DRUG INFORMATION

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Databases to support drug therapy in pregnant and lactating women

- The Gravbase and Lactbase databases provide up-to-date information for clinicians planning drug therapy for pregnant and lactating women.
- In many cases, clinical safety data on drugs improves families' compliance with drug therapy.

When assessing a pregnant or lactating woman's need for pharmacotherapy, the clinician must inevitably consider several matters. What are the effects of the drug on fetal growth and development during the different stages of pregnancy, and to what extent is the infant exposed to the drug and what is the significance of that? Nowadays, women become pregnant at a relatively advanced age, and an increasing number of pregnant women have primary diseases requiring drug therapy. New research data on drugs become available on a continuous basis. The choice of drugs has also increased, and a larger number of drugs that are safe to use is available. On the other hand, what is known as the gray area has also expanded, and there is an increasing number of drugs where the clinician must weigh the benefit the mother receives from taking the drug and the adverse effects caused to the fetus or infant.

The Gravbase and Lactbase databases are very useful in performing this task. Active use of these databases improves patient safety and reduces the number of consultations sought from maternity and prenatal clinics and also the number of telephone consultations sought from experts. The amount of conflicting information mothers receive is also reduced, reducing their anxiety.

The databases and the search characteristics

Use of the Gravbase and Lactbase databases is chargeable. They contain information on the safety of approximately one thousand drugs, vitamins, vaccines and ordinary stimulants, including substances of abuse during pregnancy and lactation. In addition to drugs available on the Finnish market, the databases also contain numerous preparations requiring a special license. The databases are updated monthly; Medbase Ltd is responsible for their content. Heli Malm, MD, Specialist in Obstetrics and Gynaecology was the teratological advisor.

On the databases' front page is a training video, giving the user an example of how to start using the databases quickly. This enables the clinician to use the databases to his or her best advantage from the start.

The databases allow the user to review the information on the use of a specific drug during pregnancy and lactation, or to assess which drug in a certain group of drugs has been found to be the safest to use during pregnancy and lactation.

The safety of drugs is classified into a system containing four categories (A–D). The safest alternatives during pregnancy and lactation are classified under code A, while potentially harmful drugs are classified under code D. The colour coding system that has become known through the SFINX drug-drug interaction database (Tables 1 and 2) is also in use.

Data can be sought using one or two search words simultaneously. Searches can be performed by the trade name, generic drug name or ATC code.

TABLE 1.

Gravbase – classification of the safety of drugs during pregnancy

A	Controlled studies or large patient materials fail to demonstrate an increased risk for malformations *or* for direct or indirect fetal adverse effects after exposure during 1. trimester. Also, there is no evidence of a risk after exposure during 2. or 3. trimester.
B	There is only a limited amount of information on the use during pregnancy and there are no controlled studies in pregnant women. Animal teratology or limited human data indicate no evidence of increased risk of malformations or direct or indirect fetal adverse effects.
C1	There is only a limited amount of information on the use during pregnancy and there are no controlled studies pregnant women or the information is conflicting. Animal teratology data indicate increased risk of malformations or direct or indirect fetal effects *or* animal teratology data are missing.
C2	Animal teratology or limited human data indicate no evidence of increased risk of malformations, but late pregnancy use may pose a risk of adverse effects during the neonatal period or during childhood.
D	There is a strong suspicion or direct evidence of malformations *or* direct or indirect human fetal adverse effects. The drug is usually contraindicated during pregnancy, but in some cases the benefits may overweigh the risk.

Following the drug being searched, the database informs the user of the classification during both pregnancy and lactation. By clicking the mouse, the user can select whether he or she would like to review the drug's safety during pregnancy or during lactation.

A short recommendation on the use of the drug during pregnancy or lactation is available under "Recommendation" in end-users native language. The recommendation is based on published research data. Guidance is also provided for using another drug in the same group of drugs if there is more clinical evidence available on the safety of that drug.

Under "Find alternative drug", you will find information on drugs that are in the same group of drugs. The classification code following the drug name provides guidance for the selection. Under "Products", you will find the preparations for the drug in question. Under "Background", you can find a short English summary containing the essential evidence-based information on the use of the drug. In addition, literary references are listed so that the user may use to familiarize yourself with the studies in more detail, if you so desire.

What are the grounds for the recommendations?

Pregnant women or infants cannot of course be exposed, in the name of research, to different drugs for the purpose of following up on what happened. Thus the golden standard of a randomised clinical trial cannot be used for collecting data. The information backing the recommendations is based on collected and published data on exposure that has already taken place, congenital malformation registers, studies on breast milk, drug levels measured in infants and the results of pre-clinical animal studies.

It is clear that exposure to drugs that have been on the market for a long time and that are commonly used has been greater than exposure to drugs that are used less commonly. Also, the number of people who were exposed is larger, and the follow-up periods are longer for the children who were born. The available information is highly reliable.

The newer the drug, the smaller the number of people who have usually been exposed, and the follow-up periods are also shorter. Consequently, the results should also be viewed slightly more critically. The clinician's decision to use the drug is certainly also influenced by the planned duration of drug therapy, whether the drug in question will be used continuously or as needed, the stage of the pregnancy, and whether lactation will be exclusive or partial.

For example, in the case of antidepressants, therapy is usually of a long duration and exposure continuous.

Clinical evidence on SSRI drugs is available from several decades, published studies are widely available, and the number of pregnant women who have been exposed to the drugs is several thousand.

