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Drug–Induced Congenital Defects

Strategies to Reduce the Incidence

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Abstract

Approximately 1% of congenital anomalies relate to pharmacological exposure and are, in theory, preventable. Prevention consists of controlled administration of drugs known to have teratogenic properties (e.g. retinoids, thalidomide). When possible, prevention could take the form of the use of alternative pharmacological therapies during the pre-conception period for certain specific pathol-

ogies, selecting the most appropriate agent for use during pregnancy [e.g. haloperidol or a tricyclic antidepressant instead of lithium; anticonvulsant drug monotherapy in place of multitherapy; propylthiouracil instead of thiamazole (methimazole)], and substitution with the most suitable therapy during pregnancy (e.g. insulin in place of oral antidiabetics; heparin in place of oral anticoagulants; α-methyldopa instead of ACE inhibitors). Another strategy is the administration of drugs during pregnancy taking into account the pharmacological effects in relation to the gestation period (e.g. avoidance of chemotherapy during the first trimester, avoidance of nonsteroidal anti-inflammatory drugs in the third trimester, and avoidance of high doses of benzodiazepines in the period imminent to prepartum).

The incidence of congenital defects is estimated to be approximately 5% of all births. A congenital defect is generally defined as an anatomic anomaly but may also be a metabolic or functional (including mental retardation) anomaly caused by a genetic alteration or by a physical, chemical or infectious agent reacting during prenatal life.[1]

It is possible to define the cause of a congenital defect in only an estimated 10% of cases while for the remaining 90% the origin remains unknown. Among identifiable causes it is probable that drugs contribute to 1% or less of all congenital defects. The importance of drug-induced malformations is that they are all potentially foreseeable.[1] Furthermore, knowledge of the teratogenic risks inherent with certain drugs not only renders it possible to reduce the incidence of congenital defects by correct and medically controlled use of such agents, but also contributes to a reduction in the number of abortions performed because of fear of defects or incorrect information regarding presumed and untenable risks.

It is vital that evidence from animal models be taken into account when assessing teratogenic risk linked with specific drugs, especially data from primates. Even so, it is obvious that only direct experience in humans will furnish conclusive data on the safety or teratogenic nature of a specific substance; in this sense, results of controlled studies with numerically significant cohorts and of controlled cases are of particular value.[2,3] Teratogen Information Services (TIS), operating in many countries, have provided over a period of time an important contribution to the improvement of knowledge by reporting numerous cases of women who are more frequently exposed to certain pharmaceuticals during pregnancy.[4]

In clinical practice, drugs are classified on the basis of their risk to the fetus, and one of the definitions of risk is that used by the US Food and Drug Administration (FDA) which takes into account animal studies, controlled trials in pregnant women and the risk/benefit ratio resulting from use (table I).[5] Considering that a drug should only be used during pregnancy when absolutely necessary and is of proven efficacy, the first step in a correct strategy for reducing drug-induced congenital defects is the individualisation of drugs recognised as teratogenic and ensuring their controlled administration in women of fertile age. The second step, in the event of necessary chronic therapy with teratogenic drugs, could be suspension or the modification of treatment by using pharmaceutical preparations more suitable for use during pregnancy as well as during the pre-conception phase. The third step consists in using, during pregnancy, drugs that are safer for the fetus and still efficacious for the mother. A fourth and final step would be to take into account the effects of the drugs during the different stages of the gestation period, avoiding their use during critical phases, such as the embryonic or peripartum periods.

1. Controlled Administration of Known Teratogenic Drugs

Considering that approximately 40 to 90%[4,6]

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Table I. Definitions used for pregnancy risk categories as defined by the US Food and Drug Administration[5]

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 women 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

of pregnant women consume pharmacological substances (and self administration is not rare), all teratogenic drugs should be prescribed with extreme caution in women of fertile age (table II). The leaflet accompanying a drug that is supplied by the pharmaceutical company should contain clear and precise information, and the prescribing specialist must also provide appropriate information. Information should include not only the possible risks but also the waiting periods before an eventual conception.

Among the most known teratogenic pharmaceuticals are thalidomide, retinoids and high doses of retinol (vitamin A).

