LEADING ARTICLE

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Assessing the Safety of Drugs in Pregnancy

The Role of Prospective Cohort Studies

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Abstract

Since, for obvious reasons, systematic testing of the teratogenic properties of drugs in humans is not possible in the premarketing phase, the epidemiological approaches to postmarketing risk evaluation are of major importance. Cohort studies, with their prospective exposure assessment, their ability to study even exposure to drugs not commonly used in pregnancy, and their ability to monitor both adverse and beneficial fetal outcomes, seem to be the most promising study type from a methodological viewpoint. Although there are numerous cohort studies on the harmful effects of drug use in pregnant women, only a few have been able to demonstrate a risk in terms of an increase in the prevalence of malformations. Most studies with significant findings were those investigating the risk potential of one group of drugs, the anticonvulsants. The lack of cohort studies showing a risk for drug use in pregnancy, however, is not necessarily indicative of some methodological deficiency. Rather, it may suggest that, for the majority of drugs, their use in pregnancy is not associated with an increased risk of congenital malformations.

Only some decades ago, the general opinion was that the placenta served as a barrier to protect the fetus from harmful agents. The rubella embryopathy in the 1940s, however, demonstrated that external factors such as maternal diseases or even unapparent infections can affect the child's development.[1] The thalidomide catastrophe in the 1960s, with the birth of several thousands of severely malformed babies, clearly showed that preparations used by the mother can cross the placenta and can have untoward effects on the fetus.[2,3] The consequence of the thalidomide disaster was an increased awareness of the potential for drugs to cause congenital malformations and other developmental disorders and the necessity to investigate this.[1] Since thalidomide, 30 drugs have been proven as being teratogenic, not all of which are currently in clinical use.[4] The drugs and their effects on the embryo, fetus or neonate are summarised below:

- ACE inhibitors: prolonged renal failure in neonates, decreased skull ossification, renal tubular dysgenesis
- aminopterin (not currently in clinical use), methotrexate: CNS and limb malformations
- anticholinergic drugs: neonatal meconium ileus
- antihyperglycaemic drugs: neonatal hypoglycaemia
- antithyroid drugs [propylthiouracil and thiamazole

1 The terms 'congenital malformations' or 'teratogenicity' used within the text include all other untoward effects on the newborn or the potential to cause them.

(methimazole)]: fetal and neonatal goitre and hypothyroidism, aplasia cutis (with thiamazole)
- carbamazepine: neural tube defects
- cyclophosphamide: CNS malformations, secondary cancer
- danazol and other androgenic drugs: masculinisation of female fetuses
- diethylstilbestrol (not currently in clinical use): vaginal carcinoma and other genitourinary defects in female and male offspring
- lithium: Ebstein's anomaly
- misoprostol: Moebius sequence
- nonsteroidal anti-inflammatory drugs: constriction of the ductus arteriosus, necrotising enterocolitis
- paramethadione (not currently in clinical use): facial and CNS defects
- phenytoin: growth retardation, CNS deficits
- psychoactive drugs (barbiturates, opioids and benzodiazepines): neonatal withdrawal syndrome (when taken in late pregnancy)
- systemic retinoids (isotretinoin and etretinate): CNS, craniofacial, cardiovascular and other defects
- tetracyclines: anomalies of teeth and bone
- thalidomide: limb-shortening defects, internal organ defects
- trimethadione (not currently in clinical use): facial and CNS defects
- valproic acid (sodium valproate): neural tube defects
- warfarin: skeletal and CNS defects, Dandy-Walker syndrome.
- Knowledge of the safety of drugs in pregnancy is extremely important. In some instances, pregnant women may have an existing condition requiring medical treatment, such as epilepsy, diabetes mellitus or asthma, or they may develop a pregnancy-induced condition. In both situations drug use during pregnancy cannot be avoided, and it is important to choose a preparation that represents the least risk to both mother and child. Further, a substantial proportion of pregnancies (about 50% in North America)[5] are unplanned, so that exposure to drugs takes place before the pregnancy is diagnosed. The consequence of an inadvertent exposure can be massive anxiety for the woman, which might lead to additional diagnostic measures, such as amniocentesis, and even the termination of otherwise wanted pregnancies. In addition, a woman who gives birth to a child with malformations after having taken medication during pregnancy may develop feelings of guilt which could have been avoided if reliable information on the risk potential of the drug in question had been available.

