Perspective

A Pediatrician's Opinion on the Need for More Data on Medicines in Pregnancy

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The safety of medicines in pregnancy and the neonatal period cannot be taken into consideration in isolation. Medicines given in pregnancy, as we all know can produce adverse events that only become apparent in the neonate/baby at a much later stage, e.g. diethylstilboestrol and clear cell adenocarcinoma of the vagina. In this historical case, the medicine was given to prevent or treat pregnancy-related problems (such as miscarriage), but medicines may also be needed for non-pregnancy related reasons in women of child-bearing age who either are pregnant or could become pregnant. Of course, it is also important to take into account the maternal and obstetric medical history when administering an investigational medicine to a neonate in order to be able to fully assess the risks and benefits of that medicine and the causality of any adverse event that occurs.

During pregnancy, the women's body undergoes many physiological changes, which makes it particularly important to study the pharmacokinetics of medicine during pregnancy since the clearance and thus the drug levels in the bloodstream are not necessarily the same as they would be in a non-pregnant woman. It is also important to consider clinical trials looking at the level of drug in cord blood at birth and/or the placenta. Similarly, a premature neonate at different gestations will have a different body composition from a term baby, and this will change as the baby develops.

As a pediatrician, one of the first times I was introduced to the close interplay between obstetrics and neonatal research was when I was the research fellow on an antenatal trial in the mid-1990s(1). This was a trial looking at the use of antenatal Thyrotrophin Releasing Hormone (TRH) to try and reduce the incidence of respiratory distress syndrome in premature neonates. I was in the privileged position of being the only pediatrician work-ing in the University of Liverpool Obstetric Department as there was a need to ensure data on the babies born to the mothers included in the study was collected accu-rately. Many years later, I also had the pleasure of work-ing closely with obstetricians in an industry-sponsored antenatal trial to try and prevent recurrent miscarriage. In both these cases, I felt it was invaluable to have a neonatology experienced pediatrician involved. By coincidence neither of those studies had a positive outcome, but I think this also emphasized to me that negative trials can be just as important – not least to avoid the use of medicines in pregnancy when there is insufficient evidence of the benefit/risk to justify their use. In this article I am going to focus on the need for more evidence on medicines given in pregnancy and why I feel this is so important.

An area of particular interest for me is the maternal immunization. Up until quite recently, it would not have been considered feasible to conduct randomized controlled trials with an investigational vaccine in pregnant women. However, the worldwide H1N1 flu pandemic in 2009 led to the recognition that there was a high rate of hospitalization and some deaths when influenza was contracted in pregnancy (2). Subsequently, there was a change in perception concerning the vaccination of pregnant women against influenza, and the current recommendations by the Center for Disease Control and Prevention in pregnancy are for both influenza and TDaP (tetanus, diphtheria and acellular pertussis) vaccinations to be given during pregnancy since the benefits outweigh the risks(3).

In addition, there are currently several investigational vaccines in development for maternal immunization. These include vaccinations to protect against Respiratory Syncytial Virus and neonatal Group B streptococcal infections. These two infections account for much morbidity and mortality in the neonatal period globally, and their prevention would be welcomed by neonat-ologists and obstetricians alike. Benefits could include not only the reduction of these infections in newborn babies but might also help in the fight against antimicrobial resistance, and the term preventative neonatology has been applied to refer to this type of intervention(4).

An interesting recent target for vaccination is the Zika virus. Although the main aim of immunization would be to reduce the serious impact of maternal infection on the developing fetus, the target population, in this case, would be adolescent girls so that they are protected in advance of a pregnancy. It is the most effective way of prevention since the harmful effects of the Zika virus occur very early in pregnancy. There are several Zika vaccines currently in development (5).

Whereas in the past, the approach has been to avoid all medicines in pregnancy, there is increasingly a recognition that there are several situations where it is either essential or desirable to give medicines during pregnancy. This includes situations where the mother has epilepsy when the risk of fits in pregnancy will often

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outweigh the risk of taking medication for pregnant women or those planning a pregnancy. Medication during pregnancy may also be needed in other conditions such as cystic fibrosis, multiple sclerosis, or in HIV infected mothers, where there may also be risks to the unborn child of transmission of infection.

As an example, sodium valproate has been used for many years in the treatment of epilepsy and although some of the adverse effects were well known, the full extent of the risks to the unborn child when it is taken in pregnancy have only recently been fully acknowledged and addressed (6). Although for epileptic women planning a pregnancy there are other anti-epileptics drugs (AEDs) available, the dilemma for a doctor considering changing anti-epileptic medication (apart from the risk of a change in fit frequency) includes the lack of data for use in pregnancy for many of the other AEDs. In many cases, the data comes from registries where there can be difficulties interpreting the data because of the problem to find an appropriate comparator group (which should ideally be untreated epileptic mothers and their babies), and lack of data on terminations carried out for fetal abnormalities, etc. A recent publication (7) presented a descriptive drug utilization study covering a 10-year period (1st Jan 2007 – 31st December 2016) of anti-epileptic prescribing in 3 European countries (Italy, France, and the UK). This study found that of the pregnant women prescribed AEDs (incidence between 3 and 7.8 per 1000 pregnancies), there was a slight decrease in valproate prescriptions over the study period. About a third of the women in the UK and France were on lamotrigine. Worryingly there was an increase in prescriptions of gabapentin and pregabalin in pregnancy where the risks to the embryo or fetus are not well known.

Similarly, the MHRA (Medicines & Healthcare products Regulatory Agency) recently published a statement on the use of Fingolimod (a disease-modifying treatment for multiple sclerosis) in pregnancy advising against use in pregnancy and in women trying to get pregnant due to the increased risk of major congenital malformations(8). However, there is limited data available on other disease-modifying agents in pregnancy.

These 2 cases illustrate the need to investigate not only new investigational products that are anticipated to be prescribed in pregnancy and/or women of childbearing potential but also to review the evidence available for older medications such as sodium valproate and consider whether new trials should be conducted. Clinical trials may not always be feasible, so other ways to collect evidence for use in pregnancy may need to be considered, e.g. registries or real-world studies (recognizing the limitations that were mentioned earlier). The Food and Drug Administration (FDA) has a list of pregnancy exposure registries available on its website (9).

To emphasize the need to include pregnant women in clinical trials, the FDA has published draft Guidance in 2018 (10). This document mentions the need to focus on medication indicated for conditions that occur commonly in women of childbearing potential and the guidance points out that currently most labeling information for pregnant women is based on nonclinical data with limited human safety data. We have seen through the examples I mention, the potential consequences for mothers and babies if we fail to include pregnant women in clinical trials. I hope that as we have increasingly seen maternal immunization clinical trials being conducted, we will now start to see an increase in clinical trials of new medicines in pregnancy. This should enable an adequate assessment of the benefit/risk to be made available for physicians and women planning a pregna-ncy and result in better outcomes for mothers and babies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper

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