Ann. Ist. Super. Sanità, vol. 29, n. 1 (1993), pp.131-137

Risk assessment of drug use in pregnancy: prevention of birth defects

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Summary. - Some developmental disorders are preventable by primary prevention, i.e. by avoiding exposure to microorganisms or chemicals that cause developmental disorders. This is not only important for physicians prescribing drugs, midwives monitoring pregnancies, but especially for parents taking the responsibility of having a baby; moreover, this fact is of importance for teratogen information services and public health authorities, both having preventive roles to play. Knowledge of the different pre- and postnatal developmental stages and the reproductive cycle is essential to understand this statement. The basic principle in reproductive toxicology and teratology is that the response of an organism to a teratogen depends upon the nature and the dosage of the substance, the stage of development of the embryo/fetus and its genetic make up. Chemical agents of different nature can induce developmental disorders either via the mother and perhaps via the father. The common consent that the vulnerable stage of development is only the first trimester of pregnancy is not correct. From oogenesis and spermatogenesis to at least the first years of life the developing organism is susceptible to harmful effects of chemical agents, including drugs. Developmental disorders include not only malformations visible at birth, but also spontaneous abortions, fetal death and functional deficits including behavioural defects. Studies both in the human and in laboratory animals make it possible to select substances to avoid exposure to developmental toxicants which are already on the market or still under development. This implicates a multi-step procedure leading from risk-evaluation, risk-assessment, and risk-communication to risk-perception and the according action (risk-management).

Key words: reproductive toxicology, embryogenesis, organogenesis, pregnancy, drugs, risk assessment, birth defects.

Riassunto *(Valutazione del rischio legato all'uso dei farmaci in gravidanza: prevenzione dei difetti congeniti).* - Alcuni difetti dello sviluppo embrio-fetale sono prevenibili attraverso interventi di prevenzione primaria: evitando l'esposizione a microorganismi o agenti chimici che causano difetti congeniti. Ciò è importante non solo per il personale medico ma anche per le coppie che desiderano un figlio. Inoltre la prevenzione dei difetti congeniti è l'obiettivo dei servizi di informazione sui teratogeni (TIS). Per poter minimizzare i rischi riproduttivi è importante conoscere i dettagli dello sviluppo pre e post-natale. Il principio di base della teratologia è che la risposta di un organismo ad un agente teratogeno dipende dalla natura e dalla dose della sostanza, dallo stadio di sviluppo dell'embrione e dalle sue caratteristiche genetiche. Agenti chimici di varia natura possono indurre anomalie dello sviluppo sia attraverso la madre che, forse, attraverso il padre. La comune opinione che lo stadio vulnerabile dello sviluppo embrionale è limitato al primo trimestre di gravidanza forse non è del tutto corretto. Dall' oogenesi e la spermatogenesi sino almeno al primo anno di vita può esistere la suscettibilità ad effetti nocivi degli agenti chimici, inclusi i farmaci. Le anomalie dello sviluppo comprendono non solo le malformazioni visibili alla nascita, ma anche aborti spontanei, morte fetale e deficit funzionali compresi quelli del comportamento. Esiste una serie di studi che possono essere condotti sia sull'uomo che sugli animali da esperimento che permettono di identificare molte sostanze chimiche che devono essere evitate, che sono già nell'ambiente o che possono essere immesse nel futuro. La prevenzione dei difetti congeniti implica una procedura complessa che comprende la valutazione del rischio, la comunicazione del rischio al pubblico, la percezione del rischio da parte del pubblico, e una serie di procedure per minimizzare le possibilità che il rischio di anomalia di sviluppo si verifichi.

Parole chiave: tossicologia riproduttiva, embriogenesi, organogenesi, gravidanza, farmaci, valutazione del rischio, difetti congeniti.

Introduction

Most prescribers and users of drugs are familiar with the warning against the use of drugs during the first trimester of pregnancy. This phrase has been introduced following the thalidomide disaster that took place some 25 years ago. However, being careful only during the first three months of pregnancy is short-sighted and in fact impossible. Firstly, because chemicals are able to interfere with all the different stages of development in the reproductive cycle (Fig. 1), and secondly, because at the moment a woman learns that she is pregnant, the stage of organogenesis has already progressed a great deal and for example, the neural walls are closed, hence the early embryonic period was inadvertently exposed to maternal drug treatment.

