COMMENTARY

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Antibacterial Use in Pregnancy

Timothy M.A. Weller[1] and *Elizabeth N. Rees*[2]

1 Department of Medical Microbiology, City Hospital, Birmingham, England
2 Department of Microbiology, Russells Hall Hospital, Dudley, West Midlands, England

The treatment of any condition during pregnancy is difficult, as drugs may pose a danger to the fetus or neonate. It is estimated that around 5% of birth defects are induced by maternal drug therapy.[1] With the risks of teratogenicity and dysmorphogenesis ever present, clinicians are cautious in the products that they employ. Despite this, over 60% of parturient women consume therapeutic agents not directly related to their pregnancy.[1] In all cases the risk to the unborn child from the treatment must be balanced against the maternal or fetal need for the drug. The selection of an appropriate antibacterial agent is no exception to this.

1. Physiological Changes in Pregnancy

Prescribing difficulties are compounded by the host of physiological changes found in the pregnant woman that result in altered pharmacokinetics. Intravascular and extravascular blood volume undergo a 40% increase by the 20th week of gestation, which may affect the efficacy of those antimicrobials that are totally eliminated between every dose. At the same time, there is an increase in glomerular filtration rate and hepatic capacity, so that agents are eliminated at a faster rate. To confuse matters, this may be reversed in toxaemia of pregnancy. Furthermore, there is a relative lowering of albumin concentration in pregnancy and, thus, more free drug in maternal than in normal adult plasma. It is clear, therefore, that the pharmacokinetics of a particular drug cannot be accurately predicted in pregnancy.

Drug solubility, ionisation and protein binding influence placental transfer and the amount of drug reaching the fetus. Only the fraction of drug not bound to plasma proteins nor carried in red cells is available for transfer. All antimicrobial agents cross the placenta, in varying degrees, by diffusion. This is largely dependent on a simple concentration gradient, but it is also related to the surface area of the membrane and the diffusion constant for the substrate being transferred. The latter is dependent on the molecular weight and spatial configuration of the drug. Antimicrobial agents have low molecular weights and cross the placenta easily, producing therapeutic concentrations in the fetus almost as soon as in the mother.

Antimicrobials are frequently used in pregnancy. Increased susceptibility to infection in these patients is the result of the physical changes in pregnancy or of ill-defined immunological mechanisms. This relative immunosuppression leads to an increased maternal risk of serious sequelae following infection with pathogens such as varicella-zoster virus and malaria. Organisms normally considered of low virulence, such as *Listeria monocytogenes*, can also cause devastating infection in the parturient woman. It is well documented that asymptomatic bacteriuria is a common consequence of the physical changes in pregnancy. If untreated it leads to the development of pyelonephritis, which is associated with premature delivery.[2] Administration of antibacterials will, therefore, be of benefit to both mother and child. There are also infections, such as toxoplasmosis, that largely pass unnoticed in the mother but may do considerable harm to the fetus. Treatment is consequently of no direct benefit to the mother.

2. Assessment of Drug Safety in Pregnancy

The clinician who wishes to use any therapeutic agent during pregnancy must bear in mind that the results of trials in healthy volunteers or nonpregnant patients are not necessarily valid. The differences in maternal physiology alter drug pharmacokinetics and there is the possibility of unpredictable adverse effects on the fetus. In an ideal world no drug would be available for use before it has been thoroughly tested for safety and effectiveness in a double-blind, randomised, placebo-controlled trial in parturient women. However, pregnant women are traditionally excluded from drug trials, due to ethical concerns about patient welfare and financial concerns about the risk of litigation. Consequently, most drugs that are used in pregnancy have not been rigorously assessed in that condition, but must still be given because there is no alternative available.

In order to feel confident enough to prescribe for parturient women the clinician must look at indirect measures of safety and efficacy. These may come from experiments *in vitro*, animal models or clinical experience.

The mode of drug action can provide a theoretical basis from which to forecast likely adverse effects. For instance, it is not difficult to predict that cytotoxic drugs, such as the antifolate methotrexate, will produce a high incidence of abnormalities. However, some agents that may seem to have a risk attached to them in theory do not, in practice, cause any ill effects. An example of this is metronidazole, which interacts with the DNA in bacterial cells whether or not they are susceptible to the drug. This implied risk of teratogenicity has led to the advice that metronidazole should not be used in the first trimester. Several large studies of incidental usage have not, however, detected any excess risk of adverse events in the offspring of those taking this antimicrobial.[3] Conversely, some agents have unpredictable teratogenic effects unrelated to the mechanism of action associated with their primary function. The problems with thalidomide, for instance, were unexpected, particularly as serious malformations were caused by very small doses administered only once or twice during early pregnancy.

