# A DATABASE MODEL OF DRUG USAGE IN PREGNANCY AND LACTATION ACCORDING TO USER INFORMATION REQUIREMENTS

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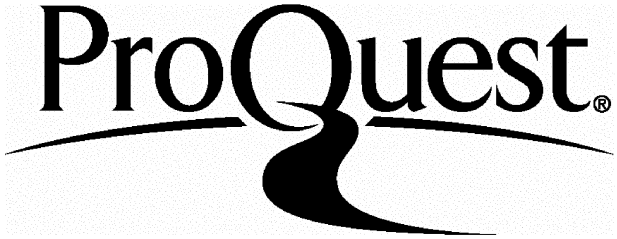

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# ABSTRACT

The information needs of a population of gynaecologists and obstetricians concerning drug administration in pregnancy and lactation, were investigated, employing the triangulation approach. This involves the application of three analytical tools: content analysis, focus group interviews and a structured questionnaire.

Content analysis was performed on queries submitted to two representative Drug Information Centres (DICs); the focus group interviews (FGIs) of gynaecologists and obstetricians were conducted in hospital departments; and the questionnaire was distributed among the majority of Israeli gynaecologists and obstetricians. The combination of complementary methods used constitutes a powerful tool for data assembly and for validation of conclusions.

Statistical analysis of the results reveals a relation between information usage and background variables, such as country of study, place of work and teaching position. In addition, a relation was found between information usage and attitude towards drug administration. Based on this analysis, a typology of users' profile was drawn and their information needs defined. A scheme of the pattern of drug information usage was delineated, leading to the designing of a database model to meet the information requirements.

Several drugs were selected to be included in the model, representing various pharmaceutical groups, different degrees of risk for the fetus and different amounts of available information about potential teratogenicity and toxicity. AskSam+ hypertext software was chosen to create the database due to its flexibility, ease of updating and enhanced text retrieval capability. Data are stored in a network of nodes connected through links. Each structured node contains all the information on a single drug: its names, risk factor, teratogenicity, fetal toxicity, mutagenicity and oncogenicity, all based upon and followed by a bibliographic list. These attributes are each assigned to a structural node and related hierarchically to body systems, organs and related pathology.

The database is user friendly, allows rapid retrieval of information and is easily installed on a PC in the gynaecologists and obstetricians' office. This model can also be readily adapted to other medical disciplines, according to their specific needs.

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## Definitions used in this thesis of terms describing fetal damage*

**Teratogenicity**
The potential to disrupt the formation of fetal organs (embryogenesis) resulting in congenital, functional or anatomical defects in body systems.

**Mutagenicity**
Damage caused to some chromosomes or to their organization, resulting in a permanent change in their genetic structure (mutation).

* Based upon definitions in:

Dorland's illustrated medical dictionary, 1994.

Briggs, Freeman and Jaffe, 1990.

# Chapter 1

# Introduction

## 1.1 Background for the Project

The practising physician is faced nowadays with a proliferation of pharmaceutical products having similar or overlapping properties. The utilization of this ever growing armamentarium, albeit beneficial, calls for special attention to the risks involved in its use, as the enhanced functional potency of the new drugs is often accompanied by numerous side effects. The process of selecting the most appropriate drug for a patient is thus becoming increasingly complex. An additional complication lurks in the large potential for interactions between different drugs administered to the same person. Physicians find it increasingly difficult to keep updated on these issues, and many lack the means for immediate consultation on the matter.

The problem is exacerbated when treating pregnant or lactating women. Drug metabolism and secretion may be considerably altered by the hormonal and metabolic changes during pregnancy, thereby increasing or decreasing the potential risks of teratogenicity and toxicity of the drugs to the fetus. Most of the drugs taken by a lactating woman find their way into breast milk, thus posing a potential danger to the nursing baby. Although the majority of drugs either do not reach significant concentrations in breast milk, or are not absorbed through the gastrointestinal tract of the infant, the list of drugs potentially harmful to the baby remains sizeable. The physician may face the dilemma of whether to recommend the continuation of breast feeding while withdrawing an important medication or the continuation of medication at the expense of breast feeding (Reisner, Eisenberg, Stahl & Hauser,1983).

In spite of potentially harmful effects, 35-100% of pregnant or lactating women take prescribed or over-the-counter medication (Rurak, Wright & Axelson, 1991). Of even greater significance is the fact that 40% of pregnant women take medication during

the first trimester, when the risk of teratogenicity is highest (Beeley, 1987). On average, women take almost four drugs during each pregnancy, not including nutritional supplements (Golbus, 1980). It is interesting to note in this context, that as early as the third century B.C. Greek physicians were aware of the problem of drug administration to pregnant women and have delimited its most dangerous periods quite accurately as revealed by the Hippocratic Corpus text: "Drugs may be administered to pregnant women, if required, from the fourth to the seventh month of gestation. After that period, the dose should be less." (Hippocratic Writings, 1978).

The public's increasing awareness of the problems associated with medical intervention has led patients to reject the traditional doctor's paternalistic approach (Emanuel & Emanuel, 1992). Many insist now upon sharing the available information, and become involved in the decision-making process leading to the choice of a particular treatment. An additional burden is thus placed on the physician, who is compelled to deliver updated information. This aspect of the physician-patient relationship is especially prominent in obstetric practice in pregnancy.

The problems associated with drug administration in pregnancy are so severe and common that several international projects have been created with the purpose of collecting data about various aspects of the issue. The World Health Organization has established an "International Cooperation Drug Utilization Study", the goals of which are stated as follows: "...to assess the pattern of drug use in pregnancy through standardized interviews of women admitted for child delivery to sample hospitals in different countries... to establish a permanent research network with centres where obstetric and perinatal care is delivered, to constitute a readily available resource to test/validate therapeutic or prophylactic measures, and drug safety issues." (Collaborative Group on Drug Use in Pregnancy, 1990).

Another institution, the European Network of Teratology (ENTIS), coordinates the activities of the existing Teratology Information Centres and Services and the

gathering of data about birth defects in fourteen countries, including Israel (Vennewald & Schaefer, 1991).

Modern medical care delivery is closely associated with the supply of readily accessible and concise information. This is demonstrated, for example,, by the finding that in complex medical situations 85% of the physician-patient encounter is spent on information gathering and processing (Hoskins, 1984), while a mere 15% is devoted to medical procedure. An important part of the physician's work comprises the gleaning of information from medical literature and other sources, which in obstetric practice has the special characteristics described above.

However, several obstacles are met on the physician's way to information. The relevant information is often scattered amongst a multitude of heterogenous journals (Haynes, 1990). Sometimes data might be presented as epidemiological surveillance studies, with little relevance to the individual case; much of the available data are contradictory, or at least inconclusive (Conner, 1986). This state of affairs is the outcome of several converging factors, such as: varying results of similar tests in different studies; widely differing methodologies employed in studies with similar purposes, variation in the study populations and lack of rigid scientific criteria in some research projects (Conner). Finally, controversial evidence should be presented to the physician as such, for him/her to decide what is relevant to the case.

A major obstacle is presented by current tools for the retrieval of information; the commonly available ones are cumbersome, time consuming and not always user-friendly (Howard & Hill, 1979). The practitioner cannot rush to the library or consult a complicated computerized system while attending to a difficult clinical problem.

In devising a solution to this problem, the special characteristics and needs of the population of physicians in question have to be determined. In Israel, gynaecologists and obstetricians work in public community clinics, hospitals (most of them affiliated to universities) and private clinics. The information needs of such a heterogenous

population had to be studied with appropriate tools which are described later. The results of this study would lead to the design of the solution, which in our case, is a user-friendly database on drugs in pregnancy and lactation.

## 1.2 The Health System of Israel

The area of Israel is 21.501 $km^2$ and the population is about five millions. Since the formal establishment of the state in 1948, there has been a constant flow of immigrants from a large number of countries. About 80% of the population is Jewish. The majority of the non-Jewish population are Moslems and the remainder are Christians, Druze and smaller religious groups.

While Israel does not have a national health care system, 95% of its population is covered by comprehensive health insurance. Seventy percent of the population are insured by Kupat Holim Klalit, the General Workers' Sick Fund, which is owned and managed by the Histadrut, the largest trade union in the country. Twenty five percent are insured by three smaller sick funds that provide similar services. The remainder are insured by the State Social Security. The insurance includes curative and preventive ambulatory care and hospitalization coverage. Most hospitals are owned either by the Health Ministry, Kupat Holim Klalit or Municipalities. Some hospitals are run by charitable or religious organizations. The larger hospitals are teaching hospitals, affiliated to university medical schools.

All medical services are located in the vicinity of the residential areas of most users. The extent of the private medical services varies according to speciality; most of the dental care, for instance, is delivered privately, as it is not included in the insurance package.

Ante- and post-natal, maternal and child care are central to Israeli society, and an extensive network of freely accessible facilities for preventive care exists in all communities, including rural ones. For many years there has been a systematic decline in infant mortality - congenital malformations and prematurity being the major causes of death in the Jewish population. Follow up of high risk pregnancies is carried out mainly in hospital outpatient clinics and the remainder in community-based ambulatory medical centres. In general, medical care of good quality is available to

the majority of the population and preventive services are well developed (Tulchinsky, 1985).

A new National Health Law is has taken effect during 1995, which will insure all Israeli citizens in existing sick funds and provide basic medical services to all.

## 1.3 Aims and Purposes

The aim of this work is to analyse thoroughly various aspects of information usage by gynaecologists and obstetricians in Israel and to derive a model for a database of drug use in pregnancy and lactation.

This includes the following sub-goals:

1. To assess the sources of information used by the population of gynaecologists/obstetricians under study.

2. To examine the physicians' practice in using drug information and its influence on drug administration in pregnancy and lactation.

3. To evaluate the influence of the physician's personal profile (age, training and position) on usage of drug information and the correlation to patterns of drug administration.

4. To search for typological groups in the population of gynaecologists/obstetricians , with distinctly different attitudes to drug usage and information needs.

5. To define the users' needs of information on drug use in pregnancy and lactation based on data obtained in items 1-4.

6. To characterize and establish a database model for drug use in pregnancy and lactation, according to the definition in item 5.

# Chapter 2

# Study Methodology

## 2.1 The Population of Gynaecologists/Obstetricians under Study

The study population encompassed 959 gynaecologists/obstetricians in Israel. A partial list of names and addresses was obtained from the ministry of health and then completed using other sources - the physicians' professional association and the pharmaceutical industry which promotes their products to this population. It may be assumed that the list included almost all the practitioners in the field. Some gynaecologists/obstetricians took part in more than one of the data gathering approaches used (as described in section 2.2), while others contributed only to one method.

## 2.2 The Triangulation Research Method

The approach to data collection and analysis may be quantitative or qualitative. The former involves deductive closed hypothesis testing by rigid quantitative and statistical methods, while the latter is an open-ended inductive process whose advantage lies in its greater flexibility; however, it may sometimes lack in accuracy and reproducibility of data (Krueger, 1988, pp. 37-44; Patton, 1987, pp. 7-11). This drawback can be corrected by using multiple methodologies in an approach called "triangulation" (Krueger, p. 40; Patton, pp. 60-69; Basch, 1987) so that ideally, two or more methods are used at each research step. Thus triangulation can be applied to:

- Data - by using multiple sources for data collection.
- Investigators - where a number of researchers with different or similar backgrounds collect and process data together or in parallel.
- Theory - by having a set of data or a given problem examined by various theoretical approaches.
- Methodology - by applying different methods to the study of a single problem.

Conceivably, triangulation can also include a mix of qualitative and quantitative methods. Thus, in a study using an overall open-ended triangulated inductive design, a specific set of data can be examined by a deductive, quantitative method. The three following methods were applied to the investigation of the information needs of physicians who treat pregnant and lactating women:

1. Retrospective studies - facet analysis of clinicians' inquiries addressed to drug information centres.
2. Focus Group Interviews (FGI) - a qualitative technique for investigating individual patterns of information usage within an interacting group setting. In this project, FGIs preceded the application of the quantitative method of questionnaires. The participants were hospital gynaecologists and obstetricians.
3. Questionnaire - a quantitative method that serves to gather data about information usage from a wide section of the population under study. In the present study, the questionnaires were sent to most of the gynaecologists/obstetricians practicing in Israel.

The combination of these three complementary methods constitutes a powerful tool for data assembly and for validation of the conclusions.

# Chapter 3

# Content Analysis of Inquiries about Drugs

Krippendorff (1980, p. 27) describes the technique of content analysis: "...the task is to make inferences from data to certain aspects of their context and to justify these inferences in terms of the knowledge about the stable factors in the system of interest. It is by this process that data become recognized as symbolic or are rendered informative about something of interest to the analyst."

The purpose of the content analysis here was to search for a stable pattern in inquiries about drugs in pregnancy and lactation. In order to serve the treating physician, the clinical aspect was stressed in the choice of inquiries for analysis and in the analysis itself.

## 3.1 Information Centres which Contributed the Inquiries

The inquiries which constituted the study material for the analysis have been addressed to the Computerized Information Unit at the Tel-Aviv University School of Medicine which is located in the central and most densely populated part of Israel. The services provided by the information centre encompass a wide spectrum of subjects, including drug information for clinical use and for research. The professionals by whom the inquiries were addressed are part of the research population participating in this project.

Although the purpose of this user study was to learn the information needs of a certain population of physicians in Israel, it is interesting to compare the structure of the inquiries to those received in information centres in another country. The centre which was chosen for comparison is the Drug Information Centre of the Wolfson Unit at the Royal Victoria Infirmary, University of Newcastle upon Tyne, because out of several Regional Drug Information Services in the UK, Newcastle received a high

proportion of inquiries on pregnancy and lactation (15.9% of all drug inquiries) (Marlowe, 1983, p.63).

## 3.2 Categories of Questions

The following issues are most often mentioned when information about drug use in pregnancy is requested: side effects, teratogenicity, dose related phenomena such as metabolic changes, the influence of the increased blood volume and renal clearance, dosage and ways of drug administration.

Grace and Wertheimer (1975) studied questions received at a university drug information service, and have been able to categorize them as judgmental or non-judgmental: "Judgmental questions required the integration of data or knowledge and experience in the process of making decision regarding a specific therapeutic problem." Non-judgmental questions refer to objective physical information such as the available forms of the drugs. According to these definitions, the majority of questions addressed to both centres in this study are judgmental.

## 3.3 Facet Analysis — Criteria which Form the Content Units

Seventy inquiries from Tel-Aviv and two hundred and thirty eight from Newcastle were analysed (Appendix A). Facet analysis was performed on all inquiries according to the following context units:

I - Name of drug

II - Drug risk factor

III - Name of a disease

IV - Pregnancy /Gestational age /Lactation

V - Miscellaneous remarks

### 3.3.1 Drug names

There are different types of drug names in common use, hence the use of universal nomenclature is essential for a study of patterns of drug prescription and provision of information. The American Pharmaceutical Association states: "In general, drug names fall into one of three main broad categories: chemical name, nonproprietary name and proprietary or trade name... The chemical name is usually the full systematic organic chemical name for the drug substance... The nonproprietary name serves as a convenient and concise name for use in identifying the drug substance... Generic name has a wide use as a synonym for the nonproprietary name... More precisely, generic names refer to families of very closely related compounds." (Bailey & Shoff, 1976).

All topics included in the inquiries were screened and counted according to those drug categories, in order to learn the usage patterns of drug names in queries to the drug information centres (Table 1).

Table 1: **The use of drug names in queries to drug information centres**

| | Nonproprietary Name | Trade Name (proprietary) | Chemical Name | Group of Drugs with Similar Activities | Use of Two Names |
|---|---|---|---|---|---|
| T.A. % | 59.4 | 23.2 | 7.2 | 18.8 | 8.6 |
| N.C. % | 76.4 | 7.6 | 4.9 | 8.4 | 0.4 |

Tel-Aviv N=69

Newcastle N=263

A preference for nonproprietary names stands out in this analysis. The main reason for this could be the bewildering proliferation of proprietary names of the same compound by different manufacturers. The use of generic or nonproprietary names facilitates communication between interested users and helps maintain a uniform

terminology. More than 25% of those who contacted the Tel-Aviv centre used trade names. In some cases, both proprietary and nonproprietary names are used. Although it seems that their disadvantage of being lengthy and cumbersome is outweighed by far by their advantage of being more accurate and scientific, the least used form at the two centres was the chemical name.

Sometimes questions refer to a group of drugs rather than to a specific one, as in certain cases information about a whole family of drugs with similar activities allows for a wiser choice of a single drug.

### 3.3.2 Risk factors of drugs

Risk factors have been assigned to drugs used in pregnancy based on the level of risk posed to the fetus by the drug. The drugs are rated A - D and X. Briggs et al. (1990) quote the definitions for risk factors put forth by the FDA in 1980 (Appendix B). A different classification, based on the TERIS database, was suggested by Friedman et al. (1990), assigning risk ratings such as "none", "minimal", "high" etc. The TERIS risk rating is not suitable for the purpose of this project, as it deals only with patients who have already been exposed to an agent, and considers only the teratogenic risk to the fetus. The FDA categories are intended to provide therapeutic guidance as well.

Most of the drugs in this study were assigned a risk factor according to the Briggs classification. The drugs included in category A are those that do not demonstrate a risk to the fetus; category X, which lies on the opposite end of the scale includes drugs clearly contra-indicated in pregnancy due to overwhelming evidence of fetal damage. In these two groups the definitions are clear-cut and can serve as a reference basis to the user. As expected, the number of questions on drugs rated A or X was the smallest in both centres, as demonstrated in Table 2 which lists the percentage of inquiries regarding drugs in each of the risk categories.

Table 2: **The percentage of inquiries of drugs according to the risk factor A-D,X).**

| | A | B | C | D | X |
|---|---|---|---|---|---|
| T.A. % | 12.0 | 28.0 | 36.0 | 20.0 | 4.0 |
| N.C. % | 2.1 | 22.1 | 49.6 | 20.0 | 6.2 |

Tel-Aviv N=50

Newcastle N=145

Drugs in category B draw more interest as there are no controlled studies on their use in pregnancy. Most of the controversial drugs are classified C or D, and those are the ones on which most of the information is requested: 56% of the questions addressed to the Tel-Aviv centre and 70% in Newcastle.

Questions with a disease name as a starting point were quite rare: 4.2% at Tel-Aviv and 6% at Newcastle.

### 3.3.3 Pregnancy

Questions on drug use in pregnancy were sometimes presented in a very general way, such as the name of the drug and the term "pregnancy" alone, or as a vague description of timing, such as "early" or "late" pregnancy. Otherwise, the trimester of pregnancy was defined or, even more precisely, the gestational week (Table 3).

Table 3: **Distribution of inquiries according to the gestational age**

| | Pregnancy* | Early/Late Pregnancy | Trimester | Week of Pregnancy | Fetus, |
|---|---|---|---|---|---|
| T.A.% | 42.9 | 3.2 | 20.6 | 1.6 | 31.7 |
| N.C.% | 69.8 | 6.5 | 17.7 | 2.3 | 2.8 |

*Gestational age not specified

Tel-Aviv N=63

Newcastle N=215

Organogenesis is all but completed after the first trimester of pregnancy (Berglund, Flodh, Lundborg, Prame and Sannerstedt, 1984) with the exception of the central nervous system and the endocrine system. Thus, inquiries limited to the first trimester of pregnancy, or early pregnancy, dealt almost exclusively with teratogenicity. The number of questions specifying the week of pregnancy is small: 1.6% in Tel-Aviv and 2.3% in Newcastle.

Using the term embryo (0-2 months of pregnancy) or fetus (3-9 months of pregnancy) was common (31.7%) in queries to the Tel-Aviv centre, but rare in those addressed to the Newcastle centre (2.8%). It was assumed that, when these terms are used in the context of drug administration, the intention was to learn about teratogenicity.

### 3.3.4 Lactation

Drugs used for the treatment of a breast feeding mother are classified into four groups (numbered I to IV). Group I includes drugs that do not permeate into breast milk at all; drugs of group II permeate into milk but do not affect infants at therapeutic doses; drugs of group III may affect the infant in the concentration found in milk when therapeutic doses are used; no information is available on drugs in group IV (Berglund et al., 1984). However, this classification was disregarded here because the number of questions on lactation was small.

The mechanism of drug transfer into milk, which depends essentially on transmembranal diffusion, is influenced by several factors: maternal plasma concentration, pH of the milk, the amount of milk consumed by the infant, intestinal absorption and drug metabolism in the infant (Berglund et al., 1984).

The Oxford Dictionary defines lactation as "production of milk from breasts or udders" and breast feeding as "feeding a baby from the breast". At the Tel-Aviv centre, most inquirers used the term "lactation", while at Newcastle the term "breast feeding" was prevalent. Although the terms are essentially different, it is obvious that they were used interchangeably.

**Miscellaneous remarks**

In addition to the subjects discussed so far, other aspects exist which have been assembled in the present analysis under the title "miscellaneous remarks" (Appendix A). Some of the inquiries were non-judgmental, for example,: topical use, blood concentration, etc. Several questions address specific aspects of drug which were used: "follow-up studies on infant" or "effect on uterus".

Questions on environmental pollutants or natural products sold over-the-counter were found only in the Newcastle centre. About one third of the inquiries to the Tel-Aviv centre, contained a specific request for human or animal studies.

## 3.4 Conclusion

The results of content analysis of the inquiries are clusters of categories, which enable to discern a clear and homogenous structure of question. In most questions, one facet deals with the drug itself and another with pregnancy or lactation. Some questions showed an additional facet, focusing on specific aspects of the characteristics of a given drug. Comparison of the inquiries between Tel-Aviv and Newcastle showed similar patterns, but some differences could be discerned as follows:

a) The use of proprietary names was much wider at Tel-Aviv, with a tendency towards searching drugs of similar activities.
b) In both centres, a bell-shaped distribution of questions with regard to risk factors (A-D,X) was observed, the majority of queries being on drugs in category C, use of which is problematic.
c) At the Tel-Aviv centre, a more specific terminology was often used with regard to the target of the risk, such as embryo, fetus and teratogenicity. At the Newcastle centre, the general term "pregnancy" was used more often. This tendency is probably an indication of the different population of physicians addressing the centres that is, mostly general practioners at Newcastle and mostly Gynaecologists-Obstetricians at Tel-Aviv.

# Chapter 4

# Focus Group Interview

## 4.1 Methodology

Focus group interview (FGI) was one of the methods employed in order to find out the information needs of physicians, along with their attitudes and drug prescription patterns. Finding out how they were obtaining information for use when reaching decisions in this context was another important goal.

FGI is a qualitative research technique, effective in small groups, for obtaining data about feelings and opinions of individual participants regarding a given issue, for example, a problem, a service or a product (Basch, 1987). In practice, groups of the target population are assembled for guided discussions about the subjects of interest. By responding to pointed questions, participants reveal important clues to their decision-making processes and choice criteria.

FGI ingredients were summarized by Krueger (1988, p. 27) as "(a) people, who (b) possess certain characteristics, (c) provide data (d) of a qualitative nature (e) in a focused discussion". Qualitative research is often said to provide the facts and hypotheses to be later validated by quantitative methods. Patton (1987, pp. 51-52) defines the difference between quantitative and qualitative sampling studies. The power of FGI, he says, lies in selecting information-rich cases by purposeful sampling for in-depth study.

Calder (1977) identifies three different approaches to FGI:

a) **Exploratory** - acquires pre-scientific knowledge, for example, pilot testing for the generation of hypotheses or ideas.

b) **Clinical (judgmental)** - generates quasi-scientific knowledge and constructs by applying scientific theory to explain human behaviour, without using quantitative measurements.

c) **Phenomenological** - provides a systematic representation of everyday knowledge as grasped subjectively by individuals. FGI introduces a social factor into this approach by causing interactions among participants and between them and the moderator.

FGI should not be confused with the technique known as "brainstorming" (BS). The two seem similar - both being based on the convening of several professionals for an intensive discussion; they differ profoundly, however, in their goals, the end-product and the manner in which the discussions are conducted. While FGI aims at eliciting the knowledge, opinions or the feelings of the participants, the purpose of BS is to attack a given problem with a "collective brain" by recruiting the mental resources of capable individuals in an interactive and co-ordinated fashion (Telem, 1988).

The group situation has several advantages. Folch-Lyon and Trost (1981) note that participants are encouraged to disclose behaviour and attitudes that they might not consciously reveal in an individual interview. Higginbotham and Cox (1979, pp. 17-18) emphasize the main characteristics of FGI as being the only research technique in which the subjects (the participants in the research) are encouraged to interact with each other. In most other types of social research, too much discussion among participants is considered as a possible source for distortion of results.

The technique had been discussed some decades ago, but recognition of its value came only later. FGI is applied primarily by marketing research organizations to collect data from consumers, but serves also as a research tool in a variety of other human activities, such as health care services, pre-testing public education material and, in general, to gain insight on attitudes of specific population subgroups.

FGI has been employed for a number of applications in Library and Information Sciences: online searching by the end user (Schwerzel, Emerson & Johnson, 1982), users advisory groups in the online industry (Van Camp, 1992), users evaluation of library service (Widdows, Hensler & Wyncott., 1991), and others.

Basch (1987) suggests to assemble groups that are homogenous with respect to demographic, socio-cultural or other common characteristics. Higginbotham and Cox (1988, pp. 38-39) suggest that FGI should limit the number of participants, as large groups are much more difficult to control than small ones, and it is often hard to stimulate an effective group interaction in a large heterogenous gathering. The recommended group size is eight to ten participants.

An outline of the topics to be discussed should be prepared carefully. The success of this technique partially relies on the moderator's skill in inspiring a relaxed and supportive atmosphere, thus encouraging interactions among group members and expression of individual views. FGI should be recorded and transcribed for content analysis.

Goldman (1962) points out the advantages of leading FGI with physicians, the target population in this study: due to the many constraints on their time, it is difficult to interview them at length as individuals. However, in group discussions with other physicians on topics that raise their interest, they seem more inclined to cooperate and are less impatient. Simon (1987) cautions against inadvertently challenging the physicians' authority, which they take for granted, and advises the moderator to "speak their language".

Four Gynaecology & Obstetrics departments, each in a teaching University Hospital in central Israel, were selected for this study. All four are involved in teaching undergraduate medical students and residents. Each department has twenty to thirty physicians, some in rotation, servicing about thirty beds. In addition, each department

has developed ambulatory outpatient clinics such as high risk pregnancy clinics, oncology and specialized emergency services.

Owing to the physicians' heavy workload, the group interviews took place during the weekly staff meeting in the departmental seminar room. Any deviation from the weekly routine would have reduced attendance. About twenty to twenty five physicians participated in each focus group. They were notified about the meeting a few weeks in advance. Seating during the meeting was around the room, in an informal atmosphere. The discussions were led by one moderator who kept visual contact with all participants. The discussion was recorded, and notes of significant remarks were taken. Each group interview lasted about ninety minutes.

At the beginning of each meeting, all participants were handed a written explanation of the purposes of the research project, stressing the importance of each participant voicing his/her views (Appendix C.1). In addition, each participant received a list of questions, such as "which of the following drugs are safe for use during pregnancy?" That question was followed by a list of drug names, from which one had to choose the appropriate answers. The purpose of this short pre-test was to introduce the group into the atmosphere of the discussion that was to follow.

Two sources of information were presented to the participants, reflecting two methods of answering questions such as the one mentioned above. One type of source summarizes the professional literature and includes a mini-review about each drug, for example, Briggs' "Drugs in Pregnancy and Lactation". The other type of source comprises pharmacological data banks, such as BIAM (Banque d'informations automatisee sur les medicaments), which report briefly on the prevalence of given birth defects.

The focal points of the discussion were:

1. Problems requiring information.
2. Types of information requested.

3. Situations in which information is required and the urgency in obtaining it.
4. Updating and follow-up.
5. Sources of information and their reliability.
6. The professionals whom the participants consult.
7. Persons who consult with the participants.
8. Requirements regarding a computerized database.

The discussion of the above points was guided by questions such as: "How do you know that a drug you prescribed to a pregnant woman is safe?", "When in doubt, what do you do?". During the discussion, unexpected questions emerged without disturbing the logical sequence of points under consideration. The proceedings of the discussions were recorded on audio cassettes and then transcribed. It should be noted that the topics brought up were stimulating and participation was lively.

Content analysis was performed on the transcription according to key ideas, in order to formulate categories of subject matter. The quotations for each category are given verbatim in Appendix C.2 as the raw data being marked only by the department (denoted by a letter), without reference to individuals. Items which have been mentioned repeatedly were noted only once, so more raw material is found in the first departments interviewed.

## 4.2 Summary and Analysis of Focus Group Interview

Summarized below (sections 4.2.1 - 4.2.8) according to the points of dicsussion are the essential views and wishes that were expressed by participants in the Focus Group Interview discussions.

### 4.2.1 Problems requiring information

Fifty years ago, no drugs were given routinely in pregnancy; today, however, every pregnant woman receives at least iron and vitamins, which are not commonly

regarded as drugs but are such nonetheless. Many chemicals are ingested in food and we are all exposed to atmospheric radiation, yet there is no proportional increase in birth defects in the human population. As a result, physicians are less apprehensive about prescribing drugs in pregnancy. Diabetes mellitus is a good example: in the past, diabetic women were strongly advised against child bearing, while nowadays they are treated with insulin. Physicians should bear in mind, though, that the relative reduction in birth defects is due, in part, to the development of better pre-natal diagnosis, and also that the protocols for testing drugs for toxicity and teratogenicity prior to their release have been significantly improved.

The clinical situations in which drug administration is indicated may be categorized as follows:

1. Life-threatening problems or malignant diseases.
2. Urgent vaccination (for example, yellow fever for a traveller to Africa).
3. Acute conditions (for example, urinary and respiratory tract infections).
4. Chronic diseases requiring continuous medication (for example, epilepsy, diabetes, thyroid disorders).

The different categories require different types of information: for categories 1 and 2 priority is given to urgent health problems of the woman, whereas most problems requiring detailed information arise in categories 3 and 4. In any case, information is needed whenever a drug is vital for treatment of a pregnant woman.

The use of teratogenic drugs is not permitted, except for emergency situations for the pregnant woman. Some drugs are used because a long cumulative experience points to their safety. Drugs are classified according to their risk factor to the fetus, from A to D and X, by increasing order of risk (Berglund et al., 1984). The most controversial drugs are classified C or D, and are the ones requiring information for the most part. These are also the drugs whose use is prone to litigation. The same is true for the use of new drugs, for example, new types of antibiotics. When there is no information

about a specific drug, it may prove useful to refer to the information available on the generic group to which the drug belongs.

Unexpected situations give rise to difficulties in providing relevant information, as in the case of snake bites or ingestion of toxic materials.

When a pregnant patient reports post factum that she has taken a drug or another chemical, detailed information about the drug or the chemical must be sought before a decision is made whether to induce abortion or not.

### 4.2.2 Types of information requested

The drug information requested by the physicians is the "state of the art" information related to drug toxicology and teratogenicity.
Opinions differ on the nature of the subjects to be included in a drug review or update and about the scope of the necessary information.
For example, when no information is available on effects in humans, opinions vary as to the usefulness of including animal teratogenicity studies as indicative against the use of the drug.
Dosages administrated to animals in these experiments are very high and extrapolation to humans is often not valid.
The risk for humans can be evaluated hypothetically, but can not be confirmed by experimental and statistical data. Still, some gynaecologists/obstetricians emphasized that such information is of some value for decision making.

It is important to compare the number of case-reports on malformations following drug ingestion in pregnancy with the data on spontaneous prevalence in the general population.

It has been noted that case reports can prevent misinterpretation of data about malformations and can be valuable if they enable exact determination of the

gestational age in which malformations were induced, thus focusing the tools for pre-natal diagnosis. One should distinguish between malformations that affect the whole system, such as the central nervous system, and minor defects that can be treated successfully later .

Information requirements are mostly concerned with drugs whose safety record is equivocal. Even when statistical data are available, significance is difficult to evaluate and only specific qualitative information can assist in decision making. Regarding drugs with controversial safety data, citations from the literature are needed to support any view on their use.

