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Therapeutic Drug Use During Pregnancy: A Comparison in Four European Countries

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ABSTRACT. A drug utilization study was performed using data of the OECM study on Occupational Exposures and Congenital Malformations, which was conducted in six European Registries of Congenital Anomalies (two in France, two in Italy, one in Great Britain, and one in The Netherlands): the mothers were interviewed after delivery for exposures during pregnancy, including use of therapeutic drugs. The analysis of drug use considered only the 1134 control mothers of healthy newborns, and focused on the first trimester of pregnancy: 36.2% of the interviewed mothers used at least one drug (excluding vitamins and minerals) during the first trimester. This rate varied from 22.5% in Glasgow to 50.3% and 44.2% in the French centers. Anti-infectives were the most frequent drugs (12.3% of mothers), then antinauseants (10.6%), and treatments for threatened abortion (5.5%). Important variations between countries were observed, reflecting different medical attitudes towards drug use during pregnancy. J CLIN EPIDEMIOL 52;10:977–982, 1999. © 1999 Elsevier Science Inc.

KEY WORDS. Drug utilization, pregnancy, epidemiology, Europe, teratogenic risk, anti-infectives

INTRODUCTION

Many important drugs have been discovered over the last 50 years, and their usefulness in the treatment of previously fatal diseases has been an undeniable progress for human well-being. Even though there are no potent drugs without any side effects, most of these are minor, and the benefit-risk ratio is usually positive.

After the thalidomide disaster in the 1960s, attention was focused on the potential teratogenic risk of drugs during the first trimester of pregnancy [1]. Since then, however, only a very few new teratogens have been identified [2]; these include valproic acid and isotretinoin.

Most of the drug utilization studies available were performed in the 1970s and the 1980s [3–11] and found high levels of use during pregnancy. Because of the variety of methods in these studies, performed in various countries, no between-country comparisons were possible. Only the CGDUP Study [12–14], a multicenter investigation, allowed comparisons between European countries.

The present analysis uses data from the OECM study

[15], a multicenter study of occupational exposures during pregnancy; its objective is to compare drug utilization during pregnancy, especially in the first trimester, across six centers in four European countries.

METHODS

The OECM study was a multicenter investigation of Occupational Exposures and Congenital Malformations, carried out between 1989 and 1992 in six areas covered by six Registries of Congenital Anomalies involved in the EURO-CAT (European Registration of Congenital Anomalies) network [16]: Paris and Bouches-du-Rhône in France, Glasgow in Great Britain, Emilia-Romagna and Toscana in Italy, and Groningen in The Netherlands.

Cases were fetuses or babies with major malformations and controls were healthy newborns matched by date and place of birth. The methods and results about occupational exposures, especially glycol ethers, have been previously reported [15].

Mothers were interviewed after either delivery or termination of pregnancy following prenatal diagnosis. A standardized questionnaire asked about occupational exposures during pregnancy. Drugs, recorded as a potentially confounding factor, were investigated for the month before

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conception, and the first, second, and third trimesters of pregnancy. The interview included specific questions about treatments for chronic diseases, infectious diseases, and such conditions as vomiting, insomnia, depression, venous disorders, and threatened abortion. There was also an open question about any other drug. Although no information was recorded about dose and duration of treatment, the interviewers were requested not to record a medication taken only occasionally, for example, one aspirin for a headache. For each indication, the reported treatments were classified at the central level into groups of drugs according to the Anatomical Therapeutic Chemical (ATC) classification.

The comparison of exposure to drugs between cases and controls, searching for associations between malformations and drugs, will be reported separately.

For the present drug utilization study, we analyzed drug intake for the mothers of 1134 healthy controls only, in order to avoid the recall bias linked to the status of the newborn (malformed or normal). This study first examined global drug use, overall and for each trimester of pregnancy, and then focused on the first trimester, looking in detail at drug use by center for various indications. The percentage of drug users was analyzed, regardless of how many different drugs each woman took. Regular use was not distinguished from discontinued use for one or more periods. No distinction was made between prescribed and self-administered drugs. Vitamins and minerals were excluded from the analysis.