For example, the Swedish Medical Birth Registry comprises over 11,000 children whose mothers received SSRI therapy during their early pregnancy. Fluoxetine was used by 1,753 women, sertraline by 3,835 women, citalopram by 4357 women, escitalopram by 224 women and paroxetine by 1297 women. Of these, children born to mothers who were taking paroxetine were found to have twice the occurrence of cardiac anomalies compared to the expected frequency. The other drugs were not found to increase the risk of malformations. Similar studies have been published, among other places, in Holland and Canada, although confirmation by meta-analyses is lacking on the matter. All of these drugs may be associated with an increased risk of neonatal

TABLE 2.

Lactbase – classification of the safety of drugs during lactation

A	The drug is not excreted into breast milk in significant amounts *or* there is evidence that indicates lack of adverse effects in the infant, when the mother uses the drug in recommended therapeutic doses.
B	There are no studies on the excretion of the drug into breast milk. There is only a limited amount or no data on the safety of the drug during breastfeeding.
C	The evidence suggests that a clinically relevant amount of the maternal drug dose is excreted into breast milk. Therapeutic maternal drug doses during breastfeeding pose an increased risk for infant adverse effects. The decision on breastfeeding should be made individually considering the potential benefits in relation to the potential risks.
D	Breastfeeding is contraindicated while using the drug. The use of the drug during breastfeeding may cause severe adverse effects on the suckling infant.

pulmonary hypertension, premature delivery and low birth weight. Use of these drugs during late pregnancy may cause neurological and respiratory symptoms; for this reason, the lowest effective dosage should be used. In this group of drugs, for example, a few studies have been published on fluoxetine in which children who were exposed to the drug in utero (n = 44–66) were monitored up to the age of 6–7 years. No difference was found in the children's intelligence quotient or social or verbal development in comparison to the group that was not exposed to the drug.

Exposure during lactation has been studied by measuring drug concentrations in mothers and in breast milk, and in some studies, in infants as well. In these studies, the number of participants is clearly smaller, usually not more than a few dozen. Of the SSRI drugs, slightly more fluoxetine is passed into breast milk than paroxetine, sertraline, fluvoxamine or citalopram. Mild adverse effects, such as irritability and colic, have been described in some studies; however, during monitoring, the drugs in question did not appear to have an adverse effect on the child's psychomotor development or learning.

Data on the risks related to the use of newer antidepressant drugs, such as duloxetine, during pregnancy and lactation are usually based on solitary case histories or studies consisting of a few dozen mother-baby pairs. Because of the small number of those exposed, the results should be considered as primarily suggestive. In such situations it would seem sensible to select, whenever possible, a drug on which more evidence is available.

When searching for a drug in the databases, it is recommended that the clinician, at least for the first time, in addition to reading the summary text, glances through the English-language summary of the research results on which the recommendation is based. This will allow the clinician the opportunity to assess the degree of reliability of the documentation himself. If one is still feeling uncertain, or if a recommendation could not be given, teratological specialist should be consulted.

Research data also helps the parents

The questions the maternity clinic and the general practitioner are most frequently faced with concern the use of the most widely used drugs during pregnancy and lactation. These drugs include antibiotics, analgesics and antipyretics, antimigraine drugs, allergy and asthma drugs, drugs used to treat gastrointestinal symptoms, antihypertensive drugs and, increasingly, mood-altering drugs.

Many of the mothers who visit prenatal clinics are monitored at specialised care polyclinics because of their primary illness. Typically, they are patients at rheumatic disease, neurology, psychiatry and pain control clinics.

For this reason, physicians treating women of a fertile age should actively ask about their patients' wishes for pregnancy, so that drug therapy could be modified well ahead of a possible pregnancy. Gravbase also helps the clinician in his work in this regard. Most physicians probably have a few preparations from each group of drugs that they are quite familiar with and usually in favour of. If a pregnant or lactating mother is already taking another preparation whose continued use is considered, or if the medication must be changed because of inadequate effectiveness or adverse effects, Gravbase and Lactbase are helpful when considering the risks that may be associated with the use of the drug. The databases also facilitate the selection of the safer of two otherwise equal drugs.

Both parents are frequently worried about the mother's drug therapy, even though in the physician's view, it is a matter of justified and safe pharmacotherapy. In such instances, the clinical safety data related to the use of the drug can be shown to the parents as well. This will improve compliance to the treatment in most cases. Occasionally, even the instructions of a doctor may have been misunderstood and, consequently, the mother has stopped taking her asthma medication or a mother suffering from severe depression has stopped taking her

antidepressant drug. In such cases clear, unbiased evidence based data helps in clarifying the matter and restarting the necessary drug therapy.

In support of early mother-child attachment, the clinician should exercise caution in prohibiting breast-feeding unnecessarily just to be on the safe side, especially in the case of mothers who are suffering from psychological disorders and are undergoing drug therapy.

Most drugs can be found in the databases under their trade names. If a search under the trade name does not produce results, try searching under the generic drug name or under the group of drugs suited to the intended purpose. This will generally produce results. Different natural products – used by a surprisingly large number of mothers – are the most problematic. The mothers using them do not always even comprehend that these products could impact the fetus or the infant. In the case of expectant pregnant or lactating mother, the clinician should intervene in the use of natural products, because there is very little research data available on the subject.

Summary

The Gravbase and Lactbase databases are useful to the clinician planning and titrating the drug therapy doses to be used during pregnancy and lactation in order to make them optimal in terms of quantity, quality and timing, with the aim of achieving a benefit from the drug therapy that is greater than the risks or adverse effects caused by it. One should, however,
also keep drug-free treatments and other supportive measures in mind to enhance the family's well-being. ■