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Pregnancy outcome following maternal exposure to pregabalin may call for concern

Ursula Winterfeld, PhD
Paul Merlob, MD
David Baud, MD, PhD
Valentin Rousson, PhD
Alice Panchaud, PhD
Laura E. Rothuizen, MD
Nathalie Bernard, PharmD
Thierry Vial, MD
Laura M. Yates, MBChB
Alessandra Pistelli, MD
Maria Ellfolk, PhD
Georgios Eleftheriou, MD
Loes C. de Vries, MD
Annie-Pierre Jonville-Bera, MD
Mine Kadioglu, MD
Jerome Biollaz, MD
Thierry Buclin, MD

Correspondence to Dr. Winterfeld: ursula.winterfeld@chuv.ch

ABSTRACT

Objective: To investigate pregnancy outcomes following maternal use of pregabalin.

Methods: This multicenter, observational prospective cohort study compared pregnancy outcomes in women exposed to pregabalin with those of matched controls (not exposed to any medications known to be teratogenic or to any antiepileptic drugs). Teratology Information Services systematically collected data between 2004 and 2013.

Results: Data were collected from 164 exposed pregnancies and 656 controls. A significantly higher major birth defect rate in the pregabalin group was observed after exclusion of chromosomal aberration syndromes, and when cases with exposure during first trimester of pregnancy were analyzed separately (7/116 [6.0%] vs 12/580 [2.1%]; odds ratio 3.0, 95% confidence interval 1.2–7.9, $p = 0.03$). The rate of live births was lower in the pregabalin group (71.9% vs 85.2%, $p < 0.001$), primarily due to a higher rate of both elective (9.8% vs 5.0%, $p = 0.02$) and medically indicated (5.5% vs 1.8%, $p = 0.008$) pregnancy terminations. In the Cox proportional cause specific hazards model, pregabalin exposure was not associated with a significantly higher risk of spontaneous abortion.

Conclusions: This study demonstrated a signal for increased risk of major birth defects after first trimester exposure to pregabalin. However, several limitations such as the small sample size, differences across groups in maternal conditions, and concomitant medication exposure exclude definitive conclusions, so these results call for confirmation through independent studies.

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GLOSSARY

CI = confidence interval; **HR** = hazard ratio; **IQR** = interquartile range; **MBD** = major birth defect; **OR** = odds ratio; **TIS** = Teratology Information Services.

Pregabalin is widely prescribed in neurology, psychiatry, and primary health care, and was granted marketing approval as an adjunctive therapy for partial-onset seizures, neuropathic pain, and, in some countries, generalized anxiety disorder.[1,2] Explored off-label uses include the treatment of restless legs syndrome and psychiatric conditions such as cyclic mood disorders. Recreational use of pregabalin has also been reported.[3] A recently published study assessed characteristics of patients receiving pregabalin in Sweden. The majority were women (63%), and off-label use was common (60%).[4] Several studies confirm that in many countries, a high number of women report conditions potentially relieved by new antiepileptic drugs such as

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Supplemental data at Neurology.org

From STIS (Swiss Teratogen Information Service) and Division of Clinical Pharmacology (U.W., A.P., L.E.R., J.B., T.B.), Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; BELTIS Rabin Medical Center and Sackler School of Medicine (P.M.), University of Tel-Aviv, Israel; Materno-Fetal and Obstetrics Research Unit (D.B.) and Institute of Social and Preventive Medicine (IUMSP) (V.R.), Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; Centre Régional de Pharmacovigilance (N.B., T.V.), Hospices Civils de Lyon, France; UKTIS (L.M.Y.), Regional Drug and Therapeutics Centre, Newcastle upon Tyne Hospitals NHS Trust, UK; Centro di Riferimento Regionale di Tossicologia Perinatale (A.P.), Azienda Ospedaliero Universitaria Careggi, Florence, Italy; HUCH Teratology Information Service (M.E.), HUCH Emergency Care, Helsinki, Finland; Poison Control (G.E.), Bergamo, Italy; TIS (L.C.d.V.), Netherlands Pharmacovigilance Centre Lareb, Den Bosch; Unit of Pharmacotherapy & Pharmaceutical Care, Department of Pharmacy, University of Groningen, the Netherlands; Centre de Pharmacovigilance de Tours (A.-P.J.-B.), CHRU, Tours, France; and Department of Pharmacology (M.K.), Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey.

