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Advice on Drug Safety in Pregnancy

Are there Differences between Commonly Used Sources of Information?

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Abstract

Background and Objective: Safety regarding use in pregnancy is not established for many drugs. Inconsistencies between sources providing drug information can give rise to confusion with possible therapeutic consequences. Therefore, it is important to measure clinically important differences between drug information sources. The objective of this study was to compare two easily accessible Norwegian sources providing advice on drug safety in pregnancy – the product monographs in the Felleskatalog (FK), published by the pharmaceutical companies, and the five regional Drug Information Centres (DICs) in Norway – in addition to assessing the frequency of questions regarding drug safety in pregnancy made to the DICs according to the Anatomical Therapeutic Chemical (ATC) classification system.

Methods: Advice on drug use in pregnancy provided by the DICs in 2003 and 2005 were compared with advice in the product monographs for the respective drugs in the FK. Comparison of advice was based on categorization to one of four categories: can be used, benefit-risk assessment, should not be used, or no available information.

Results: A total of 443 drug advice were categorized. Seven out of ten of drugs frequently enquired about, according to the ATC system, were drugs acting on the nervous system (group N). For 208 (47%) of the drugs, advice differed between the DICs and FK. Advice from the FK was significantly ($p < 0.01$) more restrictive than advice from the DICs. There were no differences in the level of consistency of advice between drugs that were newly introduced and those that had been on the market for a longer time, advice regarding use of drugs in the first trimester and advice regarding use of drugs in the second or third trimester, or between advice provided during 2003 and during 2005.

Conclusions: The results of this study show considerable differences between two Norwegian sources providing advice on the use of drugs in pregnancy. Based on the knowledge that healthcare providers choose sources of information in a random manner, our results may be of clinical importance. We believe that the

problem with heterogeneous drug information on this subject is not confined to Norway and that our results should be of international interest.

Background

Safety regarding use in pregnancy is not established for many drugs. This is largely due to the ethical concerns of including pregnant women in randomized clinical trials and the relative infrequency of most birth defects. Animal studies are usually requested prior to the approval of new drugs, but they are limited in their ability to predict human teratogenesis.[1,2] Consequently, the literature that addresses the issue of teratogenicity is mainly derived from case reports or series, case-control studies or cohort studies. However, these types of studies are associated with inherent weaknesses.[2] Thus, there is a lack of strong evidence of either safe or harmful effects for most drugs when used during pregnancy.[3] Furthermore, there is compelling evidence that lack of treatment of some maternal conditions during pregnancy can lead to increased fetal risks, including malformations, intrauterine growth restrictions and stillbirth. Optimal therapy includes evaluation of continued use of safe drugs or discontinuation of either unsafe or unnecessary medications.[4]

In the product monographs provided by the pharmaceutical industry and in the regulatory-approved Summary of Product Characteristics (SPC), drug use during pregnancy is seldom recommended.[5,6] Consequently, the term 'contraindicated' in these sources does not always reflect an established teratogenic risk associated with a drug. In spite of this, the product monographs represent a first-line source for counselling of pregnant women. Inconsistencies between sources providing drug information can give rise to confusion and thereby counteract the intention of the drug information with possible therapeutic consequences.[7] Therefore, it is important to measure clinically relevant differences between drug information sources. The aim of this study was to compare two easily accessible sources providing advice on drug use in pregnancy – the product monographs in the Norwegian Pharmaceutical Product Compendium (Felleskatalog [FK]) and the Norwegian regional Drug Information Centres (DICs) – in addition to assessing the frequency of queries regarding the use of drugs during pregnancy made to the DICs according to the Anatomical Therapeutic Chemical (ATC) classification system.[8]

Methods

RELIS is the name of the five regional DICs in Norway. A main aim of these five DICs is to provide answers to clinically oriented drug-related questions from health care providers. All questions and answers to DICs are documented in a web-based, full-text, question-answer database (the 'RELIS' database), where approximately 12% of the questions concern the use of drugs in pregnancy. An alternative and frequently consulted source of information on drug safety in pregnancy is the FK, published by the pharmaceutical companies.

