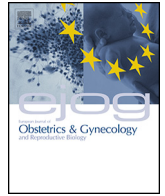


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## Position statement from the European Board and College of Obstetrics & Gynaecology (EBCOG)



### The use of medicines during pregnancy – call for action<sup>☆</sup>

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#### ABSTRACT

Less than 10% of medicines approved by the FDA since 1980 have provided enough information as regards risks for birth defects associated with their use (Adam et al. (2011) [1]). Nevertheless, it is estimated that over 90% of pregnant women take over-the-counter (OTC) or prescription medication (Ke et al., 2014 [2]). Considering the fact that the use of medication in the period before conception and during lactation can also influence the development of the child, information on the impact of their usage during reproductive life is important for everyone. The lack of clear information on this topic results in situations where life-saving medication is discontinued, withheld or used in a reduced dosage by pregnant women, while on the other hand medicines with (potential) toxic effects are taken. This is unacceptable and it is a major public concern that must be addressed.

Currently, Europe lacks a robust and comprehensive information system about medication use in reproductive life (from preconception, during pregnancy and during lactation). In order to improve maternal health, and subsequently the health of our next generation, reliable and up to date information should be made available. It should be readily accessible for both health care providers and women who are considering getting pregnant or who are already pregnant.

In order to tackle this gap in public health, this paper describes current knowledge of the use of medicines before and during pregnancy. It calls upon all stakeholders involved in medical care, research and medicine regulation, such as policy makers, regulators and governmental agencies, to take action to protect patients and improve public health.

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#### Introduction

Pregnant women want to do their best to protect their unborn babies. This often means making careful choices about what to take

during pregnancy. Prescription and OTC medications, herbal products, food supplements, topical creams, inhalers, vitamins, alcohol, nicotine and “street drugs” can cross the placenta into the fetal blood circulation. Sometimes these drugs can have unintended consequences that can cause birth defects or other health problems. Moreover, some medications can have adverse effects without ever passing through the placenta, i.e., immunosuppressant drugs do not pass through the placenta, but may allow infectious agents to cause life threatening infections because of an impaired maternal immune system and harm the developing fetus.

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Although a number of antenatal medication exposures are known to cause birth defects, like thalidomide and diethylstilbestrol, there is insufficient information available on the risks and safety of the vast majority of medicines (prescription or OTC) known or available to patients and their health care professionals. Pregnant women are often not included in clinical studies to determine the safety of medications before they are marketed [3]. It has been reported that a prolonged post marketing surveillance period is required to determine the true risk to the fetus, even for those drugs deemed to be safe initially by FDA or classified as having an “undetermined” risk before being assigned a more precise risk (27 years). It has been proposed that a more active approach to post-marketing surveillance to determine teratogenic effects is necessary [1]. Because of a lack of this information, pregnant women may unknowingly take a medication that poses a risk to their fetus. On the other hand, anxiety about the potential teratogenic effects of medications may discourage women or physicians from continuing to use essential treatments and they may even consider termination of pregnancy.

The prevalence of chronic diseases during pregnancy, like diabetes, hypertension, epilepsy or depression for example, is increasing (25% and more). These women may be inadvertently exposed to medication before finding out that they have conceived. In addition, the intercurrent medical issues like an infection or an accident for example, cause an estimated 90% of women to use medicines while pregnant or wishing to get pregnant. Almost all of the medicines used in these situations are off-label. The resulting medical and legal concerns drive inconsistent medical practices, suboptimal outcomes, and low patient satisfaction and – at their worst – endanger the lives of both mother and child.

This lack of knowledge regarding the use of medicines in pregnancy is a problem for society. It is the responsibility of the medical world, governments and regulators to better protect pregnant women. By minimising risks, we can maximise the chance of safe pregnancy outcomes, and protect both mother and child to ensure a healthy next generation.

