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Teratology and Developmental Phamacology: Why Should Paediatricians Care?

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Abstract It is important to adopt an evidence-based approach to support rational use of drugs during pregnancy and lactation, both to prevent malformations and to correct misperceptions about drug use during this critical period of life. To demonstrate the clinical effectiveness of a teratology information service and its relevance to the local child health practice, we use five clinical scenarios to illustrate the spectrum of issues commonly encountered by medical professionals of different disciplines from paediatricians, obstetricians to family practitioners. We discuss the service gap that exists in Hong Kong and the key issues, the necessary steps to introduce and sustain a local teratology information and drug counselling service to pregnant or breast-feeding women and their health care providers regarding the risks to the growth and development of their babies.

Key words Breastfeeding; Congenital malformations; Drug-exposed infants; Lactation; Teratology

Background

Paediatricians are often involved in the counselling of women who are exposed to drugs during pregnancy. The risk-to-benefit ratio is often difficult to determine due to lack of evidence or even paucity of information regarding the long-term impact of fetal drug exposure. The deleterious effects of a drug on the fetus depend on the chemical and physical nature of the drug, the extent of fetal exposure and importantly the stage of embryological development at the time of exposure. Typically there are no data on fetal effects of drugs at the time of marketing and data from animal studies may therefore constitute the initial guidelines. Understandably these data are difficult to be extrapolated to humans. Sometimes the first accounts of adverse fetal outcomes are published as case reports while in some situation, literature search often results in studies with design pitfall[1] including inadequate sample size to draw conclusion, unaccounted confounding effects of maternal diseases, pharmaco-genetic modifiers for drug disposition and significant recall bias in retrospective studies.[2] Often pregnancy safety data provided by the Food and Drug Administration (FDA) risk categories are insufficient to guide clinical decisions in pregnancy.[3] Law, Bozzo, Koren, and Einarson reported that 91% of medication approved by FDA between 1980 and 2000 were classified as "undetermined" in terms of safety for pregnancy use.[4] Furthermore the FDA categories are intended to guide drug choice before fetal exposure, rather than how to manage pregnancy after drug exposure.

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It is well known that a significant proportion of pregnancies worldwide are unplanned.[5,6] And with the societal changes and medical advances, more women with chronic medical conditions may get pregnant and require pharmaceutical treatment during pregnancy. We are now taking care of more children with fetal exposure to prescribed or recreational drugs, born by assisted reproductive technologies, or have mothers who are organ transplant recipients or long-term survivors of cancers. Paediatricians working in this era need to have knowledge in teratology/developmental pharmacology, because we are involved in the risk management of pregnant women with drug exposures and importantly we also act as the health advocates of children who may be affected with the long-term impact of exposure of medications during fetal development.[7,8] There is a need for accurate, evidence-based teratogenic information for physicians to provide effective management of maternal medical conditions without causing long-term negative impact to the unborn children.

Teratology Information Service – A Global Perspective

Teratology Information Service (TIS) provides health care professionals and the public with information regarding the safety and/or risk of exposures during pregnancy and lactation. As TIS are relatively new health services, operations vary among different centres. Counselling usually occurs over the telephone but it may also include in-person counselling at clinics.

Information on TIS in North America can be found in the website of Organization of Teratology Information Specialists[9] while those in Europe can be found in European Network of Teratology Information Services.[10] Among them, the Toronto's Motherisk Program[11] is the largest TIS in North America. It provides telephone counselling service >200 women/week and their website is visited 200,000 times/month. The program has published over 900 manuscripts in medical journals and 15 medical books. It has trained 65 doctors from 35 countries and helped initiating TIS service in 6 countries. To our knowledge, there are TISs in Asia including the Korean Motherisk Program based in the Sungkyunkwan University School of Medicine in Seoul.[12]

Surveys of the practices in the provision of teratology information have been conducted in North America[13] as well as internationally.[14] Majority of TIS are located in teaching hospitals within departments of paediatrics, obstetrics, and clinical pharmacology and toxicology. The most common type of employee is telephone counselors who are physicians or pharmacists by training, in consultation with paediatricians, epidemiologists, obstetricians/gynaecologists, clinical geneticists and infectious disease specialists.