This study was presented as an oral communication at the 2nd International Conference of the Organization of Teratology Information Specialists and the European Network of Teratology Information Services (September 19–21, 2014, Toronto, Canada) and at the 12th Congress of the European Association for Clinical Pharmacology and Therapeutics (June 27–30, 2015, Madrid, Spain).

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pregabalin.[5–7] Since a significant number of pregnancies are unplanned, widespread use of pregabalin may regularly lead to inadvertent exposure during early pregnancy.

Animal studies have suggested reproductive toxicity for this agent, with skeletal malformations, neural tube defects, increased rates of spontaneous abortions, growth retardation, and behavioral anomalies reported.[1,8–10] Data on pregabalin use during human pregnancy are scarce. A recent database study that included 30 monotherapy pregabalin exposures documented a major malformation in one exposed infant, and although overall major birth defect (MBD) rates were not increased above those of the unexposed control cohort, analysis was limited by the small sample size.[11] Preclinical observations have raised similar concerns regarding structural teratogenicity for the related compound gabapentin. A recent publication on human exposures did not find a significantly increased malformation rate but observed an increased risk for low birthweight and preterm birth in the gabapentin-exposed patients compared to a general control group.[12] Patients in the gabapentin group had a variety of neuropsychiatric disorders and received concomitant medication in many cases.

The aim of this study was to address the risks associated with exposure to pregabalin during pregnancy.

METHODS Eight participating Teratology Information Services (TIS) in different countries collected data for this multicenter, prospective, observational study: France, United Kingdom, Italy, Finland, Switzerland, the Netherlands, and Turkey. One TIS and 18 pharmacovigilance centers that use similar procedures collected data in France. TIS offer expertise on potential risks related to medication exposure during pregnancy at the individual patient level.[13] Case and control patients included in the study were women who themselves or whose physician contacted one of the centers.[13] Data were collected between 2004 and 2013.

We used the same methodology as the one described in previous studies.[13,14] Maternal characteristics (age, tobacco use, alcohol consumption, medical and obstetric history) and information on medication exposure (indication, timing in pregnancy, duration, dose, and concomitant medication) were collected at initial contact.[13,14] After the expected date of delivery, follow-up was achieved through a structured telephone interview or mailed questionnaire to the patient or her health care professional.[13,14] Collected data included pregnancy outcome, gestational age at delivery, birthweight, birth defects, and neonatal complications.[13,14] Pregnancy outcomes of pregabalin-exposed women were compared with the outcomes of women who were not exposed to an antiepileptic drug (the control group).[13,14] Exclusion criteria for both groups included exposure during pregnancy to any known major teratogen or fetotoxicant (acitretin, isotretinoin, mycophenolate, or thalidomide; angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists during second and third trimester) and to any treatment for malignancy.[15] A subset of randomly selected controls was matched to cases with a ratio of 4:1 according to center, year of contact, maternal age, and stage of pregnancy at time of call. Data collection methodology at first contact and follow-up was the same for both groups.[13]

The primary outcome of interest was the rate of MBD.[13] Two independent specialists (P.M. and D.B.) blinded to information on drug exposure classified birth defects as major or minor using 2 standard classifications.[16,17] In cases of discordant classification, consensus was achieved through discussion. Neither minor nor total birth defect rates were calculated, as minor birth defects are known to be largely underreported.[13] Secondary endpoints included the rates of live births, spontaneous abortions, pregnancy terminations, preterm deliveries (<37 weeks of gestation), and infant gestational age and birthweight at delivery.[13] Gestational age was calculated using last menstrual period or first trimester ultrasound dates.

