Drug utilization studies in pregnancy
Jong-van den Berg, Lolkje Theodora Wilhelmina de

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2006

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 31-03-2019
Chapter 1

SCOPE OF THE STUDY

Drug consumption during pregnancy can be regarded as the "raison d'etre" for drug safety monitoring and at the same time as its Achilles heel.¹
Introduction

The history of drug registration in most developed countries has been strongly influenced by the dramatic ‘thalidomide disaster’. At the end of the fifties thalidomide was marketed as a hypnotic drug which, it was claimed, could be used safely also during pregnancy. Shortly after its marketing however, a dramatic increase was seen in the frequency of a previously rare birth defect, phocomelia.† Precisely because this type of birth defect had been so very uncommon in the past,‡‡ the association with the use of thalidomide was detected relatively ‡ ‡ ‡ easy and relatively early in its history.²³

This case, and other experiences with drugs which had proved injurious in various ways in practice, led Drug Regulatory Agencies to prescribe a series of extensive preclinical toxicological tests which, it was considered, should be performed before a drug was tested in humans, and three phases of clinical testing to be performed on those drugs which proved toxicologically acceptable. Unfortunately however these procedures, although they represented an adequate approach to the question of drug safety as a whole in the light of the methodology then available, failed to solve the very problem which had led to their adoption, i.e. the safe use of drugs in pregnancy.

The risk of having a child with a birth defect has been estimated from 2 to 7 percent by different authors.⁴⁵ This wide variation can be explained by the inclusion or exclusion of minor abnormalities or birth defects with a known aetiology, such as chromosomal and recessive disorders. Finally the follow-up time after birth may considerably influence the assessment of the incidence of birth defects registered. EUROCAT†† which registers within one year after birth all birth defects interfering with physical health, estimates the incidence at 2 to 3 percent.⁴ Other authors who used different registration sources, i.e. hospital discharge diagnosis for children under 7 years, found higher figures. An incidence of 4.7 percent was found when birth defects of known causes were excluded and 6.1 to 7.2 percent if known causes are included.⁵ In 60 percent of all birth defects the aetiology is unknown, only two percent is probably caused by the use of known teratogenic††† drugs.⁶

The preclinical testing of drugs in pregnant animals proved to make only a very limited contribution to the prediction of risks in human pregnancy. Firstly, most drugs which have been found to have teratogenic properties in animal studies will

† Phocomelia: literally “seal like-limbs”; the limb defects actually observed may range from minor defects of the digits to the entire absence of some or all limbs.

‡‡ Systems for monitoring congenital anomalies are the European Registration of Congenital Anomalies and Twins (EUROCAT) and the International Clearinghouse for Birth Defects Monitoring.

††† Teratogenicity is a manifestation of development toxicity, representing a particular case of embryo/foeto- toxicity by the introduction of, or an increase of the frequency of, structural or functional disorders in the progeny.
never reach the market, and one will therefore be unable to determine whether they
are similarly teratogenic in humans. Secondly, where drugs have been admitted to
the market despite their proven teratogenicity in animals, there has proved to be
no consistent correlation between these findings and their effects on the human
foetus; some, such as isotretinoin and etretinate, have indeed been found to be
teratogenic in humans.\textsuperscript{7,8} Certain other widely used drugs, such as acetylsalicylic
acid and the corticosteroids, which had come into use before teratogenicity studies
became obligatory, and which have not been found to induce organ malformations
in humans\textsuperscript{9,11} have subsequently been shown to give positive results in teratogenic
tests in some animals.\textsuperscript{12,13} Such findings indicate that information on teratogenicity
in animals is not of great predictive value for the human situation.

In this respect the history of the thalidomide experience itself is particularly illus-
trative. Before the drug was marketed, no pre-marketing teratogenicity studies had
been performed, but following the recognition of human teratogenicity in man, ini-
tial attempts to reproduce these defects in ordinary laboratory rats and mice proved
negative.\textsuperscript{14,15} When, however, such studies were repeated in New Zealand white
rabbits, thalidomide proved to induce similar birth defects in these latter animals;\textsuperscript{16}
later work did identify means of eliciting the same defect in other species, but it
would not have emerged in routine screening. The results of teratogenicity studies
are thus dependent upon the species studied; even the strain of the species seems
to be important. It has been suggested that of all mammalian species man is the
most sensitive to thalidomide teratogenicity, but even if that is true it may not be
the case for other drugs;\textsuperscript{17} examples, cited above, suggest that for some drugs the
reverse may hold true.