Further indirect reassurance may come from animal studies. These data must, however, be viewed with caution for 2 reasons. First, the large drug doses administered in animal trials may not reflect the therapeutic concentrations that would be used in humans, leading to an overestimate of the fetal abnormality rate. Trials conducted in animals revealed that high doses of sulfonamides cause malformations in rats and mice.[4] Such malformations have not been recorded in humans, despite heavy usage in the early years of the century. Secondly, differences in drug metabolism and kinetics between the species make the results difficult to interpret. Large scale experiments can be performed in rats and mice, but trials in larger animals and primates give a more accurate indication of what will occur in humans. Unfortunately, these studies are more expensive and time consuming, as the life cycle of larger animals is considerably longer than that of a rodent. Furthermore, the studies may still produce misleading results, as in the case of vitamin A, an excess of which is teratogenic for pigs but not for humans.

In reality, most information about the safe administration of drugs in pregnancy comes from a history of long term use with no reported poor outcomes. This method of drug selection has been supported by studies in the 1970s that showed no clear relationship between antimicrobial use and adverse events.[5] Most practitioners are happy to prescribe penicillin and its derivatives, for instance, although there are no data from formal trials. The danger associated with this approach is that a harmful effect with an incidence only marginally above the background level may not be recognised. Equally, the problem may not be immediately apparent, such as the occurrence of vaginal adenocarcinoma in teenage girls whose mothers had been treated with diethylstilbestrol during pregnancy.

3. Special Problems with Antibacterials

The use of antibacterials is complicated by the presence of micro-organisms in the equation that

for other pharmacological agents only includes the host and the drug. Selection of antibacterials is, therefore, influenced by the susceptibility of the pathogen isolated. Many of the older, low-risk, antibacterials have been rendered obsolete in certain situations because of changing resistance patterns. In the 21 years between 1971 and 1992, the susceptibility to amoxicillin of urinary *Escherichia coli* isolates in the UK decreased from 88 to 57%.[6] With such a high risk of treatment failure, this low risk antibacterial is now far from ideal as the drug of choice for empirical therapy in pregnancy. There are increasing numbers of new drugs being marketed for the treatment of infection, but it will be several decades before enough experience has been amassed to wholeheartedly endorse them. This is especially true for those broad spectrum agents that are reserved for serious infections in hospital, and in consequence are not used very often. With resistance to antibacterials on the increase, there is a need for clear guidance as to which of these drugs are considered to be low risk and those about which there should be more concern.

A recent paper published in this journal attempted to monitor retrospectively the effects on the fe tus of cefuroxime axetil given during pregnancy.[7] As the authors themselves comment, the number of patients assessed was very small. An adverse event associated with cefuroxime, or indeed any cephalosporin, is likely to be a rare occurrence and would, therefore, only be detected by a cohort study including thousands of patients. Consequently, although an increasing number of pregnant women are being treated with antibacterials that are not licensed for use in pregnancy, no single centre alone will be able to gather enough information to provide solid evidence of drug safety. This could only come from data collected on a national or international basis. Some groups, such as the National Teratology Information Service in the UK, strive to gather such data but depend upon clinicians to alert them to suitable cases. To be fully effective this system would require each pregnant woman given a particular antibacterial to be registered and followed up to ensure that evidence of harmful effects was not missed. It is unrealistic to assume that this could happen.

An alternative approach would be to combine and reanalyse results from small studies, as has been done for anticonvulsants.[8] The power of the evidence is increased, but difficulties arise when different methodologies and end-points have been employed. In addition, there are many antibacterials for which there would still not be sufficient numbers of patients studied.

The answer may lie in the systematic use of case-control studies. Although the evidence is not as robust as that from a randomised controlled trial or cohort study, the results can be obtained far more quickly and with fewer patients. The association between vaginal adenocarcinoma and maternal diethylstilbestrol use was highly significant in a study containing only 8 cases and 32 controls.[9] This approach is not without its problems, as separate studies would be needed for each type of abnormality. It would not be easy to avoid the inclusion of confounding factors; for instance, each patient will have had some sort of infection that may itself have been the cause of the anomaly. The identification of suitable matched controls can also be difficult.

4. Conclusions

The appropriate use of drugs in pregnancy is hindered by the paucity of information available on safety. The thalidomide scandal has taught clinicians to be cautious, but may also lead to the most appropriate treatment being withheld in the absence of trial data. In the current political climate it seems very unlikely that any change will occur in the practice of drug companies excluding pregnant women from their studies. It is time that commonly used agents, such as antibacterials, underwent a formal risk assessment so that problems can be identified and reassurance given where possible.

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Correspondence and offprints: Dr *Timothy M.A. Weller*, Department of Medical Microbiology, City Hospital, Dudley Road, Birmingham B18 7QH, England.
E-mail: T.M.A.Weller@bham.ac.uk