A special field is related to the risk assessment of drug use in pregnancy, including fertility: reproductive toxicology. Toxicology recognizes several disciplines such as carcinogenicity, mutagenicity and reproductive

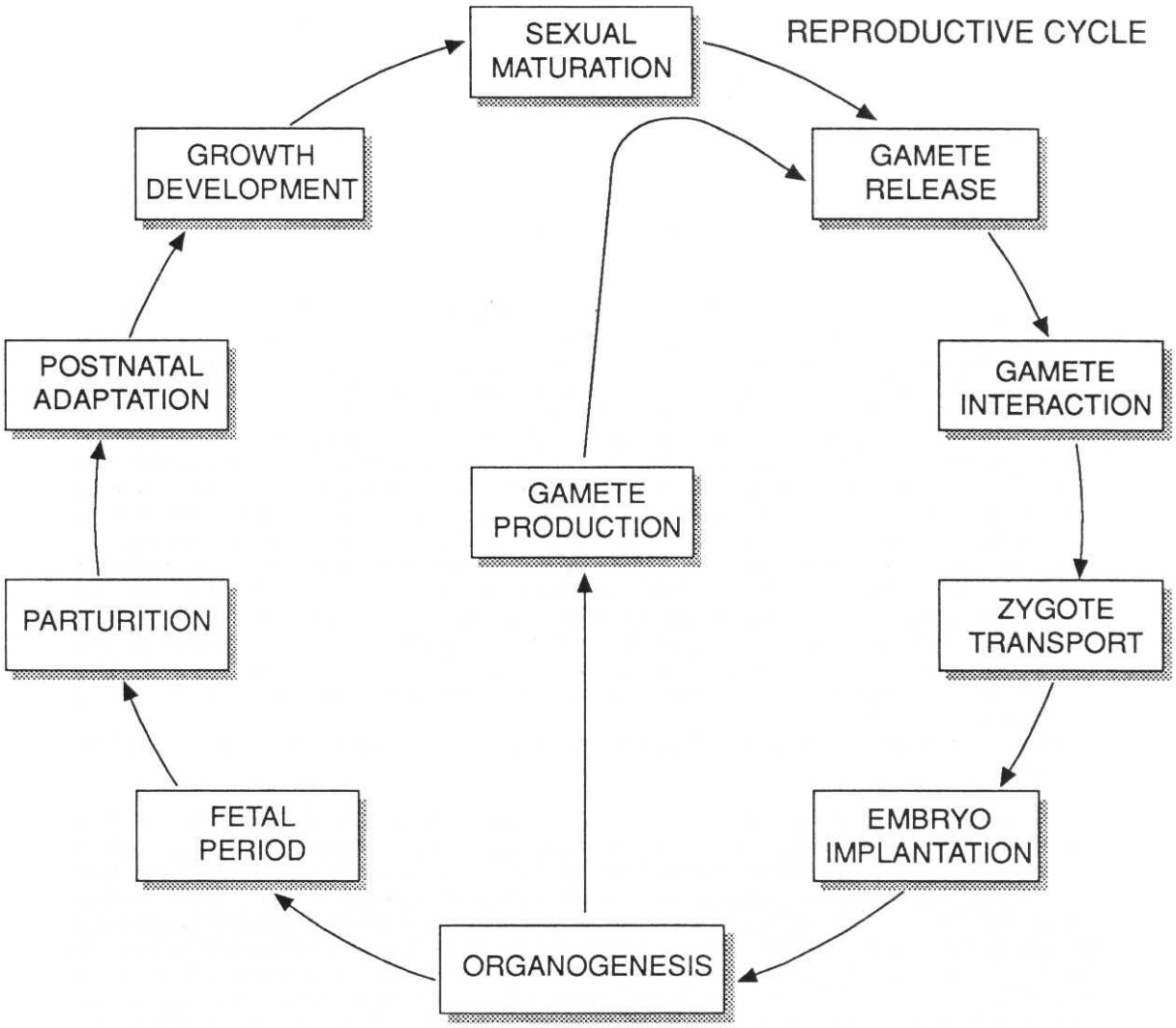

Fig. 1. - The reproductive cycle. A schematic representation of the individual processes in reproduction.

toxicology. Reproductive toxicology is concerned with possible effects of substances on the reproductive process, i.e. on sexual organs and functions, endocrine regulation, fertilization, transport of the fertilized ovum, implantation, and embryonic and foetal development.