In conclusion, current techniques for predicting the safety of drugs in human
pregnancy on the basis of animal studies, while they cannot be abandoned, are of
limited value, and the effects of many drugs in human pregnancy therefore remain
unknown when they are first given to human subjects.

Unfortunately, this shortcoming of animal studies is not compensated by pre-
marketing studies in human subjects. For obvious ethical reasons, pregnant women
are excluded from participation in the three phases of clinical testing; it would
clearly be immoral to deliberately expose a pregnant woman to an experimental
drug in order to determine its possible effects on the unborn child, and even though
very occasionally exposure may occur in this phase where pregnancy has gone un-
recognized, the limited observations which may result are unlikely to provide useful
evidence.

It follows from the above that, in almost every instance, new drugs are necessarily
released onto the market without any knowledge having been obtained as to their
possible effects in human pregnancy. This lack of knowledge is well illustrated by
the statements on the issue which are made in data sheets, package inserts and
forms of drug information at the time when a drug is approved for marketing; most
of them are so vague as to be useless. In one way or another, the data sheet will
customarily discourage use of the drug in women who are or may be pregnant, even
though the compound concerned may have passed its animal toxicological studies
with auspicious results. The text will either advise the prescriber against its use during pregnancy because of a theoretical risk of teratogenicity, or it will advise the user to consult a physician before use.

In spite of such warnings, it is evident that a large proportion of the drugs on the market will, sooner or later, be used in pregnant women; sometimes the pregnancy will have gone unrecognized when the treatment is prescribed, in other cases the risk may knowingly be taken because of pressing need, and in yet other instances the drug may, without the physician’s knowledge, be taken by a woman unaware of the warnings which relate to it. Whatever the cause, the ultimate consequence is that risks are frequently taken under uncontrolled conditions; as it has been put so strikingly in a report from the World Health Organization: “Experiments in human teratogenicity are going on all the time but the results are not being studied”\textsuperscript{18}.

The knowledge ultimately acquired as to the safety and efficacy of a drug in pregnancy is thus derived from experience in practice. Unfortunately, sometimes at the expense of dramatic disasters, such as in the case of thalidomide and of diethylstilbestrol. The risks of the latter, indeed, became manifest only decades after the drug had been taken by the women concerned\textsuperscript{19}. The only means of decreasing such risks for the future will be a better mobilization of such knowledge as does emerge in this way, so that conclusions can be drawn and risks identified at the earliest possible stage. That will involve the systematic registration of data on drug use on the one hand and on birth defects on the other, so that correlations can be sought, i.e. a specialised form of post-marketing surveillance is required. It may take many years before all the necessary information has been obtained, but with a proper approach it will be obtained without any avoidable delay. A continuous approach is needed in order to incorporate also new drugs.

**Study designs for investigating drug use in relation to pregnancy**

How can one best study the problem of teratogenicity in humans? The answer necessarily depends in part on the specific phenomenon concerned. In some instances, the type of birth defect which occurs in association with drug use is so characteristic and is so exceptionally rare in the absence of drug exposure (e.g. phocomelia and thalidomide) that it is relatively simple to establish a causal relationship. The relationship will be most rapidly and readily established when the defect induced occurs in a high proportion of exposed cases, when it is physical in nature (e.g. as opposed to behavioural changes) and when it is immediately recognizable at birth. In many instances, however, not all those conditions will pertain. An example is the complex of vaginal changes, sometimes proceeding to clear cell adenocarcinoma occurring in young women exposed in utero to diethylstilbestrol; these are only likely to become evident when the offspring attain puberty or adulthood. This fact explains, why some decades elapsed before the association was recognized\textsuperscript{19}. In yet other cases, the defects are not physical in nature but behavioral\textsuperscript{20,21}. Some complications are not specific for a given drug, or they comprise variable clusters of abnormalities.
which are not easily recognized (e.g. the so-called VACTERL syndrome, described in association with exposure to sex hormones, as discussed further below). In such circumstances extensive, systematic and long-term follow-up of the newborn can detect or exclude an adverse effect of a specific drug; which in turn must then be tested by case-control or cohort studies.