Some regulatory bodies such as the FDA and Health Canada have recognised the lack of robust quality information for medical professionals and patients with regard to the use of medication during reproductive life. The FDA has recently revised its existing system and has introduced its new “Pregnancy and Lactation Labelling Rule”, which became effective on June 30, 2015. This labelling system will force pharmaceutical companies to provide information about the potential benefits and risks for the mother, the fetus and the breastfeeding child [4].

The FDA rules will require that product labelling should be continually updated when additional information becomes available. In addition, information on pregnancy exposure registries will be added to product labelling. Furthermore a new section titled “Females and Males of Reproductive Potential” will include information on infertility, contraception recommendations and pregnancy testing. These changes will facilitate the availability of clinical data in product labelling and help clinicians consider risks and benefits when prescribing drugs to pregnant women.

We call upon European Commission to urgently follow the example of the FDA and set out guidance with regard to post marketing surveillance, in order to develop a uniform policy across Europe and North America.

### **Important steps to obtain information on the use of medication in preconception, pregnant and lactating women**

#### 1. Analysis of current situation in EU

It is estimated that over 90% of pregnant women take medicines in pregnancy [2]. However there are no data available on the use of medicines, either prescription or OTC, herbal products, food

supplements and creams in each EU country. National Professional Societies and consumer organisations should set up a working party to investigate mechanisms to capture data on the current situation in Europe.

#### 2. Improve registration of data

Registration policy regarding safety, dosage advice and data on adverse events is poor. There are different reasons for this lack of registration. Firstly, many patients use OTC drugs and do not tell their treating physician – either because doctors do not ask about it, or because patients are afraid of the reaction/advice of their doctor. Secondly, many obstetricians/midwives do not systematically register details of medication or supplements used by pregnant women in their obstetrical medical files. Thirdly, many drugs are routinely used (like a painkiller or nasal spray for a cold) and quite often women do not remember the exact name or dose used as the treatment had already finished at the time of the consultation. Finally, the pharmacovigilance reporting of adverse events in pregnant women is relatively poor. Since the medication is used off-label, doctors or pharmacists who prescribe or dispense the medication to a patient often prefer not to report the side effect because they fear legal problems.

The implementation of a general register of medication use in European pregnant women will show which supplements and medications are safe to use. What we lack most today is the denominator that is needed to assess the risk. With over 5 million babies born in Europe and up to 90% of those having been exposed to medication in utero, we should find some reassurance in having those denominators. Without the denominator, every unfortunate case can lead to misguided conclusions and decisions.

#### 3. Preconception counselling of young women

Young women should be advised to talk to their doctor even before stopping contraception. This is an important opportunity to discuss healthy lifestyles (stopping smoking, alcohol consumption, having a healthy diet to achieve a normal BMI before getting pregnant), update the vaccination status, start folic acid to reduce the risk of spina bifida and to discuss the preventive measures to take into account to avoid fetotoxic infections in pregnancy such as toxoplasmosis, CMV or hepatitis B, for example. Moreover, this is the moment for doctor and patient to go through the past medical history, which medicines or supplements have been taken, etc. Preconception is an important time to consider potential risks for the future child (genetic problems, teratogenic problems) and replace teratogenic medicines with safer alternatives. While the exact rate of pregnancy termination due to fears of adverse fetal effects of xenobiotics or radiation is not known, there is indirect evidence that this is not uncommon.

It should be communicated very clearly to pregnant women that they should not stop or start to take medication (by prescription, OTC or supplements) without consulting their treating physician.

Additionally, patient organisations and non-governmental health organisations (NGOs) can play an important role highlighting specific issues to young women with chronic diseases.

#### 4. Interdisciplinary consultation

In order to improve medical care for women who are planning a pregnancy, and those who are pregnant, the different physicians involved in their care should communicate with each other. In case of doubt about the safety of specific medicines, they should contact experts in the field. For patients it is very important to get clear and consistent advice on the medications they take.

