

Introduction

There is a lack of information about the safe use of medication during pregnancy and lactation for both women and their healthcare professionals. The U.S. Centers of Disease Control and Prevention (CDC) provide some information. The CDC estimates that 9 in 10 women use some form of medication during pregnancy and about 7 out of 10 take at least one prescription medicine.¹ In contrast, Europe lacks an official information and advice resource; the website of the European Medicines Agency is silent on this topic. However, many women need to take medication during pregnancy to manage their health condition, so "in some cases, avoiding or stopping medication use during pregnancy may be more harmful than taking a medication."² As more women postpone pregnancy the use of medicines during pregnancy is likely to increase.

"The health of women has a direct bearing on the health of the future generation, their families, and communities, and ultimately, the health of societies."

~National Institutes of Health, Office of Research on Women's Health³

The Paradox

The protection of mother and child is of paramount importance. Since the Thalidomide tragedy of the early 1960s when the teratogenic effect of a morning sickness medication resulted in birth defects and death in babies, teratogenicity testing in animals is a mandatory requirement before medicines can be authorised and prescribed. While animal studies are a good indicator of some side effects, they do not offer certainty on the safety in use and application. Moreover, women remain under represented in clinical studies, and generally pregnant women are excluded from clinical trials for safety reasons. Yet, in reality, many pregnant women must take medicines during pregnancy for pre-existing chronic conditions - such as asthma, diabetes, hypertension, and depression -or for short-term conditions -such as infection, cold or toothache. Robust evidence of how a medicine works in pregnant women and its appropriate dosage is lacking. Thus, paradoxically, the very reason that pregnant women are excluded from clinical trials - to protect them - results in a safety concern and lack of protection for both mother and child during pregnancy.

The Risk of Birth Defects

Teratogenicity—the risk of congenital anomaly (malformations at birth)—is a major concern with regard to the safety of medicines during pregnancy. During the first trimester of pregnancy, often before pregnancy is confirmed, the foetus undergoes a period of organogenesis, the formation and differentiation of organs and organ systems during embryonic development. This period extends from approximately the end of the second week through the twelfth week of gestation in humans. During this time, the embryo undergoes rapid growth and as a result, is extremely vulnerable to environmental hazards and toxic substances. Any interference with the sequential processes involved with organogenesis can cause an arrest in development and results in one or more congenital anomalies.^{4,5} Consequently, pregnant women should be careful about their medication use during this period. Late exposure may also cause neurodevelopmental effects, which is of increasing concern.



A Pregnant Woman Consulting with Her Doctor⁶

The Impact of Birth Defects

It is estimated that over 5 million women give birth each year in Europe; in 2010, about 140,000 fetuses and babies in the EU-27 had a major birth defect. Birth defects⁷ are estimated to have accounted for 11% of the European neonatal deaths in 2008.

Why Action is Needed

Promoting healthy pregnancy and safe childbirth is a goal of all European healthcare systems. Therefore, it is surprising how little information is available about the use of medicines during pregnancy.

Birth defects, stillbirth, and death are a harrowing experience for both women and their families. Women and their physicians need comprehensive safety information to make informed decisions about medication use during pregnancy in order to prevent birth defects from happening in the first place.

The safe use of medication during pregnancy is an unmet medical and societal need. There is little information available to determine the risks to both mother and child. Instead, the package information leaflets that accompany medicines carry a general warning that the medicine has not been tested in pregnant women and women are advised to consult their doctors. Approximately 90% of medications currently have no information about their potential to cause birth defects.^{8,9}

Europe lacks a robust and comprehensive regulatory and information system that addresses safe medicine use during pregnancy. Most medicines have not been tested in pregnant women, unless they are specifically intended for use during pregnancy. In order to improve maternal health and the health of the future generation, reliable and up-to-date information should be available and easily accessible to women who are planning to become pregnant or are already pregnant as well as to the health professionals who advise them. When a medicine receives its marketing authorisation, information about reproductive toxicity is only available from animal studies, which are limited in their ability to predict human teratogenesis. As pregnant women are mostly excluded from clinical trials, the safety of many medicines has not been established at the time of approval for use in pregnancy. Therefore, most medicines prescribed for pregnant women are either counter-indicated or used off-label and rigorous, systematic pharmacovigilance reporting is lacking. For some medicines, pregnancy registries have been established; however they are generally too small and do not have sufficient power to detect moderate medication-related congenital anomaly risk.

EUROmediCAT: Recommendations for a Comprehensive Pharmacovigilance System

EUROmediCAT, a four-year FP7 project, aims to build a European system for reproductive safety evaluation in order to systematically and comprehensively identify possible adverse effects of medicines used in pregnancy, at the earliest stage post-marketing, as well as to monitor and evaluate safety measures taken in Europe. The project utilises data from fourteen population-based EUROCAT congenital anomaly registries and seven healthcare databases.

EUROmediCAT focused on four medication groups for chronic conditions for which women and clinicians need evidence to balance benefit and risks of different treatment choices: anti-epileptics, insulin analogues, anti-asthmatics, and anti-depressants. Importantly, EUROmediCAT highlighted the need and importance for preconception care.^{10,11}

The findings of EUROmediCAT and its recommendations inform current regulatory practice, pharmacovigilance, research, and health policy and practice in order to do the following:

- Improve future pharmacovigilance
- Inform future drug safety measures
- Raise the level of reproductive pharmacovigilance to meet women's expectations

Key EUROmediCAT Recommendations^{12,13}

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 foetus, 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. (see all EUROmediCAT recommendations.^{14,15})

The New EU Clinical Trials Regulation: A Major Step Forward in Patient Safety

The new 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.¹⁶ It contains new rules for the inclusions of pregnant and breastfeeding women in clinical studies under strict protective measures.