1. Methodological Issues

There are some specific methodological issues involved in the investigation of the teratogenicity of drugs. One is the sample size that is required to be able to draw sound conclusions. Although the prevalence of major malformations (those requiring medical treatment and/or impairing quality of life) is relatively high (about 5 to 7%),[6-8] it can be difficult to collect a sufficiently large number of cases if only certain types of malformations are to be studied. For example, in Europe, neural tube defects, which show a pronounced regional variability, occur with an average prevalence of 6.7 per 10 000 live births, and cleft lip (with or without cleft palate) occurs with an average prevalence of 7.8 per 10 000 live births.[9] Khoury et al. calculated the sample size needed in a population-based cohort study to detect a certain increase in the prevalence of malformations due to a teratogenic drug.[10] They showed that for uncommon drug exposures with a frequency of less than 1 per 1000 pregnant women [such as with valproic acid (sodium valproate)] and a low background malformation prevalence of 0.001, detection of the teratogenic effects would require more than 1 000 000 births to be monitored, even though the relative risk associated with the drug may be as high as 20 (i.e. leading to a 20-fold increased risk of a certain malformation). In contrast, for preparations which are commonly used in pregnancy (e.g. by 2% of women as was the case with thalidomide) and which are associated with an extremely high relative risk

(such as 175), 1000 births would be sufficient to detect the teratogenic potential, even when the background malformation prevalence was as low as 0.0024.[10]

Another important issue is the temporal relationship of drug exposure to the effect on the embryo/fetus. Exposure to harmful agents in very early pregnancy (up to 15 days post conception) generally leads to abortion of the embryo that may not be apparent to the woman. During organogenesis, i.e. days 15 to 60 post conception (in humans), the embryo is especially sensitive to teratogens.[2] The various organs and organ systems are susceptible to teratogens at different times during this period. Neural tube defects occur rather early, during weeks 3 to 5 of organogenesis, whereas cleft lip (with or without cleft palate) occurs relatively late (during weeks 7 and 8). Exposure to harmful substances after the period of organogenesis may lead to functional and behavioural disorders as well as minor morphological anomalies. In order to be able to postulate a meaningful relationship between drug use during pregnancy and a congenital malformation or some other untoward fetal outcome, drug intake must have taken place during a gestational period in which the organ or organ system is sensitive to harmful agents. Thus, exact information on the timing of exposure is crucial.

The temporal association of the use of a specific drug during pregnancy and the occurrence of congenital malformations does not necessarily mean that the malformation was the result of the drug. Regardless of whether a drug was or was not taken during pregnancy, malformations will inevitably occur with a frequency corresponding to the background risk. A causal relationship should only be assumed if the prevalence of malformations in the children of women using a specific drug significantly exceeded the background rate.

When analysing the harmful effects of drugs, special consideration should be given to the phenomenon of recall bias. Recall bias occurs when the reporting accuracy is dependent on the outcome.[11-13] The mothers of malformed infants may tend to remember their drug intake during pregnancy more precisely than mothers of healthy infants. Whereas, there are some studies examining the effects of drug exposure on pregnancy outcome in which bias could not be detected,[11] other studies showed exposure-specific recall bias.[13] In the paper by Klemetti and Saxen[14] recall bias could neither be proven nor, because of some methodological problems, be ruled out. The extent to which recall bias might occur is closely related to the amount of information collected on the patient's exposure to the drug being studied. The more complete this information is, the less recall bias will occur. The level of completeness is, of course, closely related to the methods used to collect the data. When investigating drug use during pregnancy, structured questions about the indications for the drug and drug names have proven superior to open-ended questionnaires.[15] With data from malformation registries, where exposure assessments are usually done retrospectively, recall bias is a common problem.