Statistical analysis. Major birth defect rates were calculated taking into account anomalies in live births, in pregnancy terminations, and in spontaneous abortions. Crude spontaneous abortion rates were calculated after exclusion of terminated pregnancies.[13] Spontaneous abortion rates and pregnancy termination rates were also analyzed using survival analysis (cumulative incidence), in order to take into account entry into the cohort at variable time intervals postconception. Spontaneous abortion, termination of pregnancy, and live birth were treated as competing risks.[14,18] Cox proportional cause-specific hazard models were also used to assess the association of exposure with spontaneous abortion, termination of pregnancy, and live birth.[14,18] Multiple imputation was used to deal with missing time data. This was done according to the observed distribution of gestational age at the time of birth outcome, separately for each of the 3 outcomes, and conditionally so that the imputed age was larger than the age results obtained over 100 analyses.

Categorical data were compared by χ^2 or Fisher exact tests.[13] Continuous data did not follow normal distribution and were compared using a Mann-Whitney test.[13] Logistic regression analysis was used to account for a possible role of cofactors.[13] Statistical analyses were performed with STATA version 13 (StataCorp, College Station, TX) and R version 3.1.1.

Standard protocol approvals, registrations, and patient consents. The European Network of Teratology Information Services scientific committee approved the study protocol. In most participating centers, this observational cohort study did not require ethics committee approval; otherwise, ethics approval was received from appropriate authorities.

RESULTS **Maternal characteristics.** The comparison of maternal characteristics between the 164 pregabalin-exposed cases and the 656 controls is presented in table 1. Significantly more patients in the pregabalin than in the control group reported tobacco use. The gestational age at initial contact was slightly yet significantly earlier in the pregabalin group.

The indication for pregabalin treatment was reported for 160 (98%) patients and included pain (most often neuropathic pain, n = 115), psychiatric disorders (depression, anxiety disorder, bipolar

Table 1 Maternal characteristics

Characteristics	Pregabalin (n = 164)	Controls (n = 656)	*p* Value
Maternal age, y, median (IQR) (n_p; n_c = 164; 655)	33 (29–37)	33 (29–37)	0.81
Tobacco use, n (%) (n_p; n_c = 129; 511)	57 (44.2)	93 (18.2)	<0.001[a]
Alcohol consumption, n (%) (n_p; n_c = 107; 409)	14 (13.1)	57 (13.9)	0.88
GA at initial contact, wk, median (IQR) (n_p; n_c = 164; 656)	8 (6–11)	8 (6–13)	0.03[a]
Previous pregnancies, n (%) (n_p; n_c = 147; 578)			0.41
0	53 (36.1)	227 (39.3)	
1	42 (28.6)	180 (31.1)	
≥2	52 (35.4)	171 (29.6)	
Previous deliveries, n (%) (n_p; n_c = 145; 574)			0.38
0	67 (46.2)	286 (49.8)	
1	44 (30.3)	183 (31.9)	
≥2	34 (23.5)	105 (18.3)	
Previous spontaneous abortion, n (%) (n_p; n_c = 143; 569)			
0	119 (83.2)	469 (82.4)	0.03[a]
1	12 (8.4)	78 (13.7)	
≥2	12 (8.4)	22 (3.9)	
Previous ETOP, n (%) (n_p; n_c = 143; 568)			
0	131 (91.6)	511 (90.0)	0.34
≥1	12 (8.4)	57 (10.0)	
Medical conditions, n (%) (n_p; n_c = 163; 450)			<0.001[a]
Pain/migraine	122 (74.3)	37 (5.6)	
Psychiatric disorders	74 (45.1)	122 (18.6)	
Infection	8 (4.9)	112 (17.1)	
Gastric/duodenal disease[b]	4 (2.4)	37 (5.6)	
Insomnia	5 (3.0)	7 (1.1)	
Epilepsy	5 (3.0)	—	
Diabetes/gestational diabetes	4 (2.4)	10 (1.5)	
Hypertension	4 (2.4)	8 (1.2)	
Inflammatory polyarthropathies	4 (2.4)	7 (1.1)	
Hypothyroidism/hyperthyroidism	3 (1.8)	13 (2.0)	
Obesity	3 (1.8)	8 (1.2)	
Asthma	3 (1.8)	27 (4.1)	
Restless legs syndrome	1 (0.6)	—	
Other	44 (26.8)	127 (19.4)	

Abbreviations: ETOP = elective termination of pregnancy; GA = gestational age; IQR = interquartile range; n_p, n_c = number of pregabalin-exposed patients and controls with information available.
[a] Significant.
[b] Including inflammatory bowel disease.

disorder, psychosis, n = 39), epilepsy (n = 5), and restless legs syndrome (n = 1). Additional medical conditions, which clearly differ across groups, are presented in table 1.

