

PRELIMINARY REPORT ON THE FIRST BRAZILIAN TERATOGEN INFORMATION SERVICE (SIAT)

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ABSTRACT

The National System of information about Teratogenic Agents (SIAT) was set up in Porto Alegre, Southern Brazil, in 1990, with the purpose of providing doctors and the general public with rapid and updated information about the reproductive risks related to exposure to teratogenic agents. SIAT, which was the first service of this kind to operate in Latin America, is also an important source of data for prospective investigations about teratogenicity in humans. In this paper we report the preliminary experience of this service and its possible contributions. The introduction in 1992 of similar services in the two main Brazilian cities (Rio de Janeiro and São Paulo) and the operation of all three services within an integrated and coordinated national network enhance the potential of this service both at the health care and research levels.

INTRODUCTION

Since the thalidomide tragedy in the early sixties, there has been a progressively increasing interest in knowledge, prevention and treatment of anomalies of human development. About 3% of all newborn infants of the human species present clinically important congenital malformations. Of these, approximately 7% are caused by intrauterine exposure to chemical, physical or biological agents, 15 to 25% are associated with gene mutations or chromosome aberrations, 20% are of multifactorial etiology, and more than 50% are due to unknown causes (Kalter and Warkany, 1983).

A teratogenic agent is any substance, organism, physical agent or deficient condition which, by being present during embryonic or fetal life, produces an alteration in the structure or function of the offspring (Dicke, 1989).

The possible relationship between the use of medications during pregnancy and adverse effects on the embryo or fetus is of considerable concern. It is estimated that a human being may be exposed to approximately 5,000,000 different chemical substances, but only 1,500 of these have been tested on animals, and a little more than 30 have been proven to be teratogenic in man (Sheppard, 1992). This small number is due to the difficulty of investigating teratogenicity in humans. Epidemiologic studies based on the monitoring of congenital defects have not been successful in the identification of new teratogens, especially because of the need for large samples and for standardized controls (Castilla *et al.*, 1985; Kallen, 1987; Robert, 1992). Furthermore, retrospective studies depend on an accurate maternal history, and the existence of "memory bias" among mothers with normal or malformed children has been clearly recognized (Clavijo, 1991).

Traditionally, experimental studies on animals provide a screening basis for the determination of the teratogenic potential of a given agent. The fundamental role of these investigations is to elucidate the principles and mechanisms of teratogenesis, but they have not been successful in the identification of human teratogens due to the genetic differences between species. For example, corticosteroids, which are powerful teratogens in rodents, are apparently safe for man; conversely, thalidomide, a powerful teratogen for man, is apparently safe for most animals. Thus, definitive evidence about whether or not a drug is teratogenic to man should be obtained in studies on humans themselves.

To date, agents teratogenic to humans have been mainly identified by initial observations made by alert clinicians in daily medical practice. This was the case, for example, for rubella and thalidomide (Lenz, 1992; Lipson, 1992). However, epidemiologic studies are fundamental to confirm or rule out these hypotheses. The detection of valproic acid as a teratogen to humans is an example of a hypothesis raised by clinical observation (Robert and Gibaud, 1982), which was immediately tested using data from local records (Robert *et al.*, 1984) and finally confirmed by epidemiologic studies in other places (Mastroiacovo *et al.*, 1983; Lindhout and Meinardi, 1984; Martinez-Frias *et al.*, 1989).

Considering that the bibliography related to teratogenicity is very ample and scattered among different types of scientific journals and requires constant updating, specialized services have arisen in Europe and North America in order to provide this type of information to physicians and patients in general. These services have multiplied, especially during the 1980's, and also represent important sources of data on the teratogenic potential of various agents from exams of newborn infants delivered by exposed mothers. The prospective character of these services avoids the maternal memory bias, and a large number of pregnant women exposed to various substances are recorded in the files (Koren, 1990; Elefant *et al.*, 1992).