The assessment of the teratogenic effects of drugs can never be complete without information regarding stillborn infants and elective abortions, among which the prevalence of malformations are usually higher than in live births. The relevant data, however, are typically difficult to acquire and it is virtually impossible to be informed about all cases.

2. Study Types Used to Assess the Safety of Drugs in Pregnancy

It would, of course, be highly desirable to systematically investigate the teratogenic properties of drugs in humans before they were marketed. However, this is not possible because ethical reasons prevent pregnant women, and quite often women of childbearing potential, from being in-

2 The length of pregnancy is usually calculated using the first day of the last menstrual period rather than the date of conception. Using that method of calculating gestational age, you have to add 14 days to the time since conception to determine the critical phases of organogenesis. For example, neural tube defects occur 3 to 5 weeks after conception which corresponds to 5 to 7 weeks after the first day of the last menstrual period.

Table I. Possible study types used to investigate the teratogenic properties of drugs

Study type	Advantages	Disadvantages
Animal/*in vitro* studies	Can provide clues concerning the safety of drugs in humans	Extrapolation of findings is questionable
Case reports	Have been useful in proving the teratogenicity of certain drugs	Findings more or less due to chance
Case-control studies	Cost efficient, fast, allow analysis of rare malformations	Retrospective exposure assessment, recall bias, generally focus on 1 congenital malformation, usually little acceptance of results
Prospective cohort studies	Prospective exposure and outcome assessment, allow analysis of rare exposures (i.e. exposure to drugs not commonly used in pregnancy), temporal relationship between drug exposure and gestational age can be determined, no recall bias, results can be extrapolated to a defined population, comparatively high acceptance of the results	Time consuming, more expensive than case-control studies, low case numbers obtained, loss to follow-up
Historical cohort studies	Less time consuming than prospective cohort studies, no recall bias	Retrospective exposure assessment, loss to follow-up
Randomised controlled trials	Most reliable methodological approach	Rarely suitable for the evaluation of teratogenic properties of drugs
Systems based on voluntary/spontaneous reporting	Possibility to investigate drugs in a 'real life' setting	Incomplete data, outcome assessment often retrospective, potential for under-reporting

cluded in phase I to III clinical trials. Even post marketing, the existing possibilities to evaluate the teratogenicity of drugs are not sufficiently used. A summary of the study types suitable to assess the safety of drugs in pregnancy is presented in table I.

Animal reproductive toxicological studies, which are mandatory in most countries, and *in vitro* studies on teratogenic effects of drugs are only of limited value for humans because of the questionable extrapolation of findings (e.g. thalidomide proved to be safe in most animals). Case reports are, from a methodological point of view, rather a weak approach. Nevertheless, there are several examples of the teratogenic properties of drugs having been discovered by case reports (thalidomide, warfarin and isotretinoin). There are, however, more systematic approaches to assess the safety of drugs in pregnancy.

Case-control studies, which are comparatively economical, represent one such approach. These studies consist of 2 groups of participants, 1 group (the cases) with the disease being studied and the other group (the controls) without the disease. The 2 groups are compared in terms of the frequency of exposure to a factor that is suspected to cause the disease. Generally, the controls are matched for certain criteria, such as age, gender of the infant, and smoking status, to take into account the effects of confounding variables. Since the starting point of a case-control study is the occurrence of a disease, this type of study readily allows investigation of diseases with long latency periods. With case-control studies it is usually possible to obtain the case numbers needed to provide sufficient power to evaluate the risks and safety of drug use during pregnancy, even when the malformation being studied is uncommon.

In spite of these advantages, case-control studies do have some drawbacks, the most important one being recall bias. Since there are studies showing that recall of drug intake during pregnancy, especially some exposures such as oral contraceptive use after conception,[13] is better in mothers of children with malformations than in those of healthy children, the value of case control studies with healthy controls is questionable. Researchers try to overcome this problem by using mothers of children with other unrelated malformations as con-

trols, thus reducing the danger of recall bias. The optimal approach suggested by some authors[16] is to select children with a variety of other malformations (of which the aetiology is already known) as controls. Another disadvantage of case-control studies is that they generally focus on the aetiology of one particular congenital malformation, and the acceptance of the study results in the scientific community is usually rather low.