The clinical effectiveness of TIS has been studied in great details. Information disseminated from TIS has been shown to improve maternal and neonatal health in the following aspect (Table 1).[15] Up to date, an economic evaluation of TIS that weighs the costs of the program against potential health benefits has not been conducted. Five common clinical scenarios are used in the following sections to demonstrate the clinical effectiveness of a teratology information service and its relevance to child health practice. Some of these issues have been addressed by Dr Koren and his team in the *Motherisk Update* published monthly as educational column in *Canadian Family Physician* since 1995. Over 150 topics have been published in this format by the Toronto's Motherisk Program as a form of knowledge transfer to family physicians.[16]

Use of Anticonvulsants During Pregnancy – Using Valproic Acid as an Example

Motherisk performed a meta-analysis on controlled cohort studies that reported the use of valproic acid during the first trimester of pregnancy from 1978 to 2005.[17] Women exposed to valproic acid during the first trimester have more than 2.5 times the risk of having babies with malformations compared to other anticonvulsants (Relative Risk [RR] 2.59, 95% confidence interval [CI] 2.11 to 3.17), untreated epilepsy (RR 3.16, 95% CI 2.17 to 4.60) and healthy controls (RR 3.77, 95% CI 2.18 to 6.52). When valproic acid was being used as part of the anticonvulsant polytherapy, the RR also increased significantly over that of other anticonvulsants despite that the polytherapy regimens varied greatly. There is compelling evidence that the risk is dose dependent. The risks appear to begin to increase at doses of 600 mg/d and become more prominent at doses above 1000 mg/d. From various reports and case series, it was suggested that valproic acid causes malformations including neural tube defects, limb and cardiovascular anomalies. Children shall be followed up in terms of his neurodevelopment as developmental delay and cognitive deficit have been reported to be associated with valproic acid use in pregnancy. In future pregnancy, it is advised that the mothers be managed by the joint care of obstetricians and neurologists if valproic acid treatment is deemed to be required for her seizure control. It shall be

Table 1 Clinical effectiveness of Teratology Information Services (TIS)

	Scope of the problem	Effectiveness of TIS
Prevention of congenital malformations	About 86% pregnant women are exposed to >1 medication[59] and about 1% birth defects are attributable to medication use in pregnancy.[60]	Primary prevention: prevention of birth defect before it develops by peri-conceptional counselling (not fully quantified). Secondary prevention: prevention of birth defect after it has occurred by pregnancy interruption or surgical correction following prenatal diagnosis. Evidence from Motherisk showed that 5 major malformations out of 94 pregnancies are secondarily prevented per year.[61]
Prevention of unnecessary pregnancy termination	Only about 20 medications currently on the market have been universally acknowledged to be teratogenic.[60] Numerous women are inappropriately advised, or decide themselves to terminate otherwise wanted pregnancies due to the perception of risk associated with apparently safe medications e.g. antihistamines.[62]	A study from Motherisk showed 78% of their counselees had a significant change of their tendency to continue pregnancy after their counselling experience from a VAS score of 34.3 to 84.5 ($p<0.00001$)/ [NB. VAS stands for a 100-point visual analogue scale from 0 (absolute tendency to terminate pregnancy) -100 (absolute tendency to continue the pregnancy)].[63] This finding was duplicated in a study by an Italian TIS.[64]
Support of optimal nutritional supplement to improve child health	Many women do not supplement with vitamin and folate regimens. Folate deficiency is associated with neural tube defects and other birth defects including cardiovascular, limb, urinary tract defects and oral clefting. Women at high risk include those with diabetes, obesity, intake of folate antagonist or presence of family history of spina bifida.	Randomised trial by Robbins et al showed a brief counselling session, supply of folate tablets and a reminder phone call significantly increased folate intake compared to no-intervention group and estimated a decrease of NTD by 11%.[65] A Motherisk study showed that counselling increased the folate update from 17% (not counseled) to 71% (counseled).[66]
Support of optimal drug therapy during pregnancy	Untreated maternal conditions during pregnancy e.g. depression, diabetes, hypertension, asthma can lead to increased fetal risk including malformations, intrauterine growth restriction and stillbirth.	A Motherisk study of women who have stopped taking anti-depressants or benzodiazapines after knowing they were pregnant were counseled regarding the safety and risk associated with their medications and 61% resumed their medication.[67] Empowering health professionals is as important as empowering the women as a study in Canada found that physicians, pharmacists, nurses rate a sample of 4 medications as unsafe in pregnancy despite a scientifically reassuring text on the medical label.[68]
Support of breast-feeding	Avoiding breast-feeding due to misconceptions about the risk may cause loss of demonstrated health benefits of breast milk in babies.	The vast majority of medications are safe during lactation and many women are discouraged from breast-feeding or decide not to breastfeed themselves due to misperception of risk.[69]
Knowledge transfer and translation	TIS are utilised by health care providers as well as patients. As excellent research resources, TIS perform and report evidence-based studies that can be applied to patient care.	A study by Viguera et al showed that 45% of 70 women with bipolar disorder had been advised to avoid pregnancy. After appropriate counselling following risk-benefit assessment, 63% women went on to persue a pregnancy.[70] Many women have been wrongfully advised to terminate pregnancies following other non-teratogenic exposures. A Motherisk study found that 91% health care providers reported repeating the information they had received from TIS to their patients.[71] This has improved the dissemination of knowledge in the field of teratology.