The case of Bendectin®/Debendox® illustrates the problem of identifying a low-grade teratogen through the limitations of the methodology of the study conducted. A number of studies suggested an association between gestational exposure to these two similar preparations (which had dicycloverine and doxylamine as their common components) and congenital malformations while other studies seemed to discount this association. The problem here was that both the nature and the incidence of the defects thought to be associated with the drugs were similar to those of congenital defects occurring spontaneously. Another example, already touched on above, illustrates the problems which exist when the possible defect includes multiple malformations. A number of studies, mostly in America, implicated first trimester exposure to exogenous progestagens and estrogens as being causally related to the development of various overlapping clusters of malformations, to which the term "VACTERL syndrome" (an abbreviation for Vertebral, Anus, Cardiac, Trachea, Esophagus, Renal, Limbs) was accorded by Nora and Nora. The child should, in the view of these authors, be classified as having the VACTERL syndrome when at least three of the seven organ systems are involved. On the other hand, several other studies failed to demonstrate an association between congenital malformations and sex hormone exposure during pregnancy. The results of all these studies show the complexity of the issue and underline that great caution should be taken in interpreting the findings. Several authors highlight the confounding variables which exist. These include the variety of hormones used in various combinations, the dosages of the drugs used, the gestation age at the time of exposure, the indication for use (inadvertent oral contraceptive use, hormonal pregnancy testing or supportive hormone therapy), recall bias and smoking.

The cases, mentioned above which represent only a small but impressive selection of an enormous series, stress the need for good study designs but unfortunately all these designs have their shortcomings. The main epidemiological techniques which can be used comprise descriptive studies such as case reports and birth defect monitoring as well as analytical studies i.e. case-control and cohort studies.

Case reports are useful for the early detection of problems, raising hypotheses which can then be tested using more formal study designs. Case reports however, even where they strongly suggest an association, do not determine whether the birth defect is related to the use of the drug itself or to the underlying disease for which the drug was prescribed, or is merely coincidental. For testing a hypothesis raised in this or other ways, a case-control study or a cohort study can be conducted.

Birth defect monitoring systems count malformations in a defined population and watch for significant changes. These registries embody a reliable mass of data on an unselected population and provide a convenient basis for testing the hypothesis of alert clinicians and for checking the results of case-control and cohort studies.
A case-control study, which compares the drug histories of mothers of children having a particular malformation with the drug histories of mothers of infants without this defect, will be efficient, rapid and usually less expensive than a cohort study. The selection of controls demands special attention. In this approach the collection of drug information is largely retrospective, data usually being obtained by interviewing the mother and thus potentially subject to bias;34 cases are more likely than are controls to recall certain risk factors. Medical and/or pharmacy records kept during pregnancy are therefore a more reliable source of input data.35

In a cohort study the outcome of pregnancy in mothers exposed to a specific drug is compared with the outcome in non-exposed mothers. This study design avoids the problem of retrospective bias but other problems arise, namely those of observation bias and confounding bias. Observation bias can be minimized by blinding the observer. The important source of confounding bias in this field of studies is the underlying disorder which was the reason for the administration of the drug. Cohort studies which predominate in research of this kind are less powerful than case-control studies.

Risk classification systems

Data sheets or other forms of information regarding the safe use of drugs during pregnancy often recommend that the patient should consult a health professional, i.e. should “consult a physician before using this the drug in pregnancy” or realise that “before using this drug during pregnancy the pros and cons of such use should be considered”. It is not clear however, how the practising health professional is supposed to follow such warnings, in view of the lack of knowledge and guidance that are at his disposal. Even where experience is available, he or she is unlikely to be in the possession of all the facts known. Such material as is available to the health professional generally fails to indicate on what evidence the recommendations are based, how reliable that evidence is and how great the risks to the mother or child really are.