1.1 Thalidomide

Thalidomide is the most well known teratogenic. Developed in the 1950s as a sleeping drug it was also used for prevention of nausea during pregnancy. Thalidomide was banned early in the 1960s when it was found to be the cause of deformed limbs in the children of mothers who were administered this drug during early pregnancy.[7-9] It has been calculated that approximately 8 thousand neonates worldwide were born with deformations due to thalidomide.[7-9] This drug is now under investigation for treatment of AIDS, tuberculosis, Behçet's syndrome, graft-versus-host-diseases, treatment of some symptoms of Hansen's disease or leprosy, and other illnesses.[10-13] In July 1998, the FDA approved its use in the treatment of a skin pathology, i.e. leprous erythema nodosum, a complication in leprosy.[13] Among the adverse effects on the human fetus are: phocomelia, amelia, hypoplasia, congenital cardiac defects, renal malformation, gastrointestinal malformations, cryptorchism, abducent paralysis, deafness, microtia, anotia, retarded growth, mental retardation and autism.[7-9] The risk of teratogenesis is approximately 20% when drug exposure occurs between the 34th and 50th day of gestation.[14] A 'safe' dose during pregnancy has not yet been established and cases of embryopathy have been observed even at dosages of 50 mg/day when the drug is administered during the critical period.[14] It should be noted in regard to thalidomide that there is a wide variability in susceptibility as demonstrated in different species in relation to teratogenic effects and there is a strict relationship between exposure time and the presence and type of defect.

Taking into account the definite teratogenic effects of thalidomide the FDA provides recommendations and regulations for controlled use of this drug. Among the recommendations for preventing fetal drug exposure, it is interesting to note the advice for a reliable method of contraception and periodical tests for pregnancy for patients of fertile age, and the completeness of information which also includes informed consent. A programme known as System for Thalidomide Education and Prescribing Safety (STEPS) has been established for this drug.[10,13,15] In Brazil, where thalidomide is mar-

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keted for treatment of leprosy, 33 new cases of embryopathy ascribable to exposure to this pharmaceutical have recently been reported.[13]

1.2 Retinoids

Retinoids are retinol (vitamin A) analogues used in the treatment of dermatological pathologies such as severe acne and psoriasis. They are teratogenic in experimental animals and humans. In fact, they are recognised as the possible cause of miscarriages, congenital structural anomalies, especially involving the CNS, and consequently, psychomotor and intellectual retardation. Therefore, they are contraindicated for administration during pregnancy and in the pre-conception period. Due to their lipid-soluble characteristic, permanence in the body is of extremely long duration after administration. This means that pregnancy must be planned following their use and it is obligatory that the correct information on teratogenic risks is available. Among the retinoids the most well known from a clinical viewpoint are isotretinoin (13-*cis*-retinoic acid), etretinate and the topical retinoids, e.g. adapalene and tretinoin.

1.2.1 Isotretinoin

Isotretinoin is an isomer of retinol, used in treatment of severe cystic acne. Well before its approval

Table II. Drugs known to be human teratogens

Drugs	Most frequent anomalies
ACE inhibitors	Renal damage, bone defects, oligohydramnios, IUGR (following second and third trimester exposure)
Aminopterin and derivatives	CNS, limbs, craniofacial defects
Benzodiazepines	Neonatal withdrawal syndrome, apnoea, hypotonia, hypothermia (following pre-partum exposure)
Busulfan	IUGR, craniofacial, cardiac, internal organs
Carbamazepine	Neural tube defects (1% incidence)
Cyclophosphamide	Miscarriage, absent thumbs, cleft palate, multiple eye defects
Coumarin derivatives	Nasal hypoplasia, chondrodysplasia punctata, bone, facial and CNS defects (10% incidence following first trimester exposure)
Diethylstilbestrol	Clear cell vaginal or cervical adenocarcinoma
Diphenylhydantoin	Facial dysmorphism, skeletal abnormalities, cleft palate, neuroblastoma, microcephaly (5 to 10% incidence)
Ergotamine (high doses)	NTD, intestinal atresia
Hormones with androgenous activity	Masculinisation of external female genitals
Iodides and Iodine-131	Goitre, hypothyroidism
Kanamycin	Auditory function disturbance
Lithium	Cardiac defects (<2% incidence)
Misoprostol	Agenesia of limbs, cranium defects, Moebius syndrome, miscarriage
Nonsteroidal anti-inflammatory drugs	Oligohydramnios, precocious closure of Botallo's duct, haemorrhage, NEC (following third trimester exposure)
Penicillamine	Cutis laxa (<1% incidence)
Phenytoin	Facial and CNS defects
Retinoids (systemic) [isotretinoin and etretinate]	Miscarriage, craniofacial, cardiac and upper/lower limbs, CNS. For isotretinoin: 18% risk of malformations; 40% risk of miscarriage
Streptomycin	Auditory function disturbance
Thalidomide	Limb defects, cardiac, renal, gastrointestinal malformations, deafness, ocular defects (20% risk during 34 to 50th gestation day)
Tetracycline	Deciduous tooth enamel defect (occurs in 50% of fetuses exposed)
Thiamazole (methimazole)	Scalp defects (1 to 5% incidence)
Trimethadione	IUGR cardiac anomalies
Valproic acid (sodium valproate)	NTD (1 to 2% incidence)

IUGR = intrauterine growth retardation; **NEC** = necrotising enterocolitis; **NTD** = neural tube defects.

