ACEI could be associated to an increase risk of congenital malformations.

Exposure to ACEI during the first trimester of pregnancy could be associated with an increase in the risk of congenital anomalies among newborns.

According to data available until recently, angiotensin converting enzyme inhibitors (ACEI), as welle as angiotensin II antagonists, were associated with fetal complications of vascular (hypotension) and renal systems (disgenesia, oligoanuria, oligohydramnios, etc) after exposure during 2nd and 3rd trimesters of pregnancy. One of the consequences of this fetotoxicity, oligohydramnios, potentialy involved secondary fetal complications such as limb deformations, pulmonary hypoplasia, or anomalies of the skull hypocalvania. In contrast, fetopathy was not reported among women who took ACEI only during the first trimester pf pregnancy. However, the results of a study published recently in the New England Journal of Medicine [1] seem to cast doubt on ACEI drug safety during the 1st trimester of pregnancy. These new data suggest an increase in the risk of congenital anomalies among new-born whose mothers were exposed to ACEI during the 1st trimester, as compared to unexposed newborns with a risk ratio (RR) of 2.7 (95% confidence interval (IC): 1.7-4.3). The increases was chiefly attributable to cardiovascular (RR: 3.72; IC, 1.9-7.3) and nervous system malformations (RR: 4.4; IC, 1.4-14.0). This was an exploratory study that included 29'507 births, data was collected from an American insurance system database (Medicaid) providing maternal medical history and medication through records of filled prescriptions, as well as infants medical and vital records. Among these births, 411 had been exposed to antihypertensive treatments during the 1st trimester of pregnancy, of which 209 specifically to an ACEI substance. The rate of congenital malformations was 7.1% after exposure to an ACEI, against 2.6% in the unexposed group to an antihypertensive treatment. This would represent a little more than a doubling in the basal risk of congenital malformations, or a number needed to harm of 23 (of 23 exposures on average would appear one malformation assignable to the treatment). The size of the group exposed to the ACEI (N=209) appears low with regards to the background noise induced by the selected data source. Because the Medicaid database is above all aimed at financial management, its coding system is perhaps not adapted for a study of this type and notably due to limited information on possible confounding factors (ex: pre-diabetes, alcohol, drugs, drugs on free sale, industrial polluting agent). This can unfortunately be regarded as a potential source of bias in this work. However, in spite of these brought up imperfections, the results of this study cannot be ignored and should be regarded as a signal. Other studies remain necessary to confirm these results.

The Food and Drug Administration (FDA) emitted a safety alert following this publication. However, the label of pregnancy category of this drug class was not modified to this date following these results (C during 1st trimester and D during 2nd and 3rd trimester). Swissmedic will closely follow the developments regarding this potential drug-related risk and will introduce, if necessary, new

modifications in the products information to reinforce safety issues concerning use of these drugs in pregnancy.

Meanwhile, so long as further observations enabling confirmation or refutation of these results are not available, it seems appropriate to avoid, when possible, the prescription of all the classes of substances acting on the renin-angiotensin system during all three trimesters of pregnancy. At present, these molecules cannot be considered as completely devoid of risk in the 1st trimester anymore, and should be replaced by another class of antihypertensive agent as soon as the pregnancy is discovered. In order to acquire knowledge in the field, exposures to ACEI and antagonists of angiotensin during pregnancy should be reported to one of the regional Swiss centers of pharmacovigilance or to the Swiss center of teratovigilance (STIS), which will inquire about the follow-up of the pregnancy.

References

[1] William O. Cooper, M.D., M.P.H., Sonia Hernandez-Diaz, M.D., Dr.P.H., Patrick G. Arbogast, Ph.D., Judith A. Dudley, B.S., Shannon Dyer, B.S., Patricia S. Gideon, R.N., Kathi Hall, B.S., and Wayne A. Ray, Ph.D. Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors. NEJM 2006;354:2443-2451.

Alice Panchaud, Thierry Buclin, 13.06.2006