An SAS software package was used for data processing. The differences between centers were assessed with the chi-square test (with appropriate degrees of freedom); when the minimum expected frequency was less than five, the data of the two Italian centers, due to small numbers, were pooled, after checking their homogeneity.

RESULTS

Mothers' Characteristics

Table 1 shows the sociodemographic characteristics of the mothers at each center. The differences between centers are statistically significant ($P < 0.001$) for each of the following variables: maternal age, parity, place of residence (urban or rural), and socioeconomic status.

The representativeness of the mothers interviewed at each center was verified there, by comparison with the available regional population data (total births in the area) for the distribution of maternal age and parity. The differences were small and nonsignificant, except that the mothers in the Groningen area were significantly older than their local counterparts ($P < 0.05$) and those in the Bouches-du-Rhône ($P < 0.005$) and Glasgow areas ($P < 0.05$) had more children. The representativeness of their socioeconomic status could not be verified for most regions, because of a lack of relevant data. The split between urban and rural residence was in accordance with the topography of each area.

Drug Intake During Pregnancy

Overall, 64.1% of the women used at least one drug during pregnancy (including the month before conception) (Table 2); 36.2% used a drug during the first trimester, and 14.2% during the month before pregnancy.

The comparisons showed that medication use was highest in France and lowest in Great Britain for each period of pregnancy (Fig. 1). During the first trimester, 50.3% of the mothers in Paris used drugs, 44.2% in Bouches-du-Rhône, and only 22.5% in Glasgow. Results fell between these ex-

TABLE 1. Maternal characteristics by center (distribution in %)

Centers	Fr/Par	Fr/BdR	GB/Gla	It/Emi	It/Tos	NL/Gro
n	374	120	244	118	60	218
Maternal age (at delivery) ^a						
<25 years	11.2	29.2	31.1	14.4	11.7	8.3
25–34 years	67.1	55.8	57.8	72.0	81.7	78.4
≥35 years	21.7	15.0	11.1	13.6	6.6	13.3
Previous births ^a						
No	45.7	35.8	35.7	62.7	56.7	44.0
1 or 2	47.6	49.2	55.7	35.6	43.3	50.9
3 or more	6.7	15.0	8.6	1.7	0	5.1
Place of residency ^a						
Urban	94.4	87.5	96.3	65.8	68.3	56.0
Rural	5.6	12.5	3.7	34.2	31.7	44.0
Socioeconomic status ^a (last employment)						
Professional and managerial	41.8	19.3	15.2	20.5	25.4	37.0
Clerks, sales, and services	44.5	35.3	66.8	45.6	45.5	56.4
Agricultural and production	2.4	5.1	15.6	12.5	21.8	5.2
Not employed	11.3	40.3	2.4	21.4	7.3	1.4

^a Differences between centers $P < 0.001$.

TABLE 2. Drug use^a by center during pregnancy at any time and during the first trimester (number and percentage of users)

Centers	N	Any time ^b		1st trimester	
		n	%	n	%
Totals	1134	727	64.1	410	36.2
France/Paris	374	302	80.8	188	50.3
France/Bouches-du-Rhône	120	89	74.2	53	44.2
Great Britain/Glasgow	244	113	46.3	55	22.5
Italy/Emilia-Romagna	118	64	54.2	34	28.8
Italy/Toscana	60	33	55.0	21	35.0
Netherlands/Groningen	218	126	57.8	59	27.1
Differences between centers		P < 0.001		P < 0.001	

^a At least one drug (except vitamins and minerals).

^b Including the month before pregnancy.

treme in the Italian centers (35.0% and 28.8%) and in Groningen (27.1%) (Table 2).

The analysis of drug use during first trimester did not evidence any statistically significant variation with maternal age, parity, place of residence (urban or rural), or socioeconomic status.