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in 1982 for use in humans the teratogenic effects in experimental animals were known.[16] Data available in humans to date indicate that exposure at 0.4 to 1.5 mg/kg/day of isotretinoin during the first week of pregnancy causes miscarriage in 22% of cases and congenital malformations in 18%.[17] The most frequently observed malformations are characterised by defects of the CNS (microcephaly, hydrocephaly, encephalocele); the ear (microtia, stenosis or atresia of the external auditory tube, dysmorphology of the ears and low implant); the heart (conotruncus defects, aortic coarctation, ventricular septal defects). Facial dysmorphism is also present in the majority of cases. Furthermore, it seems that apparently healthy neonates could present with functional defects well after the neonatal period (e.g. blindness, deafness, intellectual deficit).[18-27] Isotretinoin is therefore a potent teratogen. Since a high percentage of users are women of fertile age it is necessary to prescribe this substance only after excluding any possibility of pregnancy, and then initiating an efficacious contraceptive regimen which should continue for at least 1 month after suspension of the drug.[28,29] Before prescribing isotretinoin, a pregnancy prevention plan and full information on the teratogenic risks involved are necessary.[30-34]

1.2.2 Etretinate

Etretinate is a retinoid used in the treatment of psoriasis.[35,36] It persists in the body for an extremely long period after administration; it has been found present in the blood more than 2 years after cessation of therapy.[37-40] However, the duration of the teratogenic effect of the drug remains unknown.[19,39,40] Avoidance of conception is in any case advised for at least 6 to 12 months after conclusion of therapy.[38] Etretinate is teratogenic in experimental animals at doses similar or higher than those used in humans. Studies in humans carried out to date have associated etretinate with malformations at CNS level (spina bifida, encephalocele), malformations of the limbs and cranial-facial anomalies.[16,41-44]

1.2.3 Topical Retinoids

Topical retinoid preparations are employed in the treatment of various dermatological pathologies as well as for cosmetic use. Published information on pregnancy outcomes with congenital anomalies following exposure to topical retinoids is limited to very few case reports.[45-49] Even if controlled studies have not demonstrated a potential connection between use of topical retinoids and fetal malformation,[50,51] we recommend that their use be discouraged during pregnancy and the preconception period. In the event of exposure during pregnancy, ultrasound surveillance for typical signs of retinoic acid embryopathy is recommended.

1.3 High Doses of Retinol (Vitamin A)

Since teratogenic effects from retinoids are acknowledged, there is a strong suspicion in regard to the possibility of teratogenic risk from retinol at high doses.[41,52,53] This is an essential lipid-soluble nutrient naturally present in a variety of food products and necessary for the maintenance of tissues and functions. The daily requirement of retinol during pregnancy, according to recommendations by the Food Agriculture Organization/World Health Organization, is 3300 IU/day. The Teratology Society advises not to exceed dosages of 8000 IU/day during pregnancy.[54] This vitamin has a long half-life and is accumulative.[55] Teratology studies in animals show a dose-dependent increase in the incidence of fetal death and malformations, in particular craniofacial and cardiac defects. Up to 1986 the FDA received 18 reports of teratogenic effects from high dosages of retinol (18 000 to 150 000 IU/day) with patterns similar to those reported in association with retinoids (cardiac and cranial-facial anomalies).[56] These results contrast with a collaborative European study in 312 neonates exposed to high doses of retinol (median 50 000IU) where no type of malformation was observed.[57] In the light of the above and despite studies in laboratory animals, and the equivalence between retinoids and retinol, there is no definite demonstration of teratogenic effect. Nonetheless, the American Society of Teratology recommends, until further information becomes available, that women in fertile age should not consume retinol supplements containing more than 8000 IU/day

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and pharmaceutical companies should reduce the dose of retinol to a maximum of 5000 to 8000IU per dosage unit. Furthermore, since the average balanced diet contains about 7000 to 8000IU daily of retinol, this should be taken into consideration when recommending a supplement. In cases of high doses of retinol, women of fertile age must be informed of the possible risks connected with a pregnancy that could commence during treatment, and should be encouraged to avoid conception. Pregnancies where there is known exposure to high doses of retinol during the first months of pregnancy must be regularly followed-up by careful ultrasound surveillance.