Pregabalin exposure. The median daily pregabalin dose was 150 mg (interquartile range [IQR] 75–300). Pregabalin therapy was started before pregnancy in 77% of the patients and discontinued at a median gestational age of 6 weeks (IQR 5–11). More than half of the patients (61%) continued pregabalin treatment beyond week 6 of gestation and 33% beyond week 7. First trimester pregabalin exposure occurred in 96% of the patients. The median duration of gestational exposure was 6 weeks (IQR 4–10). In the pregabalin group, 22 (13%) patients were concomitantly treated with another antiepileptic drug (acetazolamide, carbamazepine, clonazepam, gabapentin,

lacosamide, lamotrigine, levetiracetam, topiramate, valproic acid).

Pregnancy outcome. Pregnancy outcomes are presented in table 2. Altogether, MBD were reported more frequently in pregnancies exposed to pregabalin than in the control group. A significantly higher MBD rate in the pregabalin group persisted after exclusion of chromosomal aberration syndromes and when cases with exposure during first trimester of pregnancy were analyzed separately (7/116 [6.0%] vs 12/580 [2.1%]; odds ratio [OR] 3.0, 95% confidence interval [CI] 1.2–7.9, $p = 0.03$). When limiting the analysis to the subgroup of 19 patients with pregabalin monotherapy during first trimester of pregnancy, the association with overall MBDs remained significant (3/19 [15.8%] vs 16/573 [2.8%]; OR 6.5, 95% CI 1.7–24.7, $p = 0.02$), but became nonsignificant after exclusion of chromosomal or genetic anomalies (1/19 [5.3%] vs 11/573 [1.9%]; OR 2.8, 95% CI 0.3–23.2, $p = 0.39$). After adjustment for concomitant treatment with antiepileptic drugs, benzodiazepines, antidepressants, alcohol consumption, or twin pregnancy, the OR for MBD did not change. Conversely, compared to controls, the MBD risk tended to be higher in pregabalin-treated patients who reported smoking during pregnancy (OR 9.5, 95% CI 1.9–46.9) than in patients who did not smoke (OR 1.3, 95% CI 0.3–6.0). However, the difference between these 2 ORs did not reach statistical significance based on a logistic regression model including an interaction between pregabalin and tobacco ($p = 0.08$). Details of major and minor birth defects, medication, and maternal condition in both groups are presented in tables e-1 and e-2 on the *Neurology*® Web site at Neurology.org. Only one infant concomitantly exposed to another antiepileptic drug presented a MBD. The child was diagnosed with multiple cardiac defects. In this case, however, pregabalin exposure occurred between 12 and 16 weeks of gestation, which is beyond the critical period for cardiac birth defects. The other cases of MBD observed in the pregabalin group included 4 chromosomal and 8 structural anomalies. The structural anomalies were distributed in 4 organ systems: CNS (n = 4), skeletal (n = 2), cardiac (n = 2), and skin or vascular (n = 1). The rate of CNS malformations in the exposed group was higher than in the control group (4/125 [3.2%] vs 3/570 [0.5%], OR 6.2, 95% CI 1.4–28.3, $p = 0.02$).

With exception to the previously discussed case with multiple cardiac birth defects, all the mothers with fetuses presenting a structural anomaly started pregabalin before conception. Daily pregabalin doses in mothers of fetuses with structural anomalies were similar to those in mothers of healthy children (median 113 IQR 75–350 vs 150 IQR 75–300, $p = 0.9$).