given in the lowest effective dose and folic acid supplement shall be commenced 3 months prior to conception and continued for at least the first 12 weeks of pregnancy. Fetal ultrasound, measurement of maternal serum alpha-fetoprotein, and if necessary, fetal echocardiography between 16 and 18 weeks gestation shall be arranged to rule out major malformations.

Use of Antidepressants During Pregnancy – Using Selective Serotonin Reuptake Inhibitors (SSRIs) as an Example

The post marketing reports as well as several earlier epidemiological studies did not detect any increased risk for major malformations among children exposed in utero to fluoxetine.[18-20] A prospective collaborative study by Motherisk collected and followed up 128 women exposed to fluoxetine in the first trimester of pregnancy.[18] Pregnancy outcome was compared to two control groups, one exposed to tricyclic antidepressants and one exposed to non-teratogens. The rate of major malformations was similar in the three groups and did not exceed the baseline risk in the general populations. The results also did not show an increased risk for perinatal complications or low birth weight in the fluoxetine exposed group. Motherisk conducted another prospective controlled study of 55 mother child pairs exposed to fluoxetine compared to 80 pairs exposed to tricyclic antidepressants and to 84 women exposed to non-teratogens.[21] Neurodevelopmental assessment in the offspring did not show differences in global IQ and language scores between the three groups of children ranging from 16 to 86 months of age. It shows that maternal depressive syndromes, and not medications, affect adversely child achievements. A meta-analytical review of all published epidemiological reports in pregnancy was not able to detect an increased risk for malformations.[22] There are several reports of poor neonatal adaptability (including jitteriness, poor feeding and breathing problems) in offspring of mothers who took SSRIs in the third trimester.[23, 24] In a Motherisk cohort study, third-trimester exposure to paroxetine was associated with neonatal distress (Odds Ratio [OR] 9.53, 95% CI 1.14 to 79.3).[25] Therefore, infants exposed to SSRIs near term should be observed carefully after birth. A case-control study compared 377 women whose infant had persistent pulmonary hypertension of newborn (PPHN) and 836 matched control women and their infants and found that 14 infants with PPHN had been exposed to an SSRI after completion of the 20th week as compared to 6 control infants (OR 6.1, 95% CI 2.2 to 16.8).[26] In contrast, neither the use of SSRIs before 20th week of gestation nor the use of non-SSRI antidepressant drugs at any time during the pregnancy was associated with increased risk of PPHN. When counselling patients, the risk of these adverse effects must be weighed against the risk associated with untreated depression during pregnancy.[27]

Radiation Exposure Risk During Pregnancy

Since many pregnancies are unplanned, women may not be aware that they are pregnant during routine radio-diagnostic evaluation.[28] They perceive that to be associated with very high risk of fetal malformations because of the reported adverse biological effects of the atomic bombs dropped on Hiroshima and Nagasaki during the Second World War[29] and the nuclear accident at the Chernobyl.[30]

Radiation is a dose-dependent teratogen. Below a certain threshold, pregnant women with exposure will have similar pregnancy outcome compared to those with background radiation exposure, which is usually less than 0.1 rad (or 1 mGy since 1 rad=0.01 Gy) during the 9 months' gestations. A fetus is most vulnerable to radiation-induced central nervous system damage 8 to 15 weeks post-conception. Most diagnostic imaging centres can specify the amount of radiation used for each patient and the fetal dose is calculated as that of the ovarian or uterine dose. The United States National Council on Radiation Protection and Measurement states that the risk of miscarriages, malignancies, or major congenital malformations in embryos or fetuses exposed to doses of 5 rad or less is negligible compared with the spontaneous risk in non-exposed fetuses. Spontaneous risk includes a 15% chance of spontaneous abortion, a 3% risk of major malformations, and a 4% possibility of intrauterine growth retardation. Most radio-diagnostic examinations expose fetuses to less than 5 rad of radiation (Table 2), e.g. an abdominal CT scan is associated with a fetal radiation dose of <3 rad and it is not associated with any significant increase in major malformations in pregnant women. These women should be reassured and counseled appropriately. Relevant evidence has been summarised as policy statements issued by various professional bodies including American College of Obstetricians and Gynaecologists, American College of Radiology, International Commission on Radiological Protection, and as stated above, National Council on Radiation Protection and Measurements.[31]