Information should be very precise, for example, not "early pregnancy" but the exact gestational week. The definition of teratogenicity should describe in detail the defects and should specify the body system or organ in which they occurred. All noted side effects which are possibly related to the given drug might be relevant (for example, fetal respiratory disorder).

Details about drug dosage are of special importance because the blood volume of the pregnant woman increases and metabolic changes also occur. For some drugs, such as aspirin, a large body of data has been accumulated, but final conclusions about their safety has not been reached. Nevertheless, available comprehensive information facilitates decision making. The mini-reviews in Briggs' book are insufficient. Sometimes only a short and easily obtainable answer is required, but more often the relevant literature or the abstract of an article are required. All this is true, provided the material is readily available.

Finally, inquiries on drugs are motivated by professional curiosity, the need to make a clinical decision, or medico-legal needs.

### 4.2.3 Situations in which information is required and the immediacy in obtaining it

Drug information should always be available in all medical facilities where pregnant and lactating women are treated. This includes primary care and follow-up at outpatient clinics, inpatient wards and well-baby clinics.

The availability of information is a critical issue: its absence inevitably leads to over-caution in treatment policy. In addition, one can utilize the available information on a family of drugs to make a judgement about a specific unknown compound from the same family.

Disregarding the patient's anxiety, the urgency of obtaining information on a given drug depends on the type of the medical problem. When the woman is in a life-threatening situation, the whole issue of the risk to the fetus becomes irrelevant. In situations where the patient has already taken a medication, a delay of one to three days until information is gathered is not significant.

### 4.2.4 Updating and follow-up

Routine updating is usually achieved by a regular screening of the current literature and other sources, gathering relevant articles or information items on new medications and their use in pregnancy. Usually, from such readings, only outstanding articles or facts that are bound to have a major practical impact are remembered, for example, the studies on diethyl stilbestrol (DES).

For specific cases, one may accumulate data by carefully recording all medications in the pregnant woman's file and to follow up the outcome. This approach can significantly improve the knowledge on the use of drugs in pregnancy, but it is often impractical, due to logistic and budgetary constraints.

### 4.2.5 The sources of information and their reliability

The sources of information available today are the following: special printed publications, for example, "Drugs in pregnancy and lactation" by Briggs, periodic leaflets with updated and summarized information, pharmacological literature and the Martindale Pharmacopeia. In addition, there are usage databases like MEDLINE on CD/ROM or the IOWA system, various professional journals such as the *American Journal of Obstetrics and Gynecology* or *Clinical Obstetrics and Gynecology.* Courses in continuing education at a medical school are another source of information.

Some prefer to start seeking information by searching the literature and if they do not find the answer, to consult with a colleague. Others find consultation with colleagues the most efficient and time saving method. Doubts have been expressed about the reliability of information provided by the pharmaceutical industry. Usually, out of medico-legal considerations, the company leaves a very wide safety margin: when a drug company declares a product safe, physicians feel confident in prescribing it; but sometimes a drug is prescribed despite precautionary advice issued by the manufacturer.

Some books, such as Briggs, note whether the information cited is provided only by the drug company. Some physicians ask the manufacturer for references regarding the safety of use of a drug so as not to depend solely on the information it provides. It is generally agreed that the FDA approval represents the most authoritative safety testing record to rely upon. This approval also supplies the best medico-legal cover.

### 4.2.6 Professionals whom the participants consult

Consultations have become more and more interdisciplinary, yet the gynaecologists/obstetricians are the ones who make the final decisions about administration of drugs to pregnant women.

The gynaecologists/obstetricians trust senior colleagues who show special interest in the subject and compile data about drugs, or those who are members of the committee for approving induced abortions. Specialists in the field of the pregnant woman's disease will contribute the appropriate information (for example, epilepsy will be treated by a neurologist). Other specialists that are consulted on the subject are geneticists, teratologists, embryologists, pharmacists, pharmacologists and neonatologists (for lactation). Some of the specialists are consulted in the same hospital, while others - by calling a centre which provides an information service about teratogenicity and toxicity of drugs.

### 4.2.7 Persons who consult with the participants

The obstetrician provides information to other professionals, such as internists, family physicians and often dentists (who are not interested in details), and actually to any health delivery official who has some contact with the woman during pregnancy and lactation.

The other major group of information consumers includes the patients and their spouses. In modern medical practice, the physician is expected not to impose decisions but rather to provide the maximum available information. Whenever data on the safety of a given drug are incomplete, the woman or the couple in question should participate in the decision making process, regardless of their level of education. The final decision is influenced also by factors such as the patient's personality and the medical characteristics of the pregnancy.

### 4.2.8 Requirements regarding a computerized database

The following opinions were expressed regarding theme of computerized database:

- There is a general preference to use computerized data banks to obtain information.
- There is no reason to use a computer in front of the patient.
- The material in the data bank should be organized in a modular system, in which searching can be targeted and selective.
- The information should be stored in a textual manner, in tables and in graphs, with data about the incidence and prevalence of defects in the population that has received the drug as compared to controls.
- The organs of the fetus mostly at risk in relation to the gestational age should be listed.
- Reviews of the subject are important and a bibliographic list should be added.

**Miscellaneous remarks expressed by the Focus Group Interviews participants**

Attitudes concerning prescription of drugs differ. Conservative physicians approach with apprehension the administration of all drugs with doubtful safety record until the 13th week of gestation. During lactation, the attitude is more liberal. Certain drugs, though known to be slightly teratogenic, are still widely prescribed.

Often, the long term effects of drugs can not be predicted from presently available information. It is not possible to predict how a substance absorbed by the fetus during gestation will affect the adult developed from that fetus. These problems can be solved only at the molecular biology level or through long-term epidemiological studies.

## 4.3 Conclusion

A rich and complex picture of information needs of the participants was obtained in the FGIs. The decision about the number of groups to be formed was made according to criteria of structuring a setting in which maximum information is generated. In this study, four groups were used to gain insight about the variables of the research. The individual contribution of each participant to the process could not be determined, but the overall impression was that all members of the groups became actively involved in the discussion and interacted effectively among themselves. This resulted in generation of new ideas, as expected from efficient implementation of the FGI technique.

By ensuring a structured discussion within the user group, it is possible to understand the information requirements and the difficulties the target population encounters in obtaining it.

The following main objectives were achieved:

1. Specification of information needs.
2. Identification of problems and constraints in the current use of drugs information by the population which was studied.
3. Recognition and discovery of information needs and sources.
4. Preferences and prejudices in the use of information sources.

The results obtained are of value in themselves, but here they were used to provide the basic information for the questionnaire development, which was the next step of the study.

# Chapter 5

# The Questionnaire

## 5.1 Methodology

Questionnaires, accompanied by an explanatory letter, were sent to 959 gynaecologists/obstetricians in Israel. In order to encourage a high percentage of response, attention was given to small details of convenience: the size of the envelope complied with Israeli post standards to ensure home delivery; a self addressed stamped envelope was included; the physicians were given a month to return the filled questionnaire. Reminders were sent after a month, and telephone calls were made to several dozens of questionnaire recipients.

## 5.2 The Structure and Content of the Questionnaire

The questionnaire was constructed according to the results of the focus group interviews and the outcome of the user studies. The questions were composed with the goal of addressing the following issues: the situations in which drug information is required, physicians' attitudes towards drug use during pregnancy and lactation, the means of updating on drugs (referring to printed material, computerized sources and formal and informal meetings), and the availability and reliability of the sources of information.

In order to construct a physician's profile, details were requested about their institution of study, place of work, age, etc. One chapter in the questionnaire is devoted to the desired type and form of presentation of the information in a computerized database for drugs.

Most questions are closed, but some of them offer the option to add a free form answer. The complete questionnaire appears in appendix D.

### 5.2.1 Pre-test of the questionnaire

Questionnaires were given to twenty one gynaecologists/obstetricians for pre-testing, mainly in order to check the clarity of formulation of the open-ended questions and also the time needed to answer all the questions. Consequently, some changes were made: since the minimal time required to complete the questionnaire was 20 minutes, a group of questions with a marginal contribution to the study was eliminated. In Hebrew, verbs and nouns are conjugated to gender. The questionnaire was originally written in masculine form to simplify the phrasing, but was altered to comply with a request (from a male) to include feminine form too.

## 5.3 The Population of Respondents

Three hundred and three gynaecologists/obstetricians , 34% of the target population, returned the completed questionnaires. Nine questionnaires were not deliverable due to wrong addresses; seven were returned by recipients who did not understand the language (Hebrew); three were returned uncompleted, as the function of the addressees was not suitable to the subject of the research. Altogether, 2% of the returned questionnaires were not completed.

To detect whether a bias has been introduced, a comparison was made between respondents and non-respondents in the following criteria: sex, geographical area (according to telephone area codes) and the principal place of work (hospital, public clinic, private clinic). These were the only criteria available in the original list of gynaecologists/obstetricians . The results are presented in Table 4. The majority of gynaecologists/obstetricians are men (see also the following section - 5.3.1). The distribution of the respondent population according to work-place was similar to the total gynaecologists/obstetricians population, with a slight over-representation of practitioners in hospitals and under-representation of those who work in public clinics (Table 4).

To conclude, the respondent population represents well the total population which was studied. It should be noted, that the present survey is an analytic-relational one (Oppenheim, 1992, pp. 12-13) and its purpose is to explore the relationships between particular variables, to find associations between them, to suggest explanations etc. In such a survey, a high degree of representation of the total population is not necessary.

Table 4: **Distribution of the respondents and total population according to gender (a), geographical area of Israel (b) and major place of work (c)**

(a)

| Gender | Total population | Population of respondents |
|---|---|---|
| Males | 800<br>83.5% | 272<br>91.3% |
| Females | 158<br>16.5% | 26<br>8.7% |
| Total | n=958 | n=298 |

(b)

| Geographical area | Total population | Population of respondents |
|---|---|---|
| North | 288<br>30.1% | 76<br>25.2% |
| Centre | 524<br>54.7% | 164<br>54.5% |
| South | 146<br>15.2% | 61<br>20.3% |
| Total | n=958 | n=301 |

(c)

| Place of work | Total population | Population of respondents |
|---|---|---|
| Hospital | 684<br>71.4% | 215<br>87.1% |
| Public Clinics | 232<br>24.2% | 24<br>9.7% |
| Private Clinics | 42<br>4.4% | 8<br>3.2% |
| Total | n=958 | n=247 |

### 5.3.1 Characteristics of the population of the respondents

The population of the respondents is described according to the following characteristics: age, sex, country of studies and place of work. Age - the youngest physician was 30 years old and the oldest was 82. The mean age was 43.5±9.6 years and the median 40 years. Sex - the percentage of women who had answered the questionnaire is low (8.7%), therefore, all tests were performed without taking into consideration the sex factor.

Place of study - 169 physicians (55.8%) had graduated from medical schools in Israel; 81 (26.7%) had graduated abroad and 50 studied both in Israel and abroad. This last group included mainly new immigrants and students who started their studies abroad and completed them in Israel. The majority of gynaecologists/obstetricians, 227 (74.9%), had finished their specialization in Israel. Only 25 physicians (18.3%) had finished abroad and 36 (11.9%) started their specialisation in one country and finished it in another, mostly in Israel. Nine respondents (3%) had not yet received their final diploma. The majority of physicians, 215 (87.1%), worked in hospitals. Amongst them 82 (33.2%) worked, in addition, in a clinic. Only 24 clinicians (9.7%) worked in public clinics and a minority of 8 physicians (3.2%) worked in private clinics.

## 5.4 Statistical Analysis of the Results

The answers to the questionnaire were analysed statistically using SPSS 3.1.

The following statistical tests were used in the analyses (Guilford & Fruchter, 1973; Winer, 1971):

a) T-test for independent samples which tests whether the difference between two samples is significant.

b) One-way analysis-of-variance (ANOVA) which tests whether n independent samples are significantly different. This is followed by a Duncan procedure which compares all pairs of group means to test whether there is a significant difference between them.

   This procedure is therefore, more general than the T-test which is suitable only for two samples.

c) $\chi^2$ - tests the significance of relationship between two independent samples which are measured by a non-parametric scale.

d) Pearson co-efficient of correlation is the degree of correlation between two variables, measured by an interval scale.

In order to perform the analysis, groups of questions having the same characteristics were cumulated to meaningful statistical measures which are presented in Table 5. Most measures belong to common subjects: means of updating, reliability of sources, attitudes to drug prescription, and personal data. The following information is given in the table for each measure: the cumulated questions which were used to build it; the range of scores of the measure; the method of calculating the measure from the questions (denoted by a letter); and the page number in the questionnaire in which these questions appear (for convenience of reference). The method of calculating the measure depended on the questions which were included: measures comprising a single question took the value of the answer (denoted by V); for some questions having a range of values, the mean was calculated (M); several groups of questions involved the counting of the total number of positive answers (C); for other questions addressing a single issue, the percentage of positive replies was computed (P).

Table 5: **The statistical measures of cumulated questions which were used in the analysis**

| Measure | Questions included in the measure | Range of scores | Method of calculating the measure | Page no. in the questionnaire |
|---|---|---|---|---|
| Means of updating | | | | |
| - books and journals | A6, A7,A10-A12 | 1 - 6 | M | 1 |
| - material provided by drug companies | A8, A9 | 1 - 6 | M | 1 |
| - participation in meetings | A20 - A23 | 1 - 6 | M | 1 |
| - consultation with colleagues | A27 - A31 | 1 - 6 | M | 2 |
| - use of computerized databases | A36 - A44 | 0 - 9 | C | 2 |
| Reliability of sources | | | | |
| - books | A47, A48, A50 A53, A55 | 0 - 100 | P | 3 |
| - meetings | A56 - A58 | 0 - 100 | P | 3 |
| - drug companies | A49, A59 | 0 - 100 | P | 3 |
| - local pharmacopoeia | A49, A51 | 0 - 100 | P | 3 |
| - bibliographic tools | A54 | 0 - 100 | P | 3 |
| Availability of information sources | A60 - A62, A66, A72, B07 | 0 - 6 | C | 3 - 4 |
| Initiative in obtaining information | A64, B08, B10, B11,B12 | 0 - 5 | C | 3 - 4 |
| Situations in which information is required | B17 - B21 | 1 - 4 | M | 4 |
| Frequency of drug prescription | B25 | 1 - 4 | V | 5 |
| Attitudes to drugs prescription - in pregnancy | B30 | 1 - 4 | V | 5 |
| - in lactation | B31 | 1 - 4 | V | 5 |
| Personal Data | | | | |
| Major workplace | B66 | 1 - 3 | V | 7 |
| Is the department affiliated to medical school ? | B67 | 1 - 2 | V | 8 |
| Geographical area (phone code) | B70 | 1 - 3 | V | 8 |
| Country of studies of medicine | B71 | 1 - 3 | V | 8 |
| Country of specialization in obstetrics | B72 | 1 - 3 | V | 8 |
| Academic status | B73 | 1 - 2 | V | 8 |
| Age | B76 | 1 - 2 | V | 8 |

### 5.4.1 The means for keeping up to date and the frequency of their use

The various sources of information and means for keeping up to date have been divided into four categories: printed publications, formal and informal meetings, consultation with colleagues, and machine readable databases.

Table 6 shows the percentage of physicians who stated that they use an update method either "often" or "very often" (i.e. the first two grades on a scale of 1-6 as appears in the questionnaire); the items in each category are arranged in the table in descending order of frequency of use. In the category of printed publications three groups of sources can be recognized: the first three sources are used frequently by more than two thirds of the physicians; books and advertisements are frequent sources for approximately half of the physicians; and the remaining sources are turned to by less than a third of the physicians.

An interesting observation regarding the categories of printed publications and meetings is the prominence of drug companies as sources of information which can be seen in the prospectuses and advertisements of the companies and in meetings with their representatives.

Finally, in consulting with colleagues, the physicians show a clear preference for obstetricians over other relevant professionals.

Table 6: **The means for keeping up-to-date and the frequency of their use**

| PRINTED PUBLICATIONS | very often and often % |
|---|---|
| Journals in Obstetrics | 85.1 |
| Prospectuses of drug companies enclosed with the drug | 68.8 |
| Current awareness leaflets | 67.8 |
| Books in Obstetrics | 50.3 |
| Advertisements of drug companies in professional journals | 45.2 |
| Local journal in medicine | 28.7 |
| General journals in medicine | 25.9 |
| Bibliographic tools (e.g. Index Medicus) | 17.7 |
| Books in pharmacology | 13.7 |
| Journals in pharmacology | 6.8 |
| FORMAL AND INFORMAL MEETINGS | |
| Representatives of drug companies | 51.5 |
| Professional conferences | 36.3 |
| Staff meetings | 20.8 |
| Seminars | 14.3 |
| CONSULTING COLLEAGUES | |
| Obstetrician | 82.4 |
| Teratologist | 28.6 |
| Pharmacist | 26.5 |
| Geneticist | 18.6 |
| Microbiologist | 15.6 |
| Pharmacologist | 12.0 |
| Embryologist | 10.4 |
| Machine readable databases | 51.3 |

### 5.4.2 The relation between reliability and availability of information and the frequency of information use

A Pearson coefficient of correlation has been computed between each measure of information use and the following two measures: the availability and the reliability of information sources as evaluated by the physicians. The results (presented in Table 7) show that the availability of information is significantly related to the frequency of use of databases, consultations and also meetings as sources of information. The availability of printed and advertised publications were not found to be correlated to their frequency of use. In contrast to the availability of information, reliability is only weakly related to the frequency of its use.

Table 7: **The relation between availability, reliability and the use of information**

| Measure | Reliability | Availability |
|---|---|---|
| printed publications | .12* | .06 |
| advertised publications | .06 | .02 |
| meetings | .12* | .13* |
| consultations | .09 | .28** |
| databases | -.11 | .35** |

* $p<0.05$ ** $p<0.01$

### 5.4.3 The relation between information usage and attitudes toward drug administration

In order to examine the relationship between the information usage by physicians and their attitudes towards drug administration, the following analysis was performed. The physicians were divided into four groups of attitude according to their reply to the questionnaire: group A included physicians who held a negative attitude towards drug administration; group D represented physicians who were in favour of drug

administration; and groups B and C, included physicians who approved of prescribing drugs either under the restriction of taking appropriate measures (group B) or on the condition of consulation with an expert (group C). This was done separately for pregnancy and for lactation. The four groups were compared on all measures of information usage by one-way ANOVA with Duncan procedure. The results (presented in Table 8) reveal that physicians who believe that pregnant women should not be given drugs (group A) use less information than the other groups: they conduct fewer searches in databases, make fewer consultations, and they evaluate information as less available as compared to the other groups. No differences have been found between the groups with respect to reading of advertised publications, participation in meetings and in seeking information.

Table 8: **Measures of information usage in four groups of attitude towards drug administration in pregnancy**

| measure<br>N | | A=1<br>(22) | B=2<br>(64) | C=3<br>(80) | D=4<br>(137) | Duncan<br>p<0.05 |
|---|---|---|---|---|---|---|
| printed publications | M | 3.76 | 4.15 | 4.23 | 4.09 | A<B,C,D |
| | SD | 0.74 | 0.66 | 0.70 | 0.71 | |
| advertised publications | M | 4.70 | 4.49 | 4.70 | 4.47 | A=B=C=D |
| | SD | 1.24 | 0.98 | 0.87 | 1.00 | |
| meetings | M | 3.68 | 3.86 | 3.88 | 3.83 | A=B=C=D |
| | SD | 0.95 | 0.70 | 0.81 | 0.89 | |
| consultations | M | 2.66 | 3.06 | 3.31 | 3.18 | A<B,C,D |
| | SD | 1.01 | 0.78 | 0.79 | 0.75 | |
| databases | M | 0.90 | 2.17 | 2.35 | 2.42 | A<B,C,D |
| | SD | 1.74 | 1.98 | 1.87 | 2.02 | |
| availability | M | 1.59 | 2.60 | 2.58 | 2.57 | A<B,C,D |
| | SD | 1.14 | 1.36 | 1.26 | 1.11 | |
| initiative in seeking information | M | 2.00 | 2.29 | 2.27 | 2.29 | A=B=C=D |
| | SD | 0.81 | 0.93 | 0.91 | 0.85 | |

The results regarding lactation (presented in Table 9) were similar to those in pregnancy. The physicians who advocated giving drugs to lactating women in restricted situations (groups B,C) required more information than those who did not administer drugs at all (group A); in particular, the latter made fewer consultations, they conducted fewer searches in databases, they evaluate the information as being less available as compared to the other groups and also, they had less initiative in seeking information. In contrast to pregnancy however, there was no significant difference between physicians who administered drugs always (group D) and those who did not (group A). No differences were found between the groups with respect to reading of printed and advertised publications and participation in meetings.

Table 9: **Measures of information usage in four groups of attitude towards drug administration in lactation**

| measure<br>N | | A=1<br>(10) | B=2<br>(65) | C=3<br>(84) | D=4<br>(144) | Duncan<br>p<0.05 |
|---|---|---|---|---|---|---|
| printed publications | M | 4.02 | 4.25 | 4.13 | 4.06 | A=B=C=D |
| | SD | 0.72 | 0.54 | 0.74 | 0.75 | |
| advertised publications | M | 4.75 | 4.43 | 4.52 | 4.61 | A=B=C=D |
| | SD | 1.55 | 0.97 | 1.02 | 0.92 | |
| meetings | M | 3.57 | 3.90 | 3.81 | 3.84 | A=B=C=D |
| | SD | 0.61 | 0.73 | 0.77 | 0.93 | |
| consultations | M | 2.96 | 3.11 | 3.36 | 3.06 | A<C,B=D |
| | SD | 0.71 | 0.71 | 0.75 | 0.86 | |
| databases | M | 0.90 | 2.50 | 2.46 | 2.08 | A<B;C,D=A,B,C |
| | SD | 1.91 | 1.97 | 1.91 | 2.00 | |
| availability | M | 1.40 | 2.72 | 2.66 | 2.58 | A<B,C,D |
| | SD | 1.64 | 1.30 | 1.14 | 1.20 | |
| initiative in seeking information | M | 1.90 | 2.43 | 2.11 | 2.31 | A<B;C=D |
| | SD | 1.10 | 0.86 | 0.85 | 0.88 | |

### 5.4.4 The relation between the background variables and the usage of information

The physicians were divided into four groups according to their working place, and the four groups were compared according to information needs by means of one-way ANOVA and Duncan procedure. The results (presented in Table 10) show that the physicians who work in hospitals (groups A and D) report a greater need for information: they conduct more searches in databases, they turn to consultations more frequently, they want more detailed information and they are more active in seeking it.

No differences between the groups were manifest in participation in meetings and in reading of advertised material.

Table 10: **Measures of information usage and needs in four groups of physicians divided according to their working place**

| measure<br>N | | Hospital & Clinic A<br>(133) | Public Clinic B<br>(24) | Private Clinic C<br>(8) | Hospital D<br>(82) | Duncan<br>p<0.05 |
|---|---|---|---|---|---|---|
| printed publications | M | 4.14 | 4.05 | 2.82 | 4.13 | A,B,D>C |
| | SD | 0.71 | 0.71 | 0.77 | 0.66 | |
| advertised publications | M | 4.40 | 4.54 | 4.93 | 4.67 | A=B=C=D |
| | SD | 0.95 | 1.27 | 1.59 | 0.89 | |
| meetings | M | 3.79 | 3.77 | 3.56 | 3.92 | A=B=C=D |
| | SD | 0.83 | 0.86 | 0.94 | 0.87 | |
| consultations | M | 3.10 | 2.95 | 1.95 | 3.36 | A,D>B>C |
| | SD | 0.79 | 0.64 | 0.53 | 0.76 | |
| databases | M | 1.93 | 0.45 | 0.00 | 1.97 | A,D>B,C |
| | SD | 1.25 | 0.93 | 0.00 | 1.65 | |
| availability | M | 2.96 | 1.54 | 0.87 | 2.73 | A,D>B,C |
| | SD | 1.16 | 1.28 | 1.45 | 0.98 | |
| initiative in seeking information | M | 2.33 | 1.87 | 2.00 | 2.35 | A,D>B;C=A,B,D |
| | SD | 0.88 | 0.89 | 0.53 | 0.89 | |
| various situations and information needs | M | 2.66 | 2.55 | 2.27 | 2.67 | A,D>C;B=A,C,D |
| | SD | 0.45 | 0.47 | 0.48 | 0.47 | |
| require detailed information | M | 3.81 | 3.33 | 3.00 | 3.86 | A,D>B,C |
| | SD | 0.76 | 1.04 | 1.51 | 0.92 | |

In order to examine the dependence of information usage on the place of study, the physicians were divided into three groups and compared on all measures of information using one-way ANOVA and Duncan procedure.

The results (presented in Table 11) reveal that physicians who studied in Israel (group A) use more information and express a greater need for it than physicians who graduated abroad (group B). Physicians who studied both in Israel and abroad (group C) also require more information than those who graduated abroad, but the difference is not as strong as between physicians who studied in Israel only, and group C.

No differences were found between the groups with respect to participation in meetings and reading of advertised publications.

Table 11: **Measures of information usage and needs in four groups of physicians divided according to their place of study**

| measure<br>N | | Israel<br>A<br>(169) | Abroad<br>B<br>(81) | Both<br>C<br>(50) | Duncan<br><br>p<0.05 |
|---|---|---|---|---|---|
| printed publications | M | 4.22 | 3.92 | 4.10 | A>B;C=A,B |
| | SD | 0.69 | 0.74 | 0.60 | |
| advertised publications | M | 4.52 | 4.92 | 4.73 | A=B=C |
| | SD | 0.89 | 1.18 | 0.93 | |
| meetings | M | 3.87 | 3.74 | 3.86 | A=B=C |
| | SD | 0.84 | 0.84 | 0.80 | |
| consultations | M | 3.21 | 2.97 | 3.17 | A>B,C |
| | SD | 0.78 | 0.78 | 0.87 | |
| databases | M | 1.89 | 1.32 | 1.94 | A,C>B |
| | SD | 1.45 | 1.56 | 1.47 | |
| availability | M | 2.81 | 2.07 | 2.77 | A,C>B |
| | SD | 1.15 | 1.33 | 1.14 | |
| initiative in seeking information | M | 2.35 | 2.03 | 2.36 | B<A,C |
| | SD | 0.86 | 0.84 | 0.92 | |
| various situations and information needs | M | 2.67 | 2.54 | 2.75 | A,C>B |
| | SD | 0.42 | 0.46 | 0.47 | |
| require detailed information | M | 3.81 | 3.53 | 3.88 | A,C>B |
| | SD | 0.82 | 1.02 | 0.84 | |

In order to examine the relation between the teaching activity of a physician and his use of information, a t-test for independent groups was carried out between physicians who teach and those who do not on all measures of information usage. The results (presented in Table 12) show that physicians who teach use information much more than those who do not: they perform more searches in databases, consult more with others; they evaluate information as being more available and take more initiative in seeking information. No significant differences were found with respect to reading of printed and advertised publications, in terms of participation in meetings and the definition of situations in which information is needed.

Table 12: **Measures of information usage and needs of physicians who teach and those who do not**

| measure<br>N | | Yes<br>(181) | No<br>(122) | t value |
|---|---|---|---|---|
| printed publications | M | 4.16 | 4.05 | 1.34 |
| | SD | 0.61 | 0.81 | |
| advertised publications | M | 4.54 | 4.56 | 0.16 |
| | SD | 0.92 | 1.06 | |
| meetings | M | 3.88 | 3.77 | 1.16 |
| | SD | 0.75 | 0.95 | |
| consultations | M | 3.29 | 2.94 | 3.82 *** |
| | SD | 0.76 | 0.82 | |
| databases | M | 2.76 | 1.46 | 5.86 *** |
| | SD | 1.83 | 1.95 | |
| availability | M | 2.96 | 2.05 | 6.63 *** |
| | SD | 1.11 | 1.23 | |
| initiative in seeking information | M | 2.39 | 2.08 | 3.09 ** |
| | SD | 0.88 | 0.85 | |
| various situations and information needs | M | 2.67 | 2.62 | 0.93 |
| | SD | 0.43 | 0.46 | |
| require detailed information | M | 3.85 | 3.55 | 2.88 ** |
| | SD | 0.81 | 0.98 | |

** $p<0.01$ *** $p<0.001$

In order to examine the influence of working at a hospital which is affiliated to a medical school on the use of information, a t-test for independent groups was carried out between physicians who work at these hospitals and those who do not, on all measures of information usage.

The results (presented in Table 13) show that physicians who work at hospitals which are affiliated to medical schools use information more than those who do not, according to the number of searches in databases which they conduct and according to their evaluation of information as being more available. On the other hand, they participate less in relevant meetings. No significant differences were found between the two groups on the other measures.

Table 13: **Measures of information usage and needs of physicians who work at a hospital which is affiliated to a medical school and those who are not**

| measure<br>N | | Yes<br>(204) | No<br>(61) | t value |
|---|---|---|---|---|
| printed publications | M | 4.12 | 4.26 | 1.39 |
| | SD | 0.67 | 0.76 | |
| advertised publications | M | 4.56 | 4.41 | 1.12 |
| | SD | 0.90 | 0.98 | |
| meetings | M | 3.77 | 4.10 | 2.68 ** |
| | SD | 0.81 | 0.92 | |
| consultations | M | 3.26 | 3.12 | 1.16 |
| | SD | 0.77 | 0.90 | |
| databases | M | 2.04 | 1.49 | 2.62 ** |
| | SD | 1.42 | 1.55 | |
| availability | M | 2.98 | 2.09 | 5.67 *** |
| | SD | 1.06 | 1.10 | |
| initiative in seeking information | M | 2.36 | 2.24 | 0.95 |
| | SD | 0.91 | 0.72 | |
| various situations and information needs | M | 2.68 | 2.57 | 1.73 |
| | SD | 0.45 | 0.46 | |
| requirement for detailed information | M | 3.82 | 3.63 | 1.45 |
| | SD | 0.82 | 1.01 | |

** $p<0.01$ *** $p<0.001$

In order to examine the relation between age and the use of information, physicians were divided into those who are 40 years old and younger and those who are 41 and older (the median age). They were compared on all measures of information using a t-test for independent groups. The results (presented in Table 14) show no consistent and significant difference between the two age groups; the younger physicians evaluate information as being more available and read more printed publications, whereas the older physicians participate in more meetings.

Table 14: **Measures of information usage and needs of physicians and their relation to age groups**

| measure<br>N | | <40<br>(149) | 41<<br>(154) | t value |
|---|---|---|---|---|
| printed publications | M | 4.20 | 4.04 | 1.95 * |
| | SD | 0.75 | 0.66 | |
| advertised publications | M | 4.54 | 4.56 | 0.25 |
| | SD | 0.87 | 1.08 | |
| meetings | M | 3.74 | 3.93 | 1.96 * |
| | SD | 0.85 | 0.81 | |
| consultations | M | 3.07 | 3.23 | 1.73 |
| | SD | 0.82 | 0.78 | |
| databases | M | 2.31 | 2.16 | 0.64 |
| | SD | 1.92 | 2.05 | |
| availability | M | 2.76 | 2.43 | 2.33 * |
| | SD | 1.09 | 1.35 | |
| initiative in seeking information | M | 2.32 | 2.21 | 1.13 |
| | SD | 0.83 | 0.92 | |
| various situations and information needs | M | 2.66 | 2.64 | 0.32 |
| | SD | 0.44 | 0.45 | |
| requirement for detailed information | M | 3.74 | 3.72 | 0.17 |
| | SD | 0.84 | 0.92 | |

*$p < 0.05$

### 5.4.5 The relation between the attitude towards drug administration and the background variables

The three categories of attitude towards drug administration in pregnancy and during lactation were crosstabulated by each of the background characteristics and a $\chi^2$ test was carried out in order to examine the significance of the relation between them. In the following tables, the number of respondents corresponding to each cell appears on the left and the percentage in that column is given on the right hand side.