2. Use of Alternative Pharmacological Therapies in the Pre-Conception Period

Certain maternal pathologies require chronic therapy that is impossible to delay until after the pregnancy. Taking for granted that during a pregnancy it is not advisable to make therapeutic changes that could put the mother's health at risk, during the pre-conception phase it is possible to make excellent choices of drugs that, while ensuring good maternal treatment, involve minor risk for the fetus.

2.1 Bipolar Disorder/Depression

2.1.1 Lithium

Women requiring long term lithium therapy for bipolar disorder illustrate the problems associated with chronic treatment. Cardiovascular malformations, in particular Ebstein's anomaly, have occurred in approximately 2% or less of neonates when the mothers underwent lithium carbonate therapy during the pregnancy.[58-64] Neonatal goitre and nephrogenic diabetes insipidus, cardiac arrhythmia, congestive cardiac failure and floppy infant syndrome have been observed in neonates of women who were treated with lithium.[62,65,66] When lithium treatment is indispensable throughout pregnancy, maternal serum concentrations should be maintained at lowest possible levels and monitoring is required at least once a month for the first half of the gestation period, then weekly until after delivery. Dose changes should be limited and prenatal diagnosis by fetal ultrasound and, in particular, echocardiography should be advised. In anticipation of a pregnancy, substitution therapy with drugs that are much safer in pregnant patients should be attempted in well-selected individuals under the direct supervision of a specialist.

2.1.2 Tricyclic Antidepressants

Providing clinical conditions permit, some alternatives to lithium can be taken into consideration. An alternative could be a tricyclic antidepressant which represents the treatment of choice for depression during pregnancy (i.e. imipramine and amitriptyline). No experimental animal data, nor the extensive epidemiological studies in humans, have provided any evidence of an association between their use and specific birth defects. Use of antidepressants in early pregnancy has not demonstrated any significant risk to the baby that can be detected during the neonatal period. Only sporadic indications regarding anomalies in women who used such drugs during pregnancy are found in literature and these do not provide any valid evidence of association.[67-73]

2.1.3 Haloperidol

Haloperidol is a high potency antipsychotic drug that may be an alternative to lithium for antimanic treatment.[60] No increased teratogenic risk has been reported; however, there is a risk of tardive dyskinesia in the mother and transient extrapyramidal reaction in the neonate.[74-76]

2.2 Epilepsy

Epilepsy is another condition requiring chronic therapy. There is a doubling or even 3-fold increase in incidence of congenital abnormalities among babies born to women with epilepsy. Even if epilepsy itself may be a contributing factor, the incidence of congenital malformations has been found to be higher in mothers with epilepsy who received anticonvulsants than in nontreated ones.[77] The risk is even greater for neonates born to women treated with multiple therapies compared with those receiving monotherapy.[78-80] It is therefore highly

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recommended that women with epilepsy who are of fertile age receive: pre-conception counselling, folic acid supplementation, optimal control of seizure activity and monotherapy with the most suitable anticonvulsant drug at the lowest effective dose.[81]

No major anticonvulsant drug, i.e. phenytoin, carbamazepine, valproic acid (sodium valproate) or barbiturate, can be considered absolutely safe and free of teratogenic effects.

2.2.1 Phenytoin

The 'fetal hydantoin syndrome' will occur in about 10% of neonates born to women with epilepsy who receive phenytoin therapy during pregnancy.[82-85] The most common features of this syndrome include ocular hypertelorism, flat nasal bridge, and distal digital hypoplasia with nail hypoplasia. Nonetheless, some controversy with regard to the phenytoin syndrome exists.[82-85] The possibility of a minimum increase in the risk of neuroblastoma and other neoplasms has been observed in babies whose mothers had been administered phenytoin during the embryogenetic phase.[86-88]

2.2.2 Carbamazepine

Neural tube defects in neonates of women who received carbamazepine treatment during pregnancy have been observed with increased frequency.[89-93] In fact, the incidence of spina bifida ranged from 0.6 to 1.7% in cohort and prospective studies.[94,95]

