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Frequently asked questions on epilepsy, pregnancy and lactation: A EURAP-NL report

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ABSTRACT

Purpose: To describe the questions addressed by participants and physicians to the International Registry of Antiepileptic Drugs and Pregnancy centre in the Netherlands (EURAP-NL).
Methods: All incoming questions during the study period were systematically inventoried. Characteristics of the inquirer, antiepileptic drugs (AEDs) indicated, question topic, indication for which AEDs were (to be) prescribed, and timing of the question relative to pregnancy were evaluated.
Results: Healthcare professionals posed the majority of questions. Lamotrigine, levetiracetam, valproate and carbamazepine were the drugs most frequently referred to. Common reasons to contact EURAP-NL were congenital malformation risks associated with specific AEDs, requests for information updates when available guidelines were considered lacking, and concerns regarding breastfeeding while using AEDs.
Conclusions: There is an evident demand for additional information regarding AEDs and pregnancy. Pregnancy registries like EURAP can be a useful tool to identify information deficits and may serve as an information source for the development of guidelines to facilitate common practice among healthcare professionals.

1. Introduction

A rational management of antiepileptic treatment is of major importance for women in the context of pregnancy and lactation. In utero exposure to antiepileptic drugs (AEDs) is estimated to increase the risk of major congenital malformations in the newborn two to three times relative to the general population.[1] A substantial number of pregnant women (approximately five out of 1000) are diagnosed with epilepsy. Women with epilepsy need to adhere to antiepileptic treatment.[2] Since AEDs are prescribed for other indications as well, the proportion of pregnancies exposed to AEDs is even higher. In a survey among practicing neurologists and psychiatrists from the UK, half of each specialty group reported that AED-treated women of reproductive age represented one quarter of their consultations within the past year.[3] In order to provide optimal treatment for women of reproductive ages, information is critical for healthcare professionals especially when balancing the beneficial effects of drug treatment against potential negative effects of AEDs on pregnancy outcome.[4] Whereas personal consultations are preferred in the case of patients' medical questions,[5] clinicians' questions are best answered by clear medical guidelines, and, when available, by additional information from recent studies.

The teratogenic risk of AED therapy is present from the first weeks of pregnancy, often before the woman is aware of being pregnant. Information should be provided proactively by healthcare providers to all women of childbearing potential using AEDs in order to accomplish treatment adjustments prior to conception.[6] Clinicians should be aware that the teratogenic risks are (at least partially) related to the type, dosage, and number of AEDs.[7,8] Strategies to prevent teratogenic sequelae aim to achieve seizure control with as few AEDs as possible, at the lowest effective dose. It is recommended to limit the administration of old-generation AEDs during pregnancy because potentially severe teratogenic effects are associated with AEDs such as valproate and carbamazepine.[9,10] On the other hand, for newer generation AEDs such as lamotrigine and levetiracetam, and for most, if not all, of AED combination therapy, data available regarding their safety during pregnancy and lactation are more sparse. While updates on management of women using AED in pregnancy are often being released,[11–14] the need for information on the side of involved parties, patients as well as clinicians, has not yet been determined adequately.

In this article, we defined the information demand among patients and clinicians in regard to the prescription and use of AEDs during pregnancy and lactation. To this aim, we evaluated enquiries concerning the use of AEDs to the International Registry

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of Antiepileptic Drugs and Pregnancy centre in the Netherlands (EURAP-NL).

2. Materials and methods

The International Registry of Antiepileptic Drugs and Pregnancy (EURAP) is the largest observational cohort study concerning the use of AEDs in pregnancy.[14,15] EURAP systematically records data from pregnant women who use AEDs during pregnancy aiming to estimate the relative risk of major foetal malformations associated with the exposure to AEDs during pregnancy.

EURAP-NL commenced in 2001 under the coordination of the Department of Clinical Genetics, located at the University Medical Centre Utrecht. During the entire study period, coordinators of the study centre have been available for participating physicians and participants, as well as for the general community, to answer questions concerning AED use in relation to pregnancy. Information to healthcare professionals and (future) participants relied on most recent literature reviews resulting from searches in medical research and drug databases as well as on evidence from the EURAP database. (Pregnant) women in need for information regarding their personal treatment were advised to attend medical counselling with their family physician or medical specialist in charge.