Table 15: **The attitude toward drug administration in pregnancy and during lactation and its relation to the place of work**

| Pregnancy | Hospital No. | % | Non-hospital No. | % | |
|---|---|---|---|---|---|
| A | 8 | 3.7 | 8 | 25.0 | $\chi^2 = 21.75$ |
| B+C | 97 | 45.1 | 14 | 43.8 | p<0.01 |
| D | 110 | 51.2 | 10 | 31.2 | |
| **Lactation** | **Hospital No.** | **%** | **Non-hospital No.** | **%** | |
| A | 2 | 0.9 | 6 | 18.7 | $\chi^2 = 28.47$ |
| B+C | 102 | 47.5 | 11 | 34.4 | p<0.01 |
| D | 111 | 51.6 | 15 | 46.9 | |

Table 15 shows that the two groups differ significantly in their attitude towards drug administration both in pregnancy and during lactation, a negative attitude (category A) being more common amongst physicians who do not work at a hospital, whereas a positive attitude (categories B+C, D) is more characteristic of hospital physicians.

The results (presented in Table 16) show that physicians who teach differ significantly in their attitude towards drug administration from those who do not teach, both in pregnancy and during lactation; conditional administration (category B+C) being the prevailing attitude amongst physicians who teach, whereas a negative attitude towards drug administration in pregnancy (category A) is more pronounced in the non-teaching group who also prefer unconditional administration during lactation (category D).

Table 16: **The attitude toward drug administration in pregnancy and during lactation and its relation to teaching activity**

| Pregnancy | Yes No. | Yes % | No No. | No % | |
|---|---|---|---|---|---|
| A | 3 | 1.6 | 19 | 15.5 | |
| B+C | 95 | 52.5 | 49 | 40.2 | $\chi^2 = 2.80$ |
| D | 83 | 45.9 | 54 | 44.3 | $p<0.01$ |
| **Lactation** | **Yes No.** | **Yes %** | **No No.** | **No %** | |
| A | 2 | 1.1 | 8 | 6.6 | |
| B+C | 103 | 56.9 | 46 | 37.7 | $\chi^2 = 14.92$ |
| D | 76 | 42.0 | 68 | 55.7 | $p<0.01$ |

As Table 17 shows, in pregnancy the tendency to prescribe drugs despite the risk (category D) is more frequent amongst physicians who work in a hospital which is affiliated to a medical school, whereas the frequency of conditional drug administration (category B+C) is higher in the other group of physicians. In lactation, no significant difference between the two groups of physicians was found with respect to their attitude towards drug administration.

Table 17: **The attitude toward drug administration of physicians who work at a hospital which is affiliated to a medical school, and those who do not**

| Pregnancy | Yes | | No | | |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| A | 5 | 2.4 | 4 | 3.6 | |
| B+C | 94 | 46.1 | 36 | 59.0 | $\chi^2 = 6.80$ |
| D | 105 | 51.5 | 21 | 34.4 | $p<0.05$ |
| **Lactation** | **Yes** | | **No** | | |
| | No. | % | No. | % | |
| A | 2 | 1.0 | 0 | 0.0 | |
| B+C | 105 | 51.5 | 31 | 50.8 | $\chi^2 = 0.62$ |
| D | 97 | 47.5 | 30 | 49.2 | $p<0.05$ |

Table 18 shows that amongst physicians who studied abroad (only), a negative view towards drug administration (category A) is more frequent and conditional administration (category B+C) is less frequent compared with physicians who studied in Israel, both in pregnancy and lactation.

Table 18: **The attitude toward drug administration in pregnancy and during lactation and its relation to the place of study**

| Pregnancy | Israel | | Abroad | | Both | | |
|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | |
| A | 6 | 3.6 | 12 | 14.8 | 3 | 6.0 | |
| B+C | 84 | 49.7 | 36 | 44.4 | 24 | 48.0 | $\chi^2$=10.77 |
| D | 79 | 46.7 | 33 | 40.7 | 23 | 46.0 | p<0.05 |
| **Lactation** | **Israel** | | **Abroad** | | **Both** | | |
| | No. | % | No. | % | No. | % | |
| A | 1 | 0.6 | 8 | 9.9 | 1 | 2.0 | |
| B+C | 87 | 51.5 | 33 | 40.7 | 29 | 58.0 | $\chi^2$=17.24 |
| D | 81 | 47.9 | 40 | 49.4 | 20 | 40.0 | p<0.01 |

The two age groups were compared in their attitude towards drug administration both in pregnancy and in lactation and were found to differ significantly (as shown in Table 19): a negative attitude (category A) is more frequent amongst older physicians, whereas a positive attitude (categories B+C,D) is prevalent in the younger age group.

Table 19: **The attitude toward drug administration in pregnancy and during lactation and its relation to physicians' age groups**

| Pregnancy | <40 | | 41< | | |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| A | 4 | 2.7 | 18 | 11.7 | $\chi^2$=9.21 |
| B+C | 73 | 49.0 | 71 | 46.1 | |
| D | 72 | 48.3 | 65 | 42.2 | p<0.01 |
| **Lactation** | **<40** | | **41<** | | |
| | No. | % | No. | % | |
| A | 0 | 0.0 | 10 | 6.5 | $\chi^2$=10.02 |
| B+C | 76 | 51.0 | 73 | 47.4 | |
| D | 73 | 49.0 | 71 | 46.1 | p<0.01 |

### 5.4.6 A typology of physicians

Based on the preceding analyses, a "typology" of physicians has been constructed. The term "typology" is used to define group characteristics and intergroup differences. Three dimensions have been used to define the groups:

a) place of work - hospital vs. non-hospital

b) teaching activity - yes or no

c) place of study - abroad only vs. in Israel or both,

yielding eight groups (2 x 2 x 2). The four groups of physicians who do not work in a hospital have been combined into one (denoted by E), because the number of physicians in each group was too small for statistical analysis. The final typology consists, therefore, of five groups: group E above, together with the following four groups which comprise physicians who work in hospitals:

| | | Place of Study | |
|---|---|---|---|
| | | Israel | Abroad |
| Teaching | Yes | A | B |
| | No | C | D |

The five groups were compared on all measures of information usage and needs by means of one-way ANOVA with Duncan procedure. The results (presented in Table 20) reveal that physicians who work in a hospital and teach (groups A and B) evaluate information as being more available, perform more searches in databases and turn to consultations more frequently than the other groups. Physicians who work in hospitals (all four groups A,B,C,D) read publications such as books and journals more than physicians who do not work in a hospital. The remaining measures did not yield significant differences between the five groups.

Table 20: **Comparison of typological groups with respect to information usage and needs**

| measure<br>N | | A<br>(96) | B<br>(55) | C<br>(35) | D<br>(29) | E<br>(32) | Duncan<br>p<0.05 |
|---|---|---|---|---|---|---|---|
| printed publications | M | 4.16 | 4.13 | 4.20 | 4.00 | 3.75 | E<A,B,C,D |
| | SD | 0.69 | 0.54 | 0.82 | 0.78 | 0.90 | |
| advertised publications | M | 4.51 | 4.54 | 4.37 | 4.56 | 4.39 | A=B=C=D=E |
| | SD | 0.88 | 1.02 | 0.90 | 0.79 | 1.36 | |
| meetings | M | 3.90 | 3.80 | 3.62 | 3.97 | 3.71 | A=B=C=D=E |
| | SD | 0.75 | 0.71 | 1.10 | 1.02 | 0.87 | |
| consultations | M | 3.29 | 3.26 | 2.94 | 3.08 | 2.70 | A,B>C,D,E |
| | SD | 0.78 | 0.76 | 0.79 | 0.80 | 0.75 | |
| databases | M | 2.75 | 2.85 | 2.17 | 1.55 | 0.50 | A,B>D,E |
| | SD | 1.79 | 1.77 | 1.97 | 1.90 | 1.16 | |
| availability | M | 3.05 | 3.12 | 2.51 | 2.27 | 1.37 | A,B>C,D,E |
| | SD | 1.11 | 1.03 | 1.06 | 0.88 | 1.33 | |
| initiative in seeking information | M | 2.39 | 2.30 | 2.28 | 2.27 | 1.90 | A=B=C=D=E |
| | SD | 0.87 | 0.95 | 0.85 | 0.84 | 0.81 | |
| various situations and information needs | M | 2.65 | 2.70 | 2.70 | 2.60 | 2.48 | A=B=C=D=E |
| | SD | 0.45 | 0.44 | 0.46 | 0.49 | 0.48 | |
| require detailed information | M | 2.95 | 3.09 | 2.85 | 3.03 | 2.75 | A=B=C=D=E |
| | SD | 0.79 | 0.67 | 0.77 | 0.90 | 0.98 | |

### 5.4.7 Information to be included in the database and its form of presentation

The opinions of the clinicians varied regarding the required level of completeness and detail of the information which would be given in a database dedicated to the topic. The distribution of the respondents according to various items of required information is presented in Table 21.

The majority of physicians want to know the source from which information is cited. Other data too, are desired by a high percentage of physicians; for example,, the size of a population under study, and even reports about sporadic cases (on issues where this is the only available documentation). A smaller interest has been expressed in material about vertebrates. The overall picture of a desire for depth of response and detailed information is enhanced by the fact that only 20% would be satisfied with a brief yes/no answer, such as "yes, the drug has potential teratogenicity".

Table 21: **The level of detail of information provided by the database**

| | STATEMENT | % AGREEMENT |
|---|---|---|
| 1. | "Yes" or "no" answer will suffice. | 20.3 |
| 2. | I would like to know the source of the information. | 94.7 |
| 3. | I would like to read the source document. | 68 |
| 4. | I would like to know the size of the population under study. | 86.5 |
| 5. | When no controlled study is available, I would like to know the sporadic cases. | 84.5 |
| 6. | When no human data are available, I would like to receive data on vertebrates. | 63 |
| 7. | When no vertebrate data is available, I would like to receive data on invertebrates. | 8.9 |

The majority of physicians prefer to use the generic name of a drug, some prefer the trade name, only a few mentioned that they preferred to use the chemical name, and several find it useful to create a list of all brand names of a drug. (Table 22)

Table 22: **Preference of drug names for use in the database**

| Drug name | % agreement |
|---|---|
| Generic name | 47.7 |
| Trade name | 21.9 |
| Chemical name | 1.3 |
| Any name | 13.9 |
| Generic + Trade | 14.2 |
| Generic + Trade + Chemical | 1.0 |

As for the presentation of the information, the attitude is flexible and one can notice (Table 23), that a combined presentation of text and graphs or tables is convenient.

Table 23: **The preferred form of presentation of the information in the database**

| Form of presentation | % agreement |
|---|---|
| Text | 22.4 |
| Tables | 6.1 |
| Combined (including graphs) | 53.4 |
| Any form | 18.1 |

## 5.5 Conclusion

Despite the fact that only a third of the gynaecologists/obstetricians completed the questionnaire, the statistical analysis showed that this sub-population was not biased for the variables tested and that it represents well the total target population, except for the low percentage of women responders relative to the total population. This fact does not contradict the assumption that, in general, more enthusiastic users of information would be more motivated to spend time contributing to research on the subject.

In a comparison of various sources of medical information, books on obstetrics and pharmacology were found to be a major source of reference in specific situations of doubt regarding the use of a drug. However, for continuous update, books are surpassed by other means. Obstetric journals constitute the leading source for continuous update, but were not mentioned at all as an information source for specific problems. It should be noted however, that a sample analysis of some of the journals mentioned by the responders revealed that a relatively small number of articles are dedicated to the topic of drug usage.

Thus, it seems that the physician uses the most readily available source, without applying a critical content analysis. Among all professionals approached for consultations, gynaecologists-obstetricians were rated as first priority for both categories: keeping up-to-date and acquiring information for a specific problem or situation.

The typology of physicians was characterised based on an analysis of correlations between the measures of information usage, the attitudes toward drug administration and the personal background of physicians. "Correlations" are used here to define statistical associations between the mentioned characteristics. The variables that were found to be significant in physicians' profiles are the place of work (hospital vs. clinic), teaching activity and the country of study. No consistent differences were found between the various groups, with respect to the demand for information that should be provided in a computerized database and the required level of detail.

Regarding the age factor, it has been found that older physicians tend to refrain from prescribing drugs in pregnancy and during lactation, in clear contrast to younger physicians. At the same time, older physicians read less than their younger colleagues, except for advertised publications for which no differences were found between the age groups.

It should be noted that advertised publications are a popular source of information, despite the dubious reliability attributed to them by many physicians. It appears that the availability of information is a determinative factor in its level of use.

The use of databases on CD/ROM has recently known significant increase, as a result of which the data reported in this study have restricted implication. Due to these fast changes, it is recommended further studies on this subject be conducted in the future.

# Chapter 6

# Drug Information Centres (DICs)

## 6.1 What Are DICs?

Drug Information Centres (DICs) originated in the 1960s in the US and were located mainly in hospitals. They were later imitated in Europe and elsewhere (Gallo & Wertheimer, 1985). The principal functions of DICs were defined by Amerson (1986) as follows:

a) to complement the region's existing information services on adverse reactions and toxicology;
b) to improve the feedback to reporting doctors;
c) to identify local problems that require further investigation; and
d) to provide regional statistics.

Some DICs also deliver continuous education to physicians and pharmacists (Smith, 1987).

In reply to the questionnaire described in the previous chapter, a high percentage of physicians noted that when in need of drug information they approach a clinical pharmacologist, a pharmacist or a drug information centre. Pharmacists, in turn, glean information from printed and computerized sources. Such activities, however, do not meet the criteria for designating drug information centres, as they lack most of the attributes required of such centres.

Structured interviews were conducted with the staff of three representative DICs in order to assess their contribution to the clinical activities of physicians (all the questions of the interviews are given in Appendix E). Each interview session lasted approximately ninety minutes. The main issues of interest were: the percentage of queries on drug usage in pregnancy and lactation out of the total number of queries; characteristics of the queries, e.g. whether they are general or specific; the sources

that supply the answers; the means by which answers are delivered (by phone, in writing); whether the answer is provided as data or as a reference source.

This evaluation of DICs in Israel showed that only two of them - The Beilinson Medical Centre in Petach-Tikva and the Hadassa Medical Centre in Jerusalem (also representing ENTIS) - specialize in drug use in pregnancy and lactation. (For the detailed questionnaire see Appendix E). Other centres refer queries to the two above. The individual features of the two centres are summarized here according to their specialization.

## 6.2 Beilinson Medical Centre

This DIC was founded in 1978 and is located in the hospital pharmacy. The numerous duties of the centre are fulfilled by a pharmacist and a clinical pharmacologist and the service it provides is free of charge to all physicians in the country. Questions on drugs in pregnancy are asked mostly by gynaecologists/obstetricians and occasionally by physicians who treat pregnant women for specific problems. Questions on breast feeding are brought up mainly by neonatologists. The majority of questions are asked by phone, and a mere few arrive by post. The answers are usually given over the phone as well, and consist mostly of a reference, without supplying detailed data. Most questions on drugs in pregnancy are concerned with teratogenicity and are roughly of two types:

a. The pregnant woman, unaware of her pregnancy, took a certain drug. What is the risk to the fetus?
b. Is it allowed to prescribe a certain drug in pregnancy?

Questions regarding lactation are of two types as well:

a. Does a certain drug diffuse into breast milk?

b. Should a woman breast feed while taking a certain drug?

In comparison, general questions not related to pregnancy deal mostly with adverse effects or interactions between drugs and with matters of dosage.

The clinicians tend to use the generic name of the drug, although sometimes the trade name is used - but never the chemical name. The sources of information used are mainly specific books on the topic, e.g. Briggs et al. (1990) and comprehensive reviews presented by international committees. These documents are organized in vertical files. The data bases used are Medline and the Drugs-Pharmacology section of Excerpta-Medica, both on CD/ROM. Inquiries for research purposes are referred to the hospital library. The pharmacist consults with geneticists, teratologists and neonatologists, avoiding information provided by the pharmaceutical industry.

Some questions and answers of special interest are stored in print. The DIC members participate in international collaborative studies and meetings of ENTIS, and are involved in educational projects about the use of drugs in pregnancy both for physicians and for the general public.

## 6.3 Hadassa Medical Centre

This centre, operating since 1987 at the Hadassa Medical School, is defined as "Teratology Information service". The activities in the centre include research and consultation; the latter being provided by three physicians and a teratologist. The inquiries are presented by physicians (70%), the majority of which are gynaecologists/obstetricians and psychiatrists, pharmacists (10%) and patients (20%). The questions are asked by phone, in writing or by appointment. Inquirers use mostly trade names of drugs. The majority of the questions concern drug therapy in pregnancy, and the answers include all the information available on the topic, an

evaluation of the specific case and recommendations for treatment or further diagnostic tests. All answers, about 200 per month, are also sent out in writing and stored in a computerized database. Pharmacopoeias and specific sources on the topic are used and bibliographic searches are performed on CD/ROM. The Hadassa centre is active in ENTIS, especially by contributing the epidemiological data accumulated from follow-up on all inquirers.

## 6.4 Sorasky Medical Centre

This is not a recognized DIC, but the pharmacists, when consulted, provide information to the house staff. It is an example of a hospital pharmacy that serves as a source for information on drugs, even though it does not have the attributes of a DIC. This reflects the situation in most of the hospitals in Israel.

Most questions address problems of drug interactions and side effects. Usually, the trade names of the drugs are used. Questions regarding medication in pregnancy are concerned with teratogenicity and with safety of administering a certain drug at a given gestational age. Questions regarding lactation are rare. Queries refer to long-used medicines as much as to new ones. The physicians who consult with the pharmacist belong to various departments, although the majority are gynaecologists/obstetricians. Answers are taken from printed sources, including pharmacopoeias, specific books on the topic and sometimes articles from professional journals. The physicians are interested in any kind of available information, including sporadic case reports.

## 6.5 Conclusion

The three centres described above contribute, each with its own specific characteristics, to improving the safe usage of drugs. In addition, by providing information to physicians, they help them make informed decisions when considering measures such as an induced abortion, and enable them to relieve anxieties of pregnant women.

The DIC at Beilinson Medical Centre fulfils the tasks defined for and expected from such a centre. The teratology centre at Hadassa Medical School functions mainly as a consultation unit specifically dedicated to that field. The Sorasky Medical Centre, despite being a central hospital in the most populated area of the country, relies on the pharmacists who are overwhelmed with other tasks. This situation is quite common in Israel and indicates a deficiency calling for correction.

# Chapter 7

## Gynaecologists/Obstetricians User Studies and the Implications for the Database Model

In order to define the information needs of the gynaecologists/obstetricians, the triangulation research methodology was chosen. It included the following: a content analysis of queries directed to drug information centres (DICs) regarding the usage of drugs in pregnancy and lactation; focus group interviews; a questionnaire sent to the target population; and structured interviews performed in representative drug information centres.

A broad pattern of characteristics emerged from the content analysis of the queries:

a) proprietary names of drugs were most commonly used.
b) most of the queries referred to drugs which carry some risk, but not such that precludes their use.
c) queries have basically two facets, one being the name of the drug, the other being pregnancy (sometimes in a more specific term, such as the exact gestational age) or lactation. Some queries contain an additional facet specifying the type of injury or disease.

The FGIs yielded a complex pattern of information needs. In general, participants voiced a preference for the use of computerized databases, which should provide detailed and updated information backed by readily available documentation. However, the majority screen printed publications, with long-term prospective studies being considered more reliable than anecdotal case reports.

On the whole, a rather permissive but cautious attitude (depending on appropriate information) towards drug prescribing in pregnancy has emerged. Regarding lactation, the general pattern is similar.

The results of the FGIs contributed to the design of a questionnaire which was sent to 959 gynaecologists/obstetricians in Israel. 34% of them responded, providing a rich array of information. The major contribution of the questionnaire, besides bringing quantitative data, was the opportunity it provided for focusing on specific topics and discriminate sharply between different opinions, motivations and types of information usage.

The responders were divided into four groups, according to attitudes towards drug prescription in pregnancy. Those varied between an objection to any prescription (A) to various degrees of more liberal attitudes (B,C,D). A progressive increase in the expression of information needs was found from A to D. A greater need for information was also demonstrated by individuals participating in academic teaching activities, by physicians who studied (55.8%) or specialized (74.9%) in Israel and by those working in hospitals (87%) - as opposed to those working in community clinics. Similar findings were reported by Hull and Marshall (1987), who state that "Attitudes towards drugs and prescribing are likely to be affected by many factors, including the health care system, differences between training schemes in different countries...".

Age was not found to be a significant factor affecting information usage, although younger physicians appear to make greater use of medical literature. Similar data were found in a study by Gruppen (1990).

The initiative to seek information and the use of databases correlated with their availability. It is of interest to note that only a weak connection was found between the above factors and the physicians' perception of the reliability of information sources.

A general scheme of information usage has been obtained from the results described above (see Figure 1). Several variables were found to influence the frequency and type of information sought. A major factor was found to be the physician's personal attitude towards drug treatment in pregnancy. This, in turn, is influenced by the physician's backround - his country of study, the type of institution he works at, as well as his academic position or teaching activities.

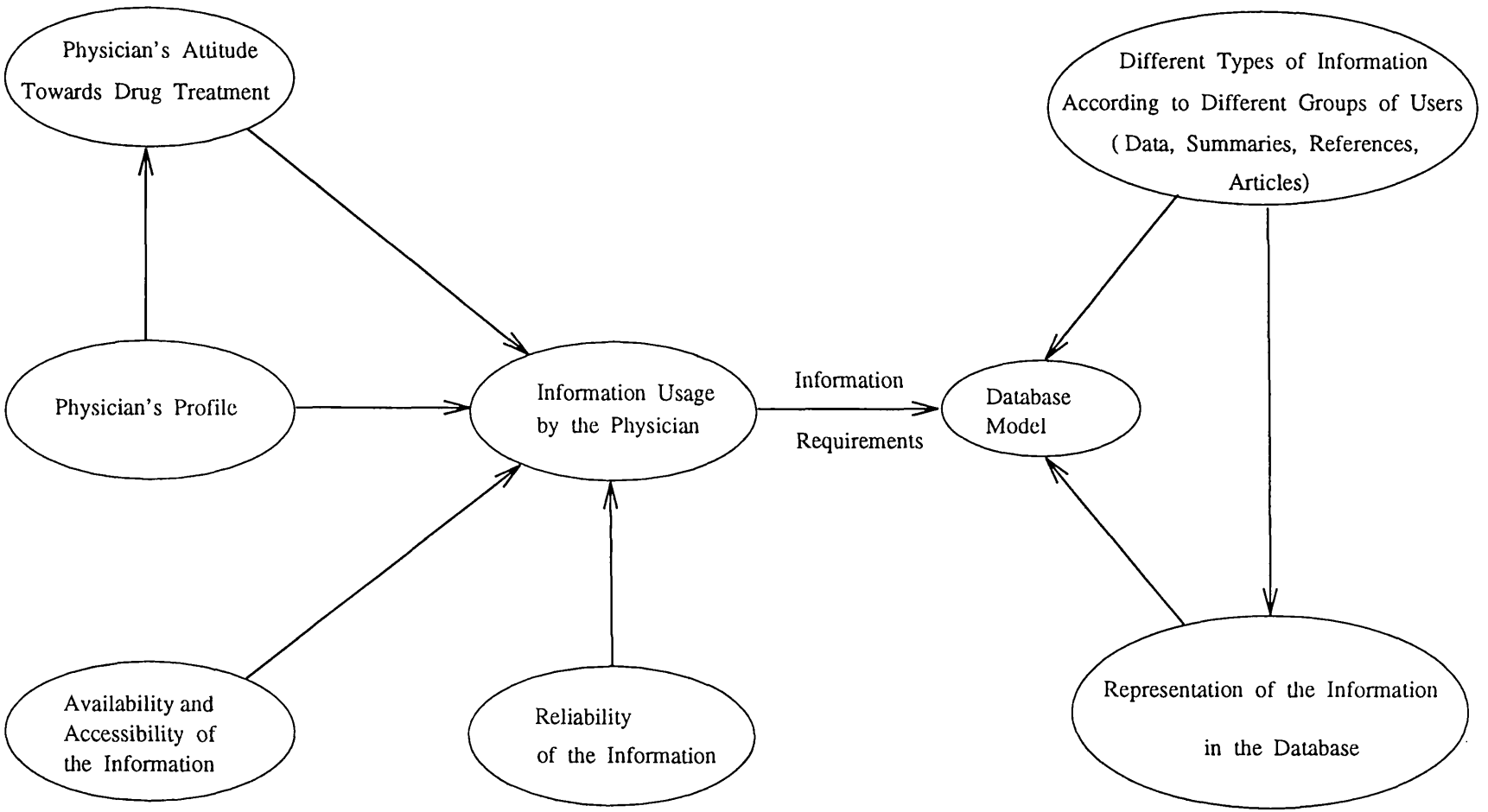
The database model described in the next chapter has been designed to meet information requirements of physicians based on the above findings. It contains information tailored and represented according to the needs of various users.

The needs of the user were the guide in the design of the database. It was found that the level of detail required varied from user to user,and it isassumed that this is true for the same user in different interconnected levels.

The aspect of reliability of the information raises two questions:
The first, what is the importance ascribed by the physician to the reliability of information? According to the direct research method (FGI), physicians emphasize the importance of data reliability. (However, this finding has not been corroborated by the indirect method, statistical analysis of the questionnaires). The next question is then -

how to guarantee the reliability of data from the point of view of the physician? By being provided with references to all the stated facts about drugs in the database, the physician can verify their validity and judge whether they are well based.

**Figure 1: Implications of the information requirements to the database model**



# Chapter 8

# The Database Model

The model addresses the problem of coping with large amounts of drug information, some of which is possibly contradictory or insufficient for assisting in clinical decisions. There were several technologies available for the creation of the database, from which hypertext has been chosen because of its special characteristics as explained in the following sections.

## 8.1 Hypertext Software

Smith and Weiss (1988) describe hypertext as "an approach to information management in which data is stored in a network of nodes connected to links. Nodes may contain text, graphics, audio, video as well as source code or other forms of data". The concept is that text can be structured, stored, edited and accessed in an associative, rather than sequential or random mode of action. The association is created according to the content of the ideas exhibited in the text.

A major feature of hypertext is the flexibility it allows in updating the system and in introducing changes at will: information in individual nodes can be updated, new nodes can be added and new links created. The application of this technology has greatly increased in recent years, and a growing amount of software based on it has become available. Hypertext tools are increasingly applied in textbook production, construction of databases for teaching, etc. (Frisse, 1988; Raymond & Tompa, 1988).

### 8.1.1 AskSam+

As the present database includes mainly textual material, the most appropriate tool is one that has a powerful text retrieval capability with hypertext features. The software that fulfils these requirements is AskSam (Access Storage Knowledge via Symbolic Access Method) - a product developed by "Seaside Software". AskSam+ is an extension developed in Israel from the 5.1 version in agreement with the parent company. It is a shell written in C and forms an interface between the original AskSam software and the user. This version is particularly user friendly, and its exceptionally easy-to-use bilinguality makes it suitable for non-English speaking countries.

## 8.2 Hypertext Nodes

The basic unit of information in a hypertext system is the node. In the present system, three types of nodes may be defined: structured, unstructured and structural. Shneiderman, Kreitzberg and Berk (1991) suggest that the optimal size of each node, be a few screens long.

### Structured Nodes

A structured node comprises structured information, namely information divided into fields. In the current database, structured nodes are used for storing the data related to drugs. Each node contains all the information about a drug in the form of a minireview, which is divided into the following fixed fields: the pharmacological class, teratogenicity, fetal toxicity, mutagenicity and oncogenicity; these are the permanent attributes of the drugs. An example is shown in Figure 2; (the complete information about the drugs used in the database model is given in Appendix F).

Figure 2: **Structured nodes contain the complete information about a drug either in pregnancy (a) or during lactation (b) and is organized in fields (their titles appearing in capital letters).**

GENERIC NAME: PHENYTOIN

PHARMACOLOGICAL CLASS: Anticonvulsant

TRADE NAMES: Dilantin (Parke Davis)
Epanutin (Parke Davis)

CHEMICAL NAME: 2,4-Imidazolinedinedione,5,5-diphenyl-

RISK FACTOR: D

PREGNANCY

TERATOGENICITY

Phenytoin is a hydantoin derivative introduced in 1938, whose potential teratogenicity has been recognized since 1964 (1, 2), resulting in a cluster of malformations, designated as the Fetal Hydantoin Syndrome (FHS). FHS is characterized by craniofacial anomalies, mainly clefting, mental retardation and sometimes neural tube defects, growth deficiencies, cardiac malformations and limb deformities, mainly distal (3, 4). Cognitive disturbances can constitute a late expression of the syndrome (5). All studies have demonstrated an increased teratogenic risk of 2.2% to 26% associated with anti epileptic drugs (AED) (3, 6), as compared to a two to threefold increase in congenital malformations (7) and perinatal mortality (8) in non treated epileptic pregnant women. It is generally accepted that AEDs increase this risk, which may be dose dependent. This includes mainly carbamazepine, phenytoin and especially suggested valproic acid (6). Thus, excessive phenytoin plasma levels were associated with a higher incidence of congenital defects (9). Teratogenicity increases with the number of administered AEDs, especialy those mentioned above (6). In addition to FHS a plethora of other malformations has been described in association with phenytoin in individual case reports (10).

Phenytoin may also be used to treat digitalis induced arrhythmias in pregnancy (11) and for anti convulsant prophylaxis in severe pre-eclampsia (12); such short exposure may not be associated with fetal damage. Phenytoin does not affect placental function (1). Various mechanisms for phenytoin's teratogenicity have been sugested. The drug increases liver folic acid metabolism and may cause a reduction in the vitamin's plasma level (14, 15), which has been associated with a 15% incidence of fetal malformations, which could be prevented with folic acid supplementation (16, 17). Recently, intermediary oxidative metabolic derivatives of phenytoin have been identified in an animal model as compounds which are possibly responsible for most of the drug's teratogenic effects (18).

Low fetal activity of epoxide hydrolase seems to be associated with an increased risk in humans too (19).

FETAL TOXICITY

An animal study has demonstrated vascular disruption and fetal tissue hypoxia following phenytoin exposure (20). Noteworthy is the possible occurrence of early haemorrhagic disease of the newborns of phenytoin treated mothers, which may necessitate vitamin K prophylaxis in such infants (21). Phenytoin may affect vitamin D and calcium in maternal and in fetal metabolism (22) but without a demonstrable clinical effect.

ONCOGENICITY

Phenytoin has been determined as a human transplancetal carcinogen, the main tumour being Neuroblastoma (23, 24). Other neuroectodermal tumours (25, 26), Wilm's tumour (26), lymphangioma (27) and ependymoblastoma (28), have also been described. As tumourigenesis may be delayed, children who were exposed in utero to phenytoin have to be followed for a few years.

MUTAGENICITY

No chromosomal aberrations have been found in a battery of cytogenetic assays following phenytoin exposure (29). In two groups of epileptics, treated or not with phenytoin, a similarly increased frequency of sister-chromatid exchanges was found, as compared with healthy controls (30).

DOSAGE

Lander and Eadie (31) claim that plasma levels of anti-epileptic drugs are reduced in pregnancy, hence their dosage should be increased accordingly; Folb and Dukes (32) make the distinction between bound and unbound drugs. This is especially important in anti-epileptic agents such as phenytoin, where plasma protein binding is decreased, causing an increase in unbound drug levels (33). Hawkins (34, 35) recommended not to increase the dosage of these drugs during pregnancy. Yerby et al. (36) confirmed that drug-protein binding of anti-epileptic drugs is altered during pregnancy, resulting in a decline in their mean total concentration. However, the free fraction of all drugs tested was elevated. The authors suggest to monitor the free fraction and not the total concentrations.

REFERENCES

1. Janz D, et al. Are anti epileptic drugs harmful when given during pregnancy? German Med Monogr 1964;9:20-3.
2. Committee on Drugs American Academy of Pediatrics. Anticonvulsants and pregnancy. Pediatrics 1977;63:331-3.
3. Hanson JW, et al. Fetal hydantoin syndrome: current status. J Pediatr 1982;101:816-8.

