usually recorded in the prescription database by the mother's personal identification number, which means that some of the drugs prescribed for a mother may have been used for treating an older child in the family. To eliminate this possibility of misclassification, we restricted the analysis to women without previous births.

In order to evaluate change in prescribing habits due to pregnancy, we included prescriptions redeemed before conception. The prescription pattern for each woman was described from 12 weeks before conception to 12 weeks postpartum. According to the date of birth and the predicted time of conception, each pregnancy was divided into five periods: 1) preconception (12 weeks); 2) first trimester, weeks 0–12 (organogenesis); 3) second trimester, weeks 13–28 (maturation); 4) weeks 29–40 (rapid growth); 5) postpartum (12 weeks).

The proportion of women who redeemed at least one prescription within ATC groups during a period was described as the prescription proportion. Measures were dated according to the day at which the prescription was redeemed. Thus, prescriptions that covered more than one period were counted only in the first. It should be taken into consideration that all the periods were equally long (12 weeks), apart from period 3 (16 weeks).

The study was approved by the local ethics committees in the Counties of North Jutland and Viborg (Reg.nr. 95/187).

Results

In the County of North Jutland 15,756 primiparae gave birth from 1991 to 1996. The data include 34,334 prescriptions, of which 19.0%, 16.2%, 21.1%, 15.2% and 28.6% were redeemed during the preconceptional period, first, second, and third trimesters, and the postpartum period, respectively. According to the Swedish risk classification, 87.7% of the prescriptions could be classified in the risk groups. The majority of prescriptions which were not classifiable were for ophthalmic (60%) and skin (8.4%) conditions. According to the FDA classification, 31.3% of these prescriptions were assigned to group C, which in this context means potential fetal risk, and 3.5% to group B, which means no fetal risk.

Overall drug use within risk categories during pregnancy

During pregnancy, safe (group A), potentially harmful (group BE and D), and non-classifiable drugs accounted for 40.9%, 26.6% and 28.7% of the prescriptions respectively. The proportion of women who received at least one drug with proven or anticipated harmful fetal effects (group B3, C, or D) was 17.8%; 137 women (0.9%) redeemed five or more prescriptions within these categories during pregnancy.

The overall proportion of group A prescriptions increased from 35.4% before pregnancy to 55.3% during the third trimester (Fig. 1); correspondingly, the percentage of women who redeemed a prescription in this group increased from 10.5% before pregnancy to 12.2% during the third trimester. The majority of group A prescriptions were drugs for treating infections (J01C: 26.2%), gynecological diseases (G01A: 22.4%) and asthma (R03A: 8.9%). The proportion of prescriptions for local treatment increased from 44.9% before pregnancy to 51.9%, 59.9% and 56.5% respectively, during periods 2–4.

The overall use of group B drugs decreased during pregnancy, reflecting the general trend in prescription proportion for some of the major drugs in this category; macrolide (J01F), antihistamine (R03A), antiprotozoal (P01A), and antimycotic (J02A) drugs for systemic use. Group B3 drugs,

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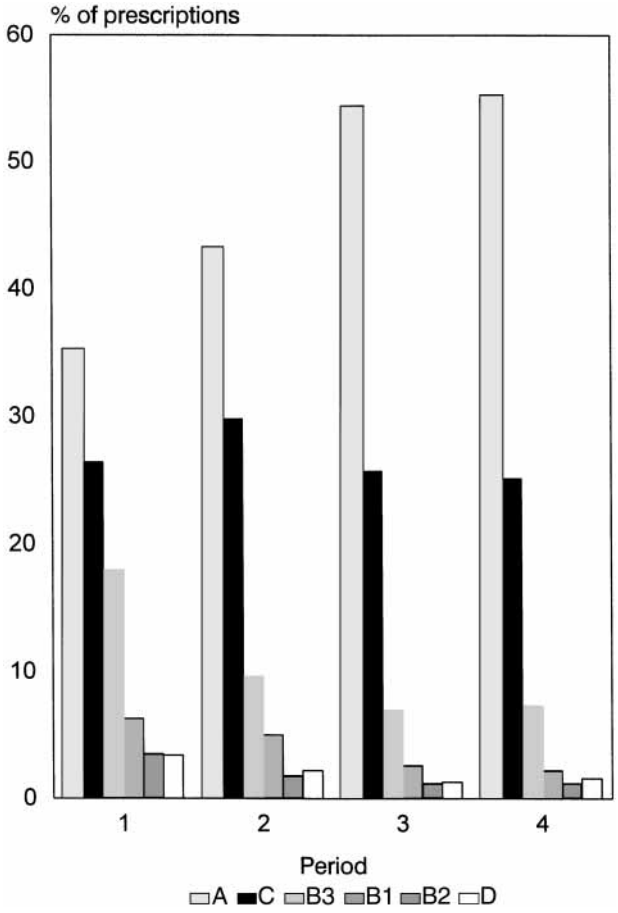