The aim of this paper is: to stress the complexity of the different stages of normal development; to mention the principles that are applicable in reproductive toxicology; to describe different drugs that might act as teratogens and reproductive toxicants; to show the broad scope of different effects caused by developmental toxicants; and to indicate methods to detect and to recognize causes of developmental defects in the expectation to prevent these disorders.

Reproductive cycle

The different stages of the reproductive cycle are in fact highlights of a continuum. These stages concern a different developmental time span each with their own sensitivity to a given toxic agent. Let us look at this cycle, starting off at the earliest moment of the origination of an individual.

Primordial germ cells are present in the embryo at about one month after the first day of the last menstruation. They originate from the yolksac-entoderm outside the embryo and migrate into the undifferentiated primordia of gonads located at the medioventral surface of the urogenital ridges. They subsequently differentiate into

oogonia and oocytes or into spermatogonia. The oocytes in postnatal life are at an arrested stage of the meiotic division. This division is restarted much later after birth, shortly before ovulation and is finalized after fertilization with the expulsion of the polar bodies. Thus, all female germ cells develop prenatally and no germ cells are formed after birth; moreover, during a female life span approximately 400 oocytes undergo ovulation. The embryonal spermatogenic epithelium, on the contrary, divides slowly by repeated mitoses, these cells do not differentiate into spermatocytes and do not undergo meiosis in the prenatal period. The onset of meiosis begins at puberty. Spermatogenesis continues throughout (reproductive) life. When the complexity of sexual development and female and male gametogenesis are considered, it becomes apparent that prenatal and postnatal drug exposure is a special toxicological problem. The specificity of male and female developmental processes also accounts for different reactions to toxic agents, such as drugs, in each sex.

After fertilization of the oocyte by one of the spermatozoa in the oviduct there is the stage of cell divisions and transport of the blastocyst into the endocrine-prepared uterine cavity. After implantation the bilaminar stage is formed and embryogenesis starts. These next 7 weeks are a period of finely balanced cellular events, including proliferation, migration, association, differentiation, and programmed cell death; precisely arranged to produce tissues and organs from the genetic information, present in each conceptus. During this period of organogenesis rapid cell multiplication is the rule. Complex processes of cell migration, pattern formation and the penetration of one cell group by another, characterize the later stages. Final morphological and functional development occurs at different times during foetogenesis and is sometimes completed after birth. Postnatal adaptation characterizes the passage from intrauterine into extra-uterine life with tremendous changes in, for example, circulatory and respiratory physiology. After puberty the above described reproductive cycle is closed.

Basic principles of drug-induced reproductive toxicology

The determination of whether a given chemical has the potentiality or capability to induce developmental disorders is governed by essentially three established fundamental principles. It can be stated [1], that a teratogenic response depends upon the exposure 1. to a specific substance in a particular dose; 2. to a genetically susceptible species; and 3. to a conceptus in a susceptible stage of development.

1. As in other toxicological evaluations, reproductive toxicity is governed by dose-effect relationships; the curve, however, is generally quite steep. The dose-response is of utmost importance in determining if there is a true effect. Moreover, nearly every reproductive toxic drug that has been realistically tested or that was clinically positive has been shown to have a "no-effect" level. Another aspect worthy of mentioning here is the sometimes highly specific nature of the substance. For instance, thalidomide is a clear-cut teratogen in the human and in specific species, in contrast to its analogues that never were proven to be developmental toxicants.

2. Not all mammalian species are equally susceptible or sensitive to the reproductive toxic influence by a given chemical. Inter- and intraspecies variability may be manifested in several ways: a drug that acts in one species may have little or no effects in others; a reproductive toxicant may produce similar defects in various species, but these defects will vary in frequency; a substance may induce certain developmental disorders in one species that are entirely different from those induced in other species. The explanation is that there are genetic differences that influence the teratogenic response. This might be further modified by environmental factors.

3. There exists a sensitive period for different effects, i.e. the developmental phase during which originating, proliferating and differentiating cells and organs become susceptible to a given drug. This period may not be related to critical morphogenetic periods, but may, for example, be related to the appearance of specific receptors. This explains how at an early period of development, dysmorphology is induced by a substance which, at the opposite end of the timetable of development, induces functional disorders such as those of the central nervous system.

Drugs causing developmental disorders

The nature and the application of drugs that induce reproductive toxicity are important and must be considered, but also the route by which they can reach the unborn. Drugs, in contrast to food-additives and to a lesser extent cosmetics are intentionally administered, and it has to be realized that a therapeutic drug in a pregnant woman crosses nearly always the mother-conceptus barriers. When the drug has an effect (or side-effect) for the mother, by definition, the drug or its metabolites will be a toxic agent for the unborn.