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36. Yerby MS, et al. Pharmacokinetics of anticonvulsants in pregnancy: Alterations in plasma protein binding. Epilepsy Research 1990;5:223-228.

GENERIC NAME: PHENYTOIN

PHARMACOLOGICAL CLASS: Anticonvulsant

TRADE NAMES: Dilantin (Parke Davis)
Epanutin (Parke Davis)

CHEMICAL NAME: 2,4-Imidazolinedinedione,5,5-diphenyl-

BREAST FEEDING

Phenytoin is excreted into breast milk at milk/plasma ratios ranging 0,18-0,54 (1, 2), with little risk to the nursing infant, if maternal drug plasma levels are well controlled. One case of neonatal methemoglobinemia and drowsiness has been reported in a breast fed infant by a phenytoin treated mother (3).

REFERENCES

1. Nau H, et al. Anticonvulsants during pregnancy and lactation: transplacental, maternal and neonatal pharmacokinetics. Clin Pharmacokinet 1982;7:508-43.
2. Steen B, et al. Phenytoin excretion in human breast milk plasma levels in nursed infants. Ther Drug Monit 1982;4: 331-4.
3. Finch E, et al. Methaemoglobinaemia in the newborn: probably due to phenytoin excreted in human milk. J Obstet Gynaecol Br Emp 1954;61:833.

The structure of the node is not rigid; it allows the exclusion of fields which are irrelevant to the information in a particular node, e.g. if a certain drug has no oncogenic potential, the field of oncogenicity will not be included in the drug's node. The information upon which the minireviews are based is drawn from various sources which are listed at the bottom of each minireview. The number of citations may vary markedly; for example, one node may contain three references while another may contain twenty four. Citations vary in length, depending on the cited source. Each of the structured nodes in the database contains information on the use of a drug, either in pregnancy or in lactation.

### Nonstructured Nodes

Some nodes in the system appear in free format:

- a table of the critical stages in human embryological development;
- definitions of the risk factors assigned to drugs;
- the help option.

These nodes appear on the screen upon user request, but are not subject to search as are the structured nodes.

### Structural Nodes

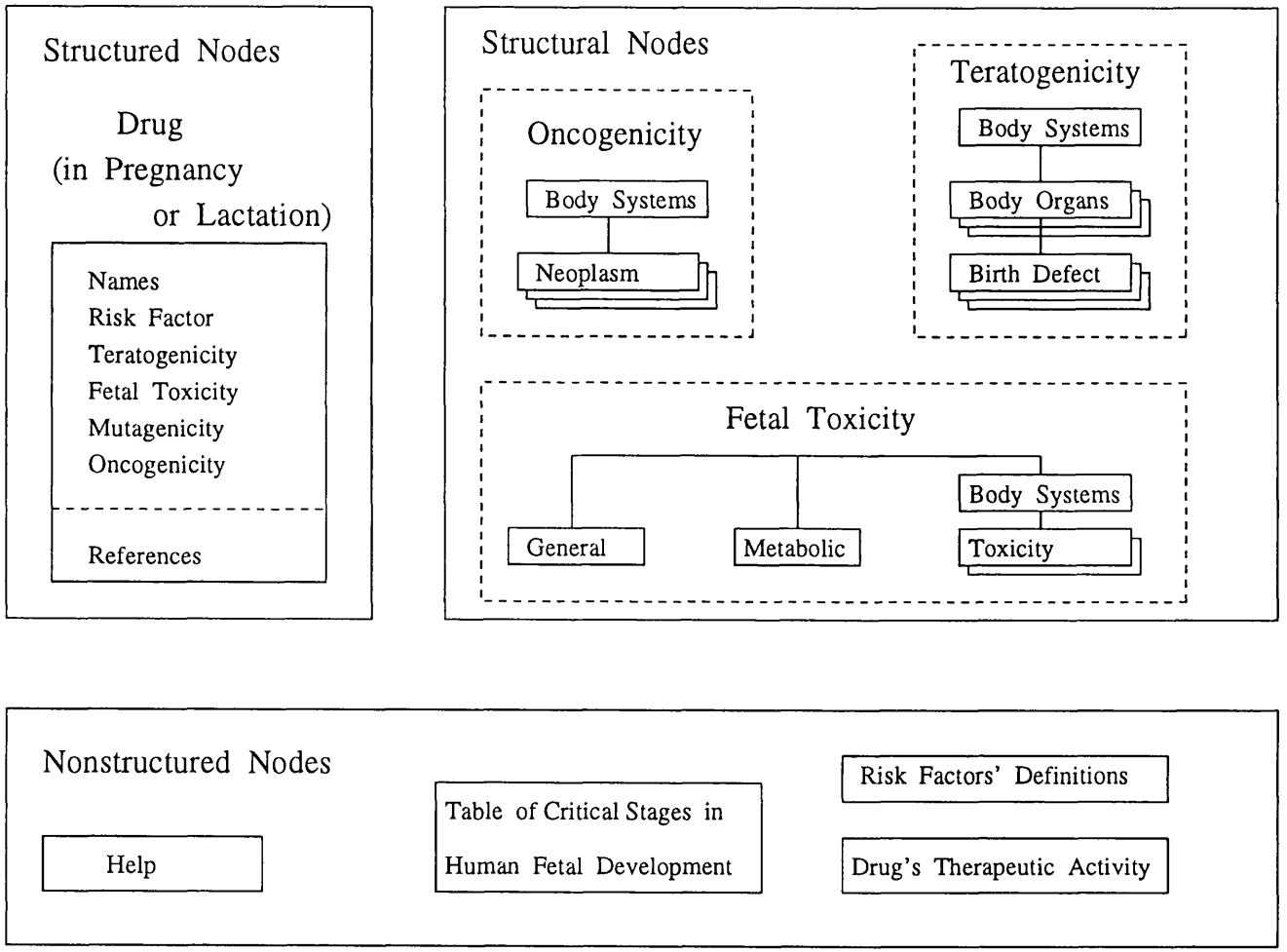
A structural node consists of hierarchical lists, by which the drugs may be accessed. There are three schemes of lists in the model (Figure 3) as described below. All schemes follow the same principle, namely a hierarchy from body systems to a localization of the lesion.

1. **Teratogenicity** is divided into three hierarchical levels:

body systems → body organs → birth defects.

The classification of birth defects used here is a simplified version of ICD-10 (World Health Organization, 1992). The arrangement is hierarchical, from major body systems to organs to birth defects. It takes into account the developmental pathology of organs. Only a limited number of birth defects were included, namely only those

**Figure 3: Hypertext nodes in the database**



which are relevant to the drugs which appear in the demonstration package (Appendix G). A special place among the body systems was reserved for the placenta due to its crucial role in pregnancy, even though it is not classified usually as a separate term.

2. **Fetal toxicity** is divided into three options.

Option "a" has three hierarchical levels:

(a) body systems → specific body system → toxicity.

Options "b" and "c" have two hierarchical levels each:

(b) metabolic → metabolic pathways

(c) general toxicity → general toxicity phenomena.

The toxicity scheme has to include these two additional levels in order to express the metabolic aspect.

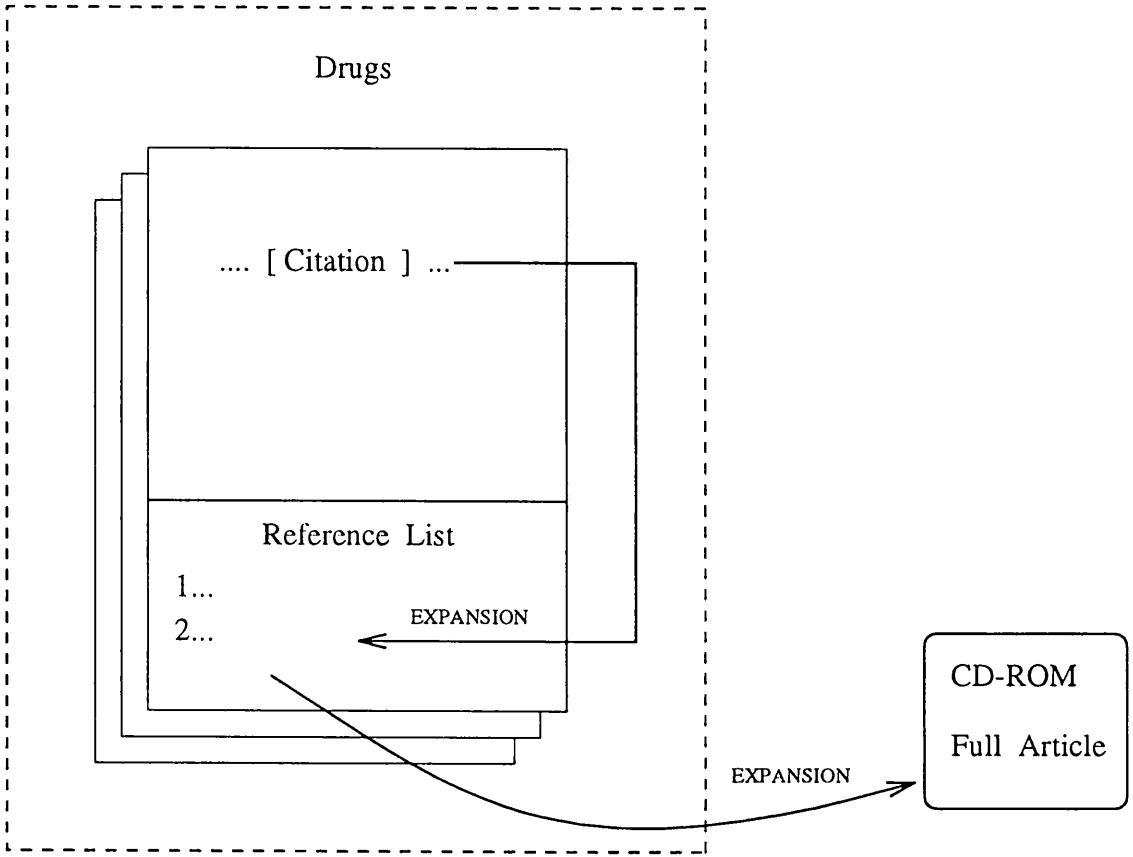
3. **Oncogenicity** is divided into two hierarchical levels:

body systems → neoplasms.

## 8.3 Hypertext Links

A link forms a connection between two nodes. Conklin (1987) distinguishes between explicit and implicit links. The explicit link includes the referential and organizational links. The referential links are logical connectors which are not hierarchical and are usually bi-directional, supporting both forward and backward movement. They connect the link "source" (the reference) with the link "destination" (the referent). The destination nodes in the referential link contain explanation, expansion, demonstration and association with the source node. Some types of referential links that are exemplified in the database are described below.

**Figure 4: Jump referential links**



## Referential Links

**Pop-up links**. Each structured node of a drug in pregnancy contains the risk factor for the drug. A referential link connects the risk factor to the referent node which includes the definition and explanation of that specific risk factor, with a possibility for an immediate return to the source node (Fig. 4).

Another pop-up link originates in the nodes mentioned above and is connected to a graphical node that contains a table of critical stages in human fetal development. This is a "reminder"-type link (Fig. 5).

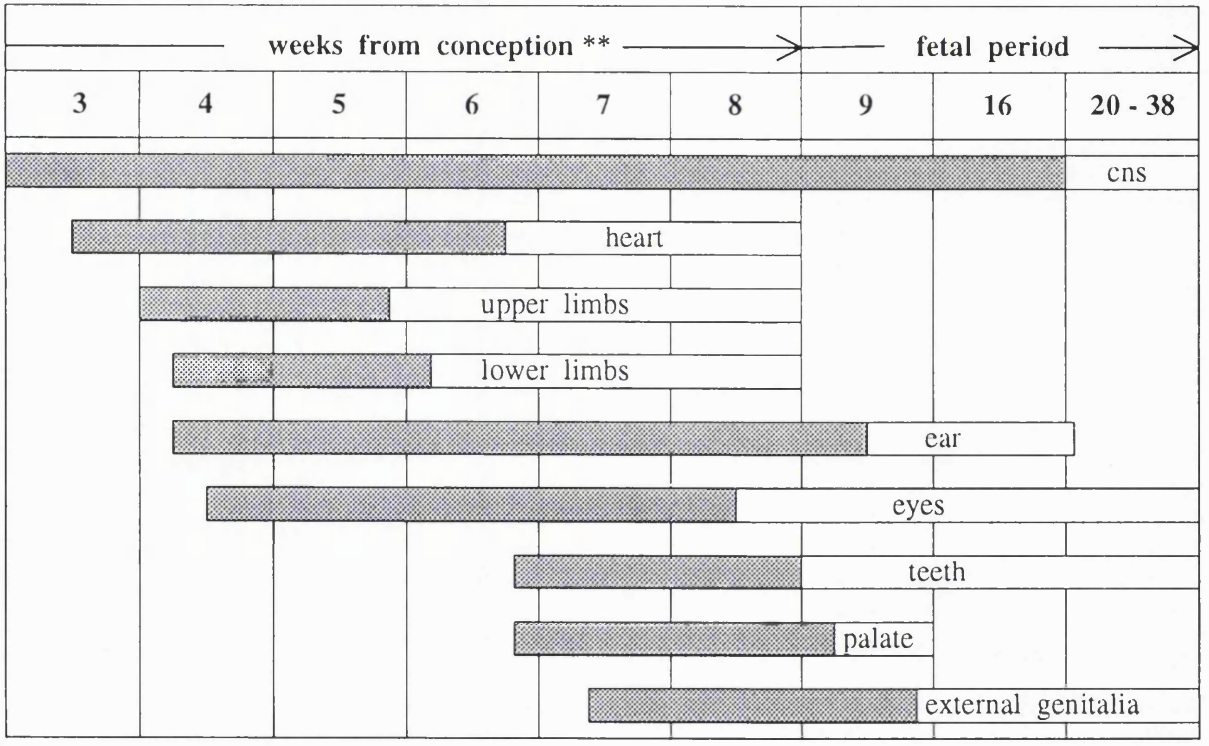
Finally, the "help" command, which is also a pop-up link provides access to information about any option in the system and can be accessed from any screen (Fig. 6). The pop-up concept was borrowed from the Windows software, but with a slight modification. In Windows, the link is created while keeping the source screen, whereas here, only the destination screen is presented.

**Jump links**. Such links allow passage from a citation mentioned in the drug minireview to the reference itself. They are "detail providing" links, permitting either to return to the source point mini-review, or to continue browsing through the reference list, or to jump directly from the citation to the full text of the referred source, which is stored in a CD/ROM; thus, they may be also considered as "expansion" links (Fig. 4). The option of accessing the full text has been programmed into the system, but may not yet be applied due to copyright restrictions.

## Structural Links

Structural (organizational) links represent hierarchical information and usually correspond to the IS_A (sub- and super-concept) relation, thus forming a tree. This type of link appears in four options in the system, in parallel to the description of the structural nodes. Such links permit a transition between levels in the hierarchy, from the base of the tree up to its highest levels, upon request.

**Figure 5: Critical stages in human fetal development ***



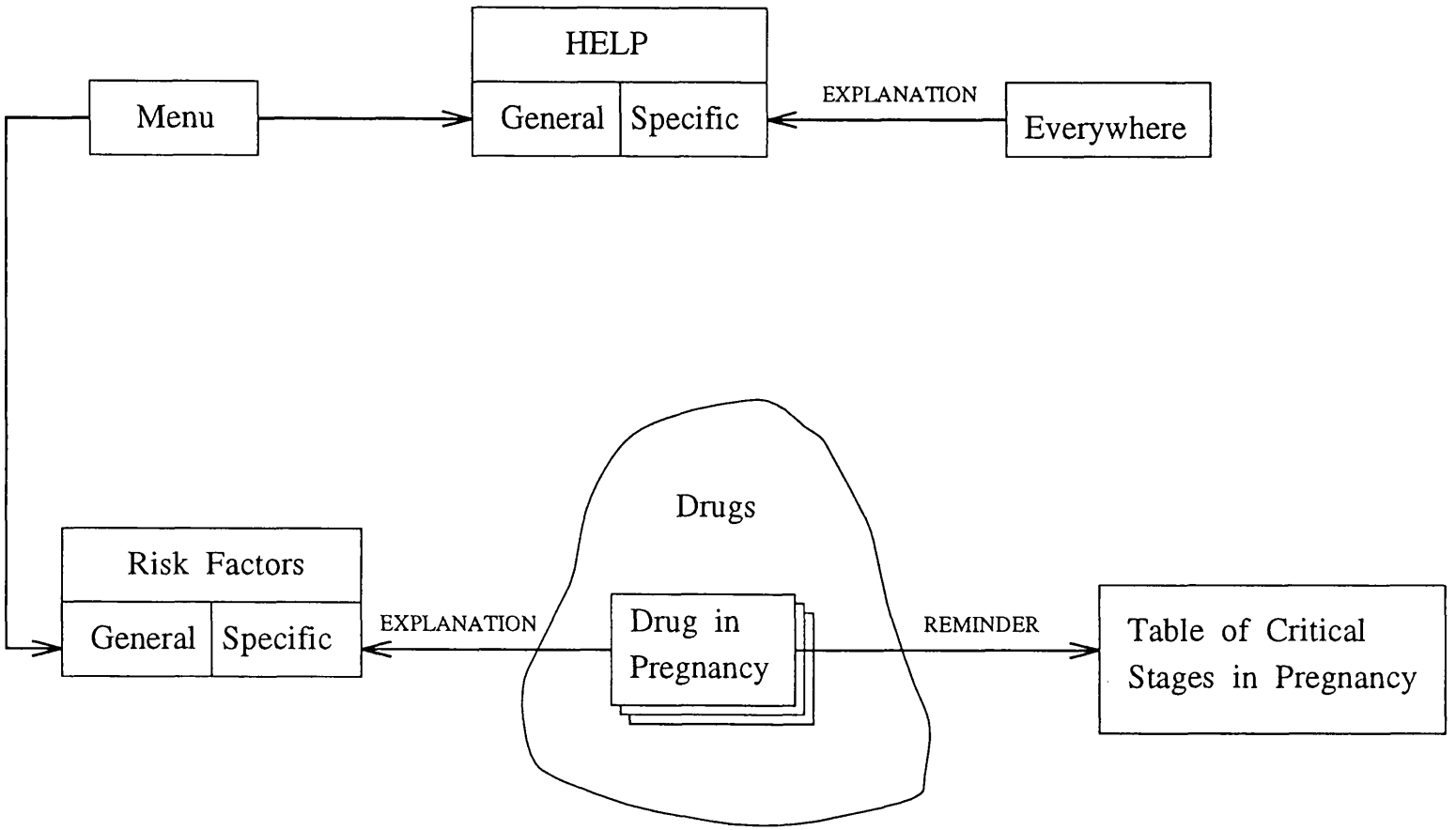

* The First and Second Embryonal Weeks are not Susceptible to Teratogens.

** For Menstrual Age (Gestational) Add Two Weeks.

Major Congenital Anomalies

Minor Congenital Anomalies and Functional Defects

**Figure 6: Pop-up referential links**



Conklin (1987) suggests we should regard the keyword or string search as an implicit link as the main characteristic of such a link is the capacity to lead to many nodes. Each term in the tree is a key word that may be used in a search.

## 8.4 Criteria for Choosing Sources For the Database Model

The evaluation of drug-related literature is a complex task, so criteria must be set which will enable a choice of relevant sources. Several bodies have passed regulations or made recommendations in order to facilitate the task. The FDA regulations, as reported by Collins and Lasarus (1975, pp.30-31), provide an example. They state firstly, that the purpose of the study must be clearly and precisely defined, and secondly, that the protocol must provide an adequate method of selecting subjects for study.

Numerous and diverse sources of information exist. A representative sample was chosen for the present study: (Briggs et al., 1990; Koren, 1990), books (Moore & Persaud, 1993), pharmacopoeias (Medic, 1972-; Martindale, 1993; Swiss Pharmaceutical Society, 1992), bibliographic databases (MEDLINE) and data banks (BIAM). Regarding drugs for which there are a large number of references, the ones chosen were those that: a) represent major studies; b) are in English and c) show numeric relations amongst raw data. The criteria of originality and comprehensiveness of a report have proven to be superior to the criterion of the date of its publication.

Where information on humans was scant, case reports and animal experimentation data were included. In cases of controversial or indecisive published information, the different views and data were cited so that the user may base the decision on all available information.

Knowledge about the effects of drug exposure through breast milk is largely based on results from small series or even just a single case (Giacoca & Catz, 1988).

## 8.5 The Drugs in the Model

The drugs chosen for the model belong to common groups of medications encountered by the obstetrician in daily practice. They were selected so as to represent various risk levels to the fetus, and thus demonstrate the various degrees of complexity in processes of drug evaluation by clinicians.

*Carbamazepine & Phenytoin*

Epilepsy is a relatively common and pharmacologically treatable disorder. Accepted wisdom suggests that, once a balance is achieved with a certain drug regimen, it should not be interrupted. However, some of the drugs prescribed for epileptics carry a risk of teratogenicity, especially phenytoin and valproic acid. This risk must be weighed, though, against the potential damage to the fetus caused by uncontrolled seizures in pregnancy. At present, carbamazepine is considered the safest anti-epileptic in pregnancy.

Numerous articles have been published about the potential teratogenic effects of phenytoin and carbamazepine and about their use in pregnancy. In addition, many chapters in books and supplements in journals deal with this subject.

*Reserpine & Captopril*

Two drugs were selected to represent two of the modes of action of anti-hypertensives: reserpine (catecholamine depletion) and captopril (ACE inhibition). Both are associated with numerous side effects, but reserpine is classified as a high risk agent for teratogenicity, while captopril is considered to carry a lower risk. After the first publications about the high teratogenic risk of reserpine appeared in print, few further studies of that drug's effects on pregnancy outcome have been performed and the use of this drug in pregnancy was discontinued gradually. The shift towards captopril in the treatment of hypertension in pregnancy resulted in a large number of published studies on its effects.

*Clomiphene*

Clomiphene is an ovulation inducer widely used in treating infertility. It is, of course, contra-indicated in pregnancy, but inadvertent use during the first trimester has been reported with little consequences to the fetus. The actual risk to the fetus posed by this agent might be minor, but, as it has no therapeutic use in pregnancy, it was rated "X", namely it should not be administered at all during pregnancy.

When the combination of terms "clomiphene and pregnancy" is used in a MEDLINE search, out pours a flood of hundreds of publications that deal mostly with the ovulation induction properties of the drug. The information on its effects on pregnancy can only be discovered by screening a large volume of irrelevant information. However, a more restrictive search strategy might result in omission of relevant material.

*Thyroxine*

Some drugs are specifically indicated in pregnancy. Thyroxine, when administered to a hypothyroid woman during the first trimester of pregnancy, traverses the placenta and prevents the fetal brain underdevelopment associated with lack of maternal thyroid hormones. Once the safety of using thyroxine preparations in pregnancy had been demonstrated in early clinical trials, further studies seemed unnecessary. The drug was allotted an "A" risk level and little recent information has been published on it.

*Chlorpropamide*

In another maternal hormonal defect, diabetes mellitus, the only indicated treatment is replacement by insulin. Oral hypoglycaemic agents, such as chlorpropamide, are contra-indicated as they do not allow control of the maternal glycaemia. Furthermore, these agents permeate through the placenta, often causing severe hypoglycaemia in the fetus and in the newborn. Chlorpropamide was chosen to represent drugs whose effects in pregnancy were barely studied, and on which little teratogenicity information is available.

*Ciprofloxacin*

The quinolone antibiotic ciprofloxacin is a drug frequently used, but for which no data on teratogenicity in humans are available. However, toxic effects have been demonstrated in animals, which renders this drug contra-indicated in pregnancy, hence preventing further studies in humans. No risk factor has yet been assigned to this drug.

*Anti-Malarials*

Anti-malarials were chosen because of the world-wide resurgence of this disease. There has been a growing necessity to administer malaria chemoprevention in pregnancy, especially against *P. falciparum*, which has been displaying an ever broadening spectrum of drug resistance. This has resulted in voluminous literature on the subject, which is tedious to screen and heterogeneous in its content, therefore rendering clinical decisions difficult.

## 8.6 User Interface

The user interface is a very important element in hypertext, and considerable effort is invested in making it as simple and as convenient as possible. Burgess and Swigger (1986) stress the importance of these features of the interface when the intended users are physicians: "Doctors are accustomed to being in 'control', they are decision makers, they initiate action, it is very important therefore, that they do not feel that a computer is usurping their role. A doctor thus needs to be given sufficient information to be able to feel that he is in control of the dialogue with the machine".

The main menu of the system presents all the searching options that relate to user needs in various circumstances.

Figure 7: **The main menu of options in the database**

MAIN MENU

0 - Help and general information about the system
1 - Information on a single drug in pregnancy
2 - Information on a single drug in lactation
3 - Drugs according to a therapeutic activity
4 - Drugs associated with a given birth defect
5 - Drugs associated with potential fetal toxicity
6 - Drugs associated with potential mutagenicity
7 - Drugs associated with potential oncogenicity
8 - Drugs according to a therapeutic activity and an association with a given harmful effect
9 - Proximity search
C - Table of critical stages in human fetal development
X - Exit to DOS

### 8.6.1 The 'Help' option

Trenner (1989) offers some guidelines for online "help": it should be readily available and easy to access, and its presentation should be understood easily accommodating to different levels of users. These guidelines were followed in the design of the 'help' optison.

The first option in the main menu (Figure 7) presents the general information about the system, including a description of the scope of the database and of the method of hypertext software. Basic definitions of the terms used in the database are also included.

The paragraph of general information is followed by the help sections of the specific options of the system in consecutive order. Displaying all this information under one command has the advantage of exposing the user to a variety of pathways for finding the answers he/she is searching for.

The user may access any specific 'help' command from each step in the search, from any screen, and then return to the source screen. This is done via a pop-up link.

### 8.6.2 Search options

While seeking information on a specific drug in pregnancy or lactation, options 1 and 2, respectively, are used. The search is initiated by entering any of the drug names: generic, trade or chemical (Figure 8). As the field of trade names can be voluminous, it was decided to list only drug trade names used in Israel.
Recall, that the information on pregnancy and on lactation is presented in separate nodes. All the other search options are cross-horizontal, namely the search is performed in a particular field of each node (Figure 9).

**Figure 8: Scheme of a search on a specific drug**

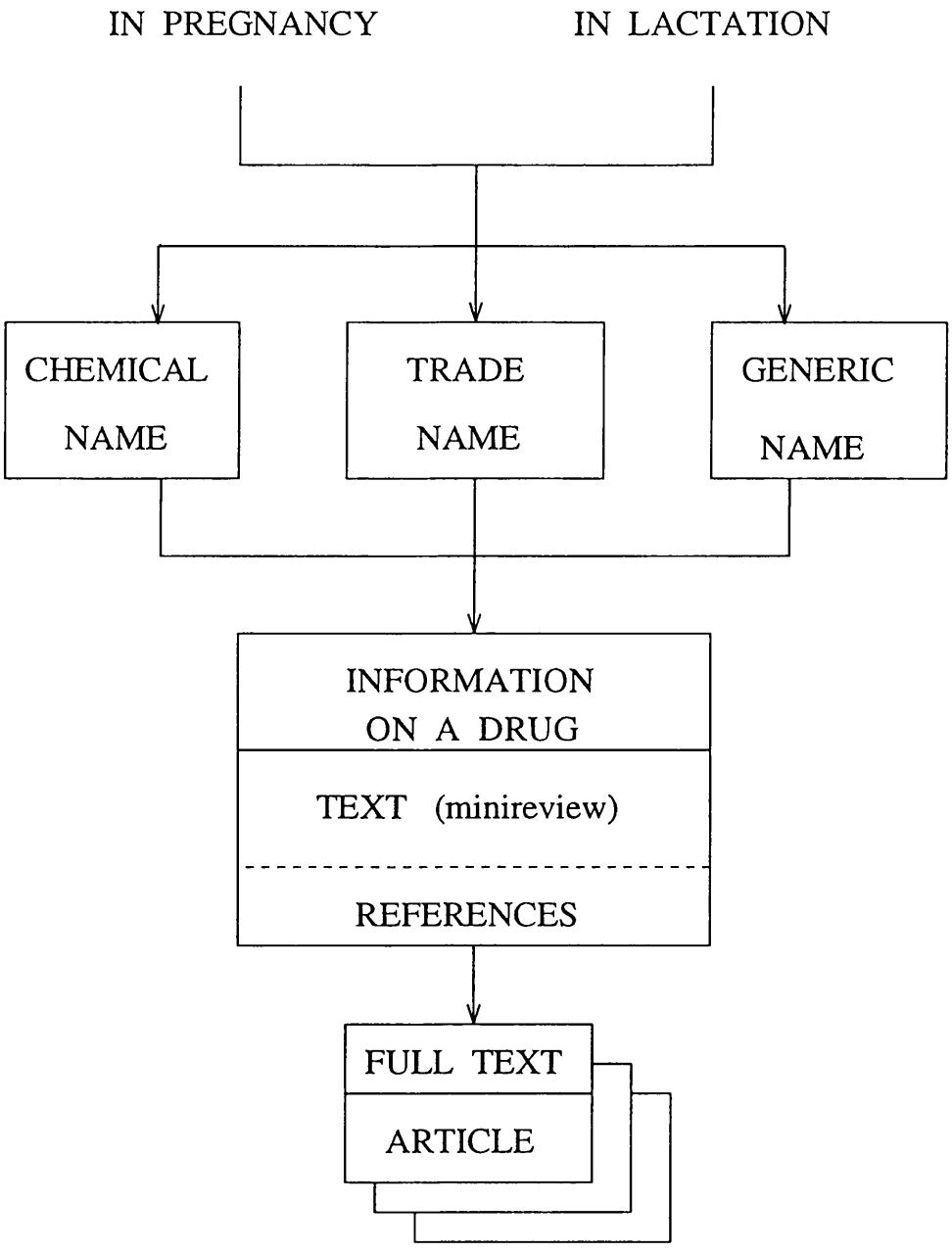
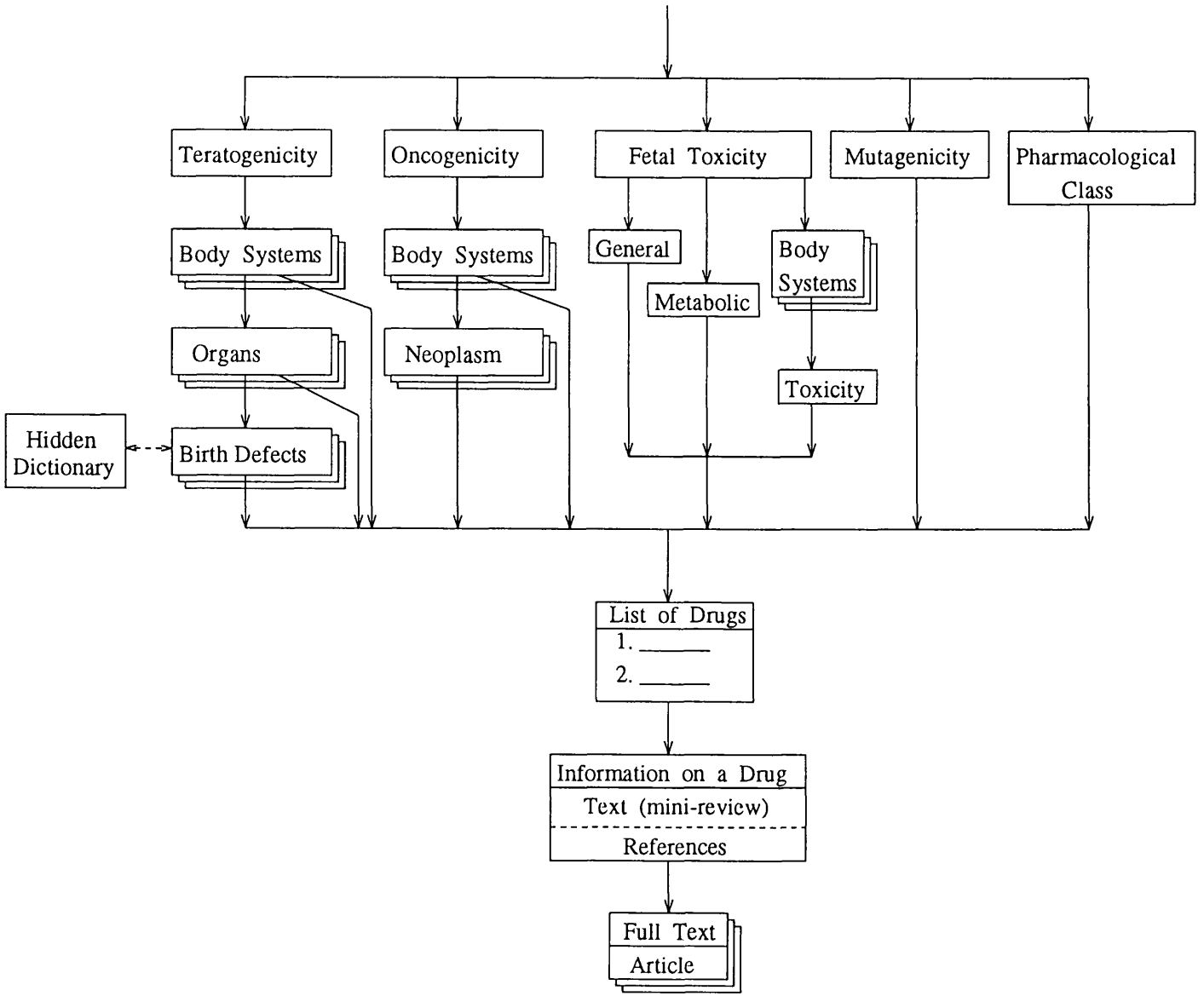


**Figure 9: Search according to various criteria**



Option 3 supplies a list of drugs according to their therapeutic activity as shown in Table 24. This is done by typing the name of a therapeutic activity or by choosing one from an alphabetical list of therapeutic activities. The activities whose name begins with the prefix "anti" will appear under the name preceded by the prefix; e.g. "anti-hypertensive" will be listed as "hypertensive". Antibiotic, however, is listed as such for obvious reasons.

