

## 2. EUROmediCAT Recommendations: European Pharmacovigilance concerning Safety of Medication Use in Pregnancy

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### PURPOSE

This paper sets out the Recommendations from the EUROmediCAT project for European and national medicines regulatory agencies, public health authorities and professional clinical bodies

- To improve future pharmacovigilance
- To inform future drug safety measures

The recommendations are designed to help make better use of current data, networks and infrastructures in Europe, to achieve a more integrated system and better dissemination of knowledge and to raise the level of reproductive pharmacovigilance to meet women's reasonable expectations.

These recommendations concentrate particularly on safety in early pregnancy in relation to the risk of congenital anomalies. Wider perspectives should also be taken with respect to other adverse pregnancy outcomes (such as miscarriages, preterm birth or intrauterine growth retardation) and particularly neurobehavioural effects of medication exposure in pregnancy, with respect to the effects of the diseases/conditions themselves on pregnancy outcome, with

respect to herbal medications and with respect to the period of lactation, but these are not the specific focus of these recommendations.

### GENERAL REGULATORY AND PUBLIC HEALTH CONSIDERATIONS

- (1) The scarcity of information on medication safety in pregnancy, in relation to risk of congenital anomaly but also neurobehavioural and other effects, is unacceptable and must be remedied by more investment in research and pharmacovigilance. A mechanism whereby pharmaceutical companies contribute to an independent pharmacovigilance and research funding pot with ring-fenced use for pregnancy and lactation is urgently needed. This would both monitor new medicines and remedy the deficit of information on medicines in common use.
- (2) All new medicines on the market should be accompanied by specific monitoring of their effects on the fetus, infants and women when prescribed during pregnancy and lactation. Regulatory powers should include revoking of licences should this information be of insufficient quantity, quality or timeliness, taking into account frequency and characteristics of prescribing or use.
- (3) When severe, the effect of the untreated disease on the fetus may confer greater harm than the teratogenic risk of the medicine. Provision of safety information must be prioritised for existing and new medicines for chronic or severe conditions, to inform the choice of the medication with optimal benefit-risk profile, specific to the indication and its severity.
- (4) As congenital anomalies are rare, and many medication exposures in pregnancy are rare, European collaboration in pharmacovigilance is essential in order to facilitate the collection of sufficient data for effective and timely pharmacovigilance. The EUROmediCAT partnership is committed to playing a key role in achieving this. Data protection regulations in Europe should allow the sharing of data across borders for pharmacovigilance. To gain

knowledge on safety of medication use in pregnancy, valuable data sources already exist. Combining these data sources between countries (pooled databases) is key to obtaining timely and continuous information on possible risks associated with medication use in pregnancy.

- (5) Medication safety targets ought to be developed and included in future strategies for public health and wellbeing, relating to implementation of the measures included in these recommendations.
- (6) Professional bodies (medical, nursing and midwifery, pharmaceutical) should work together to increase training and knowledge of pregnancy-related medication safety issues among their members. Multidisciplinary education is required to empower staff to competently and confidently deal with women's need for more accurate and evidence based information about medication usage in pregnancy.
- (7) Residents of all European countries should have access to a phone and internet supported Teratology Information Service with responsibility to give evidence-based advice on medication safety tailored to individual need. Social media should be used where appropriate to ensure maximum penetration of key messages to pregnant women.
- (8) Purchase of medication via internet presents growing risks. The relevant national authorities should work together to agree policies for monitoring and tackling online purchasing of prescribed medications, in particular those medications with a high teratogenic risk. Professional bodies need to make their members aware of the risks of internet purchase. Evidence that isotretinoin, a highly teratogenic and commonly used medication for acne, is currently available for internet purchase without prescription or safety precautions should be acted on urgently as a first step towards this goal.
- (9) Information on medication safety in pregnancy, including the need to consider medication use before pregnancy and in the very early stages of pregnancy, should be considered part of preconceptional care for all women, and should feature in the secondary school curriculum.