All incoming questions and the corresponding answers were systematically inventoried. For analysis, the following data were retrieved from each query: characteristics of the person submitting the query, AEDs in question, topic of the query, prescription indication of the AEDs, and timing of the question relative to a pregnancy. Descriptive data are presented as frequencies and counts (where appropriate).

A total of 222 consecutive questions were received by the EURAP centre in the Netherlands from January 1, 2002 until November 17, 2010 and they were paralleled by 1600 registered pregnancies. Of all questions, four regarded participation to the EURAP study, three concerned the teratogenicity of non-AEDs only (i.e., sertraline and pimozide), and two did not mention any medication at all. The remaining 213 questions referred to one or more AEDs and were selected for analyses.

3. Results

Healthcare professionals as well patients asked for AED-related information. Healthcare professionals posed questions most frequently (64.3%, $n = 137$). Neurologists represented the majority among the healthcare professionals (52.3% of all queries, $n = 67$), followed by gynaecologists/obstetricians (15.6%, $n = 20$) and clinical geneticists (14.1%, $n = 18$). Only 5% ($n = 7$) of all queries were addressed by psychiatrists. Approximately one-third of the questions were asked by pregnant women using AEDs (32.4%, $n = 69$) or by their relatives (3.3%, $n = 7$).

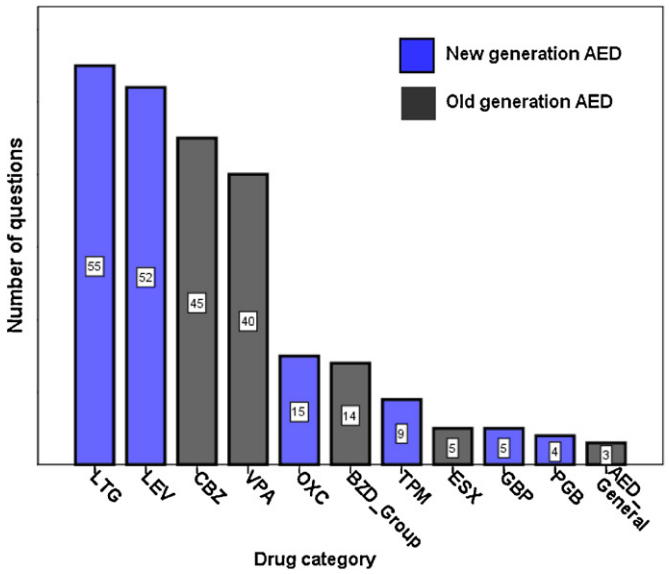

Fig. 1. Categories of antiepileptic drugs on which information has been requested. LTG, lamotrigine; LEV, levetiracetam; CBZ, carbamazepine; VPA, valproate; OXC, oxcarbazepine; BZD, benzodiazepine; TPM, topiramate; ESX, ethosuximide; GBP, gabapentine; PGB, pregabaline; AED, antiepileptic drugs in general. Data labels indicate the count of questions mentioning each drug category. Some questions involved more than one drug, e.g., for comparison purposes.

Fig. 1 gives an overview of the drug groups that elicited an enquiry. Lamotrigine, followed by levetiracetam, valproate and carbamazepine were most frequently mentioned. The most frequently asked questions (34.7%, $n = 74$) concerned observed malformations, or risk estimates of malformations in offspring of AED treated women. Second most prevalent (13.5%, $n = 28$) were requests to update information about specific AEDs. The latter category of queries originated exclusively from clinicians. Questions regarding breastfeeding associated risks in the newborn infant ranked as third (8.9%, $n = 19$). In 4 out of 213 questions, participants explicitly stated that divergent counselling opinions among different physicians had prompted their query. An extensive list of topics is shown in Table 1.

Table 1
An overview of topics on which questions were asked.

