Drug safety during pregnancy

EUROmediCAT - building a European system for the reproductive safety evaluation of medicines
The first trimester of pregnancy represents a crucial stage in the development of unborn infants. As organs are formed and the structure of the body begins to become recognisable, pregnant women must be particularly careful about which medications they use in order to avoid an increased risk of birth defects.

Unfortunately, for this very same reason pregnant women cannot be included in clinical trials for medicines. Human safety data about risk to the foetus when taken in early pregnancy is therefore not readily available when a drug is released to market, and so pregnant women are often presented with the unenviable option of either taking a medication without knowing its potential risk to their unborn child, or avoiding medication altogether and exposing themselves and their child to other potential risks. Between 40-90 per cent of women use at least one medicine during pregnancy, making this a common problem for expectant mothers.

It is fair to say that the amount of human safety data available before the marketing of drugs is not adequate for pregnant women. It is thus of great importance to continue to monitor the safety of drugs as they enter mainstream use. Professor Helen Dolk of Ulster University, however, believes that current efforts to provide this post-marketing safety data are underfunded and inadequate. “There is a rather ad hoc approach to reproductive pharmacovigilance in general in Europe, with too little investment in research and surveillance,” she says. “A lot relies on the initiative of individuals to build systems. Many groups exist – for example congenital anomaly registries collect medication data, and teratogen information systems that provide information about medication safety to women or clinicians also collect data – but there is little coordination

Safety of medication use in pregnancy

Teratogenicity – the risk of congenital anomaly – is of great importance when making decisions about whether medicines are safe to use during pregnancy. When medicines first become available, however, there is little information to advise women and clinicians about which are safer than others. The EUROMediCAT consortium has been working over the last four years to combine data sources from around Europe in order to create a permanent and reliable platform for providing this kind of advice.
and investment to ensure that a systematic and early warning system is in place.

**Building a system for reliable advice**

Dolk has led a pre-existing congenital anomaly registry network called EUROCAT, covering nearly one third of births in the European Union, for the last fifteen years, but it has not had sufficient funding to develop its postmarketing medication safety surveillance. However, a recent European project called EUROmediCAT has helped to change this. It has combined data from EUROCAT with existing healthcare data and expertise in order to develop and test an efficient system for safety evaluation of drugs during pregnancy.

Linking registry data to electronic prescription data has been an integral part of the project’s push to systemise and formalise the use of available resources. Electronic health databases are widely used across Europe and are easier to access than ever before, but until now the opportunity to use these valuable resources in conjunction with data on congenital anomalies had not been taken. “As this had not been done before, a large portion of our work in EUROmediCAT has been proving the concept that a system can be created that will bring an improvement to the information provided about certain drugs,” explains Dolk.

The focus on system building illustrates the project’s ambition to create something more long lasting than a standalone piece of research. It is of great importance that information is available on each one of the many new drugs that enter the marketplace each year, and to perform this sizeable task to the high standard that is required it must be done methodically and reliably. The incidence of any congenital anomaly due to a specific type of medication is often low, and so with smaller datasets it is easy for some risks to go undetected. It is only after the analysis of large pools of data using a variety of controlled studies that patterns start to emerge. The pooling of information in EUROmediCAT will thus help to identify specific risks associated with new drugs as quickly as possible.

**Chronic diseases during pregnancy**

It is important that treatment of chronic diseases during pregnancy does not stop due to concerns about dangers posed by medications - the risk of harm to the mother and child will often be greater if they go untreated. Epilepsy, diabetes, asthma and depression are four common chronic conditions that the project has focused on to provide better data about the risks of associated medications. The research has highlighted that there is a need for preconception care for women with these chronic diseases, where they can discuss the safest medication choices with their doctor before they become pregnant.

“We now have a better idea of exactly which congenital anomalies are associated with these medications,” says Professor Lolkje de Jong-van den Berg of the University of Groningen. “We have also been able to show that risks associated with antidepressants and antiasthmatics are small, and that the benefits of treating severe cases of these conditions would far outweigh the teratogenic risk for both mother and baby.”

The research has also highlighted that more efforts need to be made to stop the use of the antiepileptic drug valproic acid during pregnancy, where there are well known associated risks. In terms of diabetes, the findings from EUROmediCAT have shown that newly introduced insulin replacements do not confer any detectable risk to the foetus, and seem to offer adequate control of the disease, which is essential.

**The unregulated internet**

The accessibility of the internet has naturally made it the first port of call for many mothers seeking medical advice on medication safety. This is in itself not a bad thing, but at present there are questions as to the reliability of the information that can be found. Even more worryingly, the purchase of high-risk medicines online without a prescription is now easy in some countries including the UK, and this will often come without any warnings of the harm they can cause to unborn children. As such, one of the projects within EUROmediCAT was to survey the internet for sites that sell the highly teratogenic acne drug isotretinoin (commonly known as Accutane).

“Having access to medicines such as isotretinoin without professional medical

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“If drugs are bought online, then all of the precautions put in place are meaningless,” says Dolk. “For drugs such as these which are known to present high risk during pregnancy, Pregnancy Prevention Programmes have been developed.” These programmes allow only some clinicians to prescribe high-risk medicines, and only after going through a number of processes to ensure that the woman is not pregnant and will not subsequently become pregnant. Women who become pregnant while taking medication are at risk as the key period of development of the unborn baby is very early in pregnancy. If these medicines are bought online, however, then all of these precautions are meaningless, which is why the researchers consider this a very serious issue.

The future of pharmacovigilance

The EUROmediCAT project will soon come to an end, but the coordinators believe that the impact of their work will be long lasting. The organisation of such a coordinated effort into improving the use of data and other issues surrounding reproductive pharmacovigilance is unprecedented, and has helped to raise visibility of the issue of medical safety during pregnancy among policy makers, clinicians and the general public. They now hope to continue this valuable work, possibly with the aid of a new source of funding. “We believe there is a need for an independent funding mechanism in which funds are provided by the pharmaceutical industry to a central fund which can then be awarded to aid independent research and surveillance relating to medication safety in pregnancy,” says Dolk. “This will ensure that the issue is taken seriously and will provide the means for a systematic process for assessing drug safety at the post-marketing stage.”

Helen Dolk

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