Treatment Categories During the First Trimester

Treatment during the first trimester (Table 3) was most often for acute disease (31.9%) and only occasionally (7.8%) for chronic disease (including a variety of drugs: antihypertensives, drugs for asthma, thyroid disease, etc.). For acute disease, the most common medications were anti-infective agents (12.3% of all mothers), a majority of which were antibiotics (6.5%); then anti-nauseant drugs (10.6%), treatments for threatened abortion (5.5%), vaso-

protectives (3.1%), and psychotropic agents (2%). Various “other” medications were prescribed to 9.1% of mothers: the main category was analgesics (3.1%), followed by gastrointestinal agents (1.9%). This group also included homeopathic treatments and the few cases (1.4%) in which the mother knew that she had taken medication but did not remember the name or category of the drug. Moreover, 29% of the drug users took more than one treatment.

Variations Between Centers for Drug Classes

The frequency of treatment for chronic disease during the first trimester differed significantly between centers (P < 0.001), from 3.3% in Glasgow to 11.5% in Paris. The centers also differed significantly in the proportion of drug us-

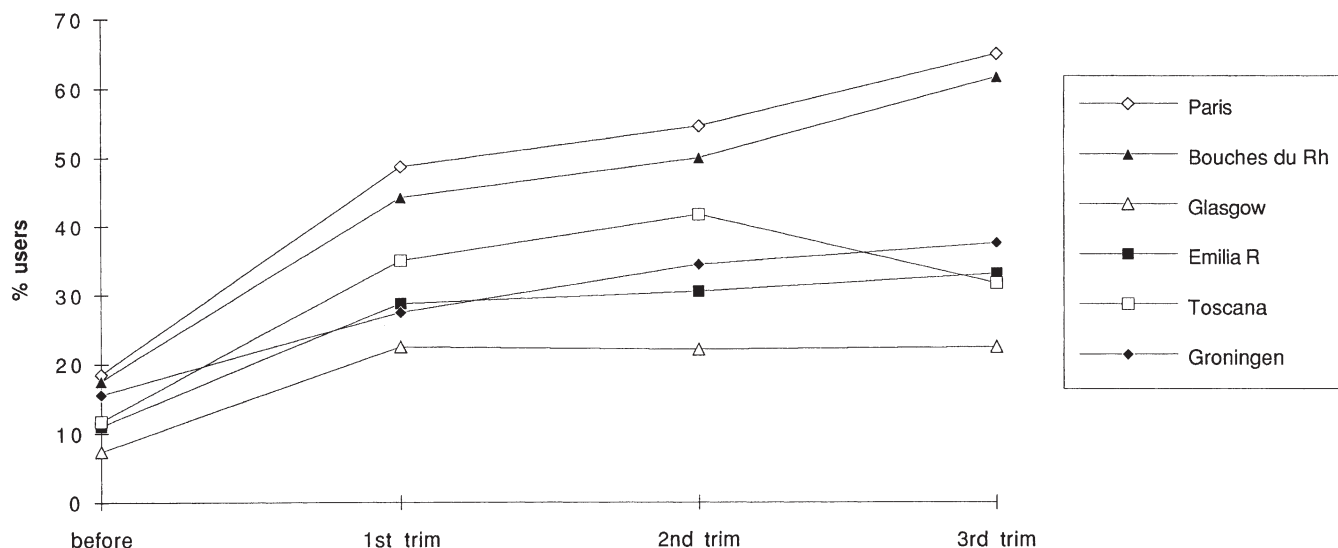


FIGURE 1. Drug use by center during pregnancy.

