CEOG Clinical and Experimental Obstetrics & Gynecology

General Section

Medication exposure and spontaneous abortion: a case-control study using a French medical database

D. Abadie, C. Hurault-Delarue, C. Damase-Michel, J.L. Montastruc, I. Lacroix, the French Regional Pharmacovigilance Centers participating to TERAPPEL

Department of Medical and Clinical Pharmacology, Faculty of Medicine, Toulouse (France)

Summary

Purpose of investigation: Few studies have been conducted to investigate drug effects on spontaneous abortion risk. The objective of the present study was to evaluate the potential association between first trimester drug exposure and spontaneous abortion occurrence. *Materials and Methods:* The authors performed a nested case-control study using data from TERAPPEL, a French medical database. Cases were the women who had a spontaneous abortion (before the 22nd week of amenorrhea) and controls were women who gave birth to a child. Analyzed variables were: maternal age, obstetric history, tobacco, and alcohol and drug consumption during the first trimester of pregnancy. For comparison of drug exposures between cases and controls, the authors calculated odds ratios (ORs) by means of multivariate logistic regressions adjusted on age and on other drug exposures. *Results:* The study included 838 cases and 4,508 controls that were identified in the database. In adjusted analyses, cases were more exposed than controls to "non-selective monoamine reuptake inhibitors" [OR=2.2 (CI95% 1.5-3.3)], "anti-protozoals" [OR = 1.6 (CI 95% 1.1 - 2.5)] and "centrally acting anti-obesity products" [OR = 3.4 (CI 95% 1.9 - 6.2)]. Conversely, controls were more exposed than cases to H1 antihistamines [OR = 0.6 (CI 95% 0.4 - 0.9)]. *Conclusion:* This exploratory study highlights some potential associations between first trimester drug exposure and risk of spontaneous abortion. Further studies have to be carried out to investigate these findings.

Key words: Spontaneous abortion; Drug exposure; Case-control study.

Introduction

Spontaneous abortion can be defined as the spontaneous loss of the conceptus before 20 weeks gestation [1]. It is one of the most frequent adverse outcomes in human pregnancy [2]. The incidence of spontaneous abortion reported by several authors among clinical pregnancies is approximately 10-20% [2, 3], however prospective studies on conception and early pregnancy have reported fetal loss rates approaching one-third [4].

Some factors have been associated with spontaneous abortion [2, 5, 6]. However, they are difficult to evaluate because many pregnant women are not closely followed-up during early pregnancy and may never present for care if they experience a spontaneous abortion. Most of spontaneous abortions are due to a conceptus with an abnormal number of chromosomes [1, 7, 8]. Uterine anatomic defects are another well known spontaneous abortion etiologic factor [9]. The rate of spontaneous abortion also seems to increase with immunological factors (autoimmune diseases [7]), endocrine abnormalities (diabetes [10], thyroid diseases [11]), thrombophilia [12], various environmental exposures (tobacco [13], alcohol [14] and moderate-to-heavy caffeine use [15]), and other maternal conditions (age [16, 17], obesity [18], infertility [19-20], and increasing number of previous spontaneous abortions [21]).

Pregnant women are often exposed to medication, sometimes inadvertently, especially during early pregnancy when they do not yet know that they are expecting a child. Various studies have reported that an elevated number of drugs are prescribed to a woman during her pregnancy (an average of six to 16 different drugs) [22-23]. Few studies have been conducted to specifically investigate a relationship between drug exposure and spontaneous abortion risk, consequently little is known about this topic.

The French Regional PharmacoVigilance Centers (CRPVs) are regularly questioned about potential drug exposure risks during pregnancy. Many of these questions relate to early pregnancy exposure. Follow up is performed and pregnancy outcomes are registered in TERAPPEL, a database shared by several CRPVs, enabling the follow up of early drug exposed women. The present study was conducted using this database in order to obtain further data on the potential relationship between first trimester drug exposure and spontaneous abortion.

Revised manuscript accepted for publication March 17, 2014

Materials and Methods

The authors performed a nested case-control study using the French database TERAPPEL. Since 1984, this database has been used to record health professionals' requests from the participating CRPVs concerning women exposed to drugs during pregnancy and breastfeeding. Data concerning the pregnancies leading to questions to the CRPV are collected prospectively and registered in the database (up to December 31st, 2010, 31,000 questions had been registered in the database). From the first contact (most of the time, a telephone contact), the health professional informs the CRPV on the pregnancy progress and drug exposures of the pregnant woman. Two paper questionnaires designed to complete data on potential risk factors during pregnancy (such as maternal diseases and drug exposures) are subsequently sent by the CRPV to the correspondent. The first questionnaire is sent just after the health professional's call and the second when the woman is supposed to deliver. Thanks to these questionnaires, TERAPPEL contains information about the call purpose, woman's state of health, medical history, drug exposure (including period of exposition) according to the ATC classification, and pregnancy outcome.