Interestingly, despite the fact that all common radio-

diagnostic procedures are not associated with an increased risk of fetal malformation, the perceived risk is often much higher. A survey done by Motherisk program showed that women who underwent diagnostic imaging procedures assigned a 25.5% teratogenic risk for major malformations, and a non-exposed control group assigned a 15.7% teratogenic risk associated with diagnostic imaging procedures in pregnancy, which is much higher than the 3% baseline risk of major malformation in general population.[32] Studies of physicians also showed a higher perceived risk of teratogenicity associated with diagnostic imaging. Using the example of an abdominal CT, a study has shown that 61% of surveyed family physicians and 34% surveyed obstetricians estimated the risk associated with a CT scan to be 5% or greater. Importantly, 6% of family physicians and 5% obstetricians would recommend an abortion after a CT scan during early pregnancy.[33] This high risk perception in both women and physicians could lead to unnecessary increase in stress and anxiety in the pregnant women, delays in appropriate management in pregnant women and even inappropriately informed choice of termination of pregnancy.

Table 2 Estimated radiation doses from common diagnostic imaging procedures

Test, area	Fetal dose, rad
Radiograph	
Upper extremity	<0.001
Lower extremity	<0.001
Upper gastrointestinal series (barium)	0.048-0.360
Cholecystography	0.005-0.060
Lumbar spine	0.346-0.620
Pelvis	0.040-0.238
Hip and femur series	0.051-0.3070
Chest (2 views)	<0.010
Retropyelography	0.800
Abdomen (kidneys, ureter and bladder)	0.200-0.245
Urography (intravenous pyelography)	0.358-1.398
Barium enema	0.700-3.986
CT scan	
Head	<0.050
Chest	0.100-0.450
Abdomen (10 slices)	0.240-2.600
Abdomen and pelvis	0.640
Pelvis	0.730
Lumbar spine	3.500
Other	
Ventilation-perfusion scan	0.06-1.00
Potentially teratogenic dose	**5.00**

Adapted from Ratnapalan S, Bentur Y, Koren G. "Doctor, will that X-ray harm my unborn child?". Can Med Assoc J 2008;179:1293-6.[72]

Maternal Substance Misuses During Pregnancy – Using Methadone as an Example

A comprehensive review of existing literature since 1970s showed that amount of methadone in breast milk appeared to be very small and such results contribute to the recommendation of breastfeeding for methadone-maintained women.[34] Previous studies have not just reported that the concentrations of methadone in breast milk are low, but they would also remain stable over time.[35-37] A study by Meites[38] published in the Motherisk Update reported that methadone doses of 25 to 180 mg/d produced concentrations in milk ranging from 27 to 260 ng/mL, leading to an average daily methadone ingestion of 0.05 mg. This was based on an infant's estimated milk intake of approximately 500 mL/d. And the ingested amount would be equal in a 5-kg baby, to the ingestion of less than 1% of the maternal weight-adjusted dose, as typical adult dose is 40 to 180 mg/d. Neonates have slower clearance rates of methadone in comparison to adults, even after adjustment the relative infant dose would not exceed 5% of the maternal weight-adjusted dose.

Methadone offers significant therapeutic benefits to the population of opiate-dependent pregnant women which far outweighed the potential risk of minimal excretion of the drug into breast milk. In 1983, the American Academy of Pediatrics (AAP) initially recommended that methadone was only compatible with breastfeeding at maternal doses below 20 mg/d.[39] Since September 2001, the AAP revised its recommendation based on more updated evidence and concluded that methadone is considered to be compatible with breastfeeding at any maternal dose in the new statement.[40]

Breast milk is optimal for infant nourishment. The practice of breastfeeding promotes positive early infant attachment experiences[41] and reduces maternal stress responses.[42] Malpas et al[43] suggested that breastfeeding may well be beneficial in the treatment of neonatal abstinence syndrome. Previous research found that the intake of breast milk was associated with reduced neonatal abstinence syndrome severity in infants born to drug-dependent mothers.[36] However, it is uncertain that if this is purely of the beneficial effects of breastfeeding or because of the low concentrations of methadone present in breast milk which reduced the withdrawal. In regard to methadone exposure during lactation, women undergoing methadone treatment regardless of the dose should not be discouraged from breastfeeding, provided that she is not taking any heroin or psychotropic drugs.