To provide the health care professional with as much guidance as possible it is necessary that the evidence be either summarized or interpreted, preferably using a standard classification system to indicate, in a clear and unequivocal manner, the size of the risk which is supposed to be related to a given drug as regards its use in pregnancy. Such risk classification systems exist in Sweden, the USA and Australia,36-38 and their wider adoption has been proposed.39 The risk classification system employed in Australia is presented in Table 1. The purpose of such a classification scheme is to provide standards to assure that currently available information regarding the drug is made available to physicians, pharmacists and other health professionals in a complete and orderly form. Each drug is classified into one of the risk categories according to the degree of risk to the fetus. A weak point is that to date most of the drugs are unavoidably classified in group B, since only animal data, with its inevitable shortcomings, are available. The results of post-marketing
surveillance and drug utilization studies will be of great importance, since they will lead to an improvement of the classification system and eventually to reclassification of the drug(s) involved.

Table 1  The Australian Risk Classification system 1989

<table>
<thead>
<tr>
<th>Category A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs which have been taken by a large number of pregnant women and women of child-bearing age without an increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs which have been taken by only a limited number of pregnant women and women of child-bearing age without an increase in the frequency of malformations or other direct or indirect harmful effects on the human foetus having been observed</td>
</tr>
</tbody>
</table>

As experience of effects of drugs in this category in humans is limited, results of toxicological studies to date (including reproduction studies in animals) are indicated by allocation to one of three subgroups:
1. Studies in animals have not shown evidence of an increased occurrence of foetal damage
2. Studies in animals are inadequate and may be lacking, but available data show no evidence of an increased occurrence of foetal damage
3. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans

<table>
<thead>
<tr>
<th>Category C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs which have caused an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug that have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy</td>
</tr>
</tbody>
</table>

**Drug utilization research and pharmaco-epidemiology**

The fact that data obtained in clinical practice do accumulate progressively in course of time is not a fully satisfactory solution to the problems of evaluating drug safety in pregnancy. That is particularly clear when one examines the attempts which have been made to analyze and interpret both experimental and practical data in a comprehensive manner, e.g. by Folb and Dukes (1990). Despite the fact that a vast amount of information has been collected and studied systematically in order to render it accessible and of practical use, the deficiencies in the starting material are, as the authors repeatedly stress, all too evident. Such work underlines the need for a broad and systematic research approach, such as can be undertaken today using the methods of drug utilization research and pharmaco-epidemiology. The World Health Organization has defined drug utilization research as relating to “the marketing, distribution, prescription and use of drugs in a society with special
emphasis on the resulting medical, social and economic consequences". Attention is also devoted to the non-pharmacological (i.e. social, anthropological, behavioural and economic) factors that influence drug use. The general objectives of drug utilization research comprise the identification and analysis of problems, in particular their cause, significance and consequences. Pharmaco-epidemiology which found its origin in the USA, has been defined as the study of the use of and the effects of drugs in large numbers of people. To date, most research on pharmaco-epidemiology has focused on the study of drug effects, particularly with the intention of examining adverse effects. Other areas needing further development are the evaluation of the efficacy and toxicity of drugs in classes of patients usually excluded from premarketing testing, e.g. children, the elderly, and pregnant and breastfeeding women. According to the definitions mentioned above drug utilization studies and pharmaco-epidemiology have much in common and not surprisingly, researchers tend to mix them up. In both areas whatever the precise definition may be, results rely to an important extent on retrospective analysis rather than on prospective studies.

What can drug utilization studies and pharmaco-epidemiology contribute to the knowledge of — and as such, to the safety of — drug use during pregnancy? The answer is in fact simple; everything can and must be learned from it, since virtually no information is available prior to marketing. Both share the idea that actual use of drugs in large populations is an important tool in understanding drug use, its determinants and its effects. Stroms' remark that the most important contribution of pharmaco-epidemiology is the reassurance of drug safety is especially relevant in relation to drug use during pregnancy. Even if a particular drug proves to have been taken during gestation by a large number of mothers who subsequently gave birth to healthy babies, one will still need such systematic study to determine whether it indeed can be used safely during pregnancy by all women.

It is important all the same, to recognize that drug utilization studies and pharmaco-epidemiology comprise more than the registration of adverse drug reactions, despite the fact that the latter receive the bulk of the political and public attention bestowed on this field. Besides this, studies of drug use during pregnancy can also teach us about the prescribing behaviour of the physician and about the pattern of drug consumption by the patient. How often is a drug actually being used and what are the determinants of changes in use? This may provide important indications as to excessive or incorrect drug use in pregnancy i.e. the extent to which avoidable risks are being taken.