The National System of Information about Teratogenic Agents (SIAT) was set up at the Hospital de Clínicas of Porto Alegre in August 1990 and is the first system of this nature operating in Latin America. The SIAT is a telephone service which provides, free of charge, information about reproductive risks related to the exposure of pregnant women to chemical, physical and biological agents, and is directed to pregnant women, physicians or researchers in general. Starting in 1992, two similar services linked to the SIAT of Porto Alegre were created in Rio de Janeiro (at the Federal University of Rio de Janeiro) and São Paulo (at Escola Paulista de Medicina) to cope with the demand for information.

In this paper we present the methodology and initial results of the operation of the SIAT.

MATERIAL AND METHODS

Operational system

The SIAT is a service basically operated by telephone. Interviews are conducted by members of the medical team of the SIAT (consisting of physicians and medical students on a scientific initiation fellowship) who apply a directed questionnaire for the verification of the following variables (when a pregnant woman calls): a) identification and characterization of the caller (name, address, origin, educational level, profession; b) major reason for the call: period of exposure and, in the case of drugs, dose and medical prescription; c) other reasons: other exposures, use of other drugs and time of use, doses and indication; d) obstetric history: previous children, previous abortions; e) regularity in attending a prenatal care service; f) other risk factors: maternal age, consanguinity, other malformed individuals in the family, chronic or acute diseases during pregnancy, alcohol intake or cigarette smoking.

The replies are given within a maximum of 72 hours, also by telephone after a careful review of the literature and of specific data banks such as REPROTOX (Koren, 1990). When a particular risk is detected, the patient is called for a personal interview or her doctor is contacted so he may plan an evaluation of possible damage to the fetus.

Newborn follow-up

After the predicted date of birth of the child, all pregnant women who contacted the SIAT are recontacted by telephone and questioned about the following variables: a) general birth conditions: live birth, stillbirth, abortion, perinatal death; b) sex, twinning, birth weight and length, Apgar score; c) presence of malformations; d) discharge conditions and postnatal course.

When there are signs of alterations, or in cases of high or unknown risk an attempt is made to perform a direct examination of the newborn infant or, if the patient cannot come to the SIAT, the child's pediatrician is contacted.

Data analysis

The data referring to the pregnant women and their newborn infants are stored in a dBase III file in a PC-AT 386 computer. The classification of the Food and Drug Administration is used for the characterization of risks related to drugs (Table I) (Briggs *et al.*, 1990). The identification of one or more of the following items is also considered as a risk factor: maternal age of more than 35 years, consanguinity of the child's parents, malformed individuals in the sibship of the parents or of the newborn infant, maternal infection during pregnancy, chronic diseases such as diabetes, hyperthyroidism etc., smoking habit, alcohol intake, or the use of other drugs.

Table I - Risk Classification according to the Food and Drug Administration (FDA).

Category	Risk factors
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.
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 risk in later trimesters).
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.
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).
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.

Reproductive damage is considered to be present when the following facts are observed during evaluation of the newborn infants: pre or perinatal death, birth weight of less than 2500 g, congenital malformations, and neurofunctional disorders.

RESULTS

During the period from August 1990 to December 1991, the SIAT recorded a total of 523 calls (Table II), most of them related to pregnant women (N = 402, 76.9%). The other classes included women who wished to become pregnant (N = 46, 8.8%), children with congenital defects suspected to be caused by teratogenic exposure (N = 30; 5.7%), and finally investigators seeking general information about certain agents (N = 45; 8.6%).

A total of 283 infants born to the 402 pregnant women (six twin births) were evaluated. It was not possible to recontact the mother in 44 cases (10.9%), and at the time of data analysis 82 pregnancies (20.4%) were still in progress (Table III).

Table II - People who requested information from SIAT: 1990-1992. N = 523.

Class	%
Pregnant women	76.9
Women who were planning pregnancy	8.8
Women with children with congenital defects	5.7
Investigators	8.6

Table III - Follow-up of pregnancies. N = 402.