Other pregnancy outcomes. The rate of live births was lower in the pregabalin group, primarily due to a higher rate of both elective and medical pregnancy terminations. The crude spontaneous abortion rate was also higher in the pregabalin group. When cumulative spontaneous abortion rates were estimated by the cumulative incidence function, a rate of 22% was obtained in the pregabalin group and 18% in the

Table 2 Pregnancy outcome

	Pregabalin	Controls	Crude OR (CI)	p Value
Live-born infants, n	119	564		
Multiple gestations, n	1 twin set	5 twin sets		
Pregnancies resulting in live-born infants, n (%)	118/164 (71.9)	559/656 (85.2)	0.4 (0.3-0.7)	<0.001[a]
Elective termination of pregnancy, n (%)	16/164 (9.8)	33/656 (5.0)	2.0 (1.02-3.9)	0.02[a]
Medical termination of pregnancy, n (%)	9/164 (5.5)[b]	12/656 (1.8)[c]	3.1 (1.1-8.2)	0.008[a]
Spontaneous abortion,[d] n (%)	21/139 (15.1)	52/611 (8.5)	1.9 (1.1-3.4)	NS[e]
Major birth defects,[f] n (%)	12/125 (9.6)	16/573 (2.8)	3.7 (1.5-8.6)	<0.001[a]
Major birth defects not chromosomal or genetic,[f] n (%)	8/125 (6.4)	11/573 (1.9)	3.5 (1.2-9.7)	0.005[a]
Preterm delivery, n (%)	11/119 (9.2)	40/559 (7.2)	1.3 (0.6-2.7)	NS
Gestational age at birth, wk, median (IQR) (n = 119; 559)	40 (38-40)	40 (39-41)		NS
Birthweight, g, median (IQR) (n = 109; 538)	3,300 (3,000-3,690)	3,350 (3,030-3,660)		NS

Abbreviations: CI = confidence interval; IQR = interquartile range; NS = not significant; OR = odds ratio.
[a] Significant.
[b] Reasons for medical termination of pregnancy: 2 ectopic pregnancies, 6 birth defects, 1 unknown.
[c] Reasons for medical termination of pregnancy: 2 ectopic pregnancies, 8 birth defects, 2 maternal diseases.
[d] Elective and medical termination of pregnancies excluded.
[e] Not associated with a significantly higher risk according to Cox proportional cause-specific hazards model.
[f] Total anomalies in live births, elective and therapeutic termination, and miscarriages with pathologic examination.

control group (figure). In the Cox proportional cause specific hazards model, pregabalin exposure was not associated with a significantly higher risk of spontaneous abortion (hazard ratio [HR] 1.60, 95% CI 0.95–2.71, $p = 0.08$). The cumulative pregnancy termination rate estimated by the cumulative incidence was 21% in the pregabalin group and 10% in the control group. In the Cox model, pregabalin exposure significantly increased the risk for pregnancy termination (HR 2.81, 95% CI 1.60–4.93, $p < 0.001$).

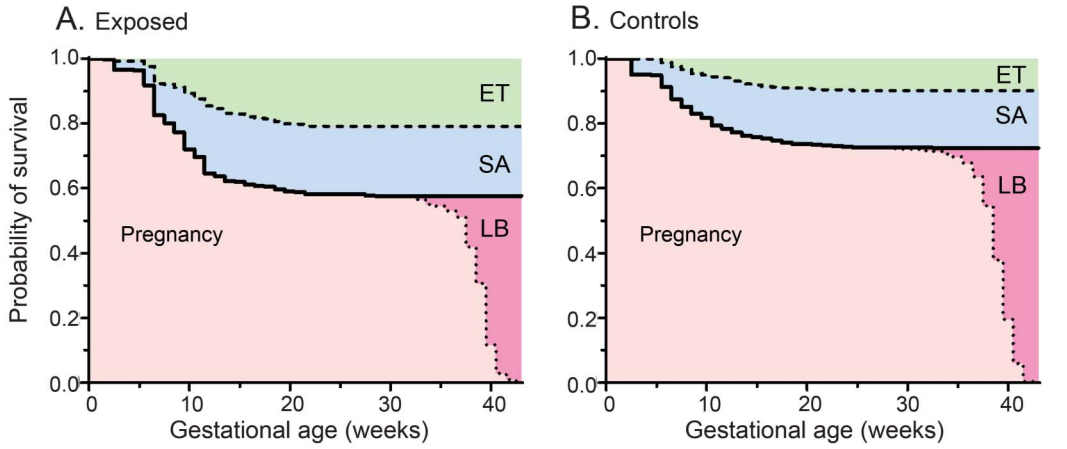
Preterm birth rates, gestational age at birth, and birthweight were similar in both groups.

