Valproic acid and pregnancy: assessment of malformations in France

A study has estimated that, in France, 2150 to 4100 live-born children who were exposed in utero to *valproic acid* or one of its derivatives between 1967 and 2016 were affected by at least one major congenital malformation.

In April 2017, the results of a French study of exposure to *valproic acid* or one of its derivatives (*semi-sodium valproate* and *valpromide*) during pregnancy and its consequences became available (1).

This retrospective cohort study was conducted in France using data on reimbursement of health care costs to insured individuals (National Health Insurance Information System, SNIIRAM) and the national hospital activity database.

8701 children exposed to valproic acid in utero between 2007 and 2014. This study included 14 322 pregnant women who were exposed to *valproic acid* or one of its derivatives in France between 2007 and 2014. During this period, the annual number of exposed pregnancies progressively declined, falling from 2316 to 1333.

The condition leading to use of *valproic acid* or one of its derivatives was epilepsy in 57% of cases and bipolar disorder in 43% of cases.

Notably, among the 8701 live-born children exposed to *valproic acid* or one of its derivatives during pregnancy between 2007 and 2014, 85% were exposed during the first two months of pregnancy (the period with the highest risk of teratogenicity). The mean duration of exposure to *valproic acid* or its derivatives during pregnancy was 117 days in mothers treated for epilepsy and 44 days in those treated for bipolar disorder (1).

Thousands of children affected by at least one major congenital malformation between 1967 and 2016. Using the hospitalisation database, 26 major congenital malformations were studied. Over the entire period from 1967 to 2016, the authors estimated that about 41 200 to 75 300 live-born children were exposed *in utero* to *valproic acid* or one of its derivatives. 2150 to 4100 of these children were recorded as being affected by at least one major congenital malformation: 1900 to 3800 children born to women who took the drug as treatment for epilepsy had an overall risk of major congenital malformation around 4 times higher than unexposed children; and 250 to 300 children born to women who used the drug to treat bipolar disorder had a 2-fold higher risk than unexposed children (2).

These numbers exclude children who were not born alive, due to reasons linked to malformations (abortions and deaths *in utero*), and those affected by neuropsychiatric developmental disorders without a major malformation. There is a study underway in 2017 which is exploring neuropsychiatric developmental disorders (including autism) linked to *valproic acid* and its derivatives (3).

A wide range of malformations observed. In comparison with children born after unexposed pregnancies, children exposed *in utero* to *valproic acid* used in the treatment of epilepsy had a significantly higher risk of spina bifida, atrial or ventricular septal defects or left ventricular hypoplasia, pulmonary artery atresia, cleft palate, anorectal atresia, hypospadias, and pre-axial polydactyly.

There appeared to be an increased frequency of other malformations in the study, but this did not reach statistical significance. These malformations included tetralogy of Fallot, cleft lip or combined cleft lip and palate, and craniosynostosis (2).

In practice *Valproic acid* and its derivatives increase the risk of congenital malformations. When there is no acceptable alternative treatment for women of child-bearing age, it is important to inform them of this risk and, as part of their care, to help them choose an effective means of contraception.

▶ Translated from *Rev Prescrire* **July 2017**
Volume 37 N° 405 • Page 513

Selected references from Prescrire's literature search

1- ANSM "Exposition à l'acide valproïque et ses dérivés au cours de la grossesse en France de 2007 à 2014: une étude observationnelle sur les données du Sniiram" 24 August 2016: 135 pages.
2- ANSM "Exposition in utero à l'acide valproïque et aux autres traitements de l'épilepsie et des troubles bipolaires et risque de malformations congénitales majeures (MCM) en France" April 2017: 11 pages.
3- ANSM "Malformations congénitales chez les enfants exposés in utero au valproate et aux autres traitements de l'épilepsie et des troubles bipolaires - Communiqué" 20 April 2017: 2 pages.