Class	%
Newborns evaluated	68.7
Pregnancies still in progress	20.4
Contact with the mother lost	10.9

The results of the postnatal evaluations are presented in Table IV. There were losses (abortion or stillbirth) in 11.7% of the pregnancies. The rate of congenital defects was 7.2%.

Table IV - Pregnancy outcomes. N = 283.

Class	%
Livebirths	88.3
Stillbirths	4.2
Abortions	7.5
Natimortality rate (excluding abortions)	4.6
Malformed babies (LB + SB)	7.2
Birth weight < 2,500 g (LB + SB)	8.0

Data about the origin, age and educational level of the mothers whose newborn infants were evaluated are presented in Tables V, VI and VII, respectively. Although most of the calls were from the Southern region, there was a considerable portion of contacts by persons residing in other regions of Brazil (N = 77; 27.9%). The modal maternal age was within the 25 to 30 year range (39.8%). With respect to educational level, there was a sharp predominance of the more advanced degrees of education, i.e., 42.1% of the mothers had completed high school and 36.9% had higher education.

The exposures recorded according to the major reason for the call were drugs, followed by maternal infections (Table VIII). The major doubts about drugs referred mainly to analgesics and to antibiotics in general. There was a significant demand for information about misoprostol, a prostaglandin of apparently generalized use in Brazil as self-medication in attempts to abort unwanted pregnancies (Table IX). The practice of self-medication was recorded in 44.0% of the 276 women.

Table V - Mothers of babies studied: place of origin. N - 276.

Place	%
Porto Alegre city	41.7
Rio Grande do Sul ¹	21.4
Southern region ²	9.0
Other regions in Brazil	27.9

¹State of Rio Grande do Sul, excluding Porto Alegre.

²Brazil's Southern region, excluding Rio Grande do Sul.

Table VI - Mothers of babies studied: maternal age. N - 276.

Age range (years)	%
< 20	6.5
20 - 24	18.1
25 - 30	39.8
31 - 34	18.9
> 34	14.5
Without information	2.2

Table VII - Mothers of newborns studied: level of education. N = 276.

Class	%
Alphabetized	1.4
Elementary school	17.1
High school	42.1
University	36.9
No information	2.5

Table VIII - Major reason for the call. N = 276.

Class	%
Drugs	66.7
Maternal infections	10.5
X Rays	5.4
Other maternal diseases	2.9
Occupational exposures	2.2
Maternal age	2.2
Other reasons	10.1

Most mothers had used some type of medication during pregnancy up to the time of their call. Table X presents the distribution of consumption of medication by FDA risk category, as well as the rate of reproductive damage observed in each category. A considerable number of pregnant women had used drugs considered to be of known teratogenic action or to have a doubtful teratogenic potential. The existence of reproductive damage, however, was statistically similar for the safer classes compared to those of higher risk.

Table IX - Major doubts: pharmacological group of drugs. N = 184.

Class	%
Analgesics	16.8
Anti-infectives	15.8
Misoprostol	11.4
Nutrients	9.8
Hormones	9.2
Anticonvulsants	8.2
Appetite suppressants	4.3
Benzodiazepines	3.3
Other central nervous system drugs	3.8
Cardiovascular drugs	2.2
Others	15.2

Table X - Distribution of consumption of medication according to FDA classification and presence of reproductive damage.

FDA class*	Use by pregnant women (N = 276)	Presence of reproductive damage
	%	%
A + B	21.4	22.0
C	30.8	31.8
D + X	30.8	25.9
No drugs	17.0	23.4

Reproductive damage includes abortion, stillbirth, perinatal death, congenital malformations, birth weight less than 2,500 g and neurobehavioral abnormalities.

*See Table I.

The directed interview permitted the detection of other risks in addition to those that motivated the call (maternal age of more than 35 years, consanguinity, malformed individuals in the family, acute or chronic diseases) in 28.3% of the mothers. Alcohol intake during pregnancy was reported in 30.4% of cases and the smoking habit in 25.4%.