All questions to the DICs received during the years 2003 and 2005 that were indexed to the category 'pregnancy' in the RELIS database were included in the study. Criteria for exclusion were questions regarding:

- drugs or substances not approved in Norway;
- a group of drugs without specification of a substance name;
- the birth defects of a born child;
- drug use by males;
- a spontaneous abortion that has occurred.

Advice on drug use in pregnancy provided by the DICs was compared with advice in the product monograph in the FK for the respective drug. Comparison of advice was based on categorization to one of four categories:

1. Can be used.
2. Benefit-risk assessment.
3. Should not be used.
4. No available information.

Furthermore, the trimester or trimesters in question and the first, third and fifth level of the ATC

system were registered for each categorized drug. The year of introduction of the generic substance in Norway was also registered. The mean and median years of introduction were 1985 and 1991, respectively. To set an arbitrary limit between newly introduced and older drugs we used the 75th percentile, which was 1997. The newly introduced drugs would then have been on the market for a maximum of 6 and 8 years in 2003 and 2005, respectively.

A pilot study was carried out to assess consistency between physicians and the DICs. The pilot study included six randomly chosen examples of drug advice and was submitted to 33 physicians, of whom 18 participated. Furthermore, two persons at a particular DIC, a pharmacist and clinical pharmacologist, categorized the initial 100 drug advice. The subsequent drug advice were categorized by the pharmacist.

Statistical Analysis

Data were analysed using SPSS version 11 (SPSS Inc., Chicago, IL, USA). The data are presented as discordant ('a' and 'b') pairs of advice from the DICs and the FK. More restrictive advice from the FK than the DICs is represented by 'a'. More restrictive advice from the DICs than from the FK is represented by 'b'. The term 'more restrictive' indicates that the majority of the advice were placed in categories 2 or 3 ('benefit-risk assessment' or 'should not be used'). We have introduced two different terms to describe the data. The term 'all advice' includes all categories (1–4), while the term 'grouped advice' is constructed by combining categories 2 and 3 (unsafe and possibly unsafe), preserving category 1 (safe use) and excluding category 4 (no information). Introducing the term 'grouped advice' allows statistical analysis of the categorized advice. The proportion of all discordant advice is represented by $(a + b)/n$, and the proportion of discordant advice where advice from the FK is more restrictive than that from the DICs is represented by $a/(a + b)$. The McNemar's test was performed to examine differences between a and b for different subgroups. Proportions of discordant advice $[(a + b)/n,\ a/(a + b)]$ were calculated for different subgroups and described. Kappa (κ) statistics (κ coefficient) were used to calculate observer agreement in the pilot study. p-Values <0.01 were accepted as statistically significant.

Results

In 2003 and 2005, there were 172 and 264 questions, respectively, to the DICs regarding drug safety in pregnancy. The number of excluded questions was 53 in 2003 and 98 in 2005; 285 questions in total were finally included in the study. The questions included categorizations of 443 (224 in 2003 and 219 in 2005) drug advice from the respective sources. Therefore, some questions to the DICs concerned two or more drugs.

Frequencies of questions to the DICs regarding drug use in pregnancy on the first level of the ATC system were as follows: N (nervous system: 182; 41%), R (respiratory system: 55; 12%) and J (antiinfectives for systemic use: 54; 12%). On the third level of the ATC system, drugs in group N06A (antidepressants) were most frequently enquired about with 62 enquiries (14% of all enquiries), followed by group N05A (psycholeptics) with 36 enquiries (8%) and group R06A (antihistamines for systemic use) with 29 enquiries (7%). Seven out of ten of the drugs where advice was most frequently sought were drugs acting on the nervous system, and four of these were selective serotonin reuptake inhibitors. The generic substance for which advice was most frequently sought was citalopram (14 questions), followed by lamotrigine (10) and prednisolone (10).