Pregnant women and women who wish to become pregnant are usually warned not to smoke cigarettes, consume alcohol or not to take any drugs that are not absolutely necessary. Their husbands or partners, on the other hand, are rarely, if ever, admonished to avoid known teratogens. Nevertheless, evidence is slowly accumulating that if males are exposed to reproductive agents before their offspring is conceived, the incidence of birth defects among those offspring may increase. So far no one is certain about the safety of substances that

after administration or via occupational exposure to males can cause birth defects. Joffe and Soyka [2] listed three possibilities: 1) the substances could damage the sperm itself genetically, impair spermatogenesis or maturation of sperm; 2) the agents might act through the semen. Many substances are excreted in semen and are present with sperm before, during but also (long) after the moment of conception; and 3) the effects of the toxic agents could be produced indirectly as a result of the action of, for example, drugs on the male. No one believes at this moment that drugs taken by males are a major contribution to developmental disorders, but many investigators conclude that these drugs could cause at least a clinically significant number of these disorders. This possible cause of developmental toxicity is essential and should not be forgotten, when stimulating primary prevention of congenital disorders.

Effects and manifestations

A wide variety of responses characterizes developmental toxicity and teratogenicity. Teratogenicity is explained here as the capacity of the substance to induce congenital malformations. Infertility, chromosomal and genetic disorders, spontaneous abortion, intrauterine death, prematurity, low birth weight, birth defects and functional disorders are effects of such drug interference with developmental and reproductive processes (Table 1). The manifestation of a reproductive toxicant or teratogen can either be seen immediately after exposure or will be expressed at a much later date. Interfering with male or female germ cell development might result in infertility, decreased sperm activity and/or libido and impaired gametogenesis. Effects on the pre-implantation stage will cause early embryonic death, extra-uterine implantation or delayed transport of the fertilized zygote.

A critical phase for the induction of structural malformations usually occurs during the period of organogenesis. In man, this critical period extends from about 20-70 days after the first day of the last menstruation period, or from one week before the missed menstruation until the woman is 44 days "overdue". It may be unwise to rely absolutely on this time period. With physical agents such as X-rays used in laboratory animals, exposure can be limited exactly to a period of minutes to discover the exact sensitive period for inducing a specific disorder. However, in drugs we are not at all sure about the time courses of absorption, metabolism and excretion. In addition, the actual proximate teratogen may be a metabolite rather than the compound administered. If the moment of final differentiation of a particular organ is known with certainty, then a teratogen must have been present prior to that time, if it is supposed to be the causal agent of the malformation.

During the fetal period the manifestations from toxicological interference are growth retardation, some forms of structural malformations, fetal death, functional impairment and transplacental carcinogenesis. The period of organ and system maturation extends beyond the period of organogenesis and even beyond the prenatal period. Therefore, the susceptible period for the induction of insults that may lead to functional deficits is much longer than that for the induction of gross structural defects. Functions that have been shown to be affected by prenatal and early postnatal exposure to chemicals include behaviour, reproduction, endocrine function, immune competence, xenobiotic metabolism, and various other physiological functions.

Fetal tissues are intrinsically highly vulnerable to carcinogens because of their high rate of cellular proliferation. This phenomenon has been demonstrated in rats, mice, hamsters, rabbits, pigs, dogs and monkeys with approximately 60 chemicals. Twenty-three compounds and groups of chemicals and 7 industrial processes have been shown to induce carcinogenic effects in human beings. However, there is convincing epidemiological evidence of transplacental tumour-induction in man for only one compound, i.e. diethylstilboestrol (DES) [3]. Exposure to DES in utero leads to the development of clear-cell adenocarcinoma of the vagina or cervix in about 1 in 1,000 of those at risk. Moreover, DES is now a recognised female genital tract teratogen. The effects of exposure to DES in utero for males are still highly controversial.

Detection and recognition of reproductive toxic drugs and teratogens

Different methods exist for assessing the reproductive toxicity or teratogenicity of medicinal products. The risk assessment process of reproductive toxic or teratogenic novel chemicals is restricted to experimental studies in laboratory animals. With respect to current chemicals, human data are of great value. It is generally considered that the predictive value of animal teratogenicity and reproductive toxicity tests in extrapolating results of chemicals into terms of human safety is less than adequate. Hence, it can be understood that not all teratogenic substances were discovered by laboratory screening methods before they were used in humans.