Use of Folic Acid During Pregnancy

Since 1960s, epidemiological studies have shown that a protective effect was found for folate supplementation against the development of Neural tube defects (NTDs), which are malformations of the cranium, spine and nervous system. Types of NTDs include spina bifida, anencephaly, meningocele and encephalocele. The Medical Research Council in the UK (1991) conducted a multicentre, randomised, double-blind trial in addressing the beneficial effects of folic acid supplementation in decreasing the risk of NTDs.[44] The aim of the study was to evaluate the efficacy of 4-mg doses of folic acid in preventing recurrent NTDs in women who had previously delivered children with NTDs. It was found that women randomised to take folic acid supplementation had a 1.0% chance of having children with NTDs (RR 0.28, 95% CI 0.12 to 0.71). However, there was no decrease in the risk of NTDs (3.49%) (RR 0.8, 95% CI 0.37 to 1.72) for women in the group without folic acid supplementation.[44, 45]

In support of the above evidence, a review of four trials has shown that periconceptional folate supplementation reduced the incidence of NTDs (RR 0.28, 95% CI 0.13 to 0.58).[46] The US Preventive Services Task Force[47] found convincing evidence that supplements containing 0.4 to 0.8 mg (400 to 800 mcg) of folic acid in the periconceptional period reduce the risk of neural tube defects. This recommendation applies to women who are planning or capable of pregnancy, but it does not apply to women who have had a previous pregnancy affected by neural tube defects or women taking certain antiepileptics.

The recommended daily dose of folate supplementation has been 0.4 mg/d for almost 20 years.[48] Prenatal multivitamins invariably contain 0.8 to 1.1 mg of folic acid, and this had led to the assumption that daily supplementation with this dose is sufficient to prevent NTDs. Wald et al[49] systematically reviewed all reports of the correlation between ingested dose of folate and resultant serum concentrations, they concluded that the current recommended daily dose of folate will render only partial protection against NTDs. According to Wald et al's analysis, 5 mg/d of folate would be necessary to render 90% protection within the populations. Folic acid might increase the risk of certain cancers for individuals with a history of or predisposition to cancer.[50] However, this would result from by long-term exposure to folate over many years, and not from several months of dosing during pregnancy.

Relevance of TIS to Paediatrics and Child Health in Hong Kong

Hong Kong follows the trends observed in the West and couples tend to get married and deliver their children at a more advanced age than decades ago. In 2010, the median age at first marriage was 31.1y for males and 28.7y for females.[51] As a consequence, child-bearing women nowadays are more likely to be affected by chronic conditions like obesity, diabetes, and cardiovascular diseases. Since many of the pregnancies are unplanned, this can be translated into increased fetal exposure to uncontrolled maternal medical conditions, medications, infections and other sources of potential teratogenicities. With advances in medicine, survivors of oncologic conditions and recipients of organ transplant can also become pregnant, when more intensive counselling and monitoring of drug use becomes critical. Together with other groups of "high-risk" pregnancies including teen pregnancies, pregnancies with assisted reproductive technologies and use of illegal drugs during pregnancy etc, these all create emerging challenges for physicians taking care of the mothers and their children.

The above scenarios illustrate the wide spectrum of clinical issues related to teratology and developmental pharmacology that are commonly encountered by paediatricians, obstetricians and family physicians. **Use of anticonvulsants during pregnancy** is probably an "older" clinical problem in which we have more evidence-based information. **Use of antidepressants during pregnancy** represents one of the newer challenges to us due to changes in the medico-social context of our society. The discussion on **radiation exposure risk during pregnancy** illustrates nicely that effective teratology information is often beyond the information itself but the effective communication and management of risk perception of our patients, as well as "ourselves" – the physicians. The discussions on **maternal substance misuses and use of folic acid during pregnancy** demonstrate that TIS must extend beyond the current pregnancy to the lactation period and must involve counselling of risk in future pregnancies, using 2 scenarios that are seen more commonly in Hong Kong nowadays.