TABLE 3. Drug use for various conditions during the 1st trimester of pregnancy (number and percentage of users)

	N = 1134	
	n	%
Total drug use ^a	410	36.2
Total treatments for chronic disease	88	7.8
Total treatments for acute disease ^a	362	31.9
Anti-infectives	139	12.3
Antinauseants	120	10.6
Treatment for threatened abortion	62	5.5
Vasoprotectives	35	3.1
Psychotropic drugs	23	2.0
"Other" treatments ^a	102	9.1
Analgesics	35	3.1
Gastrointestinal agents	21	1.9
Various (including homeopathy)	41	3.6
Unknown	16	1.4

^a Women can have more than one treatment.

ers being treated for acute disease. These differences were both global and according to drug class (Table 4). At the two French centers, the most frequently consumed drugs were antinauseants (15% in Bouches-du-Rhone and 21% in Paris) and anti-infective drugs (respectively, 12% and 19%). At the two Italian centers, the main category was treatment for threatened abortion (17%); in Glasgow, anti-infective agents (12%); and in the Netherlands, "other" treatments, including analgesics and homeopathy (13%), followed by anti-infective drugs (10%).

Classes of drugs, then, were prescribed differently in different countries. Anti-infective agents were most often prescribed in France and Scotland, and only rarely in Italy; antinauseant medication was common in France, but rare in Scotland and The Netherlands; treatment of threatened abortion was most frequent in Italy and not found in Groningen; vasoprotectives were almost exclusively used in

France. The categories of anti-infective agents also differed (mostly antibiotics in Glasgow), as did the type of treatment for threatened abortion (most often beta₂-adrenoceptor agonists in Italy and progestogens in France).

DISCUSSION

This drug utilization study, based on data collected by six centers in four European countries for the OECM study, allowed a comparison of drug use during pregnancy, because the same methodology was used to collect the data and classify the drugs; it observed quantitative and qualitative variations by center in drug use, especially during the first trimester.

We took into account possible bias related to the source of data and the design of the OECM study: the analysis concerned only controls, to avoid recall bias linked to the status of the newborn, which could influence maternal recall and interviewer's questioning. This control group had been selected by matching to cases by date and place of birth. Insofar as it is not a random sample of mothers, selection bias cannot be excluded, but mothers in the study were found to be reasonably representative of mothers in their region. Moreover, the differences in drug use between center could not be explained by local sociodemographic differences, because drug use during the first trimester did not vary significantly with any of the sociodemographic variables (socioeconomic status, maternal age, parity, and urban or rural residence).

These results suggest that these variations by center may be due to differences in health practices between countries. Support for this hypothesis comes from the similarity of drug use patterns between centers from the same country (France and Italy), despite obvious regional sociocultural differences between them (e.g., between Paris and Bouches-du-Rhône). Further studies are needed to focus specifically

TABLE 4. Intercenter comparison of drug use for acute conditions during the 1st trimester of pregnancy (number and percentage of users)

Centers	N	Anti-infectives drugs		Antinauseants		Treatments for threatened abortion		Vaso-protectives		Psychotropic drugs		Other treatments	
		n	%	n	%	n	%	n	%	n	%	n	%
France/Paris	374	69	18.5	78	20.9	21	5.6	22	5.9	9	2.4	43	11.7
France/ Bouches-du-Rhône	120	14	11.7	18	15.0	7	5.8	12	10.0	5	4.2	15	12.6
Great Britain/ Glasgow	244	29	11.9	7	2.9	4	1.6	0	0	1	0.4	15	6.1
Italy/ Emilia-Romagna	118	2	1.7	6	5.1	20	17.0	0	0	2	1.7	1	0.9
Italy/Toscana	60	4	6.7	6	10.0	10	16.7	1	1.7	2	3.3	1	1.7
Netherlands/ Groningen	218	21	9.6	5	2.3	0	0	0	0	4	1.8	27	12.5
Differences between centers		P < 0.001		P < 0.001		P = 0.001		P = 0.001		NS		P < 0.001	

on this intercountry comparison about drug use during pregnancy, with representative samples for various countries. This study is the first to show such important variations by country in drug prescription during the first trimester.

The method of investigation, that is, retrospective interview of mothers after delivery, could have led to an underestimation of drug use and to a high rate of missing or imprecise data, especially for the first trimester. Recall of exposures during pregnancy is improved, however, by direct questioning about specific exposures [17], as occurred in our study. The only important group of drugs for which there was no specific question was analgesics, which were therefore included in the general question about "other drugs." This format might explain why the rate of analgesic use was rather low compared with other studies [3,5,13].