For 214 (48%) of the categorized drugs, enquiries related to the first trimester only; for 68 (15%) of the drugs, enquiries related to either or both the second or third trimester; and for 161 (36%), enquiries were either for all three trimesters or were not specified.

In figure 1, all advice with all categories from the DICs and the FK are compared. Figure 2 shows a comparison of grouped advice where categories 2 and 3 ('benefit-risk assessment' and 'should not be used') are combined and category 4 ('no available information') is excluded. In table I, 'a' and 'b' (discordant pairs of advice) based on all advice and

		DIC			
	All advice	Can be used (n = 137)	Benefit-risk assessment (n = 251)	Should not be used (n = 55)	No available information (n = 0)
FK	Can be used (n = 34)	**32**	2	0	0
	Benefit-risk assessment (n = 252)	65	**170**	17	0
	Should not be used (n = 134)	29	72	**33**	0
	No available information (n = 23)	11	7	5	**0**

Fig. 1. All advice (n = 443) on the use of drugs in pregnancy from the five Norwegian Drug Information Centres (DICs) and the product monographs in the Felleskatalog (FK). Bold numbers represent concordant advice. The dark grey shaded area represents more restrictive advice from the FK compared with the DICs, and the light grey shaded area represents more restrictive advice from the DICs compared with the FK.

grouped advice, respectively, are shown according to the different subgroups. The proportion of all discordant advice [(a + b)/n] and the proportion of discordant advice where FK was more restrictive than the DICs [a/(a + b)] are also shown in table I. The advice from the DICs and from the FK was discordant for 208 (47%) of the drugs. The grouped advice was discordant for 23% of the drugs. The level of consistency between the two sources was highest for drugs acting on the nervous system (ATC group N) since the proportion of discordant advice was the lowest (36% for all advice and 18% for grouped advice). However, the level of consistency was among the lowest for antidepressants (N06A: 66% discordant for all advice and 35% discordant for grouped advice). There were no major differences in the proportion of discordant advice for drugs that had been on the market for a longer period of time (47% all advice, 25% grouped advice) compared with those that had been newly introduced (47% all advice, 17% grouped advice). The proportion of discordant advice for the first trimester (50% all advice, 21% grouped advice) was not substantially different from that for the second or third trimester (53% all advice, 31% grouped advice). There were no major differences in the proportion of discordant advice for advice provided during 2003 (51% all advice, 26% grouped advice) compared with that during 2005 (43% all advice, 20% grouped advice). The proportion of discordant advice where that from the FK was more restrictive than that from the DICs was close to 100% and significant for all subgroups, except antidepressants.

		DIC	
	Grouped advice	Can be used (n = 126)	Should not be used or BRA (n = 294)
FK	Can be used (n = 34)	**32**	2[b]
	Should not be used or BRA (n = 386)	94[a*]	**292**

Fig. 2. Grouped advice (n = 420) on the use of drugs in pregnancy from the five Norwegian Drug Information Centres (DICs) and the product monographs in the Felleskatalog (FK). Bold numbers represent concordant advice. **a** = more restrictive advice from FK than the DIC; **b** = more restrictive advice from the DICs than the FK; **BRA** = benefit-risk assessment; * significant difference between a and b ($p < 0.01$).

The κ coefficient for comparing the categorizations made by the physicians participating in the pilot study with those of the DICs was on average 0.67. The level of consistency between the DIC and the 18 physicians for the six randomly chosen exam-

Table I. All advice (n = 443) or grouped advice (n = 420) on use of drugs in pregnancy with regard to the Anatomical Therapeutic Chemical (ATC) classification system, introduction on the market, trimester and year of question to the Drug Information Centres (DICs)