Fig. 1. Prescribing in risk groups A, B1, B2, B3, C and D before and during pregnancy. Period 1 refers to the preconceptional period, and periods 2–4 to the first, second, and third trimesters. Figures are given as percentage of the total prescriptions during the periods.

which may be associated with potential risks of direct or indirect harmful effects to the fetus, were often prescribed during pregnancy (Table II). The proportion of prescriptions from category B3 decreased from 18% during the preconceptional period to 7.4% during the third trimester; correspondingly, the percentage of women who redeemed prescriptions for these drugs decreased from 5.5% before pregnancy to 1.9% during the third trimester. Clomiphene was the most commonly prescribed drug in group B3 before pregnancy where 1.7% of the women used this drug.

Group C drugs were the second most commonly prescribed throughout pregnancy, accounting for 26.4%, 29.8%, 25.7%, and 25.1% of the prescriptions during the periods 1–4, respectively (Fig. 1); the proportion of women who redeemed a prescription in group C was 8.5% before pregnancy, decreasing to 6.4% during the third trimester. Sulfonamide, penicillin (pivampicillin/pivmecillinam) and dermatological corticosteroid were the most frequently used drugs in category C. The most evident change in prescription proportion was seen for antirheumatic drugs (M01A); the prescription proportion decreased from 3.0% before pregnancy to 0.6% during the third trimester (Table III). The use of corticosteroid for systemic use (H01A), and of sulfonamide (J01E) also decreased during pregnancy, although to a lesser extent. Increasing prescription proportions were seen for propulsive (A03A) and for the antihypertensive drug labetalol (C07A), which was used by 0.4% during the third trimester.

Group D, which comprises drugs with potential teratogenic effects, accounted for 3.4%, 2.2%, 1.3% and 1.6% of the prescriptions during periods 1–4, respectively. The overall prescription proportion in category D was 1.2% before pregnancy, and it declined further during the first trimester. Most of the prescriptions in this category were for tetracycline; although the prescription proportion for tetracycline declined from 8/1000 before conception, 3/1000 women still received this prescriptive drug during the first trimester.

Overall drug use within risk groups during lactation

During the postpartum period, 34.2% of the women redeemed one or more prescriptions. Prescriptions from groups I, II, III, IVa, IVb and non-classifiable drugs accounted for 8.5%, 43.8%, 5.4%, 15.6%, 3.3% and 23.4% respectively of the prescriptions in the postpartum period. According to the Swedish risk classification system, drugs from groups I and II can be regarded as having no influence on the child; drugs from group III are excreted in breast milk in such quantities that there is a risk of influence on the child when therapeutic doses are used. The major drugs in groups I and II were penicillin, bromocriptine, nystatin and non steroid antiinflammatory drugs (NSAID) which accounted for 18.6%, 4.2%, 2.6% and 2.3%, respectively of the prescriptions in these groups. Group III comprised mainly oxytocic drugs (62.5%) and antihistamines for systemic use (9.3%).

Discussion

We found that potentially harmful drugs are often used in pregnancy. Our knowledge of possible fetal or neonatal adverse effects is limited for a high proportion of drugs prescribed during pregnancy and lactation. In the present study, the overall use of drugs with proven or anticipated fetal toxicity as well as the proportion of prescriptions for systemic treatment decreased during pregnancy, as has been found by other authors (12, 13). These changes presumably reflect an attempt to avoid fetal adverse effects, indicating that the medical profession

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Table II. Prescription proportion before and during pregnancy in risk groups C and D