Table 24: **The list of therapeutic activities of drugs which is used to initiate a search (option 3)**

| | |
|---|---|
| | Angiotensin converting enzyme (ACE) inhibitor |
| anti | Amoebic |
| | Antibiotic (Quinolone) |
| anti | Convulsant |
| anti | Diabetic |
| | Fertility agent nonhormonal |

Retrieval is performed only on the specific field of the drug names, which are displayed on the first screen of the node of each drug.

Option 4 provides a list of drugs associated with a given birth defect. It is possible to query either by typing the name of a birth defect, with optional right side truncation, or by choosing a term out of a three level hierarchy of terms. The three levels of terms correspond to body systems, organs and specific birth defects, as shown in Table 25. The search may be performed at any level, thus allowing a wide scope or a narrow scope at will.

Table 25: **The hierarchical list of terms used to initiate a search under option number 4. The list has three levels: body systems, organs and birth defects**

4 **********

1. Cardiovascular
2. Gastrointestinal
3. Head and Neck
4. Integumentary
5. Nervous-central (Neural tube)
6. Nervous-peripheral
7. Placenta
8. Respiratory
9. Skeletal
10. Urogenital
11. Syndromes and Multiple abnormalities

---

4.1 **********

Cardiovascular

Choose the required item:

a. Heart
b. Large vessels
   1) Patent Ductus Arteriosus
c. Peripheral vessels

---

4.3**********

Head and Neck

Choose the required item:

a. Craniofacial
   1) Microcephaly
b. Ears
   1) Preauricular Sinus

---

4.2 **********

Gastrointestinal

Choose the required item:

a. Esophageal
   1) Atresia
b. Gastric
c. Small intestine
   1) Stenosis
d. Colonic

etc.

A general problem which one faces is the lack of standardization of the medical vocabulary with some of the medical terms not having rigorous definitions. This is true for symptoms, diagnoses and even results of laboratory tests. The use of different terminology for the same phenomena is manifested in the medical language not only as the use of several synonymous words interchangeably, but sometimes also as multiple word rather than single word phrasing. The latter occurs most frequently in pathology, e.g. hypertension is the equivalent term for the expression "high blood pressure".

Understandably, this state of affairs could be a serious hindrance in full text retrieval, which employs the string-search feature (Rada, 1991, pp. 74-75). In order to overcome this obstacle, a hidden dictionary was created in the same hierachical form as the controlled list of terms as shown in Table 26, e.g. heart=cardia*. As a consequence, the search can be performed on the controlled list of concepts, on the hidden dictionary and on the full text of the field of "teratogenicity". The truncation sign of AskSam+ is an asterisk. For example, - the asterisk at the end of the word "cardia *", will retrieve the terms "cardiac" or "cardial" whichever will appear in the text.

Table 26: **The hidden dictionary of body systems and birth defects. The user may use synonyms in order to initiate a search**

4**********

Hidden dictionary of option 4

| | | |
|---|---|---|
| Heart | = | Cardia* |
| Craniofacial | = | Defective ossification of the skull |
| Nervous-central | = | Neural tube |
| Mental retardation | = | Cognitive disturbances |
| Upper limb abnormalities | = | Hand anomalies |
| Upper limb abnormalities | = | Polydactyly |
| Lower limb abnormalities | = | Polydactyly |
| Growth deficiencies | = | Development retardation |
| Renal | = | kidney |
| Spastic paraplegia | = | quadriplegia |

---

In option 5, drugs which are linked to fetal toxicity are retrieved by a search performed on terms classified in to three categories which are listed in Table 27. The choice may be a specific toxicity or a hierarchical group. The retrieval is restricted to the controlled list and to the full text of the paragraph entitled "Fetal toxicity".

Table 27: **The three categories of terms used in searches for drugs which are linked to fetal toxicity (option number 5)**

5 **********

Drugs associated with potential fetal toxicity

Choose an option:

A. Toxicity related to a specific body system

B. Metabolic toxicity

C. General toxicity

---

Option 6 is used to retrieve all the drugs which are linked to mutagenicity and is activated from the main menu. The retrieval is performed on the full text of the paragraph entitled Mutagenicity", on the truncated word mutagen*.

Option 7 provides information about drugs associated with oncogenicity. It is possible to query either by entering a name of a neoplasm, or by using a two-level hierarchy of terms corresponding to body systems and neoplasms which are listed in Table 28. The search may be done at either level, thus allowing a wide or a narrow scope. The retrieval is performed on the control list of terms and on the full text of the paragraph entitled "Oncogenicity".

Table 28: **The two level hierarchical list of terms used to initiate a search for drugs linked to oncogenicity**

7**********

1. Blood and Lymph
2. Cardiovascular
3. Head and Neck
4. Gastrointestinal
5. Integumentary
6. Nervous
7. Placenta
8. Respiratory
9. Skeletal
10. Urogenital
11. Multiple

---

7.5.1**********

5. Integumentary
   a) Melanom*

---

7.6.1**********

6. Nervous
   a) Neuroblastoma
   b) Neuroectodermal tumours

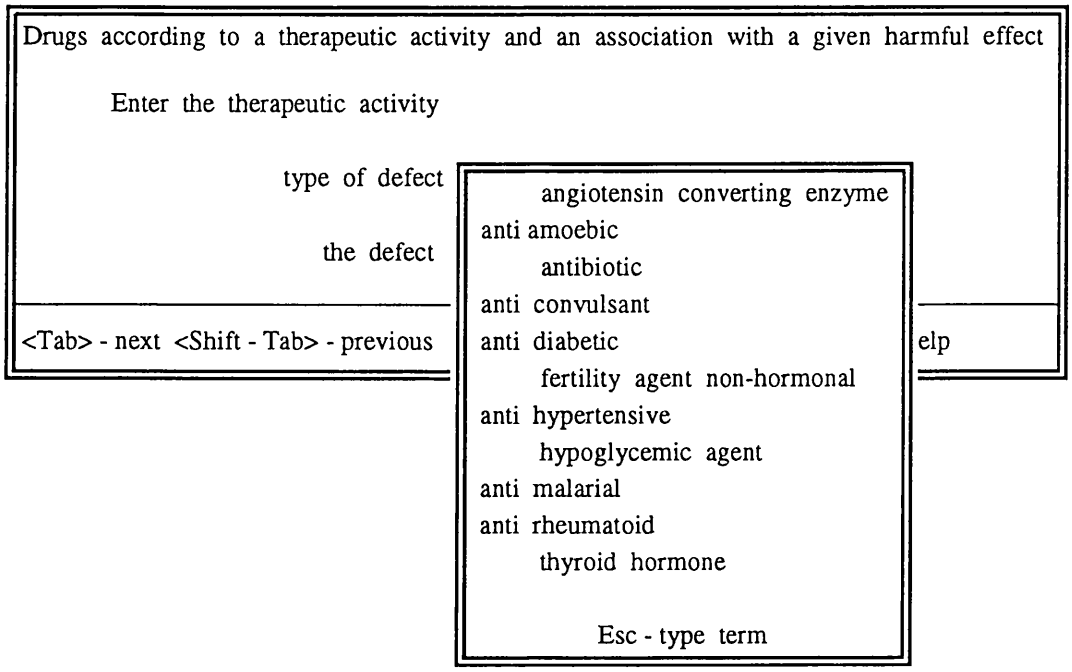
---

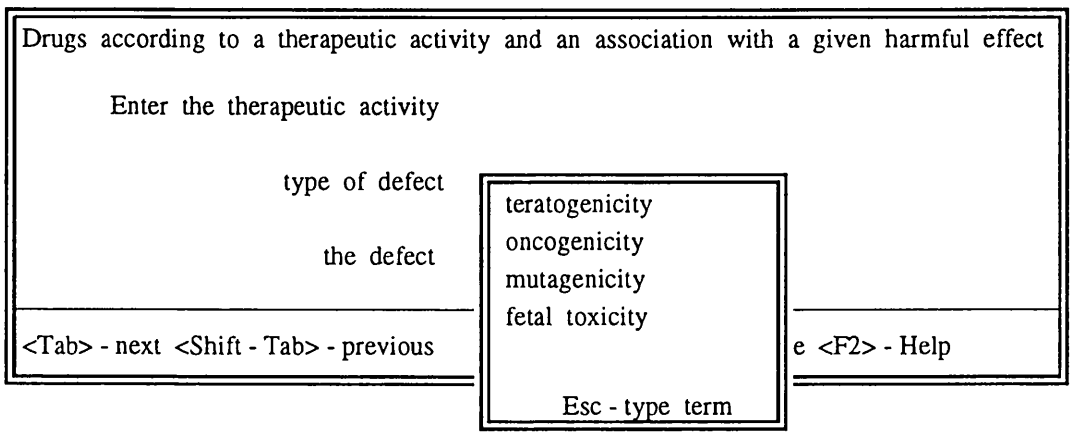
7.10.1**********

10. Urogenital
    a) Granulosa cell tumour
    b) Wilm's tumour

Option 8 unifies two options of a different character; it searches for drugs that have a given therapeutic activity and, in addition, are linked to certain harmful effects - birth defects, fetal toxicity, mutagenicity or oncogenicity (Figure 10). The required therapeutic activity and the harmful effect may be either typed or inserted from a given list. The output is a list of drugs which meet the two requirements.

**Figure 15: Search for drugs that have a given therapeutic activity and are linked to harmful effect.**



Option 9, the proximity search, allows the retrieval of drugs according to the appearance of two or more terms within a required distance and in a given order in the texts describing the drugs. For example,, the specifications could be "the words 'animal*' and 'experiment*', in this order, within the same sentence". The searches performed through this option may be saved together with their parameters for repeated use.

## 8.7 Conclusion

The question of whether physicians will accept the use of non-linear sophisticated hypertext software on their work-stations was answered by a study (Timpka, 1989), which demonstrates that they would. The study also showed that they would be especially keen if full text databases were provided and if the system provides them with information that is better suited to their needs which arise during routine practice.

The prototype of the database encompasses information intended to satisfy requirements for different levels of specificity of users' needs: data, references, and as part of future development - full text articles. It is up to the clinicians to use this information at a level compatible with the specific clinical situation.

The system is responsive to individual needs. The information which it provides is practical, clearly expressed and based on the best studies available in the literature. Special attention has been given to avoiding ambiguity in the text.

The database is organized in a modular and open way, so that it is easy to add data to each node, to form new nodes and to introduce new search options according to the developing nodes.

At present, the database contains one graphical node. In the future, though, with added graphs, figures or even videocassettes, the system may acquire characteristics of hypermedia, which are actually an extension of hypertext. Hypertext was found to be a promising medium for transfer of full text and factual information, as well as for continuous medical updating (Timpka, 1989). Future developments may also include additional subjects, e.g. the emerging field of fetal therapy, which involves direct routes of drug administration to the fetus (Miller, 1991).

The way in which this database is organized makes it suitable for loading into common PC, such as are owned by most physicians. As the demand to share

information with the patient increases, a database like the one presented here may help establish a "trialogue" between physician, patient and the computerized reference source.

# Chapter 9

## Summary and Discussion

In addition to routine supervision, a pregnant woman usually visits her physician in medical situations requiring drug treatment, or when concern arises regarding medication taken by the woman before her pregnancy became known. A visit initiates a decision making process that may result ultimately in a medical procedure - or none at all. When prescribing medical treatment to a pregnant or lactating woman, the physician must take into account all possible detrimental effects to the health of the fetus or the new-born infant.

Drug treatment in pregnancy has a number of ethical and legal implications (Stern, 1984, pp. 2-15). Many drug packages contain a disclaimer in accord with FDA regulations, stating that: "This drug has not been proven safe for pregnant women and children". As a result, physicians are reluctant to prescribe to pregnant women drugs, about whose potential teratogenicity, mutagenicity and fetal toxicity they do not have readily available information.

The general lack of supportive information about adverse effects of drugs has led to an overprotective attitude towards the fetus, rendering the mother-to-be a "therapeutic orphan" (Mucklow, 1986). Putting the information at the fingertips of the physician will ensure the best possible treatment for the woman, with as little harm to the fetus as possible. It is widely recognized that the practice of medicine and drug prescribing may be improved significantly by supplying the relevant information to the physician (Forrey, 1980; Dabanovic, 1985).

The Hippocratic Corpus (Hippocratic writings, 1978) set the tone which ruled medical knowledge for centuries, and its oath includes the statement:

> "I will hand on precepts, lectures and all
> other learning to my sons, to those of my
> masters and to those pupils duly apprenticed
> and sworn and to none other."

A mere handful of professionals were to acquire professional knowledge, and share it not with the masses. The patient was not involved in any manner in the considerations leading to the choice of medical procedure. Only recently have different approaches started to alter this perception of physician-patient relations. The paternalistic, authoritative approach is yielding to the "deliberative" one (Emanuel & Emanuel, 1992), in which the physician's duty is to fully inform the patients and to guide them through the intricacies of medical decision making. In this extremely libertarian

model, not only is the patient informed about his/her condition, but also his/her opinion carries weight in decisions, while maintaining a dialogue with the physician. An interactive triangle may be formed between the physician and the patient, who require information, and the computerized database as the information provider.

Results of users' studies, described in the previous chapters, show that attitudes of physicians to drug prescription in pregnancy and lactation vary, whence their information needs and the level of desired detailing vary as well. Prescribing habits are influenced by several factors.

The cognitive factor has to do with attitudes towards information acquisition and learning. The main effect of information acquisition is that the individual is led from uncertainty to assurance with respect to a specific problem to be solved (Whittemore & Yovits, 1973). The diligence with which a physician will seek to reduce his/her own level of uncertainty regarding a clinical problem depends upon certain qualities of that "information-seeking" physician, on the perceived benefit obtainable from the acquired information and on the qualities of the knowledge resource (Curley, Connely & Rich, 1990).

The perceived benefit obtained from the information is judged by the immediacy of the problem, the complexity and significance of the information, and the degree of irreversibility of the decision based on the acquired knowledge. The perception of the benefit is influenced also by the sense of accountability of the physician to the patient and to society.

Knowledge resources may be characterized according to a number of qualities: the extensiveness of the material, its relevance to the immediate problem and lucidity to the physician, its credibility, physical and functional accessibility and clinical applicability.

The qualities of the physician performance include his or her clinical expertise, level of motivation, familiarity with the information resource and the time it takes him or her to obtain information.

The accessibility of information is a major factor influencing its use and the decision making process. Finally, it should be noted that costs may impose serious constraints upon usage.

Additional non-cognitive factors which were found to impact the prescribing practice are: the basic attitude toward drug prescribing in pregnancy, sets of beliefs about drug efficacy, age, circumstances of training and the work environment. (Bradely, 1991)

The type of presentation of the information is important as well. Haaijer-Ruskamp, Denig and Zijsling (1987) demonstrated that printed technical drug therapy information is of little value in affecting entrenched drug prescribing habits. Denig, Haaijer-Ruskamp and Zijsling (1990) have found, that drug bulletins seeking to enhance knowledge about drug efficacy and adverse effects had a variable and unpredictable effect on drug prescribing behaviour. Interestingly, in reply to the questionnaire many expressed the need for bulletins about innovations and caveats on drug use. Plumridge and Berbatis (1989) have found that drug bulletins may improve prescribing in specific community settings. They recommend the inclusion of summaries in these publications.

The methodology of triangulation applied in the present study uses qualitative research methods. Fidel (1993) discusses in depth the characteristics of this approach, describing it as humanistic and naturalistic, dealing with "qualities of objects, persons and events that enable us to identify and classify them". This type of research is non-controlling, and its purpose is to understand a phenomenon as seen by respondents, while focusing on processes.

The appropriateness of this method for achieving the aims and purposes of this project (see paragraph 1.3) is obvious, when noting that the first purpose was to delineate the profile of a specific population and its information needs. This is precisely the kind of investigation most suitable for qualitative research, which indeed served well the task of characterizing the target population and its user needs. This, in turn, led to the design of the database model.

Two major sources of knowledge quoted by physicians are professional journals and consultations with colleagues. The relative importance of these two sources differs in various studies (Curley et al., 1990). In the present study it was found that most gynaecologists/obstetricians rely heavily on printed information in journals and are also willing to consult colleagues when necessary. Another often-quoted source, albeit of doubtful credibility, is pamphlets from the pharmaceutical industry.

It appears that almost all physicians read these pamphlets, although generally, they do not trust their content. Colvin (1990) describes a model in which the pharmaceutical industry can play an active and more positive role in providing drug information services, by staffing accredited pharmacists as drug information officers who will interact with hospital pharmacists. The model also includes guidelines for obtaining useful drug information from pharmaceutical manufacturers. Advertisements in medical journals constitute an additional source of drug information, in which the

FDA requires "a fair balance" and accurate and non-misleading information (Morris & Banks, 1989).

It is therefore recommended that pharmaceutical companies take seriously their role as providers of accurate, meaningful and credible drug information. This refers mainly to the leaflets accompanying each drug package.

One study (Finchan, 1986) has demonstrated that pharmacists rate low on a scale of importance of drug information sources, being outranked by colleagues and consultants.

Effective use of medical information is often impeded by the fact that it is scattered throughout many sources, and not always available or easily accessible to the user (Hibberd & Meadows, 1980). The multitude of problems concerning the content of the information were discussed in chapter 8: it may be incomplete, controversial or often, due to its statistical characteristics, of little relevance to a specific case. Benson, Goldstein, Fitzpatrick, Williamson and Humtzinger (1986) state that no single source of information can satisfy the needs anymore, even within a restricted medical domain. Therefore, retrieval systems should screen diverse information sources and incorporate a mechanism for unifying the resulting search.

These problems can be dealt with by selecting the material according to strict criteria, then processing it in a way that will provide various levels of specificity, such as: textual data, references to base the information upon and, ideally, the full text articles, for those clinicians who like to verify the details of the methodology used in the quoted study. In view of the increasing number of PCs found in doctors' offices, the ideal tool for doing all that is, of course, a computerized database. Extensive use of databases in the medical field may help reduce complications and resulting costs. For example,, Sager, Haug, Turner and Hebertson (1991) have developed a system for the prediction of pregnancy outcome and early identification of pregnancies at risk.

All medical database designers must overcome the obstacle of the prevalent use of natural language in professional communication in medicine. The problem is somewhat mitigated by the use of technical terms, yet still there is hardly a conformity with the rigid formalism and limited vocabulary of artificial computing languages. This difficulty is compounded by the lack of a vocabulary for expressing biomedical phenomena. Much effort is being invested in solving this problem (Gabrieli & Speth, 1990). Hypertext tools help achieve this goal thanks to their flexibility, that allows easy incorporation of free text. In addition, these tools facilitate knowledge transfer, and their use in information retrieval systems enables the user to follow almost any information path at will. The highly connected structure of nodes and links can be

exploited to build sophisticated retrieval systems (Lucarella, 1990), especially those which consist primarily of test documents. Afrati and Koutras (1990) described a formal hypertext model with a powerful supporting query mechanism. Streitz, Walker, Waterworth, Wright and Trigg (1990) stressed the capability of hypertext to meet the requirements of the human user-computer interface, thus having the potential to seed the development of a new generation of information systems.

When designing the database, a choice had to be made of a vocabulary source sufficiently flexible for the use of non-standardized medical terms, as used by practitioners, and at the same time one which is suitable for organization in hierarchical structure (Satamura & Do Amaral, 1992). The ICD-10 classification of diseases (World Health Organization, 1992), being the major internationally accepted classification system of medical diagnoses and terms, was chosen as a basis.

Information, especially on drugs, is rarely objective (Ducrot et al., 1989). Therefore, when creating a textual database such as the model resulting from this research, the literature included in it should be evaluated carefully and neutrally by a committee of highly qualified professionals. Members of such a committee should be responsible for the content of the database, and should represent the different disciplines involved in the field - in this case obstetrics-gynaecology, teratology, embryology, pharmacology, genetics and neonatology. The specialists will ensure reliable analysis and presentation of the data. Scientific integrity will be retained, despite economical pressures of the pharmaceutical industry.

A physician's office equipped with a PC, which is connected to local and world-wide telecommunications lines, has begun to appear on the Israeli medical scene. This combination of computing power and communication capabilities will enable the clinician, in the near future, to have access to most of the information required in his or her practice. The majority of physicians in the country are already using PCs. In addition, libraries of medical schools and hospitals, hospital wards and some of the clinics are using LANs for searching databases on CD/ROM. The telecommunications infrastructure in Israel is highly reliable throughout the country, and the medical community has access to world-wide sources such as Grateful Med via Internet. Medical schools contribute to the proliferation of computer systems in medical practice, by teaching students how to be intelligent users of computerized databases created for the end-user.

The convergence of the above mentioned factors will lead to a reality in which medical information systems will be integrated in daily clinical work.

One must also be aware of the fact that, in practice, the ability to access valuable information also depends on the availability of simple user-friendly interfaces to computerized systems.

The database model and the methodology used to design it may serve as a basis for development in various directions, one of them being the application to other fields. The information needs and required forms of presentation may differ between the various medical disciplines; for example,, a traumatologist working in an emergency room has different needs from those of an ophthalmologist working at an ambulatory clinic by appointments. Indeed, a Nigerian study (Osiobe, 1986) found that the use of various information sources differs widely between ten medical specialities. The system was designed according to principles which can be applied to other medical specialities, irrespective of the differences between them.

The service provided by the database can be brought to a wider public of users by means of additional technological routes. For example,, one may consider introducing such information systems into Internet. Eventually, every physician would be able to receive the required information at his or her place of work with short response time and with minimum effort. This may provide also a new ground for user needs studies in a new environment, and possibly give rise to the development of new tools.

Finally, new information processing capabilities may be developed and added to the system. Although the technology is not yet available, in the future we may be able to identify the function and activity of drugs solely on the basis of chemical moieties. An example of such developments may be seen in the implementation of a database containing chemical moieties of potential mutagenicity (Takihi, Zhang, Klopman & Rosenkranz, 1993). Thus, the implications of information technology should be harnessed to the improvement of the quality of treatment of the patients.

# Chapter 10

# Analytical and Reflective Evaluation of the Thesis

Upon the completion of the thesis, somewhat ambiguous points and some inaccuracies in the drug information database were pointed out. Hence a need arose for some clarifications and critical analysis, followed by a recommendation for improvement of similar future information systems.

## 10.1 User Studies

### 10.1.1 Focus Group Interviews (FGIs)

The FGIs were part of the user studies. The essence of this methodology is the faithful reflection of the participants' views. The author is required to summarize the contents of the proceedings without any interpretation or alteration.

The statements expressed in all sections of that chapter were opinions voiced by obstetricians participating in the FGIs; they do not reflect views of the author. This is true also for bibliographic sources mentioned, that is. the "Briggs" book, periodic leaflets produced by various health authorities, the Martindale Pharmacopoeia, databases such as MEDLINE or the IOWA system and the professional literature in pharmacology and obstetrics/gynaecology. Obviously, other sources of equal importance are available, which will be detailed in the section of bibliographic sources for the database. However, they were not mentioned by the participants, hence could not be included in the FGI section. The obstetricians mentioned, that all pregnant women in Israel were prescribed iron and vitamins. This practice was adopted following studies documenting widespread anaemia in pregnant women and infants in Israel in the 1960s (Palti & Tulchinsky, 1988). Routine iron supplementation was adopted in all prenatal clinics in Israel in the late 1970s (Palti & Tulchinsky, 1988),.reducing significantly the occurrence of haemoglobin levels below 10g/1 in pregnant women (Gofin, Adler & Palti, 1988).

An ambiguous statement, expressed in one of the FGI sessions and misunderstood, has led to mistakenly quoting insulin as traversing the placenta. Obviously, insulin is a large protein molecule that will not cross the placental barrier.

### 10.1.2 Statistical Analysis of the Questionnaire Responses - Clarifications

A number of statistical methods were applied in the study, picked for their appropriateness for the various methodologies used. The degree of correlation between measures in the questionnaire was the only parameter assessed by Pearson coefficients - a parametric test applicable to quantitative data measured by an interval scale.

Behavioural sciences deal primarily with relative and subjective values, which are ordinal and non-interval and so subject to non-parametric tests. This obstacle is commonly overcome by measuring behavioural variables by arbitrarily ranked scales, for example, by attributing the numbers 1-5 to degrees of frustration. This methodology is widely applied - the Spilberg test of anxiety and the Bender and Wecsler intelligence tests are two well known examples - thus permitting the use of parametric tools.

The weakness of this approach lies in the assumption that subjective values may be translated into interval scales of data, with a normal distribution. Even though the validity of this assumption cannot be absolutely proven in most cases, it has become the basis of statistical analysis in most behavioural studies.

The level of uncertainty may be minimized by testing whether the ranked values obtained have a normal distribution. If they do, then the use of parametric tools is acceptable. This approach, however, is not applicable to all cases.Thus, in the part of

the questionnaire that deals with prescribing attitudes, the responders were divided into four groups, A to D. The results were expressed as percentages of frequencies of each type of response. As these may not be averaged, the non-parametric $\chi^2$ test, which measures the discrimination of frequencies between groups, has been applied.

The variables assessed in the study were validated for lack of bias. Possible bias in other variables that were not evaluated is, of course, not excluded by the above practice. This limitation applies to all studies of this sort and is unavoidable.

When the distribution of data is asymmetrical and skewed by "outliers", averages are optimally expressed by "medians". In the present study, however, the distribution of responses to the items in the questionnaire were symmetrical; hence "means", which deliver more accurate information and are more sensitive to differences between clusters of data, were computed.

## 10.2 The Drug Database

### 10.2.1 General Clarifications

In defining potential hazards to the fetus from drugs administered to the pregnant woman, a distinction was made between "teratogenicity" and "fetal toxicity".

Teratogenicity is defined in this thesis as "functional or anatomical defects in fetal body systems". This is in line with Smithells' (1987) definition of a teratogen as "anything which increases the chances of a baby being born with a structural or functional abnormality".

Fetal toxicity is described as "poisonous effects on fetal metabolism or body system". This implies disruption of biochemical systems and direct toxicity, in distinction from anatomical malformations. Hawkins (1981) mentions a few examples, such as: fetal

methaemoglobinaemia may be induced by prilocaine, aminoglycoside antibiotics may be ototoxic, a platelet dysfunction may be induced in the new-born by administration of aspirin in late pregnancy (Bleyer & Berckenridge, 1970), and novobiocin may lead to inactivation of bilirubin binding sites, resulting in neonatal jaundice. However, if it is made clear that biochemical insults are part of functional teratogenicity, this additional classification is not necessary (Smithells, 1987). Much of the data in the literature concerning teratogenicity of drugs is conflicting, anecdotal or based on animal studies (Hawkins, 1981). In such cases, one is compelled to supply the available data without making any definite statement, leaving the final judgement to the clinician.

Mutagenicity and carcinogenicity occurring in offspring of mothers treated with certain drugs during pregnancy is specifically mentioned in some publications. Therefore, such subheadings were built into the database.

The effect of drugs on the fetus is influenced by maternal drug plasma levels. Most drugs cross the placenta, yet the dynamics of the transplacental transport will affect the final amount of drug reaching the fetus. Models have been proposed to study that influence (Bourget, Roulot & Fernandez, 1995). This controversial issue may not have been clarified sufficiently in the database.

Lander and Eadie (1991) claim that plasma levels of anti-epileptic drugs are reduced in pregnancy, hence their dosage should be increased accordingly; Folb and Dukes (1990, Appendix xii) make the distinction between bound and unbound drugs. This is especially important in anti-epileptic agents such as phenytoin, where plasma protein binding is decreased, causing an increase in unbound drug levels (Perucca, 1984). Hawkins (1981, 1987) recommended not to increase the dosage of these drugs during pregnancy. Yerby et al. (1990) confirmed that drug-protein binding of anti-epileptic drugs is altered during pregnancy, resulting in a decline in their mean total

concentration. However, the free fraction of all drugs tested was elevated. The authors suggest to monitor the free fraction and not the total concentrations.

### 10.2.2 Preconceptional Counselling

The issue of preconceptional counselling is ouside the strict scope of the present work. However, one can not disregard its importance in preventing fetal damage in some chronic maternal conditions, such as: diabetes mellitus, hyperthyroidism, epilepsy, chronic anticoagulation, hypertension and others. Counselling allows advance planning of treatment for the duration of the anticipated pregnancy. For example,, a diabetic woman could be switched in time from chlorpropamide to insulin, or folic acid might be added to the prescription of an epileptic patient treated with phenytoin (Kuller & Laiffer, 1994). As it happens, a large percentage of pregnancies are unplanned - above 50% in one study in the US (Jones, Forest, Henshaw, Silverman & Toreres, 1988). Israel has a high incidence of unplanned multiple pregnancies in the same families, who shun contraception due to religious beliefs. This is common in a large segment of the Jewish population and in the majority of the non-Jewish population. This might explain partially why in the user studies there was no reference to preconceptional counselling

### 10.2.3 Comments on the Drugs

**Phenytoin**

One of the commonest side-effects of phenytoin treatment in epileptic patients is hypertrophy of the gums. It may also appear as part of the fetal hydantoin syndrome (Nanda, Kaur, Bhakoo, Kapoor & Kanwar, 1989).

The best ways to prevent fetal abnormalities in women treated with anti-convulsant drugs are preconceptional counselling and folic acid supplementation. This is especially true when phenytoin is used. However, the present database is not meant to deal directly with prevention or with the side effects of drug administration in the gravid woman. It is designed specifically to assist the clinician in evaluating the risk to the fetus due to exposure of the expectant mother to a drug. The need for folic acid supplementation is mentioned in its context, but in view of its importance, it should have been further emphasized.

A more forceful and clear statement is also called regarding vitamin K prophylaxis, which is mandatory following phenytoin treatment and is nowadays a routine practice in newborns, especially if premature.

A relatively small number of anecdotal cases of malignancy in newborns of phenytoin treated mothers has been reported. Thus the statement about oncogenicity of phenytoin should be better phrased as: "phenytoin has been reported as a human transplacental carcinogen". The controversy regarding dosage of anti-epileptic drugs in pregnancy has been dealt with previously.