Prospective cohort studies follow up 2 different cohorts (one group exposed to a certain agent and the other not exposed to this agent) and analyse differences in the subsequent occurrence of the disease under study in these 2 groups (see section 3). They are more complex and generally more expensive than case-control studies, but they allow the analysis of rare exposures, i.e. exposure to drugs not commonly used in pregnancy, the collection of reliable data on exposure and outcome and the generalisation of the results to a defined population. The outstanding advantage of prospective cohort studies certainly is the prospective exposure assessment, i.e. the ascertainment of exposure takes place before the outcome is known and thus, recall bias can be avoided. In terms of studies assessing the risks of drug use in pregnancy, cohort studies allow the exact temporal relationship between drug exposure and gestational age to be established, an important prerequisite for the postulation of a causal relationship between drug intake and untoward fetal outcome.

A disadvantage of cohort studies is the low case numbers usually obtained when investigating uncommon diseases.[17] This can be overcome by using a sufficiently large cohort, a sufficiently long study period or a multicentre approach. If the study period is of considerable length, such as several years, drug use patterns may change over time, so that the data may no longer be of clinical relevance once the study is completed.[16] In addition, there is the problem of loss to follow up, and it may not be possible to obtain information on the outcome variable for some subjects enrolled in the study, especially when the study spans several years.

One possibility for assessing the safety of drug use in pregnancy in a 'real life' setting using a cohort study approach is prescription event monitoring (PEM).[18] Here, data on drug exposure are obtained from prescriptions, and outcome data are usually provided by the prescribing physicians. Thus, this study type does not lend itself to the investigation of over-the- counter drugs. PEM mainly monitors newly marketed drugs which physicians are usually reluctant to prescribe to women of child-bearing potential and whose main indications are most often not prevalent in this age group. Because of this the case numbers in PEM studies can be quite low; in 1 study with 11 000 patients, only 307 pregnancies were reported.[19]

Although the standard approach with cohort studies is to prospectively assess exposure and outcome, it is also possible to assemble the cohort using historical records (e.g. prescription data, hospital records). Such a study is called a historical or retrospective cohort study. The term retrospective describes the way the cohort is defined but not the ascertainment of disease occurrence. Although exposure assessment is based on historic information, i.e. it is done retrospectively with all the corresponding disadvantages, the cohort is defined before the disease status of the individuals is known, thus recall bias does not occur. The methods for data analysis in historical cohort studies are the same as those used in prospective cohort studies.

Randomised controlled studies are the study type that yield the most reliable results because of the experimental nature of the studies, the exact assessment of exposure, the standardised procedure and the optimal control of bias and confounding variables. Since pregnant women and women of childbearing potential are generally not included in these clinical trials, it is not easy to assess the risk of drug use in pregnancy using this approach. In the US, however, this situation has recently started to change. Efforts are now being made to include women of child-bearing age in clinical trials during the drug development process, but pregnancy or lack of contraceptive protection remain an exclusion criterion.[20] In 1993,

the US Food and Drug Administration reversed its decision to exclude women from clinical trials and permitted the participation of women of childbearing potential in Phase I and II drug trials. Meanwhile, they have progressed even further and are able to refuse the approval of trials in which the gender distribution of the study population does not reasonably reflect the gender distribution of the disease for which the drug is intended.

Another approach used to evaluate the teratogenic risk of a drug after it has been introduced to the market is a system based on health professionals voluntarily reporting fetal exposures to drug manufacturers. This method can be helpful in generating early signals about adverse and teratogenic drug reactions.[21] It allows inadvertent drug exposure to be investigated and it can be a useful tool for an initial analysis of the safety of drugs in pregnancy.[22] However, this method does have some disadvantages. Since it is based on voluntary reporting, there is always the potential danger of under-reporting. Moreover, the pregnancy rate tends to be low during the early postmarketing period. In addition, exposure assessment is generally done retrospectively, the data are often incomplete to a substantial degree and, since the total number of women exposed often remains unknown, risk assessment becomes very difficult.[5] Spontaneous reporting of alleged drug-induced congenital malformations to national or international voluntary reporting programmes currently plays only a minor role in assessing the teratogenicity of drugs because of the extremely low case numbers actually reported.[23]