2.2.3 Valproic Acid (Sodium Valproate)

An association with spina bifida has been found when mothers undergo therapy with valproic acid during the first trimester of pregnancy. This finding is supported by many epidemiological studies and clinical case reports. The estimate of risk is approximately 2%.[79,96-102] In case of valproic acid therapy, divided doses are preferred to avoid high plasma concentrations.[100-103]

2.2.4 Barbiturates

It seems that the risk of congenital anomalies does not significantly increase in women with epilepsy treated with phenobarbital (phenobarbitone) monotherapy.[71,104] In fact, in reference to those studies investigating the increased risk of congenital malformations in untreated patients with epilepsy, in particular, facial malformations and congenital heart defects, it may be hypothesised that the underlying disease rather than the treatment is the cause of the defects. However, there have been indications of an association with cardiovascular malformations and some types of barbiturates, and a long term negative effect on cognitive performances has been referred in regard to phenobarbital.[80,102,105-109]

2.3 Hyperthyroidism

Hyperthyroidism is another example of pathology during pregnancy requiring chronic pharmacological treatment.

Thionamides [propylthiouracil and thiamazole (methimazole)] are drugs used in the treatment of hyperthyroidism during pregnancy. While both are capable of crossing the placental barrier, this is inferior in the case of propylthiouracil. Recent studies have not shown any differences in therapeutic efficacy between propylthiouracil and thiamazole.[110] No differences have been found in fetal thyroid function. Follow-ups in children born to mothers treated with thionamides during pregnancy did not show any damaging effects on somatic or psychological growth or intellectual development.[110] However, what renders propylthiouracil the drug of choice as compared with thiamazole is that at least 19 cases of congenital aplasia of the skin of the scalp were found in neonates of women who had been treated with the latter agent (1 to 5%).[111-113] An association has not, however, been clearly demonstrated since hyperthyroidism could in itself increase the risk of congenital defects. Recently an unusual pattern of malformations was reported in some babies born to mothers exposed to thiamazole or carbimazole during pregnancy, and this has led to the suggestion of a rare embryopathology due to thiamazole.[114] This phenotype includes choanal and oesophageal atresia, scalp defects, minor facial anomalies and psychomotor delay.[115]

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3. Appropriate Substitution Therapy During Pregnancy

3.1 Diabetes Mellitus

Insulin is the drug of choice for diabetes mellitus during pregnancy.[5] Malformation rate ranges from 2- to 6-times that of the general population in the children of pregnant women with diabetes mellitus.[116-118] Malformations are diverse and multiple, the most common being cardiac and neural tube defects, followed by skeletal, gastrointestinal, and urinary tract abnormalities. Malformations occur during organogenesis, frequently before pregnancy is recognised, and are correlated to metabolic control. Women with these metabolic disorders who are planning pregnancy should be ensured of rigid surveillance of glycometabolic equilibrium from the pre-conception phase and throughout the pregnancy.[119-124]

Oral antidiabetics are not indicated during pregnancy because adequate control of glycaemia cannot be obtained with these agents during pregnancy and insulin release from the fetal pancreas may determine a higher risk of fetal macrosomia and high maternal and fetal morbidity.[5]

3.2 Thrombolysis

Some maternal conditions (cardiac prosthetic valve, arterial or venous thrombosis) require use of anticoagulant therapies which can cause particular problems during pregnancy with regard to both efficacy of the thromboprophylaxis and fetal risk. Oral anticoagulants such as coumarin derivatives are more efficacious than heparin in reducing maternal risk, but their use during pregnancy is associated with various fetal-neonatal problems because they cross the placental barrier.[125]

Related fetal adverse effects of oral anticoagulants consist in intrauterine growth retardation (IUGR), stillbirth, psychomotor delay, hypotonia, convulsions, nasal underdevelopment and abnormal calcification of epiphyseal bone areas (chondrodysplasia punctata), CNS and eye abnormalities and haemorrhage.[126-131] Teratogenic risk of oral anticoagulants is equal to 10% during the first trimester, with a more critical period between weeks 6 to 9 gestation and the risk is 3 to 5% during the second and third trimesters.[5,132,133] During pregnancy the best anticoagulant treatment regimen consists of replacing oral anticoagulant therapy with heparin from the beginning of pregnancy to the 16th week, then returning to oral anticoagulants up to the 36th week and again replacing with heparin therapy until delivery.[125]