ATC_4		Majority of prescriptions	Period 1	2	3	4
Overall prescription proportion C			*8.5*	*8.1*	*8.5*	*6.4*
A03A	propulsive	methoclopramide 100%	1.0	0.5	0.4	0.1
C07A	beta blocker	labetalol 55%	0.3	0.3	0.4	0.6
D07A	corticosteroid$_{D}$	group II:43% III:50%	2.0	1.8	2.3	1.5
H02A	corticosteroid$_{S}$	corticosteroids$_{S}$	0.4	0.2	0.1	0.1
H03B	antithyroid drugs	thiouracils 83%	0.1	0.1	0.1	0.1
J01C	penicillin	pivampicillin 67%	1.3	2.0	3.0	3.1
J01E	sulfonamide	sulfamethizole 100%	1.8	2.7	2.2	0.7
M01A	antirheumatic	propionic acids 83%	2.6	1.0	0.5	0.1
N02A	opiate	methadone 61%	0.1	0.1	0.1	0.1
N06A	antidepressant	serotonin reuptake inh. 83%	0.1	0.1	–	–
Overall prescription proportion D			*1.2*	*0.6*	*0.5*	*0.5*
G03D	progestogen	norethisterone 100%	0.1	–	–	–
J01A	tetracycline	lymecycline 31%	0.8	0.3	–	–
N03A	antiepileptic	carbamazepine 86%	0.2	0.2	0.3	0.3

Period 1 refers to the preconceptional period, and periods 2–4 refer to the first, second, and third trimester, respectively. Prescription proportions are given in per cent of pregnant women during the period.

Table III. Prescription proportion before and during pregnancy in risk groups B1, B2, and B3

ATC_4		Majority of prescriptions	Period 1	2	3	4
Overall prescription proportion B1			*2.0*	*1.4*	*0.7*	*0.5*
A02B	ulcer drugs	cimetidine 85%	0.3	0.3	0.1	0.2
J01F	macrolide	roxitromycin 81%	0.7	0.4	0.1	–
R06A	antihistamine$_{S}$	cetirizine 61%	0.7	0.4	0.2	0.2
Overall prescription proportion B2			*1.3*	*0.5*	*0.4*	*0.3*
A07E	intestinal drugs	mesalazine 84%	–	0.1	0.1	0.1
G01A	gynecological	terconazole 100%	0.2	0.1	0.2	0.2
P01A	antiprotozoal	metronidazole$_{S}$100%	0.9	0.2	0.1	–
Overall prescription proportion B3			*5.5*	*2.9*	*2.4*	*1.9*
C03A	thiazide	bendroflumethiazide 100%	0.1	–	0.1	0.3
D06B	chemoterapeutic$_{T}$	aciclovir 100%	0.7	0.5	0.6	0.5
G03G	ovulation inducing	clomifene 100%	1.7	0.4	–	–
J01F	macrolide	claritromycin 100%	0.1	–	–	–
J02A	antimycotic$_{S}$	fluconazole 75%	1.2	0.4	0.1	–
P01B	antimalarial	chloroquine 96%	0.2	0.1	0.1	–
R01A	decongestant$_{T}$	beclometasone 51%	0.7	0.7	0.9	0.6
R03B	anti-asthmatic$_{I}$	budesonide 84%	0.4	0.4	0.3	0.3
S01G	antiallergic$_{S}$	levocabastine 100%	0.2	0.1	0.1	0.1

Period 1 refers to the preconceptional period, and periods 2–4 refer to the first, second, and third trimesters, respectively. Prescription proportions are given in per cent of pregnant women during the period.

is aware of potential fetal side-effects of drugs prescribed in pregnancy.

The proportion of women who redeemed prescriptions for potentially harmful drugs was similar to findings from Holland where the proportion of women exposed to drugs from groups B3, C, and D was 16.7% (12). These findings were based upon the Australian risk classification (14) which is virtually identical to the Swedish system. Sannerstedt et al. found that groups A, B, C and D accounted for 27%, 19%, 7%, and 7%, respectively, among pharmaceutical products prescribed during pregnancy and lactation in Sweden (15); Addis et al. found that among 880 different drugs used in pregnancy, 30% were safe, 39% potentially harmful, and 31% were non-classifiable in regard to the risk classification system used by the FDA (16). However, the methods used in these studies differed from the present study making comparisons difficult.

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The prescribing pattern within risk groups differed. In contrast to the findings in a Dutch study (12), we found that the proportion of women who received prescriptions for group C drugs increased during pregnancy. Drugs in this category probably include a risk, particularly during the third trimester. The increase in category C was partly due to sulfonamide, which was prescribed for 0.7% of the women during third trimester. In other studies the proportion of women who used sulfonamides during the third trimester was 0.4%, De Jong-van den Berg et al. (12), 1.5%; Piper et al. (13), and 0.5%; Rubin et al. (17). The main indication for sulfonamides is treatment of urinary tract infections, which if untreated may result in significant maternal and fetal morbidity and mortality (18, 19).