Material	Number of advice (n) [all/grouped]	a		b		(a + b)/n [%]†		a/(a + b) [%]††	
		all advice	grouped advice	all advice	grouped advice	all advice	grouped advice	all advice	grouped advice
Total	443/420	189	94*	19	2	47	23	91	98
N (ATC)	182/175	64	32*	2	0	36	18	97	100
R (ATC)	55/52	25	16*	11	0	65	31	69	100
J (ATC)	54/50	33	17*	2	1	65	36	94	94
N06A (ATC)	61/58	40	20**	0	0	66	35	100	100
Introduced before 1997	328/306	145	75*	9	2	47	25	94	97
Introduced 1997 or later	115/114	44	19*	10	0	47	17	81	100
First trimester	214/203	104	42*	3	0	50	21	97	100
Second or third trimester	68/62	31	19*	5	0	53	31	86	100
2003	225/210	103	54*	12	0	51	26	90	100
2005	218/210	86	40*	7	2	43	20	92	95

a = more restrictive advice from FK than the DIC; **b** = more restrictive advice from the DIC than FK; **FK** = Felleskatalog; **N** = nervous system; **R** = respiratory system; **J** = anti-infectives for systemic use; **N06A** = antidepressants; † indicates the proportion of discordant advice; †† indicates the proportion of discordant advice where the FK is more restrictive than the DICs; * $p < 0.01$ (significant difference between a and b), ** p-value cannot be calculated.

ples of respective advice submitted was 72%, 61%, 100%, 94%, 83% and 94%.

Discussion

The main finding of this study was that in almost 50% of the cases, advice differed between the two sources providing information on the use of drugs in pregnancy. Thus, the results could be of clinical importance since healthcare providers consult more than one source of information for the counselling of pregnant women.[9] The results could also be of importance outside Norway due to the fact that other countries have a similar system with drug information from both product monographs and DICs.

Advice from the FK was significantly more restrictive than advice from the DICs. The results may to some extent be explained by the pharmaceutical industry's concern to place legally related safety issues first,[6] compared with the DICs' intention to provide advice leading to rational pharmacotherapy for the individual patient. We found that 15% of the questions to the DICs concerned the use of drugs in the second or third trimester. Advice in the product monographs in the FK seldom differentiates between trimesters, but the use of drugs in the first trimester is often of primary interest. The consequence can be that in the FK the drug is contraindicated, even though use after the first trimester may be acceptable. Although advice provided by the DICs considers the trimester in question, we found no major differences between the proportions of discordant advice provided by the two sources for the first trimester versus the second or third trimester. This could be due to a low frequency of advice for the second and third trimester.

The level of consistency was highest for drugs acting on the nervous system generally, but consistency was lowest for antidepressants that were included in this ATC group. We found no differences in the proportion of discordant advice when comparing drugs that were newly introduced on the market with those that had been on the market for a longer time. A possibility is that inconsistent drug information concerning antidepressants has continued, although experience with the use of these drugs in pregnancy has increased. Based on our current results, this may indicate a general problem with accumulated systematic documentation of safe or unsafe use of drugs in pregnancy not being communicated through drug information sources.

Some countries, although not Norway, have established risk classification systems where the drugs are categorized on the basis of teratogenicity.[10,11]

However, differences between countries in category allocation for the same drug can be a source of confusion among users of the risk classification systems.[10] Inconsistencies regarding use in pregnancy between the FK and the Norwegian SPC for the same drug and for generic drugs have previously been shown.[12] Differences were also found when comparing these sources with the Swedish SPC and product monographs. As an example, Norwegian sources advise against the use of phenylpropanolamine, while Swedish sources suggest it is safe to use.[12] We found the same difference for noscapine. Furthermore, a French study found inconsistencies concerning use in pregnancy both within the same SPC and between SPCs for generic products.[13] Other researchers have found inconsistencies between patient information leaflets regarding use in pregnancy from different brands of generically identical drugs.[7] This drug information problem is not confined to pregnancy since inconsistencies have been found between sources providing information on drug interactions[14,15] and those regarding drug use in children.[16,17]