With the exception of androgens, several antimitotic drugs, sodium valproate and vitamin A derivatives, all human teratogens were discovered earlier in man than in animals. Most of these discoveries were made by case studies and not primarily, by epidemiological studies. Hypotheses about the cause of a developmental disorder can arise from case studies, from ecological correlative investigations or from animal experiments. Specific

Table 1. - Organs and functions potentially affected by reproductive toxic agents

Reproductive stage	Female	Male	Possible end points
Germ cell formation	*Oogenesis* (occurs during fetal development of mother) Gene replication Cell division	*Spermatogenesis* Gene replication Cell division	Sterility, sub-fecundity, damaged sperm or eggs, chromosomal aberrations, menstrual effects, age at menopause, hormone imbalances, changes in sex ratio
	Egg maturation Hormonal influence on ovary	*Sperm maturation* Sertoli cell influence Hormonal influence on testes	
	Ovulation Hormonal influence on ovary		
Fertilization	*Oviduct* Contractility Secretions Hormonal influence on secretory and muscle cells	*Accessory glands* Sperm motility and nutrition Hormonal influence on glands	Impotence, sterility, subfecundity, chromosomal aberrations, changes in sex ratio, reduced sperm function
	Uterus Contractility Secretions Hormonal influence on secretory and muscle cells	Nervous system Erection Ejaculation Behaviour Libido	
	Nervous system Behaviour Libido		
Implantation	*Uterus* Changes in uterine lining Secretions Hormonal influence on secretory cells		Spontaneous abortion, fetal resorption, chromosomal aberrations, subfecundity, stillbirths, low birth weigh
Embryogenesis	*Uterus* Placenta information		Spontaneous abortion, other fetal losses,birth defects, chromosomal abnormalities, stillbirths, change in sex ratio, low birth weight
	Embryo Cell division Tissue differentiation Hormone production Growth		
Organogenesis	*Placenta* Nutrient transfer Hormone production Protection from toxic agents		Birth defects, spontaneous abortion and other fetal death, chromosomal aberrations, retarded growth and development, transplacental carcinogenesis
	Embryo Organ development and placement Growth		
	Maternal nutrition		
Perinatal	*Fetus* Growth and development *Uterus* Contractility Hormonal effects on muscle cells		Premature births, births defects (particularly nervous system), stillbirths, neonatal death, low birth weights, toxic syndromes or withdrawal symptoms in neonates
Postnatal	*Maternal nutrition* *Infant survival* *Lactation*		Mental retardation, infant mortality, retarded development, metabolic and functional disorders, developmental disabilities (e.g., cerebral palsy and epilepsy)

Table 2. - Medicinal products for which human data are available to evaluate the safety with respect to the course of pregnancy and the health of the unborn and the neonate

Category A

This medicinal product has been assessed in pregnant women and no harmful effects are known with respect to the course of pregnancy and the health of the unborn and the neonate.

Category B

B1
The safety of this medicinal product for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo or foetus, the course of gestation and peri- and postnatal development. (See explanatory text for current experience in humans.)

B2
The safety of this medicinal product for use in human pregnancy has not been established. Experimental animal studies are insufficient to assess the safety with respect to the development of the embryo or foetus, the course of gestation and peri- and postnatal development. (See explanatory text for current experience in humans.)

B3
The safety of this medicinal product for use in human pregnancy has not been established. Evaluation of experimental animal studies has shown reproductive toxicity, e.g. birth defects or other effects on the development of the embryo or foetus, the course of gestation or peri- and postnatal development. (See explanatory text for current experience in humans.)

Category C

This medicinal product does not increase the spontaneous incidence of birth defects, but it has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate (see further specific information).

Category D

This medicinal product is known or suspected to cause birth defects and/or other irreversible adverse effects on pregnancy outcome. It may also have potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate (see further specific information).

epidemiological examination in, for example, a patient-control, cohort and intervention studies might provide the final evidence of such hypotheses.

In this respect it is worth mentioning that some 15 years ago a collaboration was started among birth defects registries around the world. This International Clearinghouse for Birth Defects Monitoring Systems consists at present of 28 birth defects surveillance programs, monitoring about 4 million newborns each year. Some cooperative research is performed (eg. multi-malformed infants), but the main activity is the exchange of information collected within each program. An important aim is a world wide surveillance and in this respect the time factor is important. Preliminary data are collected within three months at the end of each quarter, while final, yearly data are also published. A primary goal of the Clearinghouse is to detect changes in the incidence of specific malformations or patterns of malformations that may indicate the presence of environmental hazards, to identify such hazards, and - if possible - to eliminate them [4].