The percentage of drug users was analyzed for the entire pregnancy and then for each trimester. Consumption before conception cannot be compared with that during pregnancy, especially for acute treatment, because of the difference in duration (the question asked about "the month before" conception). The analysis then focused on the first trimester because of its importance when considering the teratogenic risks of drugs, and a detailed analysis was made of the categories of drugs used for various indications.

Most previous studies of drug utilization during pregnancy were carried out in the 1970s and 1980s, after the thalidomide disaster. In a review of 13 epidemiological studies performed in various countries between 1967 and 1987 [3], overall drug use during pregnancy ranged from 35% to 100% when categories of drugs such as vitamins and minerals were included. Of three North American studies performed during the 1980s among large samples of mothers [4–6], two included data for the first trimester [4,6] and reported that 40% and 17% of mothers had used medication then. Among European studies [7–11], most did not give any specific information on the first trimester or include vitamins and minerals. A high level of drug consumption during pregnancy was usually reported. In Great Britain [10], drug use was rather low, 6.7% during the first trimester (excluding vitamins, minerals, and drugs during delivery) and had clearly decreased since a previous study in the 1970s. The most frequently used drugs after vitamins and minerals were found to be tocolytics (22.8%) in Italy [9] and analgesics and antibacterial agents in Great Britain [10] and in The Netherlands [11].

These studies used a variety of methods. Only the CGDUP (Collaborative Group on Drug Use in Pregnancy) study [12–14] used a standard approach that allowed drug use to be compared between countries. This multicenter drug utilization study, conducted between 1988 and 1990 under the auspices of WHO, interviewed 14,778 mothers in 22 countries, 10,258 of them in Europe (including Italy, The Netherlands, and the UK, but not France). It found that 86% of the mothers had taken drugs (including vitamins and iron) during pregnancy. In decreasing order, after

vitamins, the most frequently used medications were anti-infective drugs (19%) and analgesics (17%). In the first trimester, 6% had used analgesics, and 4–4.5%, anti-infectives. The authors commented on the high rate of prescription in Europe. The comparisons between countries were not very detailed, especially for the first trimester.

Drug use in the general population is difficult to compare between countries except from pharmaceutical data. One such study [18] examined six classes of drugs in four European countries and observed a generally higher frequency of drug use in France than elsewhere, except for a few categories of drugs. Consumption did not seem to be related to the number of drugs available—about 8000 products in France and Italy, 10,000 in the UK, and many more in Germany, where drug use was in the midrange. Other economic indicators should be considered, however. In 1992, Dickson [19] analyzed the differences in pricing policies in various European countries including the four under study: France and Italy used product price control, The Netherlands used reference pricing, and the UK used profit control. These policies affected drug prices, which were lowest in France, then Italy, intermediate in the UK, and highest in The Netherlands. Pharmaceutical expenditure, however, was highest in France, slightly lower in Italy, and lowest in the UK. Thus, the low French prices are counterbalanced by high consumption.

However, the problem of drugs during pregnancy is quite different from that of drug use in the general population, because of the potential teratogenic risk in early pregnancy. Clinical trials are not conducted among pregnant women, precisely because of the potential danger to the fetus. The recommendation for this population should be to avoid drugs insofar as possible, except when they offer incontestable benefits for serious maternal diseases.

CONCLUSION

This drug utilization study during pregnancy found high levels of drug consumption during the first trimester of pregnancy. It also observed important variations between the four countries studied, variations that reflect different attitudes towards drug use in pregnancy. Such variations suggest that the real benefit of drugs used in some countries and not in others should be reconsidered. The challenge today is to maximize drug benefits while minimizing their harm, but special caution is required in prescribing drugs to pregnant women, especially now when pregnancy is so medicalized in the developed countries.

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