It would be reasonable to anticipate that the use of medication during pregnancy would during the past thirty years have fallen to the lowest possible level, in view of the various disasters and lesser problems associated in the past with the use of drugs in pregnancy, notably those linked with thalidomide and diethylstilbestrol. There is much evidence that this in fact did not occur; in various countries and at different times investigators have adduced evidence that over-prescribing and unnecessary drug use still do occur, sometimes on a large scale. In fact, even the
avoidable problems associated with drug use in pregnancy, are not always avoided. It is as important to study these as it is to examine the use and consequences of well considered medication in this phase of life.

Objectives of the present study

Viewed against the background outlined above, there is a pressing need for better techniques to examine the pattern of drug use in or associated with pregnancy and to determine the consequences of such use. These things will, however, only be feasible if means can be found to examine data reliably on a large scale. Limited populations may not be representative for the group of pregnant women as a whole, either with respect to their drug use or to their sensitivity to drug effects. The smaller the population the less easy it will be to distinguish the nature and frequency of congenital disorders after drug intake from those recorded occurring in pregnancies where there has been no drug exposure, i.e. spontaneously occurring congenital abnormalities.

The larger the sample which can be monitored, the better equipped one will be to analyze variations in the pattern of drug prescribing in pregnancy, and to compare such prescribing with any “golden standard” which may have been established for a particular form of treatment. In this respect the Australian categorisation of risk can be used.

Studies on drug utilization in pregnancy should also include those that are concerned with the use of drugs immediately before the onset or diagnosis of pregnancy, since these may affect ovulation, ovum transport, implantation or the early development of the zygote.

Finally, there is a common misconception that the ideal strategy is the avoidance of all drug treatment in pregnancy. Clearly that is often unattainable, since drugs will sometimes be needed to ensure that pregnancy is induced or maintained or that treatment is provided for incidental or chronic disorders or complications of pregnancy itself. For various of these treatments, however, consensus as to the principles which should be applied can be defined. Properly conducted, such drug utilization studies will allow us to determine where current prescribing practice in relation to pregnancy could be improved.

The present study is designed to determine what drug utilization studies in pregnancy can contribute to safety assessment. An initial question is naturally which methods are available to study drug use in pregnant women; some methods have been developed by others and are documented in the literature, but there exist opportunities to supplement these. In particular what is needed is an evaluation of any method for studying drug use in pregnancy which might offer the prospect of large-scale applicability and the promise of reliability. Such a technique, selected for evaluation in the present study, is the mobilization of data from community pharmacies in The Netherlands.
The choice of this particular model has been determined by a number of factors; they include the particularly favourable pattern of record-keeping in Dutch pharmacies, the increasing use of computerization in this field, and the strong tradition of drug utilization studies at various centres in The Netherlands. Such trends are now evident elsewhere to a greater or lesser degree, and there is every reason to expect that an approach which proves to be valid in The Netherlands will prove to be more widely applicable internationally as well.

The study falls essentially into five parts:

- Firstly, it will seek to determine which drug dispensing data obtained from Dutch community pharmacies can be used, and in what way, for studies of drug utilization in association with pregnancy (Chapter 2).

- Secondly, the data obtained in this way are validated (Chapters 3 and 4).

- Thirdly, the pattern of drug use is examined broadly in association with pregnancy in order to determine whether the medical profession as a whole is applying both the general and specific principles which one may consider applicable if the safety of such use is to be assured (Chapters 5 and 6).

- Fourthly, a selected model is analysed, namely the pattern of use of one particular drug (clomiphene) under suspicion of exerting teratogenic effects (Chapter 7).

- Finally, and in the light of findings in the previous sections, it will seek to develop recommendations as regards methods for studying drug utilization in association with pregnancy and for a number of approaches intended to influence such use favourably (Chapter 8).

REFERENCES

13 Fraser FC, Fainstat TD. Production of congenital defects in offspring of pregnant mice treated with cortisone. Pediatrics 1951;8:527-33.