Also, the interaction between nurses/midwives, physicians and pharmacists should be improved. All too often, advice and information about the use of medicine for pregnant women are contradictory, resulting in confusion, doubt and the suboptimal treatment of pregnant women and their unborn children.

5. Set up a robust Reference and Information Centre that includes results from clinical trials, real life experience, pharmacovigilance reporting

Different organisations spread information globally via their websites, such as the Organisation of Teratology Information Specialists (OTIS), LactMed, EuroMediCat, Lareb, Cybele, Motherisk programme, Embryotox or Reprotox. These websites provide very good and useful information, mostly to assist health professionals or the general public about the potential effects of xenobiotic and radiation on reproduction, albeit that they have to work with the available data in literature, often resulting in vague recommendations. Many people still appear to prefer a search by 'Dr Google' and do not contact the specialised organisations.

Although access to a local expert would prevent these problems, research on the use of medicines in pregnancy is limited and only a small number of physicians/pharmacists/researchers have specific expertise in this field. Therefore the establishment of a recognised reference centre in each country will improve medical care for pregnant women (such as hotline intoxication centres). Such a service will, in the first instance, advise physicians, pharmacists and patients on safety, drug dose and potential alternatives. This reference centre will also improve the registration of medicine use and of adverse events, which will lead to a significant increase in the available data.

6. Elaborate research on the use of medication in pregnancy

The acknowledgement of the lack of data on the use of medicines by pregnant women and the public call to solve this problem can boost research/interest in this field.

Currently in the paediatric population, opportunistic studies are performed, whereby drug sampling is optimally performed with standard of care blood drawn in patients who have already received the drug of interest. This approach, coupled with population-based pharmacokinetic modelling methodology have allowed the use of sparse (e.g., one to five samples per patient) and scavenged (leftover samples from the routine care of patients) samples to be used for understanding drug disposition changes in pregnant women.

The recently adapted EU Clinical Trial Regulation No 536/2014 aims to create an environment that is favourable to conducting clinical trials in the EU with the highest standards of ethical and safety protection for participants. The new Clinical Trial Regulation sets out the legal conditions under which clinical trials will have to be conducted in Europe in the future. This new regulation will improve the transparency of Clinical Trial data, and will allow the inclusion of different population groups – like pregnant and breastfeeding women – under strict protective measures. Also if data from women who conceive while included in a clinical trial is collected, pharmacovigilance reporting should improve.

### Action points

What we ask from the EU politicians and legislators, clinicians and researchers:

1. An EU-wide assessment of current practice and future needs to enable the better treatment of women pre-conception and during pregnancy and lactation.
2. An EU-wide information campaign to increase awareness among the public and health care professionals (HCP) about the importance of proactive information sharing and counselling regarding medication use related to pregnancy and lactation.
3. An EU Legal framework to stimulate reporting and counselling by HCP about medication use related to pregnancy and lactation.
4. An EU Regulatory framework to improve label information about medication use related to pregnancy and lactation (i.e., make it more relevant and current).
5. An EU-wide framework to improve the quality and reliability of the information provided e.g., via the internet about medication use related to pregnancy and lactation (e.g. A central EU website with links to good sources; seal for quality information).

### References

- [1] Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. *Am J Med Genet C Semin Med Genet* 2011;157C(3):175–82.
- [2] Ke AB, Rostami-Hodjegan A, Zhao P, Unadkat JD. Pharmacometrics in pregnancy: an unmet need. *Annu Rev Pharmacol Toxicol* 2014;54:53–69.
- [3] Endicott S, Haas DM. The current state of therapeutic drug trials in pregnancy. *Clin Pharmacol Ther* 2012;92(2):149–50.
- [4] Mosley 2nd JF, Smith LL, Dezan MD. An overview of upcoming changes in pregnancy and lactation labeling information. *Pharm Pract (Granada)* 2015;13(2):605.