The Regulation, which becomes law in 2016, sets out the legal provisions under which clinical trials will have to be conducted in Europe in the future. *Article 33, Chapter V* defines the conditions for including pregnant and/or breastfeeding women in clinical trials, provided the protective measures outlined in the legislation are followed.¹⁷ As most pregnant women will still be excluded from clinical trials, there is an urgent need to conduct effective and rapid post-marketing studies for pregnant women and other vulnerable populations who otherwise would be excluded from clinical trials.

International Initiatives - The New FDA Rules on Pregnancy and Lactation

In 2014, the U.S. Food and Drug Administration (FDA) published new legislation that sets consistent standards for how information about using medicines during pregnancy and breastfeeding through the labelling of prescription drugs and biological products. Based on available information, the new labelling rule explains the potential benefits and risks for mother,

foetus, and breastfeeding child. There are three subsections: “Pregnancy,” “Lactation” and “Females and Males of Reproductive Potential.” The information is intended to help healthcare professionals make prescribing and counselling decisions.

- The **Pregnancy** subsection provides information relevant to the use of the drug in pregnant women, such as dosing and potential risks to the developing foetus, and requires information about whether or not there is a registry that collects and maintains data on how pregnant women are affected when they use the drug or biological product.
- The **Lactation** subsection provides information about using the drug while breastfeeding, such as the amount of the drug in breast milk and any potential effects on the breastfed child.
- The **Females and Males of Reproductive Potential** subsection includes information about pregnancy testing, contraception, and about infertility as it relates to the drug.¹⁸

The EUGenMed Research Project

The EUGenMed, a FP7-funded project, examined the sex and gender differences in biomedical and public health research. Within the project, the Workshop on Medicines Regulation highlighted the current information gap about women, including with regard to medicine use during pregnancy. The Workshop recommended that a robust regulatory and pharmacovigilance framework should be developed for safe use of medicines during pregnancy, which should include a comprehensive system for post-marketing data collection.^{20,21}

Where Can Reliable Advice on Drug Safety During Pregnancy be Found?

Some women must take medication for pre-existing chronic diseases, such as asthma, diabetes, high blood pressure, HIV/AIDS, etc. Often the question of treating a chronic condition during pregnancy can cause anxiety and fear in the pregnant woman. Yet if these conditions are left untreated, both mother and unborn child can be in danger. In some cases, the risk of disease may be more severe than risk of treatment; therefore, better information must be collected and the results made urgently available to inform practice.

Websites, such as the U.S. Centers for Disease Control and Prevention, advise that pregnant women should not stop or start taking any type of medication without first consulting their doctor. Some countries in Europe, such as the UK and Germany, have teratogen information systems online. Ideally, women who are **planning** to become pregnant should discuss their medication need with their doctor before becoming pregnant.

Increasingly pregnant women search for information on the Internet. It can be a dangerous if women buy teratogenic medications online. On the other hand, the Internet can also provide an opportunity to obtain information about medicines safety during pregnancy. The EUROmediCAT project examined this area and made the recommendation that the growing role of the Internet needs further evaluation to develop appropriate medication safety measures.

Preconception Information and Counselling of Women

Prevention across the lifespan is an important public health strategy. However, few prevention programmes include preconception health. As a better understanding of how the preconception environment can affect the health of the unborn child is gained, more efforts must be made to invest in prevention already at the preconception stage. The EIWH has highlighted various issues related to pregnancy, such as the dangers of smoking and alcohol consumption as well as chronic disease, including gestational diabetes. The current obesity epidemic also requires urgent action to prevent the trans-generational transmission of diabetes risk during pregnancy.

The European Board and College of Obstetrics and Gynaecology (EBCOG) recommends that young women talk to their doctor even before stopping anti-conception measures as this is an important opportunity to discuss healthy lifestyles (stopping smoking, reducing 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 preventive measures to avoid fetotoxic infections in pregnancy such as toxoplasmosis, cytomegalovirus (CMV) or hepatitis B. Preconception is also a time to motivate young women and future mothers to do the best for their baby. It is an opportunity for doctor and patient to go through the past medical history and check which medicines or supplements have been taken, etc.²²



A Woman Breastfeeding¹⁹

Steps for Action

1. Developing a comprehensive and robust European regulatory and pharmacovigilance framework for medication use during pregnancy

The lack of robust information on medicine safety in pregnancy is unacceptable. This major gap in public health needs to be urgently addressed. Information from different research projects, initiatives, agencies, networks are scattered across various websites and publications, and a European Information system is lacking. Congenital anomalies are rare; therefore, it is essential to collaborate and act at European level to improve regulatory practice and to develop a systematic and comprehensive pharmacovigilance reporting post-marketing framework.

- 2. Improve information and advice for health professionals, mothers, and pregnant women to ensure safe use of medicines during pregnancy and lactation.**
- 3. Invest in research and pharmacovigilance to evaluate and improve the safe and effective use of medicines during pregnancy.**
- 4. Execute the EUROmedicCAT recommendations.**
- 5. Create and support a comprehensive European Pharmacovigilance system that is funded by public money.**
- 6. Follow the FDA example in Europe by providing better information and labelling about use of medicines during pregnancy.**
- 7. Highlight the importance of preconception health and the need to improve information about medicine use during pregnancy by mobilising patient organisations, health NGOs, as well as the public health and health care community.**
- 8. Implement data protection regulations in Europe to allow the sharing of information across borders for pharmacovigilance.**
- 9. Empower and support young women and future mothers during preconception, pregnancy, and post-delivery to take preventative measures, to make lifestyle changes and to review their past medical history, medicines or supplement taken with their health professional for the benefit of themselves and their baby.**

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