#### IMPROVING SAFETY OF ANTIEPILEPTICS, ANTIDIABETICS, ANTI-ASTHMATICS AND ANTIDEPRESSANTS IN PREGNANCY

- (10) A strategy to increase the availability and uptake of preconception care and planning of the pregnancy

for women with chronic diseases (including epilepsy, diabetes, depression and asthma) in European countries is needed. Preconception Care includes optimising control of the disease and the choice of medication. Prescription of preconceptional folic acid to reduce the risk of congenital anomalies is also important as usage remains low in many countries. Urgent consideration is needed concerning the staffing levels needed to provide preconception care with specialist input. Further research on how to increase uptake of preconceptional care, including the design of services, is needed.

- (11) Consideration should be given in clinical guidelines to whether women who are taking antiepileptics, antidiabetics, antiasthmatics or antidepressant medications should be offered enhanced prenatal diagnostic services including diagnostic ultrasound scans with particular attention to the types of congenital anomalies associated with these medications.
- (12) Valproic acid stands out as a highly teratogenic medication, with strong evidence relating to congenital anomalies and growing evidence relating to neurobehavioural effects. Intensive efforts are required to increase awareness of all relevant medical practitioners regarding minimisation of use of valproic acid by women of reproductive age, particularly in neurology, psychiatry, obstetrics and general practice, as well as specialist and practice nurses and midwives. Where women are encouraged to switch antiepileptic medication before pregnancy, proactive monitoring and support should be offered.
- (13) Diabetes is a major risk factor for congenital anomaly and is increasing in frequency among women of reproductive age. Clinicians should seek to optimise glycaemic control for women with diabetes before pregnancy as the prime consideration. There are no known safety concerns over the use of insulin analogues to outweigh their advantages, but pharmacovigilance relating to insulin analogues and to the growing use of oral antidiabetics should continue. Gestational diabetes generally emerges after the period of organogenesis, but screening for gestational age diabetes as recommended by WHO should be part of an integrated approach to diabetes management for pregnancy, starting prior to pregnancy. Effects on reproductive health reinforce the need for intensive efforts to prevent diabetes in the population.
- (14) Antidepressants have an important place in the treatment of depression when the severity of the condition leads to the benefits of treatment for both mother and fetus outweighing the risk for the fetus. According to EUROmedICAT data, SSRI use in pregnancy has been increasing in

Europe, there are large differences between countries in their use and there is evidence of a small congenital anomaly risk related to all commonly used SSRI. Attention is needed to depression prevention and treatment for women of childbearing age and pregnant women. Further research is needed to disentangle the effects of antidepressants, depression, and co-exposures, and their possibly cumulative impacts.

- (15) It is important that health services help women with asthma achieve good control prior to conception and during pregnancy. This is to prevent harmful effects of asthma exacerbations, to both fetus and mother, and to prevent teratogenic effects of high dose antiasthmatic medication. Use of prophylactic inhaled steroids seems to be the best solution for treatment of asthma in pregnancy to prevent exacerbations and to reduce the need for beta-2 agonists. Evidence from EUROMediCAT and other studies suggests that cleft palate and gastroschisis are associated with exposure to inhaled beta-2 agonists. Further research is particularly needed regarding safety for the fetus of combined treatment with long-acting beta-2-agonists and inhaled steroids.
- (16) Continuing pharmacovigilance is essential for antiepileptics, antidiabetics, antiasthmatics and antidepressants. This should include independent confirmation of the signals generated by the EUROMediCAT project for these and other medication types. Further research is needed on the effects of polytherapy within and between drug classes; the independent and interacting effect of indication and medication on outcomes; the genetic/physiological basis of teratogenic effects of medications which may guide personalised medicine approaches in future (i.e. approaches which may identify women at most risk of adverse effects to provide alternative treatments). The comprehensive approach used by EUROMediCAT to examine use and risk of medication for maternal chronic diseases should also be extended to other conditions affecting women of fertile age, including thyroid diseases, rheumatoid arthritis and other autoimmune diseases, and hypertensive conditions.