% Questions Total = 213	Topic	Example
35%	Congenital malformation risks in foetus of AED treated woman	Can observed malformations (e.g., micrognatia, mandibular hypoplasia) be ascribed to medication?
13%	General updates from literature overviews and EURAP preliminary data	Is there new data available about the safety and teratogenicity of levetiracetam?
9%	Breastfeeding associated risks	Does quantitative evidence exist about breastfeeding associated risks for the newborn in the case of lamotrigine?
8%	Comparison between AEDs	Given that therapeutic opinions from two neurologists are contradictory, which is the optimal treatment choice between lamotrigine and carbamazepine?
6%	Vitamin supplementation	Which is the recommended dose of folic acid supplementation when previous pregnancies resulted in a newborn with spina bifida?
5%	Cognitive development risks	Do autism spectrum disorders and delay in cognitive development occur more frequently in children from mothers who were under AED treatment during pregnancy?
5%	Pharmacological interactions with hormonal medication	Should AED dose be adjusted when used simultaneously with hormonal treatment during in vitro fertilization procedure?
5%	Risks for pregnancy complications	Is there a possible relationship between medication during the pregnancy and spontaneous abortion?
4%	Dose adjustment	Does the risk for congenital malformations decrease when lowering each drug dose within an AED combination?
10%	Other	–

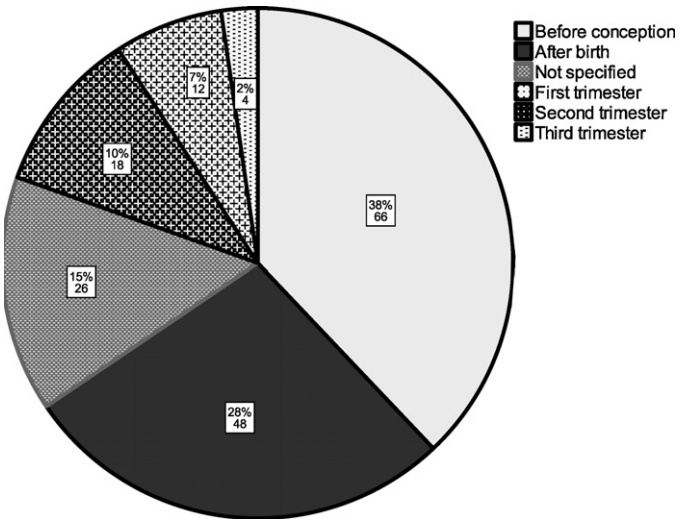

Fig. 2. Timing of the enquiry relative to the pregnancy as registered by EURAP. Solid fill – enquiries sent before and after pregnancy; crosshair patterns – enquiries sent during pregnancy of patient. Total of questions mentioning that information was needed for a particular pregnant woman is 177.

174 out of 213 questions included characteristics of a specific patient (i.e., woman being treated with AEDs) such as drugs being administered, main indication for treatment, patient's intention to conceive or pregnancy stage at the moment. The majority of these questions referred to the choice of medication for the treatment of an epilepsy syndrome (67.8%, $n = 118$). In addition, there was a small proportion of questions that specifically mentioned treatment indications other than epilepsy such as psychiatric disorders (3.4%, $n = 6$) and chronic pain syndrome (2.3%, $n = 4$).

Where the pregnancy stage of the AED treated woman in question was mentioned, queries inventoried during the first trimester of pregnancy were most prevalent. The more advanced the pregnancy stage, the fewer questions were registered. More than half of the questions were asked outside a pregnancy period of the AED treated women, either before potential conception or after delivery (Fig. 2). Notably, questions about teratogenic risks of AEDs in offspring of patients ($n = 71$) were uniformly distributed across the preconception (39.7%, $n = 29$) and postnatal period (31.5%, $n = 23$).

4. Discussion

This is the first study to evaluate frequently asked questions regarding antiepileptic drug treatment in relations pregnancy and breastfeeding. During the period analysed, EURAP-NL was contacted by many of its participants and by clinicians who needed additional, up to date information about AED use during pregnancy and lactation. Information demand was extensive as revealed by the various question topics with malformation risks, literature updates and breastfeeding related risks being the most prominent.

