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Valproate in pregnancy: comment from the SAPP

Comment on: Use of valproate in pregnancy and in women of childbearing age between 2014 and 2018 in Switzerland: a retrospective analysis of Swiss healthcare claims data. Swiss Med Wkly. 2021;151:w20386

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For the Swiss Academy for Perinatal Pharmacology (SAPP)

The SAPP thanks the authors of the study "Use of valproate in pregnancy and in women of childbearing age between 2014 and 2018 in Switzerland" [1] and would like to make a few additional comments:

Use of medications during pregnancy that are harmful to the mother and/or the unborn child should be avoided whenever possible. As the authors mention in their introduction, the teratogenic effect of valproate has been known for about 40 years. However, the spectrum of known harms could have expanded over the years due to increasingly refined diagnostic techniques. But, irrespective of this, valproate has always required and continues to require a personalised interdisciplinary discussion whenever it is used by a woman of childbearing age [2].

In the international pregnancy EURAP registry there has been a continuous decrease (of nearly 50%) in valproate therapy for epilepsy since 2005 [3]. To compare the study size with other publications, it would be interesting to see the absolute numbers. Is there a trend over the time period in increasing use of antiepileptic drugs, as reported in the cited Danish publication [4], with a decrease in use of valproate? What about other medications such as phenobarbital and phenytoin, which are still mentioned in pregnancy registers [3]?

Valproate is reserved for very specific forms of epilepsy (therapy-refractory primary generalised epilepsies). It can therefore be assumed that it is increasingly being prescribed for non-epileptic indications such as psychiatric diseases [5]. Detailed information about the indication is therefore an important requirement, but was lacking in the data shown by the authors.

All statistics used reported last menstrual day to analyse gestational age. We have known for several years that these data are inaccurate, and gestational age should be based on the first trimester ultrasound, which is routinely performed in Switzerland and covered by health insurance [6].

As has been well documented in the literature for years, treatment compliance is worse in pregnant women than in non-pregnant women, especially women with pre-existing diseases and therapies such as psychopharmacological drugs [7, 8]. A prescription recorded on the basis of billed medicines is therefore not equivalent to taking the medicine, about which there was also no information.

As the authors also mention, the effects of valproate may be dose dependent. In fact, it is crucial for valproate, as for many other (antiepileptic) drugs, that the dose is based on adverse effects on the unborn child during pregnancy and the associated postnatal developmental disorders of the child [9]. Unfortunately, there are no doses in the healthcare claims data.

There was no ethical approval because the data were anonymous. Within the Human Research Act (HRA) the Federal Council in fact regulates the requirements for correct and secure anonymisation and encryption, as well as the requirements for decryption [10]. It would have been of interest if the authors had given additional information about this procedure for the healthcare claims data, because the age of the patients is one of the parameters used.

The authors discuss the important matter of the existing reporting system in Switzerland in the form of pharmacovigilance, to which the Swiss Teratogen Information Service (STIS) in Lausanne also contributes reports on pregnancies. Because of the voluntary (e.g., spontaneous) nature of the reports (for valproate there is now a mandatory requirement), the value of its information is limited. However, a study initiated by the SAPP and published in an international journal has already shown that in the first 20 years of the reporting system, the focus of these pregnancy reports was on medicines acting on the nervous system (40% mainly antidepressants and antiepileptics) [11].

The authors compare their results with studies in Denmark, where the data used were from the national pregnancy register, which includes exact information about the pregnancies and pregnancy outcomes [4]. However, this study does not have the same extent of information concerning pregnancy and newborn follow up, and further studies with healthcare data should rely on exact data about the pregnancy.

Data from databases such as the healthcare claims database or the pharmacovigilance database are therefore suitable to give a direction. For a particularly vulnerable group such as pregnant women, we need precise data on the outcome of pregnancy, indications, dosages, etc. (e.g., verified via

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a patient dossier). For more detailed information, special registers are helpful for particularly demanding medications – these include, for example, the EURAP register for recording antiepileptic drugs (valproate, etc.) [12]. However, if it is mandatory to record *every* prescription by a doctor to a pregnant woman, breastfeeding woman, or woman of childbearing age in general, the intake by the patient should also be documented. It is possible that an electronic patient dossier could support such a procedure.

How to improve our knowledge and the recommendations concerning the safety of drugs in pregnancy (in general and not only for valproate) has been one of our main topics in the last decades. However, owing to the limited informative value of healthcare claims data, we see the focus not only on systematic monitoring, but also on prospective preventive measures. What we need for our daily work in practice are just preventive / prospective measures, namely medication guidelines in the form of evidence-based, updated data on medicines. The key points (indication, form of application, dosage and other recommendations) should be summarised in tables and freely accessible. The SAPP has been compiling such data for years (e.g., AmiKo data with reference to drug monographs) [13, 14].

The topic of medication in pregnancy is indeed still underestimated owing to its enormous complexity; this is the reason why the SAPP was founded in 2007. Since then, it has been working in an interdisciplinary manner to promote safe medication use during pregnancy and breastfeeding. As early as 2013, the SAPP approached the Federal Council and the Federal Office of Public Health (FOPH) and since then has, together with other professional societies, pleaded for official recommendations on the safety of medication for pregnant and breastfeeding women. In February 2020, following the published valproate cases, the SAPP, together with five other professional societies, submitted a further request to the Health Committee of Parliament for urgent treatment of official recommendations.

In spring 2020, the FOPH – after many years of discussions with the SAPP – began an initial inventory of already existing pregnancy data, analogous to the procedure for data on paediatrics (Swisspeddose) [15]. A joint stakeholder meeting was postponed due to the coronavirus pandemic and is currently scheduled for March 2021. Let us now hope for rapid further progress.

Disclosure statement

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