Based on our current results, we also examined the consistency between some examples of the generic products in the FK (2007 edition)[18] regarding advice on the use in pregnancy. For mirtazapine, three of four advice for generic products were allocated to category 2 ('benefit-risk assessment') and one advice to category 3 ('should not be used'). For loratadine, three products were allocated to category 2 and two to category 3. One of the generic products containing erythromycin included information that referred to recent data concerning a possible increased risk for cardiovascular malformations, while the other generic product lacked this information. This resulted in different advice. These results, in addition to the inconsistencies found by others, point to differences between and within information sources for the same generic substance. The approval of generic products by European regulatory authorities is presently based on a mutual recognition procedure and a decentralized procedure,[19] which may result in differences in drug information for generic products in all European countries. This is inconsistent with the currently perceived need for harmonization of drug information.

Management of pre-existing chronic conditions or conditions that may be exacerbated by pregnancy is relatively common in pregnancy. Examples are psychiatric and neurological disorders, hypertension and asthma.[20] We, as well as others,[21,22] have reported a high proportion of questions to DICs concerning drugs acting on the nervous system, although this proportion was notably high (41%) in our study. This could be due to the frequent use of these drugs and could also reflect a lack of information concerning the use in pregnancy for the many new substances within this group of drugs. In addition, psychiatric and neurological conditions (e.g. epilepsy) can represent a risk during pregnancy and the post-partum period.

In some cases, contraindications in the product monographs regarding drug safety in pregnancy result in queries to a DIC. Approximately 20% of the questions to Norwegian DICs regarding drug safety in pregnancy concern the assessment of indication for induced abortion due to the inadvertent use of drugs. A Norwegian DIC has previously shown that physicians find clinically aimed drug information to be of high quality and to have impact on their clinical practice.[23,24] DICs in other countries have evaluated the need for information on drug use in pregnancy.[21,22,25] This indicates that DICs are important sources for drug advice, and our current results indicate that the choice of source for drug information could be of importance.

Strengths and Limitations

The categorization of advice was carried out retrospectively by a pharmacist at a particular DIC. This could bias the results. However, the pilot study showed a substantial level of observer agreement (κ coeffiecient 0.67)[26] between the physicians and the DIC. Furthermore, two persons categorized the first 100 drug advice independently. The pilot study, as well as the initial categorizations, showed that some advice was difficult to categorize, but they appeared randomly and it is unlikely that this could explain the present results. Because of the fact that

contraindications in the FK in some cases are the reason for contacting a DIC, the discrepancies in this material could be overestimated. However, it is unlikely that this could explain the high level of discrepancy observed.

The FK was chosen as a comparative source based on its easy accessibility and its frequent use for the counselling of pregnant women. Comparison with the SPCs could have influenced the results, but the SPC is not commonly used as a source of drug information in clinical practice in Norway.

By including enquiries to the DICs from 2 different years, the amount of material was increased and possible changes in advice over time could be studied.

Further Implications

We, along with others, have shown that inconsistencies between sources providing advice on the use of drugs in pregnancy are relatively common. Initiatives should be taken to coordinate information in SPCs and product monographs for the same drug and for generic products. It should be a regulatory issue to harmonize the sources, both on a national and international level. Furthermore, an important issue is the need for actions to increase the awareness of the public on this problem. There is a need for continued evaluation of the clinical consequences of the current information practice.

Conclusion

We have demonstrated considerable differences between two Norwegian sources providing advice on the use of drugs in pregnancy. Based on the knowledge that healthcare providers choose sources of information in a random manner, our results may be of clinical importance. Consistent and adequate information on the safety of drugs is of paramount importance for physicians' therapeutic decisions. The current results suggest a need for regulatory actions to coordinate and assess the quality of sources of information on clinically important issues, such as the safe use of drugs in pregnancy. We believe that the problem with heterogeneous drug information on this subject is not confined to Norway and that our results could be of international interest.

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