3. Prospective Cohort Studies for Assessing Drug Use in Pregnancy

Taking into account the methodological issues involved in assessing the risk of drug use in pregnancy, prospective cohort studies seem to be an ideal tool for investigating this area. They possess most of the characteristics required to establish causal relationships between drug exposure and untoward pregnancy outcome (see section 2). Their only major disadvantage is the low case numbers obtained when investigating certain types of congenital malformations, e.g. cleft lip (with or without cleft palate) or neural tube defects. Nevertheless, to date, only few cohort studies have actually been able to demonstrate the risk potential of drugs in pregnancy. This may, in part, be because the use of most drugs during pregnancy is actually not associated with an increased risk of congenital malformations or other types of untoward fetal outcome. With regards to the drugs with known risk potential discussed in the introduction, only the teratogenic properties of anticonvulsants have been demonstrated by prospective cohort studies.[24-27] For the other drugs either no prospective cohort studies have been conducted or these studies did not actually prove that there was an increased risk of malformations.

A large prospective cohort study on risk factors in pregnancy was conducted by Koller and colleagues in Germany in the 1960s.[28] One of the major goals of the study was to evaluate the risk of drug use during pregnancy. Between 1964 and 1970 a total of 14 774 pregnant women were enrolled in this study and data from 7870 women were analysed. Intake of all drugs was recorded prospectively, using interviews and diaries, and investigated with regard to impaired fetal development in terms of spontaneous abortion, perinatal mortality, congenital malformations, etc. The most commonly used groups of drugs in the first trimester were female sex hormones (23%), vitamins A, B, C, iron (22.3%), laxatives (21.1%) and antiemetics and antihistamines (17.0%). After adjusting for confounding factors (e.g. maternal age), no statistically significant association between drug use during pregnancy and untoward fetal outcome could be detected. Another very large cohort study of Michigan Medicaid recipients with 229 101 completed pregnancies was conducted between 1985 and 1992. The results have not yet been published but are referred to by Briggs et al.[29] in their book on the safety of drug use in pregnancy and lactation and are used for risk evaluation.

A prospective cohort study, known as the PEGASUS-project, is currently under way in Mu-

nich, Germany to assess the risks of drug exposure in pregnancy.[30,31] A specially designed report form is posted in a prenatal care log-book which pregnant women receive from their gynaecologists. Information on all drugs taken during pregnancy (including the name of the drug, dosage, duration of treatment, reasons for use and whether it was an over-the-counter or a prescribed drug) is documented prospectively on this form by the pregnant women and/or their physicians. In Munich, about 75% of women visit a gynaecologist within the first 3 months of pregnancy so that for the vast majority of women recording drug usage starts within the first trimester. Information on the medical history of pregnancies, deliveries (i.e. delivery mode, duration of delivery, delivery-related medical problems, etc.) and fetal outcome is provided by the Bavarian Perinatal Study which routinely collects data on all births in hospitals in Munich. To date, record linkage of drug usage and fetal outcome data has been completed for 1037 children, 20 of whom have had major congenital malformations. These numbers are still too small to evaluate the teratogenic properties of single substances.

The teratology information services (TIS), that have evolved during the last few years, also prospectively collect information on drug exposure during pregnancy. For selected exposures, follow-up studies are conducted. One of the outstanding TIS is the Motherisk Programme which was established in 1985 at the Hospital for Sick Children in Toronto, Canada. They receive about 100 inquiries per day and follow up pregnancies with exposures to agents of special interest such as known teratogens or drugs for which information is still insufficient. In the past few years, they have published the results of prospective cohort studies on calcium antagonists,[5] histamine H_2 antagonists,[32] topical tretinoin,[33] mesalazine (mesalamine),[34] selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors,[35] fluoroquinolones,[36] sumatriptan,[37] and omeprazole[38] with cohort sizes ranging from 80 to 267 in the exposed groups. None of the Motherisk studies have, as yet, demonstrated an elevated risk of malformations in the children of exposed women.