Cases were all the women registered in TERAPPEL whose pregnancy outcome was "spontaneous abortion" (before the 22nd week of amenorrhea) and controls were all the women registered in TERAPPEL whose pregnancy outcome was "birth". For both groups the authors only selected pregnancies whose call purpose was "first trimester risk assessment", so that cases and controls had the same drug exposure risk during the first trimester of pregnancy. Analyzed variables were: age, obstetric history (births, ectopic pregnancies, intrauterine deaths, medical terminations of pregnancy, and spontaneous and voluntary abortions), tobacco, alcohol, and drug consumption during pregnancy. To avoid an artificial overexposure of the control group, which had a longer mean duration of pregnancy, the authors took into account the same period of drug exposure for both groups, which corresponded to the average gestation length for cases.

Data were analyzed using SAS version 9.1 software. The authors compared quantitative variables (age, number of different drugs taken by women during the study period) between cases and controls using Student tests. Categorical variables (medication use, consumption of tobacco and alcohol and obstetric history) were compared between the two groups using the Chi-square or Fischer's exact test when appropriate. For drug exposures, whenever possible, relevant confounders significantly associated with spontaneous abortion in univariate analysis were included in regression models.

Results

The present study included 838 cases and 4,508 controls that were registered in the TERAPPEL database. Spontaneous abortions were reported at a mean time of 9.4 (±3.0) weeks since last menstrual period. In the control group, length of gestation was 38.9 (±2.0) weeks since last menstrual period.

Women's characteristics

The general characteristics for the case and control groups are presented in Table 1. Cases were significantly older than controls (32.4 *vs* 30.6 years-old, $p < 10^{-4}$). The history of ectopic pregnancy, intrauterine death, voluntary abortion, and medical pregnancy termination was similar in both groups. The case group had experienced significantly more spontaneous abortions ($p = 1.10^{-4}$) and births ($p = 7.10^{-3}$) in the past than the control group.

Table 1. — *General characteristics of 838 cases and 4508 controls.*

	Group; n°.(%) of women		p
	Cases	Controls	
Characteristics	**n=838**	**n=4508**	
Age, yr, mean (SD)	32.4 (6.1)	30.6 (5.4)	<10-4
Pregnancy duration, SA, mean (SD)	9.4 (3.0)	38.9 (2.0)	
N° of drugs taken, mean (SD)	2.25 (1.8)	2.20 (1.9)	NS
Tobacco use during pregnancy [(a)]			NS
No tobacco use	168 (74.7%)	1474 (76.1%)	
At least one cigarette	57 (25.3%)	464 (23.9%)	
Alcohol use during pregnancy [(b)]			NS
No alcohol use	192 (91.0%)	1633 (89.9%)	
At least one glass	19 (9.0%)	182 (10.0%)	
N° of previous miscarriages [(c)]			1.10-4
0	217 (71.9%)	2066 (81.2%)	
>1	85 (28.2%)	479 (18.8%)	
N° of previous ectopic pregnancies [(d)]			NS
0	265 (99.3%)	307 (98.0%)	
>1	2 (0.8%)	47 (2.0%)	
N° of previous intrauterine deaths [(e)]			NS
0	264 (98.9%)	2321 (99.2%)	
>1	3 (1.1%)	18 (0.8%)	
N° of previous voluntary abortions [(f)]			NS
0	234 (82.4%)	2139 (86.6%)	
>1	50 (17.6%)	330 (13.4%)	
N° of previous medical terminations of pregnancy [(g)]			NS
0	264 (97.8%)	2317 (98.4%)	
>1	6 (2.2%)	37 (1.6%)	
N° of previous births [(h)]			7.10-3
0	221 (37.5%)	1371 (43.5%)	
>1	368 (62.5%)	1782 (56.5%)	
Percentage of missing data: [(a)] 60% [(b)] 62% [(c)] 47% [(d)] 51% [(e)] 51% [(f)] 49% [(g)] 51% [(h)] 30%			