Neonatal outcomes. Neonatal complications were reported in 5 of the 13 newborns exposed antenatally to pregabalin until delivery. All but 1 infant born at 36 weeks were term births. These included isolated respiratory distress (n = 2), withdrawal syndrome (n = 1), and clavicle fracture (n = 1). The fifth child developed respiratory distress, hypotonia, and shock with metabolic acidosis, hepatic cytolysis, and renal insufficiency and died at 6 weeks of age. The mother took low-dose aspirin until 36 weeks of gestation, followed by enoxaparin until 38 weeks of gestation. At 36 weeks of gestation, intrauterine growth restriction (<10th percentile) was diagnosed. One of the infants who presented with respiratory distress was concomitantly exposed to tramadol, morphine, and propranolol; the other child was exposed to betahistine until delivery. The infant who presented with features of withdrawal syndrome was concomitantly exposed until delivery to oxycodone, alprazolam, and paroxetine.

Information on follow-up was obtained from health care professionals and patients in similar proportions for both the pregabalin and the control group: health care professionals 35%, patients 28%, unknown 37% in both groups. Infant age at follow-up was reported for 56% of the patients in the pregabalin group and 26% for the control group. Median infant age at follow-up was 12 weeks in the pregabalin group (IQR 4–18) and 8 weeks in the control group (IQR 4–13, $p = 0.04$). The rate of loss to follow-up differed between centers: France, 7.6% and 21% in the pregabalin and the control group, respectively; United Kingdom, 0% in both groups; Florence, Italy, 7.4% and 3.5%, Bergamo, Italy, 50% in both groups; Finland, 72.5% and 55%; Switzerland, 25% and 24%; the Netherlands, 25% and 14%; and Turkey, 0% in both groups. For a sensitivity analysis, we reassessed the overall MBD risk based on the assumptions (1) of a MBD in each case and control lost to follow-up (OR 2.7, 95% CI 1.9–3.9, $p < 0.001$) and (2) of an absence of MBD in each case and control lost to follow-up (OR 3.3, 95% CI 1.4–7.4, $p = 0.001$). Under both assumptions, the effect of pregabalin remained statistically significant.

DISCUSSION To our knowledge, this prospective observational study reporting on pregnancy outcomes after in utero exposure to pregabalin is the largest one published yet. Our results raise a signal for a possible increase in the rate of MBD after pregabalin treatment during the first trimester of pregnancy.[19] The rate of CNS malformations was higher in the exposed group than that observed in the control group. All 4 cases were concurrently exposed to other substances and genetic causes have not been formally investigated. However, given that pregabalin is a centrally acting agent, the possibility that these findings may signal a teratogenic effect in humans needs to be

Figure **Cumulative incidence rates of spontaneous abortion, pregnancy termination, and live birth in both groups**



Overall survival of pregnancy over gestational weeks (solid line) differentiating the cumulative incidence of elective termination (ET, dashed line) and spontaneous abortion (SA) and showing the occurrence of live birth (LB, dotted line) in childbearing women exposed to pregabalin (A) vs controls (B).

considered. Our data are too scarce to establish whether a distinct phenotype might characterize pregabalin-induced CNS changes, and the cerebral ventricle enlargement reported in all 4 cases can still represent a fortuitous association.

Overall, the pregabalin-exposed pregnancies that resulted in malformations were exposed to more medications and had more complicated medical conditions than those in the comparison group. One of the infants was diagnosed with an atrial septal defect. The mother was concomitantly exposed to paroxetine and citalopram. There is an ongoing discussion as to whether cardiac malformations are causally associated with paroxetine use during pregnancy.[20] One pregnancy was terminated after diagnosis of multiple birth defects. However, the mother reported, among other exposures, very high alcohol consumption between weeks 5 and 8 of pregnancy. We also observed more chromosomal anomalies in the pregabalin group than in the general controls. Interestingly, a higher proportion of women in the pregabalin group reported tobacco use during pregnancy. Smoking induces hepatic enzymes, which are involved in drug metabolism.[21] However, pregabalin is not metabolized to any large extent—90% of pregabalin is excreted in an unchanged form.[1] Cigarette smoke contains an important number of toxins and potential chemoreactants including nicotine and carbon monoxide.[22] Maternal smoking has a harmful effect during pregnancy and increased risk of intrauterine growth restriction, stillbirth, preterm birth, and placental abruption were observed in some epidemiologic studies.[22] An increased risk for specific birth defects such as gastroschisis has been suggested in smoking mothers.[23] However, in our study further statistical analysis did not support an interaction between smoking and pregabalin.