3.3 Hypertension

Another maternal pathology necessitating treatment during pregnancy is high-risk chronic hypertension. The characteristics of an antihypertensive drug for use during pregnancy are efficacy, lack of negative effects on uterus-placenta circulation and renal flow, lack of short and long term effects on fetus-neonate (teratogenic, neurological, reduced capacity for stress adaptation). To date, only α-methyldopa responds to these requisites.[134] Other drugs may be used in alternative during the more advanced stages of the pregnancy such as, β-adrenergic blockers, and calcium channel antagonists. ACE inhibitors are contraindicated due to adverse fetal effects after exposure during the second and third trimesters. These effects are: insufficient ossification of head bones, kidney damage, oligohydramnios, lung hypoplasia, IUGR.[135-145] The angiotensin II inhibitors are also associated with such effects and should be avoided during pregnancy.[146]

4. Controlled Administration of Drugs During Pregnancy: Pharmacological Effects versus Gestation Period

The majority of drugs may be used during pregnancy, even if it is a good rule to avoid use during embryogenesis unless the therapy is absolutely necessary or involves well-controlled treatment with drugs with ample available data. Pharmacological treatments exist that are particularly damaging for the fetus during embryogenesis or during the peripartum period. Such drugs include: antitumour therapy during the first trimester, nonsteroidal antiinflammatory drugs (NSAIDs) during the third, or

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high doses of benzodiazepines imminent to prepartum.

4.1 Chemotherapy

The decision to carry out chemotherapy during pregnancy must consider the need for therapy for the mother and possible risks for the fetus, and this must be taken into account for the duration of the pregnancy. Antineoplastic agents have an effect on rapidly proliferating cell populations, so are potentially dangerous to the growing fetus. Administration may lead to first trimester miscarriage or congenital malformations (14 to 17%) and later, to retarded growth and fetal death. Whenever possible, it is safer to delay such therapies until after the first trimester of pregnancy with benefits which appear similar to those obtained in nonpregnant patients.[147-149]

4.2 Nonsteroidal Anti-Inflammatory Drugs

NSAIDs may be used as analgesics during pregnancy. Their occasional use does not appear to increase the natural risks of pregnancy.[150] With use of NSAIDs during the third trimester oligohydramnios and anuria in the fetus have been observed, as well as early closure of Botallo's duct with possible pulmonary hypertension, intracranial haemorrhage, and necrotising enterocolitis in the neonate; consequently they are contraindicated.[151-157]

4.3 Benzodiazepines

Benzodiazepines are included in the most commonly used antianxiety drugs. Administration during pregnancy must be clinically justified; a benzodiazapine with a short half-life and devoid of active metabolites is to be preferred. Administration during early pregnancy seems to be associated with a slight increase in cleft lip with or without cleft palate[158] while, among the effects of high doses of benzodiazepines given in the immediate pre-partum period, apnoea, hypotonia, hypothermia, neonatal withdrawal syndrome with signs and symptoms of neuromuscular excitability predominate.[158-161]

5. Conclusions

While congenital defects induced by pharmaceuticals represent only a small percentage of all anomalies, the fact that they can potentially be prevented is important. Considering that approximately 40% of pregnancies occur without any specific planning by the couple, any fertile woman should only use a drug when and if it is absolutely necessary because, while only few drugs have been demonstrated as teratogenic, all new drugs may be teratogenic. An excellent precaution would be to avoid prescribing multivitamin products containing high doses of retinol. When chronic therapies with drugs potentially harmful to the fetus are needed, the possibility of therapeutic changes in the pre-conception period by using alternative drugs, equally efficacious for the mother but with less risk for the fetus, should be carefully evaluated. Only when it is strictly necessary, and no equally efficacious alternative exists, should pharmaceuticals considered to be teratogenic be used. In this situation the possibility of a pregnancy should be excluded at the beginning of therapy, fertility should be controlled during pregnancy, and information on eventual waiting periods should be provided. If therapy is required during pregnancy, the risk/benefit ratio of the pharmacological action in relation to effects on fetus and embryo should be well assessed, taking into account the gestation period (in particular, the first trimester and peripartum). The absolutely safe drug does not exist, therefore it is preferable, when necessary, to administer drugs of proven efficacy and about which the risks associated with their use in pregnancy are already known.

In this regard it is to be hoped that TIS will soon be available in every country so as to provide adequate information for patients and medical staff. In such a service, personnel with special experience in clinical teratology, pharmacology and prenatal medicine would be able to provide pre-conception counselling, evaluate the teratogenic risk of a phar-

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macological therapy during pregnancy, or advise on the best and safest drug for any necessary therapy to be continued during pregnancy.

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