Medication exposure

The average number of different drugs used during the study period was not significantly different between cases and controls {respectively, 2.25 (±1.84) *vs* 2.20 (±1.90)}. In the two groups, the first intake of drug occurred on average during the first week of pregnancy. Table 2 shows drug exposure for cases and controls according to ATC classification. Regarding both groups, the most commonly taken drugs were for the "nervous system", "anti-infectives for systemic use", "alimentary tract and metabolism", and "musculoskeletal system" ATC classes. After adjusting for age and other drug classes associated with an increase of spontaneous abortion risk, the authors found that cases were more exposed than controls to "antiparasitic products" (OR 1.51, 95% CI 1.04 - 2.19) in particular "antiprotozoals" (OR 1.63, 95% CI 1.06 - 2.50), "anti-obesity preparations, excluding diet products" (OR 2.58, 95% CI 1.47 - 4.53) and in particular "centrally acting anti-obesity products" (OR 3.40, 95% CI 1.85 - 6.24) and to "non-selective monoamine reuptake inhibitors" (OR 2.19, 95% CI 1.46 - 3.29). Conversely, after adjusting for age, the authors found that cases

Table 2. — *Risk of spontaneous abortion associated with drug use during pregnancy.*

		No. (%) of cases and controls exposed		p	Odds ratio for spontaneous abortion (95% CI)			
No. ATC	ATC title	Cases	Controls		Crude		Adjusted	
A	Alimentary tract and metabolism	123 (14.68%)	664 (14.73%)	NS				
A08=A08A	Antiobesity preparations, excluding diet products	22 (2.63%)	40 (0.89%)	p<1.10-4	3.01	(1.78-5.09)	2.58*	(1.47-4.53)
A08AA	Centrally acting antiobesity products	21 (2.51%)	29 (0.64%)	p<1.10-4	3.97	(2.25-7.00)	3.40*	(1.85-6.24)
B	Blood and blood forming organs	42 (5.01%)	249 (5.52%)	NS				
C	Cardiovascular system	66 (7.88%)	329 (7.30%)	NS				
D	Dermatologicals	33 (3.94%)	151 (3.35%)	NS				
G	Genito-urinary systems and sex hormones	81 (9.67%)	412 (9.14%)	NS				
H	Systemic hormonal preparations excl. sex hormones and insulins	45 (5.37%)	266 (5.90%)	NS				
J	Antiinfectives for systemic use	173 (20.64%)	885 (19.63%)	NS				
L	Antineoplastic and immunomodulating agents	17 (2.03%)	107 (2.37%)	NS				
M	Musculo-skeletal system	116 (13.84%)	588 (13.04%)	NS				
N	Nervous system	357 (42.60%)	1830 (40.59%)	NS				
N05	Psycholeptics	171 (20.41%)	728 (16.15%)	p=3.10-3	1.33	(1.11 -1.60)	1.24*	(0.99-1.50)
N06	Psychoanaleptics	172 (20.53%)	742 (16.46%)	p=4.10-3	1.31	(1.09-1.58)	1.19*	(0.98-1.45)
N06A	Antidepressants	170 (20.29%)	729 (16.17%)	p=3.10-3	1.32	(1.10-1.59)	1.20*	(0.98-1.46)
N06AA	Non selective monoamine reuptake inhibitors	39 (4.65%)	88 (1.95%)	p<1.10-4	2.45	(1.67-3.60)	2.19*	(1.46-3.29)
P	Antiparasitic products, insecticides and repellents	41 (4.89%)	156 (3.46%)	p=0.04	1.44	(1.01-2.04)	1.51*	(1.04-2.19)
P01	Antiprotozoals	32 (3.82%)	110 (2.44%)	p=0.02	1.59	(1.06-2.37)	1.63*	(1.06-2.50)
R	Respiratory system	76 (9.07%)	457 (10.14%)	NS				
R06=R06A	Antihistamines for systemic use	24 (2.86%)	201 (4.46%)	p=0.03	0.63	(0.41-0.97)	0.59**	(0.37-0.94)
S	Sensory organs	10 (1.19%)	51 (1.13%)	NS				
V	Various	29 (3.46%)	171 (3.79%)	NS				
	Non aspirin NSAIDs	73 (8.71%)	407 (9.03%)	NS				
*adjusted on age and other drug exposures								
**adjusted on age								

were significantly less exposed than controls to "antihistamines for systemic use" (OR 0.59, 95% CI 0.37 - 0.94).