DISCUSSION

A Teratogen Information Service plays an important role, both by providing assistance for the primary prevention of the occurrence of congenital defects and other reproductive risks caused by the environment, and by offering appropriate information and/or follow-up when exposure to a given risk factor has already occurred. Such a service also permits the identification of a significant number of pregnant women exposed to the same risk factor, which is difficult to obtain using other methods. Furthermore, the information is collected in a prospective manner, so that memory bias is avoided. The follow-up of newborn infants is of fundamental importance. In Brazil, for example, the question of the teratogenicity of misoprostol is an example of a problem that can be effectively investigated by the SIAT (Schuler *et al.*, 1992).

During this initial period of functioning, there was good acceptance and a good demand on the part of the community and of the medical class. Some characteristics of the present sample indicate, however, that thus far we have been working with a selected group as indicated by the high educational level (80% had completed high school or had higher education), and by the greater percentage of women in more advanced age ranges (34% being above 29 years of age) when compared to the age range of the population of pregnant women of Porto Alegre in general (25% being above 29 years of age) (Clavijo, 1991). The fact that the system operates by telephone and that it was presented to the public by advertising in newspapers and on television may explain, at least in part, this peculiarity of the sample. There is a need to elaborate new strategies in order to reach the less educated segment of the population in the country.

Even considering the high educational level of these pregnant women, it is interesting to note that there was a high frequency of self-medication (44%), which seems to be a diffuse habit in Brazil, and also a high rate of consumption of medications classified by the FDA in the "C", "D" and "X" categories, a fact further supporting the idea that a service like the SIAT should play an important role in our medical system.

The types of concern reported when stating the major reason for the call, with drugs being more commonly mentioned and among them analgesics and antibiotics, are similar to those observed in similar services in Canada and Europe (Koren, 1990; Elephant *et al.*, 1992) and reflect the most common exposures during pregnancy.

The initial evaluation of the newborn infants showed a 69% success rate in recontacting the mothers. This number is considered to be satisfactory and is equivalent to the 73% rate observed by Elephant *et al.* (1992) in Paris. Analysis of the reproductive risks implied showed a 7.2% rate of congenital malformations in the present sample, a higher value than reported by the Collaborative Latin-American Study of Congenital Malformations (ECLAMC) for Latin America, which is 2.5% among newborn infants (Castilla, 1990). The stillbirth rate (4.6%) was also higher than the 1.9% rate reported by ECLAMC. These data, however, are still too few to permit any inference, since the sample is still too small for reliable statistical analyses. Furthermore, as can be seen by the results, in addition to the risk identified in the major reason for their call, a significant percentage

of women presented additional risk factors which should also necessarily be taken into consideration.

ACKNOWLEDGMENTS

SIAT is supported in part by grants from Ministry of Health of Brazil and from FIP/HCPA. Scientific initiation fellowships for medical students of the SIAT team were provided by CNPq, FAPERGS and PROPESP/UFRGS. The authors express their gratitude to Dr. Carlos Cesar de Albuquerque (President of HCPA) and to Dr. Roque Monteleone Neto (formerly at Ministry of Health) for their efforts, which enabled SIAT to operate.

RESUMO

O Sistema Nacional de Informações sobre Agentes Teratogênicos (SIAT) foi criado em Porto Alegre, no sul do Brasil, em 1990, com o objetivo de fornecer para médicos e para a população em geral informações rápidas e atualizadas sobre os riscos reprodutivos relacionados com a exposição a teratogênicos. O SIAT, que é o primeiro serviço desse tipo a operar na América Latina, é também uma importante fonte de informações prospectivas sobre a teratogenicidade em humanos. No presente trabalho apresentamos a experiência preliminar deste serviço e suas possíveis contribuições. A introdução, a partir de 1992, de serviços similares nas duas maiores cidades brasileiras (Rio de Janeiro e São Paulo) e a operação dos três sistemas como uma rede nacional integrada e coordenada aumenta o potencial desse serviço tanto a nível assistencial como de investigação.

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(Received September 24, 1993)