#### METHODOLOGY AND INFRASTRUCTURE FOR PHARMACOVIGILANCE

- (17) Population-based congenital anomaly registries are an essential tool in pharmacovigilance relating

to pregnancy and should be supported in all European countries. The key feature of such registries is the collection of validated high quality diagnostic information on congenital anomalies, including diagnoses after the neonatal period, and terminations of pregnancy following prenatal diagnosis. Unvalidated healthcare database information (e.g. from Hospital Episode data, or primary care data) on congenital anomalies should be avoided. European Member States should allocate funding to EUROCAT congenital anomaly registries to collect medication exposure information as part of registry activities, including linkage to prescription databases which improves information available from hospital medical files. Currently only half of EUROCAT registries are engaged in these activities and therefore Europe is not meeting the potential for reproductive pharmacovigilance.

- (18) Collaboration between networks addressing medication safety in pregnancy should be encouraged and supported. This should involve European networks such as EUROMediCAT, ENTIS and EURAP as well as other collaborations between countries such as the Nordic partnership and UK Epilepsy & Pregnancy register. It is important to conduct multiple observational studies with different study designs and data sources so that robust conclusions can be drawn. Similarity of findings between different study designs and populations strengthens the evidence base. Spontaneous adverse reaction reporting and industry pregnancy registries, the mainstay of previous approaches to reproductive pharmacovigilance, have been demonstrated to be extremely limited in their capacity to supply the information required.
- (19) We recommend the establishment of collaborative European pregnancy cohorts for women with chronic diseases receiving specialist care in EUROCAT registry areas, linked with congenital anomaly registries e.g. for diabetes, epilepsy and rheumatoid arthritis. These cohorts could continuously monitor new medications on the market. The presence of a EUROCAT registry would facilitate follow-up of the outcome of pregnancy, and provide a ready comparator population.
- (20) Information on prescription medications in electronic healthcare databases should be made available for research and pharmacovigilance in all European countries. Such databases can be linked to congenital anomaly registries to obtain

a highly effective pharmacovigilance database as demonstrated by EUROmedICAT. Electronic prescription databases can also be used for drug utilisation studies of the period before, during and after pregnancy.

- (21) For maximum utility for reproductive pharmacovigilance, electronic healthcare databases should allow, whether by linkage or directly:
- Identification of all women giving birth, with information on date and gestational age at delivery
  - Inclusion of pregnancies resulting in spontaneous miscarriages and terminations of pregnancy following prenatal diagnosis of congenital anomaly
  - Information on sociodemographic variables (e.g. maternal education and socioeconomic status) and principal lifestyle confounders (smoking, obesity and alcohol) and periconceptional folic acid, increasingly available in maternity databases
- (22) Particular efforts are required to improve the quality of electronic prescription data in Europe in the following areas, found to be variable between countries:
- The recording of dose and use of Defined Daily Dose (DDD)
  - The recording of indication
  - The availability of hospital prescription data (inpatient and outpatient)
  - The availability of data on hospital prescribing to pregnant women, especially as pregnant women may access their care differently during pregnancy
  - The availability of data concerning prescriptions from private practitioners
  - The use of or translation to ATC (Anatomical Therapeutic Chemical classification system) codes as a common coding system across Europe.
- (23) Electronic prescription data may not cover over the counter purchase of medicines, or internet purchase of medicine, for which other measures to improve pregnancy exposure information for pharmacovigilance must be found.
- (24) There is a need to develop specific analytical methodology to improve signal detection in pharmacovigilance of pregnant women.
- (25) Adequate data sources need to be put in place, or existing ones enhanced, to allow evaluation of the effectiveness of all components of Pregnancy Prevention Programmes (such as for the acne treatment isotretinoin). This includes, but is not limited to, the availability of data on prescribing to all women of childbearing age, prescriptions dispensed in hospital pharmacies and those issued by specialists and in secondary care, contraception use and pregnancy tests.

## ENDORSEMENT

These recommendations were endorsed by the following members of the EUROmedICAT External Advisory Board, expert panel members of the EUROmedICAT Conference, EUROCAT Registry Leaders and other EUROmedICAT participants.

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**CONFLICT OF INTEREST**

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