Discussion

Few studies have been conducted to specifically investigate a relationship between drug exposure and spontaneous abortion risk. The present exploratory study reports that first trimester exposure to "centrally acting anti-obesity products", "non-selective monoamine reuptake inhibitors", and "antiprotozoals" are associated with an increase in spontaneous abortion risk. In contrast, the study shows that controls were more exposed to "antihistamines for systemic use" than women who had experienced a spontaneous abortion.

The majority of previous studies which reported findings on medication and spontaneous abortion risk were cohort-designed to investigate the effects of specific drugs and did not study spontaneous abortion as a primary objective. The present authors conducted a first exploratory case-control designed study to generate hypothesis on the potential links between first trimester drug exposure and risk of spontaneous abortion. The case-control approach is a good design for investigating simultaneously the potential effects of different drug exposures on the occurrence of an event. This design, associated with the large population size (more than 5,000 pregnancies registered in the database), allowed the authors to have an overview of the potential effects of a wide variety of drugs on spontaneous abortion risk. Moreover, unlike studies performed on prescription or reimbursement databases, the present methodology (information on drug exposures provided by physicians who question their patients on their drug consumption) enables accounting of over-the-counter drugs.

However, the methodology of this exploratory study presents some limitations, mostly due to the source of the data. Indeed, TERAPPEL database had not initially been implemented for this specific study, and consequently some variables are missing. The first limitation that should be pointed out, is that the authors could not take into account all the potential confounding factors. First, confounding by specific indications which increase spontaneous abortion risk cannot be excluded. Other potential confounding factors such as obstetric history and alcohol or tobacco use could neither be taken into account because of the large proportion of missing data. However maternal age, a well-known risk factor for spontaneous abortion [16-17] that was significantly associated with spontaneous abortion risk in the present crude

analysis, was included in regression models. Moreover, the authors studied the differential effects of drugs associated with an increase of spontaneous abortion risk: "centrally acting anti-obesity products", "non-selective monoamine reuptake inhibitors" or "antiprotozoals". A second limitation is the possibility of a selection bias: women included had been exposed to at least one drug, which motivated the call of the health professional. However this bias is attenuated by the comparative analysis of cases and controls.

Regarding antidepressants, most of the studies failed to show a significant association between exposure to these drugs during pregnancy and spontaneous abortion [24-31]. A significant increase of spontaneous abortion risk has rarely been associated with this drug class in pharmacoepidemiologic studies [32-34]. Meta-analysis reported significant increase of the spontaneous abortion risk associated with all antidepressants [35], serotonin reuptake inhibitors [36], and specific antidepressants like paroxetine or venlafaxine [37]. Serotoninergic mechanism has been suggested, as 5-hydroxytryptamine is abortive in experimental animals [38]. However, potential confounding factors, especially maternal depression, have been inconstantly considered in the relevant studies. In the present study, the association between antidepressants and spontaneous abortion was observed mainly with imipraminic antidepressants (non-selective monoamine reuptake inhibitors), especially with clomipramine. Two prospective studies, which included a total of 378 pregnant women exposed to imipraminic antidepressants, did not report any increased risk of spontaneous abortion compared with the general population rate [27, 31]. However, the interpretation of these findings is limited as no control group was included in these studies. Other studies (case-control or meta-analysis) reported a non-significant increase of spontaneous abortion risk with imipraminic antidepressants exposure [33, 35]. As an indication bias cannot be ruled out in the present study, further analyses are needed to confirm or disprove this potential relationship.

The present results showed a significant association between spontaneous abortion risk and "centrally acting antiobesity products" or "antiprotozoals" exposures, in crude and in adjusted analyses. For "antiprotozoals", the difference was observed particularly for "nitroimidazole derivatives" but the possible indication bias, and the small numbers of pregnancies in this subclass (<10 in each group), limit the interpretation of the results. The most encountered drug of "centrally acting antiobesity products" was dexfenfluramine. A minor study evaluating the effects of phentermine/fenfluramine on approximately 100 pregnant women did not report any increase of spontaneous abortion risk with these drugs [39] and the rare literature data available on the topic do not suggest a positive link between spontaneous abortion risk and amphetamine exposure [40]. Some studies reported that spontaneous abortion risk was increased with ecstasy (another amphetamine) [41], but this data is difficult to interpret because women exposed to ecstasy often have a potentially dangerous lifestyle for the fetus. Due to potential indication bias since obesity constitutes a recognized risk factor for both maternal and fetal complications such as spontaneous abortion [42-44], it is necessary to remain cautious concerning the interpretation of the present results.