Pregabalin exposure was not associated with a significantly increased risk of spontaneous abortion in the Cox model, which takes into account possible bias arising from differences in the stage of pregnancy at which pregnancies were reported to the study centers. An increased rate of elective termination of pregnancy was observed in the pregabalin-exposed group. The decision to electively terminate a pregnancy may in some cases have been taken because of concerns regarding the drug effect on pregnancy outcome.[13] Underlying maternal disease may also have played a role.[13] Furthermore, a higher rate of unplanned pregnancies in the pregabalin-exposed group cannot be excluded, leading to poorer acceptance of the pregnancy.[13]

Only a few infants were exposed to pregabalin up until delivery. One of the infants who presented respiratory distress was concomitantly exposed to other psychotropic medication and propranolol throughout pregnancy. The infant who presented withdrawal symptoms was concomitantly exposed to other psychotropic drugs. Consequently, it is difficult to attribute the observed signs to pregabalin vs other causes. However, pregabalin discontinuation can be associated with withdrawal symptoms in adults, and 2 cases of possible poor neonatal adaptation syndrome in neonates exposed to gabapentin close to delivery have been reported in a cohort study.[12] Neonates exposed to pregabalin until delivery should be monitored after birth for withdrawal symptoms or signs of toxicity.

Interestingly, an even lower percentage of patients than in the study on pregnancy outcomes following gabapentin use received pregabalin for the treatment of epilepsy.[12]

The strengths and limitations of collaborative TIS studies have been discussed elsewhere.[24] An important strength of this study is the prospective collection of information on drug exposure during pregnancy by detailed medical history taken at the moment of first contact with the participating centers, and at follow-up. The main limitation is the absence of a control group of women who were treated for similar conditions. A disease-matched control group would have better allowed accounting for differences in maternal comorbidities between both groups.[14] However, heterogeneity in indications for pregabalin would make such a control group difficult to collect. Teratogens are considered to act in a dose-dependent manner, but we did not observe any association between pregabalin dose and birth defect risk. Further limitations include different information sources for outcome data (health care professionals and patients), the limited data on folate use and on prior pregnancy complications, and the lack of data on family history of pregnancy complications and on congenital birth defects; the lack of genetic analysis in cases of multiple MBD; the variations in timing of follow-up; the small sample size, especially in monotherapy; and the fact that this is not a population-based study. The study does, however, have a number of strengths. Importantly, the same procedure for data collection was used in both groups, thus limiting the risk of potential bias for outcomes being lost to follow-up.[13] A sensitivity analysis showed no indication that loss to follow-up could have significantly affected the results.

Although our study raises a signal for a possible increase in the risk of MBDs after pregabalin treatment during pregnancy, these results call for further confirmation through independent studies since the sample size is insufficient and differences across groups in maternal conditions and concomitant medication exposure do not allow definitive conclusions to be drawn. Pregabalin should only be prescribed in women of childbearing age on a valid indication

and after thorough risk-benefit analysis. In patients exposed to pregabalin during pregnancy, enhanced fetal monitoring may be warranted.

AUTHOR CONTRIBUTIONS

Dr. Winterfeld: study conception and design, acquisition of data, analysis and interpretation of data, drafting and revising the manuscript for intellectual content. Prof. Merlob, Dr. Baud, and Prof. Rousson: analysis and interpretation of data, drafting and revising the manuscript for intellectual content. Dr. Panchaud and Dr. Rothuizen: study conception and design, acquisition of data, drafting and revising the manuscript for intellectual content. N. Bernard, Dr. Vial, Dr. Yates, Dr. Pistelli, Dr. Ellfolk, Dr. Eleftheriou, Dr. de Vries, Dr. Jonville-Bera, and Dr. Kadioglu: acquisition of data, drafting and revising the manuscript for intellectual content. Prof. Biollaz: drafting and revising the manuscript for intellectual content. Prof. Buclin: study conception and design, analysis and interpretation of data, drafting and revising the manuscript for intellectual content, study supervision.