The prescription proportion for group D drugs was low before conception and decreased further during pregnancy. However tetracycline was prescribed for 0.8% and 0.3% respectively, before conception and during first trimester of pregnancy; these drugs should be avoided during pregnancy as safe alternatives are available. Regarding the antiepileptic drug carbamazepine, the prescription proportion was comparable with findings in other studies (12, 20, 21) and it remained stable throughout pregnancy.

During the postpartum period, safe drugs (groups I and II), drugs with possible harmful neonatal effects (group III), drugs for which we only have limited knowledge regarding neonatal effects (group IV), and non-classifiable drugs accounted for 43.5%, 4.8%, 15.9%, and 35.8%, respectively of the prescriptions in the present study. Sannerstedt et al. found that groups I, II, III, and IV accounted for 4%, 34%, 12%, and 59% respectively of drugs prescribed during lactation in a Swedish study (15). The prescription proportion for bromocriptine was 2.8% during the postpartum period, which is similar to findings in other studies (20, 21). Due to suspected risk of severe cardiovascular adverse effects, bromocriptine has been withdrawn from the market in other countries for lactation inhibition (22–24).

The main strengths of our study are its size and the population-based design. The uniformly organized health care system makes complete follow-up possible. The main limitations are that only prescribed and refunded drugs are in the database; drugs used during hospital admission are not included. Moreover, prescribed drugs are not always used and the overestimation may be considerable (as with the ovarian stimulant during the first trimester of pregnancy). Concerning drug use postpartum, the most important limitation of this study is the fact that prescriptions given to the mother during the postpartum period are probably intended for treating the child.

Conclusion. During pregnancies a high proportion of Danish women were exposed to one or more drugs in high risk categories, and present knowledge of possible fetal or neonatal adverse effects is limited for a high proportion of drugs prescribed during pregnancy and lactation. Since we have no information about the indications that led to these prescriptions, we cannot argue that the use of these drugs was unjustified, since an untreated disease may well be a worse alternative (25). Only systematically collected data within proper epidemiological designs will show whether the present prescription pattern is reasonable. Barkers programming hypotheses (26) and current evidence about long-term effects of prenatal exposure stress the need for long-term follow-up of health and development in exposed children, since prenatal exposure may be 'safe' only when the follow-up is short-term.

Appendix A (9)

Group A comprises drugs that are assumed to have been used by a large number of pregnant women, and for which satisfactory retrospective and prospective studies in pregnant women are considered to have been carried out, without any identified disturbance in the reproductive process, e.g. increased incidence of malformations or other direct or indirect harmful effects to the fetus.

Group B comprises drugs that may be assumed to have been used by only a limited number of pregnant women, without any identified increased incidence of malformations or other harmful effects for the fetus having been noted so far; however, clinical studies are sparse or lacking. As the experience of effects of medicinal products in man is limited in this category, results of reproduction toxicology studies in animals are indicated by allocation to one of three subgroups: **B1;** Reproduction toxicology studies have not given evidence of an increased incidence of fetal damage or other harmful effects to the reproductive process. **B2;** Reproduction toxicology studies are inadequate or lacking, but available data do not indicate an increased incidence of fetal damage or other harmful effects to the reproductive process. **B3;** Reproduction toxicology studies in animals have shown an increased incidence of fetal damage or other harmful effects to the reproductive process, the significance of which is considered uncertain in man. It must be emphasized that drugs are assigned to group B:3 when it is considered unclear whether the product effect observed in animals is of relevance to man. If animal experiments are con-

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sidered to indicate a certain risk to man, the product is assigned to category C or D.

Group C comprises drugs which by their pharmacological effects have caused, or must be suspected to cause, disturbances in the reproductive process that may involve risk to the fetus, without being directly teratogenic.

Group D comprises drugs that have caused an increased incidence of fetal malformations or other permanent damage in man, or that, on the basis of for example reproduction toxicity studies, must be suspected of doing so. Group D comprises drugs with primary teratogenic effects.

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Address for correspondence:

Charlotte Olesen, M.D.
The Danish Epidemiology Science Center
University of Aarhus
Vennelyst boulevard 6
DK-8000 Aarhus C
Denmark

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