**Ciprofloxacin**

There is no need to distinguish between teratogenicity and fetal toxicity with regard to this drug. “Fetal toxicity” referred to a study demonstrating degenerative arthropathy in "juvenile animals". However, extrapolation of such results to fetuses is questionable, if at all possible. On the other hand, another study (Berkovitch, Pastuszak, Gazarian, Lewis & Koren, 1994) has documented 38 cases where

quinolones were given in the first trimester of human pregnancy, without untoward effects in the infants.

**Clomiphene**

As this drug is an ovulation inducer, there is no need for a statement that "it is contraindicated in pregnancy". Clomiphene has been chosen as an example of a drug which is never indicated for use in pregnancy, but whose inadvertent administration may occur. Although side effects of drug treatment are not dealt with in this database, it should have been mentioned that clomiphene is associated with an increased risk of multiple pregnancies (Levene, Wild & Steer, 1992) and that clomiphene-induced pregnancies sometimes end in spontaneous abortion. It would have been more appropriate to cite first the studies with large series of patients, in which no significant association was found between birth defects and clomiphene administration, and then to mention the anecdotal reports possibly linking clomiphene to neural tube defects, the weight of the larger studies being much greater.

The subheading of oncogenicity refers to a late appearance of tumours in treated women. As this is not related to fetal oncogenicity, this paragraph should not not have been included.

**Chloroquine**

The incidence of fetal abnormalities potentially associated with chloroquine is low. It is considered to be the safest antimalarial agent for treatment of cases of chloroquine-sensitive P.falciparum malaria. This fact is stated in the text. Amongst the rare cases of fetal malformations, an important one is retinopathy (Hawkins, 1981; Wolfe & Cordero, 1985), which should have been mentioned explicitly. As the drug crosses the placenta, haemolytic anaemia may be induced rarely in a G-6-PD deficient newborn. Such a warning should have been included, because the incidence of G-6-PD deficiency is relatively high in most Mediterranean populations.

**Captopril**

The opening sentence of the paragraph on fetal toxicity: "Fetal toxicity seems to be fairly common" is an overstatement. The reported cases of renal insufficiency, oligohydramnios, growth retardation, prematurity and pulmonary hypoplasia were serious enough for the issuance of a warning, but their overall frequency is relatively low.

**Carbamazepine**

Of the fetal craniofacial abnormalities associated with carbamazepine, cleft palate is the commonest (Lander & Eadie, 1991). This should have been stated specifically.

**Chlorpropamid**

As explained before, the database deals with drug exposure in pregnancy, either inadvertent or therapeutically indicated for the mother. However, in the present case a note should have been added, that a diabetic woman planning pregnancy must be advised to switch from chlorpropamide to insulin prior to conception, in order to avoid exposure to chlorpropamide during the first trimester.

**Reserpine**

This drug was chosen as an example of a previously used anti- hypertensive medication which was gradually phased out from use in pregnancy, due to accumulating reports of maternal and fetal toxicity. The fact that this drug had been assigned a high risk factor (D) was indicated. However, it was not clearly stated that its use in pregnancy had been abandoned and that one of the causes was induction of extreme nasal congestion in the newborn which resulted in respiratory distress.

Upon repeated reflection, the choice of this drug may have been unwise,as it is of little relevance to present obstetric practice.

## 10.3 Sources for the Database Model

There are about 22.000 journals (current titles) in the biomedical field. Some of the journals are covered by computerized databases. The major bibliographic databases for drug treatment are: Medline, Excerpta Medica, BIOSIS, Pascal and others. A comprehensive search on a subject requires the use of all major databases, since they differ in many aspects, among which is the choice of journal coverage.

Medline is considered the authoritative source for information on drugs for the FDA, the Israeli Ministry of Health and many other organizations. Excerpta Medica has its reputation due to the section on drugs, which covers a wide scope of scientific publications with an emphasis on European literature. These two databases use a similar indexing system including the MESH vocabulary (Medical Subject Headings), which Excerpta Medica has adopted from Medline. These indexing systems are essential for an efficient literature retrieval.

Another form of computerized databases are the data banks on drugs. These provide data on various topics concerning drug treatment, with or without reporting the source of the information.

An essential source of information is the pharmacopoeias, such as Martindale's, the British National Formulary, the Physicians Desk Reference and others. These reference books include essential information on drugs, which is updated periodically, and are of much help in the treatment of patients. Books with drug information on specific topics bear a special value for the clinician: Gilstrap and Bertis (1992); Ledward, Hawkins and Stern (1991); Niebyl, 1988) and others which deal with drug treatment in pregnancy and lactation. For the model of the database, it was decided to choose one representative source from each category: a bibliographic database (Medline), a pharmacopoeia (Martindale), ecetera. When constructing a real life database for clinical use, a maximum of information sources should be used.

All the information to be included in the database, along with the sources from which it was retrieved, should be submitted for review and evaluation by highly qualified medical professionals.

## 10.4 Updating of the System

The information on the drugs included in the database should be collected by an information expert. For the updating, facilities such as the "Allert" services provided by the databases hosts should be used. Queries on specific usage of drugs by trade or generic names (according to the particular database) should be stored in several databases such as: Medline, Excerpta Medica, etc. When the database is periodically updated by the host (for example, KRI-Dialog), usually once a week, a list of new publications on the topics queried is produced. This material should be screened by the medical experts. Once the full text of the selected references has been gathered by the information expert, it should be evaluated further by the medical consultant. Only then should the information expert update the database by processing the new material into the respective records, fields and links. Thus, a successful outcome in building an effective database is dependent upon a close interaction between the information scientist and the medical expert.

An information system has a natural "life span", evolving and growing, till it reaches its maximal use; then it declines gradually, eventually being replaced by other systems developed as new technologies emerge.

## 10.5 Final Comments and Recommendations

The methodological approach to the user studies yielded the relevant information about user needs of the target population studied, namely the gynaecologists-obstetricians in Israel. The choice of the hypertext Asksam+ software allowed the design of a flexible and user friendly database, which is easy to update as well.

The main problems were encountered in the contents of the database as described. The most prominent ones were the controversial distinction between "teratogenicity" and "fetal toxicity" and the ill-conceived choice of Reserpine as one of the representative drugs. These deficiencies may be traced all to one source - the lack of a critical guidance by an experienced gynaecologist-obstetrician with a solid pharmacological background all along the construction of the database.

It is essential to obtain participation of such a professional in the design, execution and updating of an information tool destined to assist a given population of medical users. The lesson which may be derived from all the above is:

1. The construction of a user friendly drug information database forphysicians is feasible.
2. The reliability and successful outcome of such a project depends upon a collaborative effort of an information scientist and an experienced clinician.

A final caveat to keep in mind is that, even when a rigorous control is applied to the information flow, some bias can not be eliminated completetely, as each expert has his or her unavoidable professional predjudices, based on personal experience. Therefore, there is no "absolute truth" in medicine, and alternative approaches are available to almost any problem. This pluralism should find its expression in presenting information to the clinician, who will be the final judge of its use for the benefit of the patient.

# Appendix A

## Content Analysis of Queries Submitted to Drug Information Centres in Tel-Aviv and Newcastle.

TEL – AVIV

| Nonproprietary Name | Trade Name (Proprietary) | Chemical Name | Risk Factor | Group of Drugs with Similar Activity | Gestational Age/ Pregnancy | Lactaion | Disease | Human/ Animal | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 1. | Resprim | | D | | 1.First Trimester | | | | |
| 2. | | Diethylstil-bestrol | Xm | | 2.Pregnancy | | | | Follow Up Studies |
| 3. | Parlodel | | Cm | | 3. | | | | Teratogenicity |
| 4. | | | | Beta Blockers | 4.Pregnancy | | | | |
| 5.Ritodrine | | | Bm* | | 5. | | | | Teratology |
| 6.Thyroxine | | | Am | | 6.Pregnancy | | | | |
| 7.Metronidazole | | | Bm | | 7.Pregnancy | | | | |
| 8.Prostaglandine | | | | | 8.First Trimester | | | | |
| 9.Scopolamine | | | C | | 9.Foetus,Embryo | | | H,A | |
| 10.Vitamin C | | | A* | | 10.Pregnancy | | | | Dosage |
| 11.Valproic Acid | | | D | | 11. | | | | Teratogenicity |
| 12. | Bolvinon | | | | 12. | | | | Teratogenicity |
| 13.Tinidazole | | | | | 13.First/Third Trim. | | | | |
| 14.Terfenadine | | | C | | 14.Pregnancy | | | | |
| 15. | | | | | 15.Effects on Foetus | | Lupus Erythe-matosus | | Drug Therapy |
| 16. | | | | Neoadjuvant Therapy | 16.Pregnancy | | | | |
| 17.Dactinomycin | | | Cm | | 17.Third Trimester | | | | |
| 18.Methotrexate | | | D | | 18.Pregnancy | | | | |
| 19. | | | | Chemotherapy | 19.Early Pregnancy | | | | |
| 20.Ifosfamide | | | D | | 20.On Foetus | | | | |
| 21.Metronidazole | | | Bm | | 21. | | | H,A | Teratogenicity |
| 22.Aspirin | | | C* | | 22.Foetus,Embryo | | | | |
| 23.Salicylate | | | | | 23. | Breastfeeding | | | |
| 24.Cortisone | | | D | | 24.20th Week Preg. | | | | |
| 25. | | | | Anti-Inflamatory Agents | 25.Foetus,Embryo | | | | |
| 26.Valproic Acid | Depalept | | D | | 26. | | | H | Teratogenicity |
| 27.Vitamin D | | | A* | | 27.First Trimester | | | | Dosage |

| Nonproprietary Name | Trade Name (Proprietary) | Chemical Name | Risk Factor | Group of Drugs with Similar Activity | Gestational Age/ Pregnancy | Lactaion | Disease | Human/ Animal | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 28. | | | | Antimicrobial | 28.Third Trimester | | | | Treatment |
| 29.Ampicillin | | | B | | 29.First Trimester | | | | |
| 30. | | | | Antibiotics | 30. | | | | Prophylaxis to Abortion |
| 31.Diclofenac | Voltaren | | B | | 31. | | | | Teratogenicity,Side Eff. |
| 32. | | | D | Benzodiazepines | 32.Foetus, Embryo Newborn | | | | |
| 33. | | Propanolamines | | Propanolamines | 33.Pregnancy | | | A | Effects on Uterus |
| 34.Serotonin | | | | | 34.Pregnancy | | | A | Effects on Uterus |
| 35. | | Lithium Carbonate | D | | 35.Pregnancy | | | | |
| 36. | | | | Neoroleptic Agents | 36.Pregnancy | | | | |
| 37. | | | | Tricyclic Antidepressants | 37.1st Tri.,Newborn | | | H,A | |
| 38.Tetracycline | | | C | | 38.First Trimester | | | | |
| 39.Ibuprofen | | | B* | | 39.Pregnancy | | | | |
| 40.Cephalexim | | | | | 40. | Excertion to Milk | | | |
| 41.Folic Acid | | | A* | | 41. | Lactation | | | |
| 42.Primaquine | | | C | | 42.Third Trimester | | | | |
| 43. | | | | Oral Contraceptives | 43. | Lactation | | | |
| 44.Cephalexin | | | Bm | | 44.Pregnancy | | | | Adverse Effects |
| 45.Clonazepam | | | C | | 45.Second Trimester | | | | Administration |
| 46.Cortisone | | | D | | 46.Pregnancy | | | | |
| 47.Clonidine | | | C | | 47.Early Pregnancy | | | | Teratogenicity,Side Eff. |
| 48 | Clonex | | C | | 48. | | | | Teratogenicity |
| 49. | Moxypen | | B | | 49.Pregnancy | | | | Side Effects |
| 50.Cephalexin | | | Bm | | 50. | | | | Passage through Placenta |
| 51.Nafcillin | | | B | | 51.Foetus, Embryo | | | | |
| 52. | | Ascorbic Acid | A* | | 52.Foetus | | | H,A | |
| 53. | | | | | 53.Pregnancy | | Psoriasis (severe) | | Treatment |
| 54.Tinidazole | | | Bm | | 54.Pregnancy | | | | Administration |

| Nonproprietary Name | Trade Name (Proprietary) | Chemical Name | Risk Factor | Group of Drugs with Similar Activity | Gestational Age/ Pregnancy | Lactaion | Disease | Human/ Animal | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 55. | Flagyl | | Bm | | 55.Pregnancy | | | | Follow up studies on Infant |
| 56. | | | | Analgesics | 56.Pregnancy | | | | |
| 57.Aspirin | | | C* | | 57.Pregnancy | | | | Prevent Preeclampsia |
| 58.Pivampicillin | | | B | | 58.Pregnancy | | | | |
| 59. | | | | | 59.Pregnancy | | Hepatitis Non A, Non B | | Treatment |
| 60.Vitamin A | | | A* | | 60.Pregnancy | | | | Dosage |
| 61.Flucytosine | | | C | | 61.Pregnancy | | | H | |
| 62.Codeine | | | C* | | 62.Very Early Preg. | | | | |
| 63.Clonidine | | | C | | 63.Third Trimester | | | H | |
| 64.Bromocriptine | Parlodel | | Cm | | 64.2nd/3rd Tri. | | | | |
| 65. | Vermox | | C | | 65.Pregnancy | Lactation | | H | |
| 66. | Primolut-Nor | Northisterone Acetate | D | | 66. | | | H | Teratogenicity, Mutagenicity |
| 67.Somatomedin-C | | | | | 67.Foetus | | | | Fetal Blood |
| 68.Marcaine | Bupivacaine | | C | | 68.Pregnancy | | | | Maternal Neonatal Blood Concentration |
| 69. | Thalidomide | | X | | 69.Pregnancy | | | H,A | Malformations, Scientific Evidences |
| 70. | | | | Non Steroidal Anti Inflamatory | 70. | Lactation | | | |

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| Nonproprietary Name | Trade Name (Proprietary) | Chemical Name | Risk Factor | Group of Drugs with Similar Activity | Gestational Age/ Pregnancy | Lactaion | Disease | Human/ Animal | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 1. | | | | | 1. | | | | Hepatitis B vaccine prior to conception |
| 2.Paracetamol | | | B | | 2. | | | | Overdose |
| 3.Dothiepin | | | D | | 3.First Trimester | | | | |
| 4.Clotrimazole | | | C | | 4.Early Pregnancy | | | | Clotrimazole-cream |
| 5.Temazepam | | | | | 5.Pregnancy | | | | Poisoning |
| 6. | | | | Anti-Thyroid Drugs | 6. | Breastfeeding | | | Anti-Thyroid Drugs |
| 7.Benzodiaze-pines | | | | | 7.Pregnancy | | | | |
| 8.Domperidone | | | | | 8.Pregnancy | | | | |
| 9. | | | | | 9.Foetus | | | | Effects of exposure to u.v. sunlamps on foetus |
| 10.Chloropro-mazine | | | C | | 10.Pregnancy | | | | |
| 11. | Eugynon 30 | | | | 11. | | | | Conceived when taking... |
| 12. | | | | Anticonvulsants | 12.Pregnancy | | | | |
| 13.Lignocaine, Adrenaline | | | | | 13.Late Pregnancy | | | | |
| 14.Buprenor-phine | | | | | 14.Third Trimester | | | | |
| 15.Ipecacuanha | | | | | 15.Early Pregnancy | | | | Syrup |
| 16.Idoxuridine | | | C | | 16.Pregnancy | | | | |
| 17. | | Pyrazinamide | | | 17.Pregnancy | | | | |
| 18.Carbamaze-pine | | | Cm | | 18.Pregnancy | | | | |
| 19.Vitamine A | | | A* | | 19.Early Pregnancy | | | | |
| 20.Lofepramine | | | | | 20.Pregnancy | | | | |
| 21.Naftido-furyl | | | | | 21.First Trimester | | | | |
| 22. | | | | | 22.Pregnancy | | | | Turpentine Oil |
| 23. | | | | Antidepressants | 23.Late Pregnancy | | | | |
| 24.Metromida-zole | | | Bm | | 24.Pregnancy | | | | |

| Nonproprietary Name | Trade Name (Proprietary) | Chemical Name | Risk Factor | Group of Drugs with Similar Activity | Gestational Age/ Pregnancy | Lactaion | Disease | Human/ Animal | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 25.Sulpiride | | | | | 25.Pregnancy | | | | |
| 26.Warfarin | | | D | | 26.Pregnancy | | | | |
| 27.Ergotamine/ Dothiepin | | | D | | 27.Pregnancy | | | | |
| 28.Dothiepin | | | D | | 28.Pregnancy | | | | |
| 29.Pancreatin | | | | | 29.Preganacy | | | | |
| 30.Salphasalazine/ Cholestyramine | | | sulp.* choleC | | 30.Pregnancy | | | | |
| 31.Domperidone | | | | | 31.Pregnancy | | | | |
| 32.Dothiepin | | | D | | 32.Pregnancy | | | | Overdose |
| 33.Flecainide | | | | | 33.Pregnancy | | | | |
| 34. | | | | Anaestheics | 34.Pregnancy | | | | |
| 35.Carbamazepine | | | C | | 35.Pregnancy | | | | |
| 36.Phentermine Thiazide Triamterene | | | C,?,D | | 36.Early Pregnancy | | | | |
| 37.Thyroxine | | | | | 37. | Breastfeeding | | | |
| 38. | | Norethisterone | Xm | | 38.Pregnancy | | | | |
| 39.Acetarsol | | | | | 39.Pregnancy | | | | |
| 40.Flupenthixol | | | C | | 40.Pregnancy | | | | |
| 41.Metoclopramide | | | Bm | | 41.Pregnancy | | | | |
| 42. | X-Prep,Picolax | | | | 42.Pregnancy | | | | |
| 43.Tetracycline | | | D | | 43.Pregnancy | | | | |
| Trimethoprim | | | Cm | | | | | | |
| 44.Clemastine | | | C | | 44.Pregnancy | | | | |
| 45.Acyclovir | | | Cm | | 45.Pregnancy | | | | |
| 46. | | | | | 46. | Breastfeeding | | | Rubella vaccine |

| Nonproprietary Name | Trade Name (Proprietary) | Chemical Name | Risk Factor | Group of Drugs with Similar Activity | Gestational Age/ Pregnancy | Lactaion | Disease | Human/ Animal | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 47.Carbamaze-pine | | | Cm | | 47.Pregnancy | | | | |
| Minilyn | | | | | Pregnancy | | | | Overdose |
| 48.Aspirin | | | | | 48. | Breast Milk | | | In relation to Reye's Syndrom |
| 49. | | | | Antibiotics | 49.Pregnancy | | | | |
| 50. | | Diethylpropion | B | | 50.First Trimester | | | | |
| 51.Lofepramine | | | | | 51. | Breastfeeding | | | |
| 52.Trimetoprim | | | Cm | | 52.First Trimester | | | | |
| 53. | | | | Benzodiazepines | 53.Pregnancy | | | | |
| 54. | | | | Antidepressants | 54.Late Pregnancy | | | | |
| 55.Clobazam | | | D | | 55.Pregnancy | | | | |
| 56.Cimetidine | | | B | | 56.Pregnancy | | | | |
| 57. | Uniphylin | | C | | 57.Pregnancy | | | | |
| 58.Nifedipine | | | Cm | | 58.Pregnancy | | | | |
| 59.Trazodone | | | | | 59.First Trimester | | | | |
| 60.Methoxsalen | | | B* | | 60.First Trimester | | | | |
| 61.Atenolol | | | Cm | | 61.First Trimester | | | | |
| 62.Aspirin | | | C* | | 62.Pregnancy | | | | |
| 63.Cotrimoxaz-ole | | | Cm/B* | | 63.Pregnancy | | | | |
| 64.Dothiepin | | | D | | 64.First Trimester | | | | |
| 65.Indometha-line | | | B* | | 65.First Trimester | | | | |
| 66.Lithium | | | D | | 66.Pregnancy | | | | |
| 67.Nifedipine | | | | | 67. | Breastfeeding | | | |
| 68.Aspirin | | | C* | | 68.First Trimester | | | | |
| 69.Paracetamol | | | B | | 69.First Few Weeks | | | | |
| 70.Paracetamol | | | | | 70. | in Milk | | | Overdose |
| 71.Mebendazole | | | C | | 71.Pregnancy | | | | |

| Nonproprietary Name | Trade Name (Proprietary) | Chemical Name | Risk Factor | Group of Drugs with Similar Activity | Gestational Age/ Pregnancy | Lactaion | Disease | Human/ Animal | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 72. | Pondocillin | | | | 72.Foetus | | | | Implications of sentitising. Foetus |
| | | | B | Penicillins | | | | | |
| 73.Pizotifen | | | | | 73.Pregnancy | | | | |
| 74.Pyrazina-mide | | | C | | 74.First Trimester | | | | |
| Rifampicin | | | C | | First Trimester | | | | |
| 75. | Duphaston | | | | 75.First Trimester | | | | |
| 76.Menthol | | | | | 76.First Trimester | | | | |
| 77. | Gastrografin | | D | | 77.Pregnancy | | | | |
| 78. | | Arklone | D | | 78.Preganancy | | | | Occupational exposure |
| | | Methanol | | | Pregnancy | | | | |
| 79.Valproate | | | D | | 79.Pregnancy | | | | |
| 80.Arginine | | | | | 80.Pregnancy | | | | |
| Ornithin | | | | | Pregnancy | | | | |
| 81. | | | | | 81.Pregnancy | | | | Canabis |
| 82. | | Formamide | | | 82.Pregnancy | | | | Exposure |
| 83.Metronida-zole | | | | | 83. | Breast Milk | | | Adverse effects |
| 84.Thyroxine | | | | | 84. | Breast Milk | | | |
| 85. | | | | | 85.Pregnancy | | Malaria | | Malarial prophylaxis |
| 86. | | Diethylpropion | B | | 86.Pregnancy | | | | |
| 87. | | | | | 87.Pregnancy | | Shingles | | Treatment of Shingles |
| 88.Quinine | | | D* | | 88.Pregnancy | | | | |
| 89.Gentian violet | | | C | | 89.Pregnancy | | | | |
| 90.Acyclovir | | | Cm | | 90.Pregnancy | | | | |
| 91. | | | | | 91.Pregnancy | | | | Vaccines |
| | | | | | | | | | |
| | | | | | | | | | |

| Nonproprietary Name | Trade Name (Proproetary) | Chemical Name | Risk Factor | Group of Drugs with Similar Activity | Gestational Age/ Pregnancy | Lactaion | Disease | Human/ Animal | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 92.Clomiphene | | | Xm | | 92.Pregnancy | | | | |
| 93.Nifedipine | | | Cm | | 93.Early Pregnancy | | | | |
| Enalapril | | | D | | Early Pregnancy | | | | |
| 94.Atenolol | | | Cm | | 94.Pregnancy | | | | |
| 95. | | Nitrous Oxide | | | 95.Pregnancy | | | | Exposure |
| 96.Tetracyc-line | | | D | | 96. 4-5 weeks Pregnancy | | | | |
| 97.Mesalazine | | | | | 97.Pregnancy | | | | |
| 98.Amitipty-line | | | D | | 98.Pregnancy | | | | |
| 99.Phentermine | | | C | | 99.pregnancy | | | | |
| 100.Ergomet-rine | | | | | 100.Pregnancy | | | | |
| 101. | | | | | 101.Pregnancy | | | | Aniseed |
| 102. | Stilbestrol | | Xm | | 102.Foetus | | | | Exposure to male foetus |
| 103. | | | | Antiemetic | 103.Pregnancy | | | | |
| 104.Flupenthi-xol | | | C | | 104.Pregnancy | | | | |
| Lorazepam | | | | | | | | | |
| 105.Clindami-cin | | | B | | 105.Pregnancy | | | | Topical Clindamycin |
| 106. | | | | | 106.Pregnancy | | Leprosy | | Leprosy Treatment |
| 107.Rifampicin | | | C | | 107.Pregnancy | | | | |
| 108. | Hismanal | | | | 108. | Breastfeeding | | | |
| 109.Dithranol | | | C | | 109.Pregnancy | | | | |
| 110.Flumsolide | | | | | 110.pregnancy | | | | |
| 111.Diazepam | | | D | | 111.Pregnancy | | | | Ventolin Inhalor |
| Moduretic | | | | | | | | | |
| Co-codamol | | | | | | | | | |
| | Ventolin | | | | | | | | |
| 112.Thiethyl-perazin | | | Contra indicated | | 112.Pregnancy | | | | |

| Nonproprietary Name | Trade Name (Proprietary) | Chemical Name | Risk Factor | Group of Drugs with Similar Activity | Gestational Age/ Pregnancy | Lactaion | Disease | Human/ Animal | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 113.Hydroxy-zine | | | C | | 113.Pregnancy | | | | |
| 114. | | | | Antihelmintics | 114. | Breast Milk | | | |
| 115.Ranitidine | | | Bm | | 115.Pregnancy | | | | |
| 116.Midazolam | | | D | | 116.Pregnancy | | | | |
| 117.Piperazine | | | | | 117. | Breast Milk | | | |
| 118.Methoxsa-lem | | | B* | | 118.Pregnancy | | | | |
| 119.Penicilin | | | B | | 119.Second Trimester | | | | |
| 120. | | | | | 120.Pregnancy | | Migraine | | Migraine Therapy |
| 121. | Podophyllin | | | | 121.Pregnancy | | | | |
| 122.Diazepam | | | D | | 122.Pregnancy | | | | |
| 123. | | | | Antiemetics | 123.Pregnancy | | | | |
| 124.Fluphena-zine | | | C | | 124.Pregnancy | | | | Fluphenazine Injection |
| 125.Chloroquine | | | C | | 125.Pregnancy | | | | |
| 126.Chloram-phenicol | | | C | | 126.Pregnancy | | | | |
| 127.L. Trypto-phan | | | | | 127.First Trimester | | | | |
| 128. | | Amino Acids | | | 128.Pregnancy | | | | Ingestion of Amino-acids |
| 129.Hydroxyzine | | | C | | 129.First Trimester | | | | |
| 130.Pimozide | | | C | | 130.Labour | | | | to Induce Labour |
| Procyclidine | | | C | | | | | | |
| 131.Mebendazole | | | C | | 131.First Trimester | | | | |
| 132.Amoxycic-llin | | | B | | 132.Pregnancy | | | | |
| Clavulanate | | | B | | | | | | |
| 133.Naloxone | | | Bm | | 133.Pregnancy | | | | |
| 134.Vitamin D | | | A* | | 134.Pregnancy | | | | |
| 135. | | | | Cytotoxic Drugs | 135.Second Trimester | | | | |
| 136. | | | | | 136.Pregnancy | | | | Exposure to Natural Gas |

| Nonproprietary Name | Trade Name (Proprietary) | Chemical Name | Risk Factor | Group of Drugs with Similar Activity | Gestational Age/ Pregnancy | Lactaion | Disease | Human/ Animal | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 137.Ergometrine | | | | | 137. | Lactation | | | |
| 138. | | | | | 138.Pregnancy | | Scabies | | |
| 139.Papaveretum | | | | | 139.Pregnancy | | | | |
| 140. | | | | | 140.Pregnancy | | | | Hepatitis B Vaccine |
| 141. | | | | | 141.Pregnancy | | | | Occupational Exposure to Solvents |
| 142.Propantheline | | | Cm | | 142.Pregnancy | | | | |
| 143. | | Ursodeoxycholic acid | B | | 143.Pregnancy | | | | |
| 144.Piperazine | | | B | | 144.Pregnancy | | | | For Thread Worms |
| 145.Amphetamine | | | | | 145.Pregnancy | | | | |
| 146. | | | | Anticoagulants | 146.Pregnancy | | | | |
| 147.Metoclopra-mide | | | B | | 147.Pregnancy | | | | |
| 148.Dithranol | | | C | | 148.Pregnancy | | | | |
| 149.Betametha-sone cream | | | | | 149.Pregnancy | | | | Bethamethosone Cream |
| 150.Rifampicin | | | C | | 150.Late Pregnancy | | | | |
| 151. | | | | | 151.Pregnancy | | | | Treating House for Rot |
| 152.Norethiste-rone | | | X | | 152.For two weeks in pregnancy | | | | |
| 153.Betametha-sone | | | C | | 153.Pregnancy | | | | Topical Bethamethasone |
| 154. | | | | | 154.Pregnancy | | Asthma | | |
| 155. | | | | | 155.Pregnancy | | | | Cholear, Thyroid and Polio Vaccination |
| 156.Ephedrine (Nasal drops) | | | C | | 156.Pregnancy | | | | Ephedine Nasal Drops |
| 157.Nimorazole | | | Bm | | 157.First Trimester | | | | Nimorazole orally |
| 158. | Gastrozepin | | | | 158. | | | | |
| Ranitidine | | | Bm | | Pregnancy | | | | |
| Cimetidine | | | B | | | | | | |
| 159.Sulpiride | | | | | 159.First Eight Weeks of Pregnancy | | | | |

| Nonproprietary Name | Trade Name (Proprietary) | Chemical Name | Risk Factor | Group of Drugs with Similar Activity | Gestational Age/ Pregnancy | Lactaion | Disease | Human/ Animal | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 160.Dothiepin | | | | | 160. | Lactation | | | |
| 161.Ethynodiol | | | D | | 161.Pregnancy | | | | |
| Propranolol | | | Cm | | | | | | |
| Phenylpropanol-amine | | | C | | | | | | |
| 162. | | | | | 162.Pregnancy | | Nausea Vomiting | | Treatment of Nausea and Vomiting |
| 163.Chlorpheni-ramine | | | B | | 163.Pregnancy | | | | |
| 164. | | | | Decongestants | 164.Pregnancy | | | | |
| | | | | Cold Cures | | | | | |
| 165. | | | | | 165.Pregnancy | | Tuberculosis | | Antituberculosis |
| 166. | | | | | 166.Pregnancy | | Head Lice | | Head Lice Treatment |
| 167. | | | | | 167.Pregnancy | | | | Evening Primrose Oil |
| 168. | | | | Analgesia | 168.Pregnancy | | Bone Pain | | |
| 169.Nicobrevin | | | | | 169.Pregnancy | | | | |
| 170. | | | | | 170.Pregnancy | | Pseudomonas Urinary Tract | | |
| 171.Mianserin | | | | | 171.First Trimester | | | | |
| 172. | GTN | | Cm | | 172.Pregnancy | | | | |
| Isosorbide Dinitrate | | | C | | | | | | |
| 173.Mefenamic Acid | | | C | | 173.Pregnancy | | | | |
| 174. | | | | Alternative Antihistamine | 174.Pregnancy | | | | |
| 175.Disulfiram | | | X | | 175.First Trimester | | | | |
| | Chlormethia-zole | | | | | | | | |
| 176.Disulfiram | | | X | | 176.Pregnancy | | | | |
| 177.Perphenazine | | | C | | 177.Late Pregnancy | | | | |
| 178.Lobeline | | | | | 178.Pregnancy | | | | |
| 179. | | | | Antiemetic | 179.First Trimester | | | | |