To provide some idea of how these studies are conducted, the study on H_2 antagonists has been briefly described.[32] This study prospectively enrolled 230 women who contacted Motherisk between 1985 and 1993 regarding gestational exposure to H_2 antagonists. At the time of first contact with Motherisk, information on the mother, the pregnancy, duration of H_2 antagonist exposure, indication for H_2 antagonist therapy and on other drug exposures were collected. After the expected date of delivery, data on the delivery and the child, including congenital malformations and developmental disorders, were collected by telephone interview. The non-exposed cohort consisted of women who had contacted Motherisk because of exposures to agents which were not known or suspected to be teratogenic or fetotoxic, such as dental x-rays, and was matched according to maternal age, smoking status and alcohol consumption. The primary outcome variable of this study was the prevalence of major congenital malformations and secondary end-points included pregnancy outcome, gestational age at delivery, the number of preterm deliveries, birth weight, the number of neonates who were small for their gestational age, the method of delivery, the incidence of neonatal health problems and Denver Developmental Milestones (a screening test to assess whether a child's gross and fine motor, language, social-emotional, and cognitive skills are appropriately developed given the child's age). Of the 230 enrolled women, 52 were lost to follow-up, so that complete information on 178 exposed women (77.4%) was available. A significant difference could not be detected between the exposed and the non-exposed groups in any of the outcome variables. The authors concluded that H_2 antagonists do not represent a major congenital risk. A methodological deficiency in this study is that a group of drugs, rather than a single agent, was assessed. An increased malformation risk with only 1 of the agents in the class of drugs under study could easily be masked by other drugs in the same group not increasing the

malformation prevalence. Yet, such an in-depth analysis would require case numbers that are not readily obtained.

With regards to assessments of the teratogenic potential of drugs carried out by drug companies, a manufacturer of aciclovir together with the US Centers for Disease Control has conducted a study on the use of this drug in pregnancy (the Acyclovir in Pregnancy Registry).[39] A total of 1002 known pregnancy outcomes were followed prospectively between 1984 and 1996, and the results were not indicative of an increased risk of malformations with the use of aciclovir in pregnancy.

4. Conclusions

Since the thalidomide disaster it is well accepted that drugs can have adverse effects on the unborn child. Although numerous studies show that medication use during pregnancy is wide-spread,[30,31,40,41] there is still a serious lack of comprehensive and valid data on the utilisation and risks of drug use in pregnant women. As pregnant women are excluded from clinical trials, the teratogenicity of drugs cannot be evaluated in the premarketing phase. There are, however, several possibilities to assess the safety of drugs in pregnancy once they have been marketed. One of them is the use of prospective cohort studies which have a number of methodological advantages compared with other study types. Cohort studies permit the systematic investigation of drug safety on a population basis. Assessment of exposure is done prospectively, making it possible to obtain complete, detailed and reliable data on all drug intakes as well as on the gestational stage at which they were taken. Thus, the information necessary to establish a temporal relationship between exposure to a certain drug and the occurrence of congenital malformations is provided. In addition, with prospective exposure assessment recall bias can be avoided.

In every epidemiological study on the teratogenic properties of drugs it is essential to take into account the effect of confounders i.e. factors which are associated with an increased risk for congenital malformations but which are not the end-point of the study. Some such factors include maternal diseases and infections (rubella, toxoplasmosis), certain chemicals, maternal smoking, drug and alcohol abuse and genetic factors. Usually, cohort studies offer ample opportunities to control for confounding variables. One of the problems inherent in the cohort study approach is the low case numbers usually obtained when analysing specific drugs or malformations. Multicentre studies and international cooperations offer the possibility to overcome this difficulty.

It is important to note that the use of drugs in pregnancy should not exclusively be perceived as a potential risk – some drugs can also be beneficial for the child's development. The most striking example of this is probably the prevention of neural tube defects by folic acid supplementation before and during the first weeks of pregnancy. Prospective cohort studies are also a suitable tool for evaluating such benefits.

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