Comments to:
"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

Dear Editors

The SAPP thanks the authors of the study and would like to make a few additional comments:
- 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, it must also considered that the spectrum of damage can expand during the last years due to the increasingly refined diagnostic possibilities - irrespective of this, valproate has always required and continues to require a differentiated interdisciplinary discussion whenever it is used by a woman of childbearing age [1].
- Throughout the international pregnancy EURAP registry there is a continuous decrease (nearly 50%) in valproate therapies for epilepsy since 2005 [2]. 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 AED, like reported in the citated Danish publication [3] with a decrease in use of valproate? What about other medications as phenobarbital and phenytoin, which are still mentioned in pregnancy registers [2]?
- Valproate is reserved for very specific forms of epilepsy (therapy-refractory primary generalised epilepsies). It can therefore be assumed that valproate is increasingly being prescribed for non-epileptic indications such as psychiatric diseases [4]. Detailed information about the indication is therefore an important requirement but is still missing in data such have be shown by the authors.
- All statistics are based on reported last menstrual day to analyse gestational age. We know since several years that these data are inaccurate, and data should be based on first trimester ultrasound, which is routinely performed in Switzerland and covered by the health insurance [5].
- As it is well documented in the literature since years, compliance is also worse in pregnant women than in non-pregnant women especially in case of women with preexisting diseases and therapies like psychopharmacological drugs [6,7]. A prescription as it is recorded based on the billed medicines, is therefore not equivalent to taking the medicine, about which there is also no information.
- As the authors mention additionally, valproate may be dose-dependent in his effects. In fact, it is crucial that for valproate as for many other (antiepileptic) drugs, the dose applies to the adverse effects on the unborn child during pregnancy and the associated postnatal developmental disorders of the child [8]. Unfortunately, we have no doses in the healthcare claims data.
- There is no ethical approval because of anonymous data. 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 [9]. It could be of interest if the authors give additional information about this procedure for the healthcare claims data because the age of the patients is one of the used parameters.

- The authors discuss also the important point of existing reporting system in Switzerland in the form of pharmacovigilance, to which the Swiss Teratogen Information Service STIS in Lausanne also contributes with reports for pregnancy. Due to the voluntary (e.g. spontaneous) nature of the reports (for valproate there is now a mandatory requirement) it is limited in its informative value. 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 drugs of the nervous system (40% mainly antidepressants and antiepileptics) [10].
- The authors compare their results with studies in Denmark where data were used from the national pregnancy register, which include exact data about pregnancy and pregnancy outcome [3]. However, this study does not have the same quality concerning pregnancy and newborn follow up and further studies with health care data should only rely on exact data from pregnancy.
- Data from bases like e.g. the healthcare claims database or the pharmacovigilance database, are therefore suitable for a directional orientation. 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 a patient dossier). For more detailed information, special registers are helpful for particularly demanding medications - this includes for example the EURAP register for recording antiepileptic drugs (valproate, etc.) [11]. 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 would also have to be documented. It is possible that an electronic patient dossier could provide support for such an elaborate procedure.
- Like the authors, we are reflecting since many years how we can carry out future projects to improve information about the safety of valproate and about medications in pregnancy in general. However, due to the limited informative value of healthcare claims data, we see the focus not only in systematic monitoring, but rather in prospective preventive measures. What we need for our daily work in practice are just preventive / prospective measures, i.e. 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) [12,13].
- The topic of medication in pregnancy is indeed still underestimated due 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 the safety of 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 pleaded together with other professional societies 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 5 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 Pediatrics (Swisspeddose) [14]. A joint stakeholder meeting was postponed due to the Corona pandemic and is currently scheduled for March 2021. Let us now hope for a rapid further development.

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