| Nonproprietary Name | Trade Name (Proprietary) | Chemical Name | Risk Factor | Group of Drugs with Similar Activity | Gestational Age/ Pregnancy | Lactaion | Disease | Human/ Animal | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 180. | | Diethylpro-pion | B | | 180.First Trimester | | | | |
| 181.Hydrochlo-rotiazide | | | D | | 181.Pregnancy | | | | |
| Amiloride | | | Bm | | | | | | |
| 182. | Pondocillin | | | | 182.Foetus | | | | |
| | | | B | Penicillins | | | | | Implication of Senisitising Foetus |
| 183.Milpar | | | | | 183.First Trimester | | | | |
| 184.Pizotifen | | | | | 184.Pregnancy | | | | |
| 185.Pyrazinamide | | | | | 185.First Trimester | | | | |
| Rifampicin | | | C | | | | | | |
| 186.Cocodamol | | | | | 186.Pregnancy | | | | Overdose |
| 187.Phenothia-zine | | | | | 187.Pregnancy | | | | Teratogenicity |
| 188.Terfenadine | | | C | | 188.Pregnancy | | | | |
| 189.Carbaryl | | | | | 189.Pregnancy | | | | |
| Malathion | | | | | | | | | |
| 190.Tetracycline | | | D | | 190.Pregnancy | | | | Overdose |
| 191. | | | | Anticoagulants for DVT | 191.Pregnancy | | | | |
| 192.Athenolol | | | Cm | | 192.First Trimester | | | | |
| 193.Dothiepin | | | D | | 193.Early Pregnancy | | | | |
| 194.Salbutamol | | | Cm | | 194.Pregnancy | | | | |
| 195.Fenflura-mine | | | Cm | | 195.Pregnancy | | | | |
| 196.Aminophyl-line | | | C | | 196.Pregnancy | | | | |
| Prednisolone | | | B | | Pregnancy | | | | |
| 197.Phenelzine | | | C | | 197.Third Trimester | | | | |
| 198.Dothiepin | | | | | 198. | Breast Milk | | | Increasing Breast Milk Production |
| 199.Tetracosac-trin | | | C | | 199.Pregnancy | | | | |

| Nonproprietary Name | Trade Name (Proprietary) | Chemical Name | Risk Factor | Group of Drugs with Similar Activity | Gestational Age/ Pregnancy | Lactaion | Disease | Human/ Animal | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 200.Frusemide | | | Cm | | 200.Pregnancy | | | | |
| Spironolactone | | | D | | | | | | |
| Bezafibrate | | | | | | | | | |
| 201.Paracetamol | | | B | | 201.Pregnancy | | | | Overdose |
| 202. | | | | Volatile Acids | 202.Foetus | | | | Occupational Exposure to Volatile Acids |
| | | | | Anaesthetic Agents | | | | | |
| 203. | | | | Anti-TB Drugs | 203. | Breastfeeding | | | |
| 204. | Paroven | | | | 204.Pregnancy | | | | |
| 205.Trifluoperazine | | | C | | 205.Pregnancy | | | | |
| 206.Cocaine | | | C | | 206.First Trimester | | | | |
| 207.Aminocaproic Acid | | | | | 207. | Breastfeeding | | | |
| 208.Rifampicin | | | | | 208. | Breast Milk | | | Excertion in Breast Milk |
| 209.Azathioprine | | | D | | 209.Pregnancy | | | | |
| Prednisolone | | | B | | | | | | |
| | Slow-K | | | | | | | | |
| 210.Oxymetazoline | | | | | 210.Pregnancy | | | | |
| 211.Amitriptyline | | | D | | 211.Pregnancy | | | | |
| Perphenazine | | | C | | | | | | |
| 212.Timolol Eye-Drops | | | Cm | | 212.Second Trimester | | | | Timolol Eye Drops |
| 213.Captopril | | | Cm | | 213.First Trimester | | | | |
| 214.Sulthiame | | | | | 214.Pregnancy | | | | |
| 215.Cocaine | | | | | 215.Pregnancy | | | | Topical Cocaine |
| 216.Ibuprofen | | | B* | | 216.Pregnancy | | | | |
| 217.Prochloroperazine | | | C | | 217.First Trimester | | | | |
| 218.Methyldopa | | | C | | 218.Pregnancy | | | | |
| | | | | Beta Blockers | | | | | |

| Nonproprietary Name | Trade Name (Proprietary) | Chemical Name | Risk Factor | Group of Drugs with Similar Activity | Gestational Age/ Pregnancy | Lactaion | Disease | Human/ Animal | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 219.Mebeverine | | | | | 219.Pregnancy | | | | |
| 220.Disulfiram | | | X | | 220.Late Pregnancy | | | | |
| 221.Anadin | | | | | 221.Pregnancy | | | | |
| 222.Podophyllin | | | | | 222. | | Genital Warts | | |
| 223.Disulfiram | | | X | | 223.First Trimester | | | | |
| 224. | | Carbon Tetra-Chloride | | | 224. | | | | Teratogenicity |
| 225.Lorazepam | | | C | | 225.Pregnancy | | | | |
| Lofepramine | | | | | | | | | |
| 226.Pizotifen | | | | | 226.First Trimester | | | | |
| 227.Phentermine | | | C | | 227.Pregnancy | | | | |
| 228.Temazepam | | | | | 228.Pregnancy | | | | Overdose |
| 229.Vitamin C | | | A* | | 229.Pregnancy | | | | |
| 230.Betametazone | | | C | | 230.Pregnancy | | | | Topical |
| Terfenadine | | | C | | Pregnancy | | | | |
| 231.Azathioprine | | | D | | 231.Second Trimester | | | | |
| Cyclophosphamide | | | | | | | | | |
| 232.Sulphinpy-razone | | | Countra Indicated | | 232.Pregnancy | | | | |
| 233. | Senokot | | | | 233.Pregnancy | | | | |
| 234.Amodiaquine | | | | | 234.Pregnancy | | Malaria | | |
| | Fansidar | | C | | | | | | |
| 235. | | | | Cough Supressants | 235.First Trimester | | | | |
| 236.Tetracyc-line | | | D | | 236.Very Eary Pregnancy | | | | |
| 237.Mefloquine | | | C | | 237.Pregnancy | | | | |
| 238.Frusemide | | | Cm | | 238.First Trimester | | | | |
| | Nylax | | | | | | | | |

# Appendix B

## Definitions of Risk Factors as Given by Briggs et al., 1990.

## Risk Factors

Risk Factors (A, B, C, D, X) have been assigned to all drugs, based on the level of risk the drug poses to the fetus. Risk Factors are designed to help the reader quickly classify a drug for use during pregnancy. They do not refer to breast-feeding risk. Because they tend to oversimplify a complex topic, they should always be used in conjunction with the Fetal Risk Summary. The definitions for the Factors are those used by the Food and Drug Administration (Federal Register 1980;44:37434-67). Since most drugs have not yet been given a letter rating by their manufacturers, the Risk Factor assignments were usually made by the authors. If the manufacturer rated its product in its professional literature, the Risk Factor on the monograph will be shown with a subscript M (e.g., $C_M$). If the manufacturer and the authors differed in their assignment of a Risk Factor, our Risk Factor is marked with an asterisk and the manufacturer's rating is shown at the end of the Fetal Risk Summary. Other Risk Factors marked with an asterisk (e.g., sulfonamides, morphine, etc.) are drugs that present different risks to the fetus depending on when or for how long they are used. In these cases, a second Risk Factor will be found with a short explanation at the end of the Fetal Risk Summary. We hope this will increase the usefulness of these ratings. The definitions used for the Risk Factors are presented below.

**Category A:** Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

**Category B:** Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

**Category C:** Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in woman or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

**Category D:** There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

**Category X:** Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

# Appendix C

# Focus Group Interviews

**C.1 The introductory leaflet which was distributed to the participants in the FGIs**

Dear Physician,

I am conducting a research project at University College, London, on the needs of gynaecologists and obstetricians regarding information on drugs and its acquisition.
The main goal of the project is to create a database on the of drugs in pregnancy and lactation.
Since it is not possible for me to take notes during the meeting, I will use a tape-recorder to record the discussion.
I am interested in professional needs and not in personal details.
Please enable all your colleagues to take part in the discussion; the opinions of all the participants are important.
The contents of the discussion will be analysed and summarized and based on them, recommendations will be formulated for improving the access to required information on drugs.

Please stay till the end of the meeting.

Thank you for your cooperation,

Ruth Handzel

## C.2 A verbatim transcription of the discussions of the Focus Group Interviews

1. Problems requiring information

A The patient reports post factum about a drug or chemical taken during pregnancy and she asks for advice about the potential danger to the fetus. In some cases the only action that can be taken us an induced abortion.

A Problems occur when physicians prescribe drugs without asking the woman the date of her last menstruation. All those cases are referred to for counselling and for recommendation.

A We need information about a drug which is vital for the treatment of a pregnant woman due to an acute or to a chronic disease. In some rare cases when the problem is life threatening, the considerations are different.

A For antibiotics we have our policy of prescription.

A In a certain case, the woman was two weeks pregnant and took Fasign in a large dose. I spent three days gathering information and took advice from the embryologist, but still the answer was equivocal - which allowed not to terminate the pregnancy, despite the fact that some risk remains. Finally, it is up to the patient to decide.

A In cases where it is not possible to assure the woman that the drug is harmless, she and her husband have to share the decision, even if their education is inadequate or their intelligence limited. Our role is to supply all the relevant information, well organised, so that the couple can reach a joint decision.

A Even if percentage-wise the risk is low, it is not within our role to order the patient to perform abortion or not. If the pregnancy results in a malformed baby, the responsibility rests on her shoulders.

A Unexpected situations give rise to difficulties in providing relevant information. For example,: the level of safety in the use of a microwave oven or ingestion of an antimosquito spray.

A It is easier to call an information centre than to go to the library, which is time consuming, and quite often the answer is not found in the sources there. Usually we will use well tried drugs with a proven efficacy and safety record, rather than try new drugs such as new antibiotics, about which little information is available. One should refer to the information available on the group to which the specific drug belongs.

B In chronic diseases such as epilepsy we are compelled to continue the administration of drugs taken continuously.

B Chances for teratogenicity are small and there will always be sporadic reports on it, for example, valium, nevertheless it is widely used.

B In one comprehensive review, it was stated that nowadays most drugs are safe and problems are exceptional.

B Sometimes the indication of pregnancy termination is derived from the disease itself and not the drugs administered, like in some neoplastic conditions.

B Retrospectively, some fifty years ago, almost no drugs were given in pregnancy. Now every pregnant woman takes at least iron and vitamins which are also drugs. In addition, many chemicals are ingested in food and there is atmospheric radiation. Nevertheless, there is no proportional increase in birth defects in the human population. Therefore physicians are less apprehensive about prescribing drugs in pregnancy. Diabetes mellitus is a good example. In the past a diabetic woman was not allowed to become pregnant, but nowadays she is treated by insulin, which also diffuses across the placenta to the fetus and not all the effects are known. Thus the amount of available information always lags behind the needs.

B One has to remember that the reduction in birth defects is due mainly to the development of better test for prenatal diagnosis.

B One cannot predict long term effects of drugs from present information. How can we know what will be the effects of substances absorbed by foetuses, after they reach adulthood? For instance, Dr. Smith administrated, in the forties, a drug to prevent abortions, and in the next generation appeared the "Death Syndrome". What is the effect on adult females concerning cancer or extrauterine pregnancies? These problems can be solved only at the molecular biology level.

C In some situations a calculated risk is taken despite reports in birth defects.

C There is a group of drugs classified between class C and fully teratogenic (class D), about which information is insufficient.

C Controversial issues require detailed information prior to taking decisions.

C In controversial issues there is also the fear of malpractice suits.

C Even if statistical data exist on birth defects, significance can be rarely tested.

C In controversial cases, the conservative approach is safer. Anyway the mother's well-being should always prevail.

C Most drugs in pregnancy are needed to treat diabetes, various infections and thyroid disorders.

D Our attitude is usually conservative. We approach with apprehension all doubtful drugs until the 13th week of gestation.

D In young pregnant women, we often have to use antibiotics, a measure which necessitates much information.

D In the past we were very conservative about giving drugs to lactating women. Nowadays almost all drugs are given in this situation and there are practically no contradictions. Specific information is required only in special cases.

2. Types of information requested

A In some cases we can take advantage of available information in animal experimentation, when information in humans is absent.

A A woman who carries an IUD which includes cuprum becomes pregnant: documentation about teratogenicity of cuprum exists only in animals, but not in humans. This information can help the pregnant woman to decide whether she wants to keep her pregnancy or not.

A We have to remember the concentrations and dosages we administer to animals in experiments which can not be compared to human usage. Therefore we can only mention a theoretical risk without statistical data.

A Remark: Thalidomide was safe in animals.

A The question is whether information on animals helps in the process of decision making. I doubt it.

A The administration of a drug is often stopped due to the fear of it being harmful, without knowing its mechanism of action. With due time and after having learned its characteristics, the drug might be used routinely.

A We have a long-standing experience in the use of drugs but still need updated information.

A An answer that a drug is teratogenic or not, is insufficient. One has to know which system in the body is affected by it.

A Minireviews are useful.

A Information about teratogenicity only is not sufficient because the drug can have a direct toxic effect on the foetus, such as causing respiratory disorders.

A Minireviews are useful because they include concise information. However, one should differentiate between teratogenicity to a whole system, such as the central nervous system and induction of minor defects, which have a minimal effect on the foetus and are usually treatable. Therefore, one should not be content with a yes or no answer about teratogenicity. A much more detailed information is required.

A If the information is to be useful it should demonstrate a few cases, who have received the given drug, in whom the prevalence of a certain birth defect should be compared to that in the general population.

A There are thousands of single anecdotal reports of birth defects, which have occurred in pregnant women, who took various medication. Such descriptions can not help in decision making, unless they are accompanied by some positive evidence for a causal relation, such as a comparison with the prevalence of the same defect in the general population.

A It is sufficient to label drugs, which are totally contraindicated in pregnancy, as such. The same is true for drugs which are obviously permitted in pregnancy. The problems arise with controversial medications, for which more information is needed than usually available in minireviews.

A An expert opinion, such as the one of a clinical pharmacologist, helps to reach a practical decision, inspite of reports about birth defects.

A When dealing with controversial subjects, citation from the literature to support either of two different opinions are helpful, but do not solve the problem entirely.

A When "early pregnancy" is mentioned, it is not clear whether it means a gestational age of 3-4 weeks or 6 weeks. An exact definition is needed.

A One needs to know the prevalence of a given defect in comparison to the natural occurrence in large population.

A Practically every existing birth defect has been reported in conjuction with a given drug, including ovulation inducers. Even drugs which have been claimed to be associated with some defect, but its prevalence was found to be the as in the general population.

B Case reports influence my opinion as a clinician, in spite of the fact that all teratology textbooks warn against false interpretation of such reports. If a malformation is reported only in a single case, I will still look for another drug.

B That is because you do not want to be the originator of the second case report.

B In case a drug was demonstrated to induce some teratogenicity in animals, will we use it anyway? For example, tetracyclines have been shown to be teratogenic in animals, but not in humans. Nevertheless, we hesitate to prescribe these drugs during the first trimester, especially that alternatives do exist.

B The real problem is encountered when a drug was found not to be teratogenic in animals and no data is available in humans.

B If there is evidence for teratogenicity in animals but no data in humans, this should not completely prevent prescribing the drug, but it becomes a second choice.

B A central question is whether the "state of the art" reviews should also include data obtained in animal studies. In my opinion it should not, because in the latter, extremely high doses are administered and the results can not be extrapolated to humans. It is in the interest of the pharmaceutical companies to minimise drug use in pregnancy, because it is a problematic market, which exposes them to litigation. Only a few of the drugs which have been prescribed in pregnancy have passed a rigorous test of safety. However, the safety of a large group of drugs, which fall into B-C category, has not been established.

B We are in need to constantly update "state of the art" information, beyond the one included in "Briggs".

B We would like to know details about the malformations observed, therefore case-reports are valuable.

B Often we have to take a decision in cases where the woman took a drug, not knowing that she was pregnant, or without being aware of the potential danger of the substance. In these situations we need maximum possible information, including a knowledge of the mechanism of the action of the drug. Some of the malformation, which might arise as a result of the situation described above, could be diagnosed prenatally if we knew which system might be harmed by the drug.

B I prefer to obtain only the conclusions derived from the literature because often, as in the case of aspirin, the literature is so vast that after much reading, one cannot find the practical recommendations. However, answers in the form of "yes" or "no" are unsatisfactory. More detailed information is required and I would like to have an intelligent summary or a few important citation.

B In addition to an answer delivered as a short summary, one also wants the option to read the complete relevant literature, if it is not prohibitively voluminous.

B It would be interesting to screen the relevant literature or parts of it, in case it is available.

B When facing a problem which is not academic in nature, but purely practical, it suffices to receive the conclusion of the relevant research without the sources. The interest in the material grows with its accessibility.

B An abstract is sufficient for practical purposes.

C We have a group of drugs which are categorised between clearly teratogenic and class C and with which not enough experience has been accumulated. In these situation the detailed information is needed.

C The existence of statistical data does not ensure the safety of a drug, therefore maximum qualitative, as well as quantitative information is needed.

C Drug information should be divided into one which satisfies our professional curiosity and one which will provide us medicolegal coverage.

C The methodological data is important, for example,, how the population sample was selected. A statistical knowledge is a prerequisite for understanding the significance of the reported clinical series.

C The fact that malformations can be traced by ultrasound (US) helps to focus the problem.

C Information about the ingested dose is important. One has to take into account the changes in metabolism and in blood volume of the pregnant woman.

C In some cases I wish to see the whole article.

3. <u>Situations in which information is required and the urgency in obtaining it</u>

A It might take one to three days to obtain the desired information; which means, that we have to contact the patient again.

B Drug information should be available wherever we treat pregnant women, such as the outpatient clinic, inpatient wards and well-baby clinics.

B If I do not have the appropriate information I will not prescribe the drug.

B Unless relevant information about a drug is readily available, it is better to avoid using it.

B Even if a certain study points towards lack of teratogenicity of a given drug, my decision will vary in different situations. For example,, pregnancy after fifteen years of fertile treatment as compared to an unwanted pregnancy in a nineteen years old girl. All the factors must be taken into consideration with maximum available information for decision making.

C Gathering drug information is usually not urgent, provided the factor of anxiety in the patient is disregarded.

D Drug information should be available at any medical facility to which the patient arrives, either for the first time, or for follow-up, for hospitalisation or for counselling about lactation.

4. Updating and follow up

A It is useful to keep track in a pregnant woman's file of all medication administered and to follow the pregnancy and the resulting offspring. This can provide a large body of data on the effect of drugs on pregnancy. However, collecting and processing of such data is time consuming and costly.

A After having screened the literature, one usually remembers only outstanding items, such as the large studies on thalidomide or diethyl-stilbestrol.

B One screens literature routinely for new drugs, but when the need arises, cases are evaluated individually.

5. Sources of information

A Booklets published by Agis (a pharmaceutical company).

A The Israel Drug Compendium.

A "Drugs in Pregnancy" by Berkowitz.

A Lectures in perinatology, including treatment problems.

A Post-Graduate Continuing Education courses in the Faculty of Medicine.

A Consultations with colleagues.

A Various library sources.

A A list of drugs, compiled by the hospital nursery, permitted and not permitted in lactation.

A Information on computerized data based on CD-ROM.

A For some drugs Briggs reports: "no information is available". In such cases we have to look for other sources.

A Periodic leaflets of medical authorities with updated and summarized information.

B Pharmacological literature.

B If no answer has been found in the literature, I will consult with a colleague.

B The Teratology Information Centre.

B I prefer to call an information centre, rather than to go to the library, which is time consuming; in addition the available sources often do not yield the requested information.

C Martindale's Pharmacopoeia.

C IOWA System.

C Various high level professional journals.

C We approach the library for a search, not in textbooks, but rather in bibliographical tools and pharmacopoeias.

C We will ask the manufacturing company for sources of information.

C When unusual problems arise such as a viper bite, data bases are consulted.

D The periodical *Clinical Obstetrics.*

D Important information is to be found in the *Am. J. of Obstetrics.*

6. The reliability of information sources

A Some books, such as the one by Briggs, cite the drug company as the source of information when it is the only one available.
A Obviously drug companies are careful about supplying information, which might have a "boomerang effect", and they try to ensure a large safety margin.
A There is almost no drug which a company would pronounce as safe during pregnancy, due to the fear of legal suits. Therefore if it is stated as such, it is probably reliable.
A Whenever published research is cited, it enables to verify reliability of reporting by the drug company.
A I would like to check details, to be convinced about the safety of a drug.
A In the newer editions of the Briggs, the number of patients in trials cited are larger, but in practice it is does not effect the decision taken.
B The credibility of the FDA is accepted everywhere, and if on a drug appears the label "FDA approved", it signifies that the drug has passed all the FDA testing apparatus, which is also important for legal covering.
D In some cases a drug will be administered in spite of a warning to the contrary, issued by the manufacturer.

7. The Professionals whom the participants consult

A A neonatologist about the lactation period.
A Other colleagues in the same field.
A A clinical geneticist.
A The Teratology Centre in Jerusalem, where they have detailed information about drugs, and where an embryologist can be consulted.
A We call the Teratology Centre very seldom as we prefer to use local resources.
A Some colleagues (obstetricians) compile information on drug usage.
A Often a specialist who treats a specific disease of the woman will consult us.
B Consultations have become more and more multidisciplinary, however, usually the final decision about drug administration to pregnant and lactating women are taken by gynaecologists and obstetricians.
B If my colleagues can not supply the relevant information, I will search the literature.
C In case of lactation, it is advisable to consult the neonatalogist.
C I would consult a clinical geneticist, a pharmacist and a clinical pharmacologist.
D It is convenient to approach the hospital pharmacist, who has the sources of information about drugs and can also consult with other pharmacists.
D A drug should be administered after consulting the specialist who treats the woman's medical problem.
D The committees for pregnancy interruption have a very conservative approach about indications for pregnancy termination due to drug ingestion.

8. Persons who consult with the participants

A In a specific case a woman took a dose of a drug, while two weeks pregnant. It took three days to gather all the information and to consult an embryologist. All this resulted in an equivocal answer, leaving the patient to decide whether this pregnancy was very precious to her or she prefers to interrupt it. It depends a lot on the woman's personality. The gynaecologist's role is to provide accurate and comprehensive information.

A In cases where it is not possible to promise that the drug is harmless, the patient and often her husband have to participate in the decision, regardless of their level of education.

A We have to supply a lot of organised information so that a joint decision will be reached with the patient and her husband.

A If the risk is very low, it is not my duty to order the woman to perform abortion or not. If the newborn will have a defect, she will carry the brunt of it. Therefore we need to present her with as much information as possible.

A In modern medicine the physician is not supposed to impose decisions, but to provide accurate and organised information.

A A balance has to be reached between ethics and information.

A One has to diagnose the personality of the person to whom the information is to be delivered. Most situations are not black and white. If a drug carries teratogenic risk of, say, 3-3.5%, it is not possible to ensure the woman that her offspring will be perfectly normal. Without taking drugs, some risk to the foetus still exists. We have to give as much information as possible to the patient.

A Each case is a different, and the attitude toward the usage of a drug will depend whether it is a pregnancy after ten years of trials, or it is a woman who already has a few children. We have to supply the woman and her partner as much information as possible without dominating their decision.

B We are confronted by internists, family physicians and often dentists who require definite yes or no answers, without going into details.

C The specialist who treats the pregnant woman for a certain disease should not prescribe medications without consulting us (the gynaecologist).

C All medical authorities who treat a woman during pregnancy or lactation, should prescribe drugs only after obtaining the relevant information from us.

9. <u>Requirements regarding a computerized database</u>

A The process of written publications is lengthy and always lags behind, therefore computerized material is preferable.

A There is no reason not to consult computerized data in presence of a patient as it is legitimate to acknowledge lack of sufficient information or not being certain about a medical issue.

A Tables with data on incidence and prevalence of birth defects in the population which was or was not exposed to the drug. In addition, a review of the subject and the bibliographic list would be helpful.

B Graphs are easy to assimilate, accompanied with legends.

B In addition to the graphic information, which is easy to use, texts, which include more information, are also required.

C The information can be visualised with graphs, provided textual explanations are added.

C Important data, such as the prevalence of certain birth defects as a function of the gestational age, are portrayed easily in the graphic form, which will help us to concentrate on changes sensitive to ultra-sound visualisation.

D The information should have a modular organization, enabling retrieval of specific and targeted information in a selected quantity.

## Appendix D

**The Questionnaire and a Letter to the Physicians which Was Sent Together with the Questionnaire.**

Dear Physician,

I am conducting a research project at University College, London, on the needs of gynaecologists and obstetricians regarding information on drugs.
The results of this survey will influence the improvement of information services which are available to you.

The enclosed questionnaire addresses the issue. There is no need to write your name on it, as answers will serve for statistical analysis of the data only and will be treated with utmost confidentiality.

The questionnaire is sent to a number of gynaecologists and obstetricians, therefore, your participation and your opinions are essential to the success of this survey.

Thank you for your cooperation.

Yours sincerely,

Ruth Handzel.

Instructions for completing the questionnaire:

Please read carefully the questions and all possible answers to each of them. It is important that you answer all the questions for the purpose of statistical analysis. Missing answers would affect the quality of the survey.

Some questions offer multiple answers; choose the most appropriate answer and circle the number next to it.
Other questions ask you to provide an answer or invite you to express your opinion.

## Questionnaire on Drugs in Pregnancy and Lactation

For office use

| | | | | |
|---|---|---|---|---|
| | | | | 1 |
| | | | 1 - 4 | 5 |

**The following group of questions deals with your means of updating on drugs. Please encircle the appropriate answer.**

What are the sources which you use for drugs update?

| **Printed publications** | very often | often | sometimes | infrequently | extremely rare | never | |
|---|---|---|---|---|---|---|---|
| Textbooks in Obstetrics | 1 | 2 | 3 | 4 | 5 | 6 | (6) |
| " in Pharmacology | 1 | 2 | 3 | 4 | 5 | 6 | (7) |
| Advertisements of drug companies in professional journals | 1 | 2 | 3 | 4 | 5 | 6 | (8) |
| Prospectuses of drug companies enclosed with the drug | 1 | 2 | 3 | 4 | 5 | 6 | (9) |
| Current awareness leaflets (local publications) | 1 | 2 | 3 | 4 | 5 | 6 | (10) |
| Bibliographic tools (e.g. Index Medicus) | 1 | 2 | 3 | 4 | 5 | 6 | (11) |
| Journals | 1 | 2 | 3 | 4 | 5 | 6 | (12) |

Please list up to five journals which you read regulary on this subject:

1. ..... 3 9 (13)
2. ..... 4 9 (14)
3. ..... 5 9 (15)
4. ..... 6 9 (16)
5. ..... 7 9 (17)

Other printed sources of information, please specify:

..... 8 9 (18)

..... 1 9 (19)

**Formal and informal meetings**

| | very often | often | sometimes | infrequently | extremely rare | never | |
|---|---|---|---|---|---|---|---|
| Seminars | 1 | 2 | 3 | 4 | 5 | 6 | (20) |
| Professional conferences | 1 | 2 | 3 | 4 | 5 | 6 | (21) |
| Staff meetings | 1 | 2 | 3 | 4 | 5 | 6 | (22) |
| Representatives of drug companies | 1 | 2 | 3 | 4 | 5 | 6 | (23) |
| Others, please specify: ..... | | | | | | | |

(24 -26)

Consulting colleagues on drugs information:

| | very often | often | sometimes | infrequently | extremely rare | never | |
|---|---|---|---|---|---|---|---|
| Pharmacists | 1 | 2 | 3 | 4 | 5 | 6 | (27) |
| Pharmacologists | 1 | 2 | 3 | 4 | 5 | 6 | (28) |
| Geneticists | 1 | 2 | 3 | 4 | 5 | 6 | (29) |
| Embryologists | 1 | 2 | 3 | 4 | 5 | 6 | (30) |
| Others, please specify: ..... | | | | | 1 | 9 | (31) |
| ..... | | | | | 2 | 9 | (32) |
| ..... | | | | | 3 | 9 | (33) |

Use of machine-readable databases:

| | very often | often | sometimes | infrequently | extremely rare | never | |
|---|---|---|---|---|---|---|---|
| On-line information | 1 | 2 | 3 | 4 | 5 | 6 | (34) |
| CD-ROM | 1 | 2 | 3 | 4 | 5 | 6 | (35) |

Which of the following databases have you used?

| | Yes | No | |
|---|---|---|---|
| Medline | 1 | 9 | (36) |
| Excerpta Medica | 2 | 9 | (37) |
| Biosis | 3 | 9 | (38) |
| Chemical Ab | 4 | 9 | (39) |
| IPA | 5 | 9 | (40) |
| Dif | 6 | 9 | (41) |
| Diogenes | 7 | 9 | (42) |
| Biam | 8 | 9 | (43) |
| Use database but don't know the source | 1 | 9 | (44) |

Did you perform repeated searches in the same database? 1. yes 2. no 3. don't know (45)

Are you subscribed to "allert" (SDI) service? 1. yes 2. no (46)

In your opinion, how reliable are the sources you are using?

| | generaly reliable | not very reliable | don't know | |
|---|---|---|---|---|
| Textbooks in Obstetrics | 1 | 2 | 3 | (47) |
| Textbooks in pharmaclogy | 1 | 2 | 3 | (48) |
| Prospectuses of drug companies enclosed with the drugs | 1 | 2 | 3 | (49) |
| Pharmacopeia | 1 | 2 | 3 | (50) |
| Medic | 1 | 2 | 3 | (51) |
| Israel drug compendium | 1 | 2 | 3 | (52) |
| Current awareness leaflets (local publication) | 1 | 2 | 3 | (53) |
| Bibliographic tools (e.g. Index Medicus) | 1 | 2 | 3 | (54) |
| Articles in professional journals | 1 | 2 | 3 | (55) |
| Seminars | 1 | 2 | 3 | (56) |
| Professional conferences | 1 | 2 | 3 | (57) |
| Staff meetings | 1 | 2 | 3 | (58) |
| Representatives of drug companies | 1 | 2 | 3 | (59) |

## Availability and accesto information

| Is there a medical library? | Yes | No | |
|---|---|---|---|
| At your workplace | 1 | 9 | (60) |
| Close to your workplace | 2 | 9 | (61) |
| Close to your home | 3 | 9 | (62) |

Please encircle appropriate answeres.

If you have a reference or a bibliographic list, do you find the documents themselves (e.g. articles, books) in the library you are using?

1. Always 2. Frequently 3. Rarely 4. Never (63)

What do you normally do if you do not find the document at your library?

Please encircle one answer only

1. Go to another library 2. Using interlibrary loan 3. Give up searching
4. Other, please specify: (64)
5. ..... 5 9 (65)
6. ..... 6 9 (66)

Is there an online retrieval service at your workplace?
1. Yes 2. No 3. Don't know (67)

Where is the service based? Please encircle appropriate answers:

1. Library 2. Drug information centre 3. Department 4. Clinic (68) ___

5. Don't know 6.Other ,please specify: (69) ___

(70) ___

(71) ___

Is there a CD-ROM retrievalserviceat your workplace?
1. Yes 2. No 3. Don't know (72)

Where is the sevice based? Please encircle appropriate answers: (73) ___
1. Library 2. Drug information centre 3. Clinic 4. don't know

5. Other, please specify: (74) ___

For office use

| | |
|---|---|
| DUP | 3 |
| 1 - 4 | 5 |

In your opinion, how updated are the materials on drug information at the library you use regularly. Please enircle one answer only.
1. Mostly currently updated 2. Some materials are currently updated
3. Most materials are not currently updated. (6)

Is there a drug information centre at your work place? 1. Yes 2. No (7)

If yes, how frequently do you approach the centre?
1. Several times a week 2. Once a week 3. A few times in a month 4. Once a month 5. A few times in a year (8)

Have you been referred to a drug information centre <u>not</u> at your work place?
1. Yes 2. No (9)

Are you prepared, at your own initiative, to approach a drug information centre outside your work place? 1. Yes 2. No (10)

How do you follow up-to-date information about new drugs? Please encircle appropriate answers.

| | Yes | No | |
|---|---|---|---|
| Regularly reading the literature about the drugs you prescribe | 1 | 9 | (11) |
| When a specific problem occurs in treatment or prescription | 1 | 9 | (12) |

When a clinician does not have sufficient information about a drug, the reason is usually because (encircle one answer only)

1. Insufficient time for keeping up to date
2. Not all relevant sources are available when required
3. Information sources are not currently updated
4. Other, specify: (13)

4 9 (14)

5 9 (15)

6 9 (16)

**The following group of questions identifies situations in which drug information is required**

| | very often | often | sometimes | never | |
|---|---|---|---|---|---|
| Treatment with new drug | 1 | 2 | 3 | 4 | (17) |
| Drug combinations treatment | 1 | 2 | 3 | 4 | (18) |
| While symptoms occurs which could be drugs side effects | 1 | 2 | 3 | 4 | (19) |
| During the first interview with the pregnant woman | 1 | 2 | 3 | 4 | (20) |
| In each visit of the pregnant woman | 1 | 2 | 3 | 4 | (21) |

Other, please specify: .....