Discordant with the general prescription pattern in the Netherlands, the majority of questions addressed issues related to new generation AEDs such as lamotrigine and levetiracetam. The EURAP prescription figures over the period 1999–2010 show that carbamazepine (belonging to old generation AED) was the most frequently administered drug in monotherapy, followed by lamotrigine and valproate.[16] While lamotrigine and levetiracetam are relatively new drugs that clinicians may have less experience with, these drugs are not associated with high malformation risks. At present, lamotrigine is the drug of first choice for women who wish to become pregnant.[13] In contrast, valproate and to a lesser extent carbamazepine are associated with increased malformation risks and especially neural tube defects.[9,10,17] Also, the use of valproate during pregnancy is associated with a decrease in intelligence in exposed children compared to other AEDs.[18–20] In our opinion, the prescription of these drugs in pregnancy should be surrounded with extreme caution. However, the use of these drugs elicited less questions from either clinicians or patients than the use of lamotrigine or levetiracetam. Questions concerning intellectual development after prenatal exposure to AEDs were not abundant in our inventory (5.1%, $n = 11$ out of 213 questions) and were exclusively asked by healthcare professionals. Efforts should be made to disseminate awareness of these data to clinicians and women using AEDs.

Information demand was high for congenital malformations risk in the newborn, indicating that both physicians and patients were familiar with a possible causality related to AED exposure. It is quite alarming that a substantial number of questions were asked after onset of pregnancy, or even in the postnatal period of the AED exposed child. Treatment adjustment during the preconception phase of women using AEDs may result in a decrease in malformation rate as compared to interventions during a pregnancy.[6] The second most enquired topic regarded updates concerning specific AEDs without mentioning a specific pregnancy. This question category reflects the need for continuous medical education among clinicians in order to provide optimal care for both women using AEDs and their offspring. The third most frequently mentioned topic concerned AED associated neonatal toxicity during breastfeeding, mainly for lamotrigine, levetiracetam and benzodiazepines. Drug transfer to breast milk and drug half-life in infants appears to be most extensive for ethosuximide and phenobarbitone.[21] In contrast, investigations on the pharmacokinetics of lamotrigine and levetiracetam conducted so far suggested minimal or no risk of toxicity in the neonate as a consequence of breastfeeding.[21,22] Concerns about these drugs are not grounded and may be due to a lack of information on the topic.

The number of questions asked in total was not as high as might be expected over a period of eight years ($n = 222$). Unfortunately, we feel that this relatively low number reflects a lack of awareness in the medical profession of the possible adverse consequences of AED use during pregnancy. Therefore, women of reproductive age may not have actively sought for information concerning the possible adverse consequences of AED use in pregnancy.

Neurologists were the main group of health care professionals to ask questions to the EURAP-NL coordinators. Neurology has long led the way in developing and sharing information related to the use of AEDs in women of childbearing age.[12,13] Only a minority of queries came from psychiatrists. This distribution is in agreement with the participation rates from the EURAP registry since only 0.9% of women included were suffering from a disease other than epilepsy.[23] However, in daily medical practice especially older generation AEDs (such as valproate) are often prescribed to female patients by psychiatrists for mood stabilization.[24] Valproate is the AED with both an association with a high malformation rate and a worse cognitive outcome in children exposed to valproate during pregnancy.

Women being prescribed AED also asked a considerable amount of questions (32.4% of all queries). Remarkably, one of the reasons for them to ask information directly from EURAP-NL is the opinion disagreement between their physicians. For example, inconsistent advice was signalled when patients consulted two neurologists, or a neurologist and a gynaecologist.

The present paper offers a description of the issues encountered in medical practice when prescribing AEDs to pregnant women. Caution should be taken when interpreting these observations as, unlike a community-based assessment, our question inventory had a participation bias. Therefore, it is highly likely that the questions addressed to the EURAP only cover some areas of

interest, while the "silent" patients and clinicians may have an even broader information demand.

In conclusion, our study demonstrates the evident demand for information regarding AEDs and pregnancy in both patients and clinicians. The lack of information may result in divergent opinions between clinicians and delayed counselling of women using AEDs. Approaching registries like EURAP would be favourable to counteract information deficits in medical practice, and to develop improved medical guidelines.

Declaration of conflict of interests

DB has received speakers' fees from UCB Pharma and Sanofi-Aventis. AR and SB declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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