The second method to detect chemicals with reproductive toxic or teratogenic properties is the use of laboratory animals. Prior to 1960 teratogenicity testing was very limited, with foetal survival generally being the main parameter. In the wake of the thalidomide disaster, "guidelines for reproductive studies, which cover also teratogenicity tests, for the safety evaluation of drugs for human use" [5] appeared. At present, most countries require extensive information on the potential reproductive toxicological effects of a drug before a license to market is approved. Gradually, a number of internationally accepted tests have been developed covering not only intra-uterine growth and development, but also gonadal function, mating performance, implantation, parturition and lactation. In spite of shortcomings, animal testing for reproductive toxicity and teratogenicity is the only present alternative, when we deal with a novel substance. The danger of disasters such as thalidomide may however, be further diminished by close and accurate surveillance of drugs following their introduction into society and the environment (postmarketing surveillance).

Primary prevention of developmental disorders

The final aim of public health must be prevention. Primary prevention of developmental disorders can be defined as the use of methods to prevent the origin of a developmental disorder. The approach for primary prevention of birth defects is most successful when a

medicinal product prevents the origination of a disorder for example in case of rubella vaccination (prevention of congenital rubella syndrome. Moreover, primary prevention of developmental disorders can be achieved when a drug is identified as a reproductive toxicant and is not approved for marketing or is removed from the market. When thalidomide was recognized as the causal factor in an epidemic of limb defects, removal of the drug from the markets resulted in a disappearance of this embryopathy. This event was also accompanied by a drastic avoidance of general drug intake by pregnant women. Nowadays, however, there are indications that about 80% of pregnant women use prescribed or 'over the counter' drugs. There can be no reasonable doubt that, at the present day, drugs are often more widely used in pregnancy than is justifiable from the knowledge available. This may be one aspect of what is sometimes called the medicalisation of pregnancy. At times it may even seem that pregnancy is to be regarded as dangerous until proven safe, whereas drugs are regarded as safe in pregnancy until proven dangerous. Health care professionals, and also pregnant women need to develop a more critical attitude to the use of drugs during pregnancy, or better to the use of drugs during the fertile period, taking these only when essential, thereby avoiding many unnecessary and unknown risks. The same applies obviously, for social drugs like tobacco, alcohol and addictive drugs. These remarks imply that health professionals and patients need to be informed about proven safe drugs.

Since 1984 classification systems have been introduced in the USA, Sweden and also in Australia. These systems allow a general estimation of the safety of drugs in pregnancy and to reproduction. In the European Community (EC) a draft proposal for categorization of medicinal products has been prepared, that is based on available human data (Table 2). Knowledge about the (un)safety of the drug in the human is the starting point. Prolonged use of medicines during pregnancy occurs in cases of chronic diseases such as epilepsy, diabetes, thyroid dysfunction etc. There are clear indications of teratogenicity amongst these groups of medicines and epidemiological investigations of these deserve high priority. Greater uniformity in prescribing habits would enhance the likelihood of detecting causal factors of developmental disorders. The registration of new drugs developed for conditions requiring treatment during pregnancy should be based on comparative clinical trials in which not only the therapeutic but also the teratogenic properties are examined. Categorization of drugs is necessary and provokes in communities such as the EC the possibility of harmonization. But such a categorization is general and has a "ready-made" fashion. A more "tailor-made" information about the (un)safety of chemicals with respect to reproduction is given by teratology information services. In 1990 two of such organizations for collaboration have been established: in the Americas OTIS (Organization of teratology information services) and in Europe ENTIS (European Network of Teratology Information Services). A teratology information service provides health professionals and patients with information relating to the pertinent situation, illness and chemical exposure of the person involved. These services also carry out follow-up studies to learn what happened during the course of pregnancy and about the health of the newborn (postmarketing surveillance). The last examples of activities to primarily prevent drug-induced birth defects can be characterized as risk-assessment leading to risk-communication.

The knowledge gained should lead to a better risk-perception and corresponding actions. This applies for the patient, the physician, but also for public health authorities (risk-management).

Submitted on invitation.
Accepted on 25 September 1992.

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