Hong Kong is well known to be an international city with accommodation of residents from different cultural background and ethnic groups, where the risk perception, health-seeking behaviours, medicinal use related to cultural habit and tradition in care of pregnancy vary a lot and would be expected to be quite different from the experience reported elsewhere in the western world. For example, the

use of herbs, alternative therapies, and other traditional medicines, either alone or in combination of traditional western medicine, are far more prevalent in pregnancies in Hong Kong and different parts of Asia.[52] Therefore the issue of lacking TIS, drug information and counselling service during pregnancy and the perinatal period is particularly relevant and important in Hong Kong. Hence a local teratology information and drug counselling service focusing on pregnancy and subsequent child development would be really necessary. The Hong Kong Poison Information Centre (HKPIC) is a professional body established by the Hospital Authority, the Department of Health, and Chinese University of Hong Kong in the year 2005. The HKPIC collects data from voluntary reporting of all actual or potential poisoning cases from the accident and emergency department of six major hospitals in Hong Kong and answers toxicology consultations from healthcare professionals in Hong Kong.[53] However, the service mainly focuses on emergent poisoning events in general population and could not provide tailor-made teratology and developmental pharmacology information concerning pregnancy and lactation. Development of local TIS in Hong Kong would bridge this important gap and serve as a complimentary partner with the existing drug poison information service.

Although use of medicinal and natural drugs among mothers during pregnancy and lactation has become more common, there is still a lack of data on its safety and effects on the health and development of the fetus.[54] In recent few decades, there is emerging evidence on the variable effects of common medicinal drugs on children with exposure during fetal stage.[55,56] It is believed by many families and women that natural health products, being commonly used during pregnancy and lactation are safe. Tiran (2003) reported a prevalence of using herbal medicine during pregnancy of 7%-55%.[57] For many women, the use of natural health products may become a reasonable alternative to pharmaceutical drugs, as those natural drugs are often portrayed by mass media as safe products to use. In a study on the pharmaceutical drug use of 295 pregnant women, 37% of these women reported noncompliance with their existing drug regimens due to hesitations about drug use during pregnancy.[58]

Conclusions

In the past few decades, several large-scaled TIS have been developed successfully in many developed countries. "Treating the mother - protecting the unborn" is the motto of the Toronto Motherisk Program. Their mandate, as well as that of many other TIS worldwide, is to provide evidence-based information and guidance to pregnant or lactating patients and their health care providers regarding the fetal risks associated with drug, chemical, infection, disease and radiation exposure(s) during pregnancy. It is by empowerment of the mother by information and counselling that we can protect the "unborn" not only from harmful exposures but also to misconception, which may eventually lead to unnecessary termination of pregnancy or adverse long-term developmental outcomes. Much of the damage inflicted on children during fetal life or soon after birth by drugs, chemicals and infections can be prevented through public education, counselling and research. We need a TIS in Hong Kong to address important issues that are emerging worldwide and unique to the socio-cultural context and the changing epidemiology of our locality. This involves careful planning (Appendix 1) and strategic collaboration with international and local experts in order to ensure success and sustainability (Appendix 2). If we as paediatricians can take action based on currently available information, we can rescue generations of children from lives of illness and wasted potential.

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Appendix 1. Steps in establishing a local teratology information and drug counselling service

A proposed health promotion model would include 1) telephone helpline, 2) clinics and 3) brochures, booklets, websites and other educational materials and include the following components:

(1) Telephone counselling for both general public and health care providers.
(2) Clinic assessment to provide counselling to mothers and postnatal assessment of the children with prenatal drug/disease exposure.
(3) Knowledge exchange for mothers and professionals by means of printed educational material, seminars/lectures for professionals/general population and publications in peer-reviewed journals.
(4) Program website with regular information update.
(5) Development of computerised patient database for patient tracking and longitudinal follow-up and supporting research.
(6) Development of strategic collaboration with other TISs, local community service and the mass media.

Appendix 2. Success and sustainability of a local teratology information and drug counselling service – key elements

(1) Resources and manpower
(2) Collaboration with major TIS overseas and Training of staff to provide adequate counselling
(3) Preparation of updated and evidence-based information for education and counselling
(4) Cultural adaptation of existing educational materials and medical information
(5) Development of local database and ongoing research to generate evidence and recommendations with regards to local scenario, e.g. use of herbs among Chinese pregnant women
(6) Support from professionals and integration with the community