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REFERENCES

1. Pharmacology Review: Lyrica Pregabalin. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021446s002,s003lbl.pdf. Accessed August 20, 2014.
2. Tassone DM, Boyce E, Guyer J, Nuzum D. Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. Clin Ther 2007;29:26–48.
3. Schifano F, D'Offizi S, Piccione M, et al. Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. Psychother Psychosom 2011;80:118–122.
4. Wettermark B, Brandt L, Kieler H, Boden R. Pregabalin is increasingly prescribed for neuropathic pain, generalised anxiety disorder and epilepsy but many patients discontinue treatment. Int J Clin Pract 2014;68:104–110.
5. Reimers A. New antiepileptic drugs and women. Seizure 2014;23:585–591.
6. van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology and its clinical relevance. Br J Anaesth 2013;111:13–18.
7. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res 2012;21:169–184.
8. Etemad L, Mohammad A, Mohammadpour AH, Vahdati Mashhadi N, Moallem SA. Teratogenic effects of pregabalin in mice. Iran J Basic Med Sci 2013;16:1065–1070.
9. Reprotox: Micromedex. Pregabalin. Available at: http://www.micromedexsolutions.com/. Accessed August 20, 2014.
10. Centre for Drug Evaluation and Research Approval Package. Lyrica (Pregabalin): Pharmacology Review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021446_Lyrica%20Capsules_pharmr.PDF. Accessed November 19, 2014.
11. Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. J Neurol 2014;261:579–588.
12. Fujii H, Goel A, Bernard N, et al. Pregnancy outcomes following gabapentin use: results of a prospective comparative cohort study. Neurology 2013;80:1565–1570.
13. Winterfeld U, Klinger G, Panchaud A, et al. Pregnancy outcome following maternal exposure to mirtazapine: a multicenter, prospective study. J Clin Psychopharmacol Epub 2015 Mar 31.
14. Winterfeld U, Allignol A, Panchaud A, et al. Pregnancy outcome following maternal exposure to statins: a multicentre prospective study. BJOG 2013;120:463–471.
15. Weber-Schoendorfer C, Chambers C, Wacker E, et al. Pregnancy outcome after methotrexate treatment for rheumatic disease prior to or during early pregnancy: a prospective multicenter cohort study. Arthritis Rheumatol 2014;66:1101–1110.
16. Merks JH, van Karnebeek CD, Caron HN, Hennekam RC. Phenotypic abnormalities: terminology and classification. Am J Med Genet A 2003;123A:211–230.
17. Rasmussen SA, Olney RS, Holmes LB, et al. Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol 2003;67:193–201.
18. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol 2012;41:861–870.
19. Hauben M, Aronson JK. Defining "signal" and its subtypes in pharmacovigilance based on a systematic review of previous definitions. Drug Saf 2009;32:99–110.
20. Grigoriadis S, VonderPorten EH, Mamisashvili L, et al. Antidepressant exposure during pregnancy and congenital malformations: is there an association? A systematic review and meta-analysis of the best evidence. J Clin Psychiatry 2013;74:e293–308.
21. Kroon LA. Drug interactions with smoking. Am J Health Syst Pharm 2007;64:1917–1921.
22. Jauniaux E, Burton GJ. Morphological and biological effects of maternal exposure to tobacco smoke on the feto-placental unit. Early Hum Dev 2007;83:699–706.
23. Lepigeon K, Van Mieghem T, Vasseur Maurer S, Giannoni E, Baud D. Gastroschisis: what should be told to parents? Prenat Diagn 2014;34:316–326.
24. Schaefer C, Ornoy A, Clementi M, Meister R, Weber-Schoendorfer C. Using observational cohort data for studying drug effects on pregnancy outcome: methodological considerations. Reprod Toxicol 2008;26:36–41.

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Ursula Winterfeld, Paul Merlob, David Baud, et al.

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