(21-24)

Please estimate the frequency in which you prescribe a drug to the lactating woman? Please encircle one answer.

1. Several times a week 2. Once a week 3. Once a month (25)

Please estimate the frequency of pregnant women receiving any drug treatment during pregnancy ..... % (26)

Please estimate the frequency of lactating women receiving any drug treatment during lactation ..... %

(27)

**The following group of questions deals with your attitude regarding drug treatment during pregnancy and lactation**

When a pregnant patient requires drug treatment, who has the overall responsibility for the treatment? Please encircle one answer only.

1. The obstetrician
2. The specialist for the specific disease
3. Both the obstetrician and the specialist
4. Other, please specify:

(28) ⌊___⌋

When a lactating patient requires drug treatment, who has the overall responsability for the treatment? Please encircle one answer only.

1. The obstetrician
2. Paediatrician
3. The specialist for the specific disease
4. Both obstetrician and the paediatrician
5. Other, please specify:

(29) ⌊___⌋

In a situation in which the pregnant patient must be treated with a drug which may endanger the foetus; which of the following sentences reflects your opinion? Please encircle one answer only.

1. It is preferable not to prescribe drugs to a pregnant woman, because it may endanger the foetus
2. Following appropriate instructions, it is possible to prescribe drugs to pregnant women
3. Drug treatment is possible following a consultation with an expert
4. The health of the pregnant patient is most important and drug treatment should be prescribed even if this might carry some risk to the foetus

(30)

In a situation in which the lactating patient must be treated with a drug which may carry some risk to the newborn; which of the following sentences reflect your opinion. Please encircle one answer only.

1. It is preferable not to prescribe drugs to a lactating woman, because it may carry some risk to the newborn
2. Following appropriate instructions, it is possible to prescribe drugs to lactating women
3. Drug treatment is possible following a consultation with an expert
4. The health of the lactating patient is most important and it may be necessary to stop lactation.

(31)

- 7 -

In case of doubts about the action of a drug you would like to prescribe, which sources of information do you use? Please specify.

| Pregnancy | Lactation |
|---|---|
| | |
| | |
| | |
| | |
| | |

(32 - 36)

(37 -41)

In case of doubts about the action of a drug you would like to prescribe, whom do you want to consult? Please specify.

| Pregnancy | Lactation |
|---|---|
| | |
| | |
| | |
| | |
| | |

(42 - 46)

(47 -51)

Following an enquiry, you receive clear professional opinion that a certain drug may not, or may be used. Which of the following sentences describes your situation? Please encircle one answer only.

1. The answer satisfies my needs for information regarding the treatment
2. In addition I need the reasons and explanation for the opinion given
3. In addition to the reasons, I also need to know the research methods of the study used, the population, ect...

(52)

Can you think about the most recent occasion when you received information on drugs, following your request. Did the information you have received following your inquiry assist you in your decision about treatment ?

1. The information was very helpful
2. Somewhat helpful

3. Of little use
4. Was of no use at all. (53)

**The following group of questions deals with the type and form of presentation of required information**

When you inquire about the teratogenicity or mutagenicity of a drug, are you satisfied with a "yes" or "no" answer

1. The answer will satisfy 2. The answer will not satisfy

Please explain your answer ..... (54)

| | Yes | No | |
|---|---|---|---|
| In addition, would you like to know the source of the information ? | 1 | 9 | (55) |
| Would you like to read the original text ? | 1 | 9 | (56) |
| Is it important for you to know the size of the population used in the study on which the information is based? | 1 | 9 | (57) |

In which form would you prefer to receive the information on drugs?

Please encircle appropriate answers.

1. Text 2. Graphic 3. Tables 4. Combined 5. Any form (58)

| | Yes | No | |
|---|---|---|---|
| If there is no controlled study, would you like to receive information based on data derived from sporadic cases ? | 1 | 9 | (59) |
| If there are no human data, are you interested in data based on animal studies ? Vertebrate | 1 | 9 | (60) |
| Invertebrate | 1 | 9 | (61) |

When searching for information about a drug, do you prefer using:

1. Generic name 2. Trade name 3. Chemical name 4. Any name

5.Other, please specify: ..... (62)

Do you want to add any comment about types of information and its presentation regarding drugs in preganancy and lactation?

.....

.....

.....

(63-65)

The following information is needed for statistical processing.

Where do you work ? Please encircle appropriates answers.

1. Hospital (departments and clinics)
2. A clinic in a health insurance service
3. A private clinic
4. Antenatal clinic (66) ⌊__⌋

| | Yes | No | |
|---|---|---|---|
| If you work in a hospital, is the department affiliated to a medical school ? | 1 | 9 | (67) |

To which sector does the hospital belong ?

1. Sick fund (Histadrut)
2. Municipal
3. Government
4. Private (68)

Your work place is in:

1. A city 2. Small town 3. Communal village (Moshav)
4. Communal village (Moshava) 5. Village 6. Kibbutz (Community) (69)

Your work place is in area phone code:

1. 06 2. 04 3. 053 4. 054 5. 03 6. 08 7. 02 8. 051 9. 057 10. 059 (70)

Where did you study medicine ?

1. In Israel 2. Abroad 3. Both (71)

Where did you train in your speciality ?

1. In Israel 2. Abroad 3. Both 4. I have not yet finished my residency training (72)

| | Yes | No | |
|---|---|---|---|
| Do you have an academic degree ? | 1 | 9 | (73) |
| Do you teach? | 1 | 9 | (74) |

1. Male 2. Female (75)

Your age ..... ⌊__⌋ (76-77)

- 10 -

Do you have a Pc/Computer terminal? Please encircle the appropriates answers.

1. At the department in which you work

2. At the clinic 3. At home (78)

| DUP | 3 |
|---|---|
| 1 - 4 | 5 |

| What software do you use ? | Yes | No | |
|---|---|---|---|
| Word processor | 1 | 9 | (6) |
| Statistical analysis | 2 | 9 | (7) |
| Applications generator | 3 | 9 | (8) |
| Data-base (e.g. bibliographic list) | 4 | 9 | (9) |
| Records of patients | 5 | 9 | (10) |
| Lab results | 6 | 9 | (11) |

Others, please specify: (12-13) (14-15) (16-17) (18)

Thank you for your cooperation,

Ruth Handzel

## Appendix E

## Questionnaire for Structure Interview with Drug Information Centre Personnel.

# QUESTIONNAIRE FOR STRUCTURE INTERVIEW WITH DRUG INFORMATION CENTRE PERSONNEL.

**Information on the faculty**

1. When was the service opened?
2. What is the location of the service?
3. What is the professional training of the service providers?
4. Is this service their only occupation?
5. Is a fee charged for the service? If yes, which user population is charged? By which criteria?
6. Are the queries listed in a registry? If yes: Manually?
   Computerized?
7. Are the answers also registered? Manually?
   Computerized?
8. Are the original documents for the answers registered?

| Yes | No | Manually | Computerized |
|---|---|---|---|

# TYPE OF QUERIES ADDRESSED TO THE CENTRE/UNIT

What is the type of general questions on drug information?

| | Always | Very often | Often | Infrequently | Never |
|---|---|---|---|---|---|
| 1. AE | | | | | |
| 2. INTER | | | | | |
| 3. AD+DOS | | | | | |
| 4. PK | | | | | |
| 5. Which drug caused the specific symptoms | | | | | |
| 6. OTHERS | | | | | |

What is the type of questions on drug use in pregnancy?

| | Always | Very often | Often | Infrequently | Never |
|---|---|---|---|---|---|
| 7. AE | | | | | |
| 8. INTER | | | | | |
| 9. AD+DOS | | | | | |
| 10. PK | | | | | |
| 11. Teratogenicity | | | | | |
| 12. Fetal age/ Gestational age | | | | | |
| 13. Are given symptoms caused by the drug | | | | | |
| 14. OTHERS | | | | | |

What is the type of information needed about the use of drugs in pregnancy?

a. Are controlled studies relevant?

| Always | Sometimes | Never |
|---|---|---|
| | | |

b. If no controlled studies are available will case reports suffice?

| Always | Sometimes | Never |
|---|---|---|
| | | |

c. If no data are available in humans, will data available from animal studies suffice?

| Always | Sometimes | Never | Other |
|---|---|---|---|
| | | | |

16. What is the type of information needed about the use of drugs in lactation?

17. What is the percentage of questions about the use of drugs in pregnancy and lactation amongst all the queries to the centre/unit?

18. Is there a given profile of most questions asked about the use of drugs in pregnancy, such as:

    The specific drug and pregnancy

    The specific drug and gestational age

    The place of the given drug in the drug risk category in pregnancy

    Other

19. Is there a given profile of most questions asked about the use of drugs in lactation?

20. Do most questions deal with new drugs?

21. Do most questions deal with new drugs used in Israel?

22. What are the sources used for answering the questions?
    a. Manual sources:
       Books in Obstetrics
       Books in Neonatology
       Books in Pharmacology
       General Pharmacopoeiae
       National Pharmacopeiae
       Books on specific subjects, such as Briggs
       Prospects enclosed with the drugs
       Other information from the manufacturer
       Manual bibliographic touls
       Drug information pamphlets of health services providers (e.g. General Sick Fund)
    b. Other sources of drug information such as:
       Microfiches
    c. Computerized drug information sources:
       CD/ROM ON LINE
    d. What are the major data bases used?
23. Will computerized searches be performed by the centre's/unit's personnel, or referred elsewhere and to whom?
24. Are all questions answered by a computerized search?
25. What are the three most reliable sources for obtaining information?
26. What are the three least reliable sources for obtaining information?
27. Does the centre's/unit's personnel consult other professionals?
    Other pharmacists
    Pharmacologists
    Geneticians
    Teratologists
    Neonatologists
    Clinical pharmacologists
    Other drug information centers
    Others
28. The users' caterories which address your centre/unit:
    a. Who is serviced by your centre/unit?
       Physicians of the hospital in which your centre is located
       Physicians from other hospitals
       Physicians from antenatal clinics

Community ambulatory clinics

Private clinics

b. Queries on the use of drugs in pregnancy are addressed mainly by:

Gynecologists/Obstetricians

General Practitioners

Others

c. Queries on the use of drugs in lactation are addressed mainly by:

Gynecologists/Obstetricians

General Practitioners

Pediatricians/] Neonatologists

d. What is the level of seniority of hospital physicians addressing the centre/unit?

Chairmen of departments

Senior physicians

Residents

28. By which means are most queries made (by %)?

Telephone

In writing

By personal visit to the centre

29. How are the answers delivered (by %)?

Telephone

In writing

By personal visit to the centre

30. When asking about the teratogenicity or mutagenicity of a drug, what is the level of answering which is accepted by most users?

a. Answers of "Yes" or "No"

Always Often Sometimes Rarely Never

b. Are users also enquiring about the identity of the source of the information?

Always Often Sometimes Rarely Never

c. Are users asking for the actual document of the source?

Always Often Sometimes Rarely Never

31. Which name of the drug do most users quote?

Generic Trade name Chemical Other

32. What is the level of confidence in prospects enclosed with the drugs?

# Appendix F

# Complete Information about the Drugs Included in the Database Model.

GENERIC NAME: CIPROFLOXACIN

PHARMACOLOGICAL CLASS: Antibiotic (Quinolone)

TRADE NAMES: Ciproxin (Bayer)

CHEMICAL NAME: 3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-

RISK FACTOR: Not determined

PREGNANCY

TERATOGENICITY

A long term toxicological study in mice and rats (1) did not give any indication of teratogenicity or embryopathy. No such data are available in humans. Quinolones penetrate the placenta (2) and can be found in amniotic fluid at low concentration.

FETAL TOXICITY

Ciprofloxacin has been demonstrated to cause degenerative arthropathy in juvenile animals (3), therefore it is contraindicated in pregnant women and in children.

REFERENCES

1. Schluter G. Ciprofloxacin: toxicologic evaluation or additional safety data. Am J Med 1989;87(5A): 37s-39s.
2. Giamarellou H, et al. Pharmacokinetics of three newer quinolones in pregnant and lactating women. Am J Med 1989;87(5A):49s-51s.
3. Christ W, et al. Specific toxicology aspects of the quinolones, Rev Infect Dis 1988;10(suppl 1):s141-6.

GENERIC NAME: CIPROFLOXACIN

PHARMACOLOGICAL CLASS: Antibiotic (Quinolone)

TRADE NAMES: Ciproxin (Bayer)

CHEMICAL NAME: 3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-

BREAST FEEDING

The drug is secreted at a relatively high concentration in breast milk. Therefore it is contraindicated in lactating women, because of a potential joint damage to the joints of the nursing infant (1).

REFERENCES

1. Giamarellou H, et al. Pharmacokinetics of three newer quinolones in pregnant and lactating women. Am J Med 1989;87(5A):49s-51s.

GENERIC NAME: CLOMIPHENE

PHARMACOLOGICAL CLASS: Fertility agent nonhormonal.

TRADE NAMES: Serofene (Serono)
Ikaclomide (Teva)

CHEMICAL NAME: Ethanamine, 2-[4-(2-chloro-1,2-diphenylethenyl) phenoxyl]-N,N-diethyl-

RISK FACTOR: Xm

## PREGNANCY

### TERATOGENICITY AND MUTAGENICITY

Clomiphene is an ovulation inducer which is contraindicated after conception. Neural tube defects have been suspected to occur after clomiphene treatment (1). Two cases, one of a ruptured meningomyelocoele (2) and the other with oesophageal atresia, congenital heart defects and agenesis of one kidney (3) have been reported after inadvertent use of clomiphene during the first trimester of pregnancy. Other malformations have been reported after clomiphene assisted pregnancies, such as hydatiform mole (4), ovarian dysplasia (5) and Down's syndrome (6). However in larger studies (7, 8, 9), the most extensive one including 1034 pregnancies (10), no significant association between birth defects and clomiphene treatment could be established. a similar conclusion has been arrived at two newer publications (1, 11).

### ONCOGENICITY

A series of 12 patients was described, in whom granulosa cell tumour followed ovarian stimulation with clomiphene (12). In another case, a possible cause and effect was claimed between the appearance of multiple melanoma and clomiphene treatment two years earlier (13).

### REFERENCES

1. Mills JL, et al. Risk of neural tube defects in relation to maternal fertility and fertility drug use. Lancet 1990:336:103-4.
2. Yikorkala O. Congenital anomalies and clomiphene. Lancet 1975;2 1262-3.
3. Singhi M, et al. Possible relationship between clomiphene and neural tube defects. J Pediatr 1978;93:153.
4. Wajntraub G, et al. Hydatidiform mole after treatment with clomiphene. Fertil Steril. 1974;25:904-5.
5. Ford WDA, et al. Fetal ovarian dysplasia possibly associated with clomiphene. Lancet 1981;2:1107.
6. Oakly GP, et al. Increased prevalence of Down's syndrome (mongolism) among the offspring of women treated with ovulation-inducing agents. Teratology 1972;5:264.

7. Asch RH, et al. Update on the safety and efficacy of clomiphene citrate as a therapeutic agent. J Reprod Med 1976;17:175-180.
8. Ahlgren M, et al. Outcome of pregnancy after clomiphene therapy. Acta Obstet Gynecol Scand 1976;55:371-5.
9. Poecile A, et al. Treatment of anovolution in polycystic ovary syndrome with clomiphene citrate in 10-day cycles. (Spanish) Rev Chil Obstet Gynecol 1989 54(2) 94-7.
10. Kurachi K, et al. Congenital malformations of newborn infants after clomiphene-induced ovulation. Fertil Steril 1983;40:187-9.
11. Rosa F. Ovulation induction and neural tube defects. Lancet 1990; 336:1327.
12. Willemsen N, et al. Ovarian stimulation and granulosa - cell tumor. Lancet 1993;341:1345-6.
13. Kuppens E, et al. Multiple primary melanomas in a patient with familial type DNS during clomiphene induced pregnancy. Melanoma Res 1992;2:71-4.

GENERIC NAME: CLOMIPHENE

PHARMACOLOGICAL CLASS: Fertility agent nonhormonal.

TRADE NAMES: Serofene (Serono)
Ikaclomide (Teva)

CHEMICAL NAME: Ethanamine, 2-[4-(2-chloro-1,2-diphenylethenyl) phenoxyl]-N,N-diethyl-

BREAST FEEDING
No data available.

GENERIC NAME: CHLOROQUINE

PHARMACOLOGICAL CLASS: Anti Malarial
Anti Amoebic
Anti Rheumatoid

TRADE NAMES: Malaraquin (Sterling/Winthrop/Ross)
Norolon (Sterling/Winthrop/Ross)
Pfizerquine (Pfizer)

CHEMICAL NAME: 1,4-pentanediamine,
N4-(7-chloro-4-quinolinyl)-N1, N1-diethyl-

RISK FACTOR: C

## PREGNANCY

### TERATOGENICITY

Chloroquine is used mainly for antimalarial prophylaxis; it may be also used to treat extraintestinal Entamoeba histolitica and at higher doses, as inflammation suppressor in rheumatoid arthritis. Its use for malaria prophylaxis has been lately limited by the rapid emergence of chloroquine resistant strains of Plasmodium falciparum. Chloroquine crosses the placenta, with equilibrated cord/maternal plasma concentrations (0.33). The main report on the effects of chloroquine on foetuses throughout pregnancy (1), based on study of 169 infants, who were exposed in utero to a weekly dose of 300 mg chloroquine base and 454 non exposed controls. Four (0.9%) of the later were born with congenital defects, as compared to two (1.2%) amongst the exposed, the difference not being statistically significant. One woman who was treated with chloroquine during pregnancies for discoid lupus, gave birth to 3 exposed newborns with defects, one exposed and two non-exposed normal infants (2); the defects were left sided hemihypertrophy and cochleovestibular paresis (two infants). A more recent study (3) has evaluated the effect, which the administration of chloroquine in pregnancy to mothers with malaria had on birth-weight of the offspring. Placental parasitaemia, but not the drug, was associated with a reduced birth-weight.
An animal study in sheep has suggested a possible delay of lung maturation in exposed foetuses, which was reversible by hydrocortisone (4). In general chloroquine is considered to be the safest anti malarial for administration in pregnancy (5, 6).

### ONCOGENICITY

The series of the three infants of the woman with discoid lupus quoted above (2) included a case of Wilm's tumour.

### REFERENCES

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chemosuppression of malaria during pregnancy. Br Med J 1985;290:1466-7.
2. Hart CW, et al. The ototoxicity of chloroquine phosphate. Arch Otolaryngol 1964;80:407-12.
3. Cot M, et al. Effect of chloroquine chemoprophylaxis during pregnancy on birth weight: results of a randomized trial. Am J Trop Med Hyg 1992;46:21-7.
4. Okanlawon AO, et al. The effects of chloroquine on pulmonary saccular growth near term. West Afr J Med 1991;10:171-4.
5. Anonymous. Malaria in pregnancy. Lancet 1983;2:84-5.
6. Subramanian D, et al. Imported malaria in pregnancy: report of four cases and review of management. Clin Infect Dis 1992;15:408-13.

GENERIC NAME: CHLOROQUINE

PHARMACOLOGICAL CLASS: Anti Malarial
Anti Amoebic
Anti Rheumatoid

TRADE NAMES: Malaraquin (Sterling/Winthrop/Ross)
Norolon (Sterling/Winthrop/Ross)
Pfizerquine (Pfizer)

CHEMICAL NAME: 1,4-pentanediamine,
N4-(7-chloro-4-quinolinyl)-N1, N1-diethyl-

BREAST FEEDING

Chloroquine is excreted into human breast milk with a milk:blood ratio of 0.36, resulting in nontoxic consumption by the infant (1). Based on a 1000ml daily milk consumption, nursing infants are expected to absorb 2,2-4,2% of maternal dosage. It is estimated that breast feeding is safe when mothers receive anti malarial treatment with chloroquine (2).

REFERENCES

1. Akintonwa A, et al. Placental and milk transfer of chloroquine in humans. Ther Drug Monit 1988;10:147-9.
2. Ogunbona FA, et al. Excretion of chloroquine in chemosuppression of malaria during pregnancy. Br Med J, 1985;290:1466-7.

GENERIC NAME: LEVOTHYROXINE

PHARMACOLOGICAL CLASS: Thyroid hormone

TRADE NAMES: Eltroxin (Glaxo)
Levothyrox 50 (Merck-Clevenot)

CHEMICAL NAME: L-Tyrosine,O-(4hydroxy-3,5-diiodophenyl)-3,5-diiodo-

RISK FACTOR: Am

PREGNANCY

TERATOGENICITY AND MUTAGENICITY

Levothyroxine (T4) is considered a safe drug for treatment during pregnancy, especially due to low transplacental passage (1). Moreover, it may be administered intra-amniotically to prevent congenital hypothyroidism (2). The small amounts of thyroid hormones which do cross into the foetus are sufficient to prevent hypothyreotic brain damage (3).

In a large prospective study of 537 mother-child pairs, there were 780 exposures to T4 during the 1st trimester of pregnancy (4), which in nine cases were associated with cardiovascular anomalies, three cases of Down's syndrome and three of polydactyly. However, no statistical significance could be demonstrated, because maternal hypothyroidism may be associated with poor pregnancy outcome (5).

REFERENCES

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2. Perelman AH, et al. Intrauterine diagnosis and treatment of fetal goitrous hypothyroidism. J Clin Endocrinol Metab 1990;71:618-21.
3. Vulsma T, et al. Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. N Engl J Med 1989;321:13-6.
4. Heinonen OP, et al. Birth Defects and Drugs in Pregnancy. Littleton: Publishing Sciences Group 1977.
5. Pekonen F, et al. Women on thyroid hormone therapy: pregnancy course, fetal outcome and amniotic fluid thyroid hormone level. Obstet Gynecol 1984;63:635-8.

GENERIC NAME: LEVOTHYROXINE

PHARMACOLOGICAL CLASS: Thyroid hormone

TRADE NAMES: Eltroxin (Glaxo)
Levothyrox 50 (Merck-Clevenot)

CHEMICAL NAME: L-Tyrosine,O-(4hydroxy-3,5-diiodophenyl)-3,5-diiodo-

BREAST FEEDING

With one exception (1), most studies have shown low or unmeasurable levels of T4 in breast milk of treated mothers, with no effect on neonatal thyroid function (2, 3). This includes sophisticated methods of measurement, such as radioimmunoassays (4) and gas chromatography (5). In spite of these results breast feeding probably does confer some protection to children with congenital hypothyroidism (6).

REFERENCES

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2. Varma SK, et al. Thyroxine, triiodothyronine and reverse triiodothyronine concentrations in human milk. J Pediatr 1978;93:803-6.
3. Letarte J, et al. Lack of protective effect of breast feeding in congenital hypothyroidism: report of 12 cases. Pediatrics 1980;65:703-5.
4. Mizuta H, et al. Thyroid hormones in human milk and their influence on thyroid function of breast-fed babies. Pediatr Res 1983;17:468-71.
5. McOller B, et al. Identification of thyroxine in human breast milk by gas chromatography-mass spectrometry. J Clin Endocrinol Metab 1983;56:30-4.
6. Franklin R, et al. Neonatal thyroid function: comparison between breast-fed and bottle-fed infants. J Pediatr 1985;106:124-6.

GENERIC NAME: CAPTOPRIL

PHARMACOLOGICAL CLASS: Anti-hypertensive
Angiotensin converting enzyme (ACE) inhibitor

TRADE NAMES: Capoten (Squibb)
Inhibace (Taro)

CHEMICAL NAME: L-Proline, (3-mercapto-2-methyl-1-oxopropyl)-
(s)-
RISK FACTOR: Cm

PREGNANCY

TERATOGENICITY
Captopril has a low teratogenic risk. Two cases of birth defects, have been reported (1), including defective ossification of the skull, associated with ACE inhibitors. In another series of 19 infants exposed to captopril during the first two trimesters of pregnancy , one had microcephaly and encephalocoele (2). Another report described four cases of patent ductus arteriosus in 37 pregnancies by 31 women, who were continuously treated with ACE inhibitors for chronic hypertension (3). However, this minor cardiac malformation is also relatively common in the general newborn population.

FETAL TOXICITY
Fetal toxicity seems to be fairly common, resulting mainly in renal insufficiency, sometimes with oligohydramnios, growth retardation, prematurity and still births, foetal hypoxia and pulmonary hypoplasia (2, 3, 4). An earlier animal study produced similar results (5). Based on these findings, the FDA has issued a warning about the use of ACE inhibitors in pregnancy (6).

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GENERIC NAME: CAPTOPRIL

PHARMACOLOGICAL CLASS: Anti hypertensive
Angiotensin converting enzyme (ACE) inhibitor

TRADE NAMES: Capoten (Squibb)
Inhibace (Taro)

CHEMICAL NAME: L-Proline, (3-mercapto-2-methyl-1-oxopropyl)-
(s)-

BREAST FEEDING

Captopril is excreted in low concentrations into breast-milk at a milk/plasma ratio of 0.012, as measured in 12 nursing mothers who were treated with captopril (1). No effects on the infants was observed. The American Academy of Pediatrics considers captopril compatible with breast feeding (2).

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GENERIC NAME: CARBAMAZEPINE

PHARMACOLOGICAL CLASS: Anti convulsant

TRADE NAMES: Tegretol (Geigy)
Tegretal (Geigy)
Teril (Taro)

CHEMICAL NAME: 5H-Dibenzen(b,f)azepine-5-carboxamide

RISK FACTOR: Cm

## PREGNANCY

### TERATOGENICITY

A 1989 report (1) states that carbamazepine is probably a human teratogen, but as maternal epilepsy itself is associated with an increased risk of congenital defects in the offspring (2, 3), carbamazepine is nevertheless recommended as the treatment of choice for pregnant epileptic women (4). Gestational exposure to carbamazepine may result in decreased head circumference in the infants (5). A multitude of anomalies have been described in about 600 1st trimester anecdotal exposures to this drug (1, 6, 7, 8, 9, 10, 11, 12, 13), the majority being concommitantly exposed to additional anti convulsants, which is known to increase the risk for teratogenicity (14). The defects included: craniofacial abnormalities, limb defects, congenital heart disease and developmental delay. Eight infants with spina bifida were identified in a series of 1307 pregnancies with monoexposure to carbamazepine (15). This represents a nine-fold relative risk increase for neural tube defects. In a prospective study of 23 in-utero exposures to carbamazepine, one was born with meningomyelocoele and other abnormalities (16). No late effects were found on the offsprings' central nervous system development (17). Consensus guidelines of the California Comprehensive Epilepsy Program (18), state that only anti convulsant monotherapy should be administered during pregnancy, which reduces significantly the teratogenic risk as compared to anti convulsant polytherapy. A 1991 editorial (19) concludes, that although carbamazepine is a minor teratogen, the evidence for barring this drug from use during pregnancy is insufficient. It has been suggested to offer withdrawal from anti convulsant therapy to pregnant women, after a period of two years free of seizures (20).

### FETAL TOXICITY

Carbamazepine crosses the placenta, fetal levels reaching 50-80% of maternal serum, concentrating mainly in the fetal liver and kidneys, without affecting placental function (21). Some alterations in maternal-foetal metabolism of vitamin D were reported (22), but were found not to be significant. With the progression of pregnancy drug, plasma levels decrease due to changes in plasma protein binding (23).

### DOSAGE

Plasma levels of anti epileptic drugs decrease during pregnancy, due to enhanced

binding to plasma proteins; therefore the dosage of all the drugs have to be increased in pregnancy (23). Plasma levels of carbamazepine have to be maintained in the range of 15-40 mumol (24).

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GENERIC NAME: CARBAMAZEPINE

PHARMACOLOGICAL CLASS: Anti convulsant

TRADE NAMES: Tegretol (Geigy)
Tegretal (Geigy)
Teril (Taro)

CHEMICAL NAME: 5H-Dibenzen(b,f)azepine-5-carboxamide

BREAST FEEDING

Carbamazepine is excreted into breast milk resulting in low milk:plasma ratios of 0,24-0,69 (1, 2, 3, 4) without plasma accumulation. A case of infantile drawsiness after exposure to carbamazepine in breast milk has been reported (4). The American Academy of Pediatrics considers this drug to be compatible with breast feeding (5).

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GENERIC NAME: CHLORPROPAMIDE

PHARMACOLOGICAL CLASS: Hypoglycemic agent
(Anti diabetic)

TRADE NAMES: Diabenese (Pfizer-Roerig)
Diabitex (Teva)

CHEMICAL NAME: Benzensulfonamide, 4-chloro-N-[(propylamino) carbonyl)]

RISK FACTOR: D

PREGNANCY

TERATOGENICITY
Teratogenicity has been demonstrated in animal studies. In humans, the incidence of congenital defects, possibly associated with chlorpropamide, does not exceed that found in offspring of diabetic mothers, in which it is increased two to four fold, as compared with normal controls (1). However, four cases of congenital malformations, suspected of being directly associated with chlorpropamide have been reported (2, 3); they include hand anomalies, lower ileum stenosis, preauricular sinus and microcephaly with spastic quadriplegia.

FETAL TOXICITY
Chlorpropamide crosses the placenta readily, persisting in neonatal serum for days, which may result in severe neonatal hypoglycaemia (4). In addition, this drug does not provide an adequate diabetic control, therefore it is not indicated for treating pregnant diabetic women (5).

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GENERIC NAME: CHLORPROPAMIDE

PHARMACOLOGICAL CLASS: Hypoglycemic agent
(Anti diabetic)

TRADE NAMES: Diabenese (Pfizer-Roerig)
Diabitex (Teva)

CHEMICAL NAME: Benzensulfonamide, 4-chloro-N-[(propylamino)
carbonyl)]

BREAST FEEDING
Chlorpropamide is excreted into breast milk, where it reaches low concentrations. The effect on the nursing infant has not been documented.

GENERIC NAME: RESERPINE

PHARMACOLOGICAL CLASS: Anti-hypertensive

TRADE NAMES: Adelphane (Ciba Geigy)

CHEMICAL NAME: Yohimban-16-carboxylic acid, 11,17-dimethoxy-18-[(3,4,5-trimethoxybenzoyl)oxy]-,methyl ester,(3β16β,17α,18β,20α)

RISK FACTOR: D

## PREGNANCY

### TERATOGENICITY

The largest study of exposure to reserpine during pregnancy was included in the Collaborative Perinatal Project (1), which monitored 50282 mother-child pairs. Four defects were found amongst first trimester exposures (8%) which is a greater incidence than expected, but no significant association with a specific defect could be demonstrated. The same was true when all exposures during pregnancy were recorded (475) with 25 defects, which included: microcephaly (n=7), hydronephrosis (n=3), hydroureter (n=3) and inguinal hernia (n=12).

### FETAL TOXICITY

Reserpine acts by catecholamine (2), serotonin and noradrenaline depletion. Its use antepartum can result in nasal congestion, lethargy and anorexia in the newborn (3). Prenatal exposure to reserpine has been shown to induce long-term alterations in cardiovascular parameters (4) and neurobehavioural toxicity (5) in the rat model.

### MUTAGENICITY

Reserpine was found to increase the mutagenic response of a metabolically activated promutagene in an in vitro system (6).

### ONCOGENICITY

Reserpine was found to increase the incidence of mammary gland tumours in female mice (7).

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GENERIC NAME: RESERPINE

PHARMACOLOGICAL CLASS: Anti-hypertensive

TRADE NAMES: Adelphane (Ciba Geigy)

CHEMICAL NAME: Yohimban-16-carboxylic acid, 11,17-dimethoxy-18-[(3,4,5-trimethoxybenzoyl)oxy]-,methyl ester,(3β16β,17α,18β,20α)

BREAST FEEDING

Reserpine has been shown to be excreted into breast milk (1) but no adverse effects in the nursing infant have been reported.

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## Appendix G

**A Diskette Containing the Database Model (attached to the backcover).**

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