The present study does not support the conclusion that non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) use is associated with an increased risk of spontaneous abortion. The association between gestational use of non-aspirin NSAIDs and spontaneous abortion remains controversial. Three publications of pharmacoepidemiology studies have reported a positive relationship between NSAIDs use and spontaneous abortion risk [45-47]. The mechanisms suggested by authors involve the role of prostaglandins in implantation and in maintaining placental perfusion. In the Nielsen *et al.* study [45], protopathic bias was possible since the association between NSAIDs exposure and spontaneous abortion was higher when exposure occurred immediately before spontaneous abortion, and in a subsequent re-examination of results adjusting for gestational age, the observed associations were no longer statistically significant [48]. If, as suggested by the only of these three studies which included non-prescription NSAIDs [46], the relationship between NSAIDs and spontaneous abortion risk is stronger with exposure closer to conception time, it is possible that the lack of significance observed in the present study could be explained by the authors' difficulty in collecting information on exposure to drugs around conception time. However, the present study is not the only one that does not suggest a positive association between non-aspirin NSAIDs use and spontaneous abortion. Indeed, a recent cohort study of almost 3,000 pregnancies did not observe any association between early pregnancy exposure to over-the-counter NSAIDs, particularly non-aspirin, and spontaneous abortion [49]. In France, ibuprofen can be dispensed without prescription. The present method has the advantage of providing access to data on exposure to over-the-counter drugs, even if underreporting of self-medication is possible.

Surprisingly, controls were significantly more exposed to "antihistamines for systemic use" (H1 antihistamines) than cases, and the difference was still significant in the present age-adjusted analyses. Literature data on the potential link between H1 antihistamine use and spontaneous abortion risk is very limited. A prospective, controlled, and observational study of 53 pregnant women exposed to hydroxyzine and 39 to cetirizine showed no difference with regards to the risk of spontaneous abortion rate between the hydroxyzine or cetirizine groups and the control groups [50]. Some antihistamines are indicated in the treatment of vomiting and it has been described that women who experience intense nausea and vomiting in early pregnancy have less risk of spontaneous abortion than women with less or no nausea and vomiting [51]. However, in the present study, confusion by

indication does not explain the observed association. Indeed, most of the antihistamines associated with a decrease in spontaneous abortion risk in the present study are not registered for nausea and vomiting indication: only the "piperazine derivatives" (ATC code: R06AE), represented in majority by cetirizine and levocetirizine (eight out of the nine cases and 97 out of the 98 controls exposed to "piperazine derivatives"), were significantly associated with a decrease in spontaneous abortion risk. In literature, links have been reported between hyper-histaminemia and specific gestational complications such as spontaneous abortion [52, 53]. A histamine injection in pregnant cats and inhibition of diamine oxidase (the main enzyme involved in histamine metabolism at the feto-maternal interface) in pregnant rats was reported to induce spontaneous abortions [54, 55]. Observations of spontaneous abortion in women with diamine oxidase deficits and increased histaminemia levels have also been published [56, 57]. This could be explained by the contractile effect of histamine on uterine musculature or indirectly by an increased production of the uterotonic PGF2 alpha (which is thought to play a key role in the initiation and maintenance of normal labour) [52]. Treatment of threatened abortion with antihistamines has been investigated and it was shown that a combined therapy of antihistamines and antispasmodic had the same protective effect as a tranquilizer and gestagen combined therapy [58].

Conclusion

The authors report the results of the first exploratory case-control designed study performed to investigate potential associations between first trimester drug exposure and spontaneous abortion occurrence. "Non-selective monoamine reuptake inhibitors", "centrally acting antiobesity products", and "antiprotozoals" were associated with an increased risk of spontaneous abortion, but an indication bias cannot be ruled out, since the pathologies for which these drugs are used can also be involved in spontaneous abortion. In contrast, "antihistamines for systemic use" were significantly associated with a decrease in spontaneous abortion risk. This could be explained by a pathophysiological hypothesis since H_1 antihistamines could have potential protective effects on histamine-induced uterine contractions. However, further investigations are needed to specifically study this potential association.

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Address reprint requests to:
D. ABADIE, Pharm.D
Department of Medical and Clinical Pharmacology,
Faculty of Medicine
37, Allées Jules Guesde
31000 Toulouse (France)
e-mail: delphine.abadie@univ-tlse3.fr