Congenital Disorders

Background information on risk from exposure to teratogens and the impact of interventions

This document gives you a brief overview of the risk from exposure to selected teratogens, and specific interventions that may reduce the associated burden of congenital disorders caused by them. This document focuses on environmental, occupational and pharmaceutical teratogens. Documents relating to other teratogens (alcohol, rubella, syphilis and nutritional deficiencies: folic acid and iodine) are listed under specific clinical topics.

What are teratogens

A teratogen is an agent with the potential to cause abnormal development prior to birth and may affect gametes, the embryo or fetus. Consequently, the risk of congenital disorders is not limited to pregnant women; the male reproductive system may also be damaged by exposure to teratogens, which might lead to congenital disorders when fathering a child. Preconception exposure to teratogens may also have consequences for a woman by affecting her eggs, and possibly through the accumulation of toxic chemicals that could later affect a developing fetus. Teratogens encompass a wide variety of agents including alcohol, certain infectious agents, therapeutic drugs and chemicals.

Congenital disorders caused by teratogen exposure

The range of teratogenic effects is broad, covering many disorders from abnormal organ function to retarded growth. A single teratogen can cause many different types of congenital disorders. The nature of the congenital disorder will be highly dependent on the level of exposure, the gestational age at the time of exposure, and the type of agent to which the prospective mother is exposed. Figure 1 illustrates how the developmental stage of the fetus at the time of teratogenic exposure can affect the type of abnormality that results. Exposure in the first 3 to 8 weeks of pregnancy is more likely to cause major morphological abnormalities, which have a high risk of mortality. Teratogenic exposure occurring later in gestation can result in congenital disorders of a more functional and minor morphological nature which, although less likely to be fatal, can still cause significant problems throughout life.

Some of the common congenital disorders that are regularly found after teratogen exposure are:

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Neural tube defects (NTDs)

Orofacial clefts

Limb reduction defects, i.e. when part of a limb or an entire limb fails to develop correctly

Conditions specifically affecting males, such as hypospadia and cryptorchidism.

What are the sources of exposure?

Environmental exposure

Exposure to environmental teratogens can occur through multiple routes. Exposure to industrial teratogens can be caused by industrial accidents, general occupational exposure or industrial pollution. Agricultural teratogens can be encountered occupationally (e.g. by use of teratogenic pesticides in commercial production or market gardening), or environmentally when prospective parents live in a highly agricultural area where chemicals are sprayed.

Studies on the teratogenic risk posed by industrial chemicals have identified a number of chemicals as being associated with congenital disorders, including: toluene, glycol ethers and other organic solvents, methyl mercury, lead compounds, and acrylonitrile[1] [2] [3] [4] [5].

Organic solvents (including toluene and glycol ethers) are used in many different industries, for instance in the formulation of adhesives, cleaning materials and pesticides, in the photographic industry, pharmaceutical industry, metal cleaning, dry cleaning, the paint industry and many others. Occupational exposure to lead occurs in lead smelters, construction works, plastics production, in jobs involving paints and dyes, and in the printing, ceramics, and electro-technical industries. Acrylonitrile is primarily used as a feedstock in the plastics industry, where it can be used in the creation of a number of synthetic rubber compounds. These chemicals are widely used in industrial settings and therefore the potential for both maternal and paternal exposure is high.

A number of specific agrochemicals, such as DDT, have also been found to be associated with congenital disorders[6]. However, it is important to note that it is often difficult to discern the individual effect of agrochemicals, as agricultural workers tend to be exposed to many different herbicides, pesticides, insecticides or fungicides at any one time.

Occupational exposure

Numerous studies have investigated the link between specific maternal or paternal occupations and the development of congenital disorders. Maternal occupations that have

[1] Bukowski JA. Review of the epidemiological evidence relating toluene to reproductive outcomes. Regul Toxicol Pharmacol 2001;33:147-56.

[2] Cordier S, Bergeret A, Goujard J, Ha MC, Ayme S, Bianchi F, Calzolari E, De Walle HE, Knill-Jones R, Candela S, Dale I, Dananche B, de Vigan C, Fevotte J, Kiel G, Mandereau L. Congenital malformation and maternal occupational exposure to glycol ethers. Occupational Exposure and Congenital Malformations Working Group. Epidemiology 1997;8:355-63.

[3] Kondo K. Congenital Minamata disease: warnings from Japan's experience. J Child Neurol 2000;15:458-64.

[4] Sallmen M, Lindbohm ML, Anttila A, Taskinen H, Hemminki K. Paternal occupational lead exposure and congenital malformations. J Epidemiol Community Health 1992;46:519-22.

[5] Wu W, Su J, Huang M. [An epidemiological study on reproductive effects in female workers exposed to acrylonitrile]. Zhonghua Yu Fang Yi Xue Za Zhi 1995;29:83-5.

[6] Bornman R, de Jager C, Worku Z, Farias P, Reif S. DDT and urogenital malformations in newborn boys in a malarial area. BJU Int 2010;106:405-11.

been associated with an elevated risk of congenital disorders include the leather industry[7] as well as chemical professions[8,9], for example occupations involving exposure to organic solvents (e.g. in the manufacture of paint, plastics, printer inks, pharmaceuticals and agricultural products).

There is evidence that some occupations in healthcare, including work in hospitals and as veterinarians[10] (e.g. radiologists), may be associated with an elevated risk of offspring with congenital disorders[11,12,13]. Some of the roles for which no association has been identified include operating room nurses, oncology healthcare workers and women exposed to low-dose radiation in veterinary practice.

The evidence base for the association of occupational teratogen and mutagen exposure with an increased risk of congenital abnormalities is limited. Most associations found between occupational exposure and increased risks of congenital abnormalities were not significant, and were often based on a relatively small sample of workers; therefore, no firm conclusions can be made.

Medication during pregnancy

Though it is well recognised that most therapeutic substances pass from mother to fetus, the extent to which this causes harm is difficult to determine and, is in many cases, unknown. Even when evidence suggests that a drug may harm a fetus, physicians must balance this risk with the drug's intended therapeutic benefit. Further problems lie with the use of over-the-counter and alternative medicines, which can be bought without the advice of a health professional, and in the latter case are less stringently regulated than prescription pharmaceuticals.

In many low and middle income countries (LMIC) there may be an increased risk of the use of potentially teratogenic medicines, due to a lack of or poor compliance with regulation of the distribution and use of many medicines, particularly if they are not distributed by medical personnel. There may be reduced control of prescribing or, even when prescribed by a healthcare professional, a lack of knowledge surrounding medications which may be high risk.

Off-label use and self-medication can also be an issue, for example in the use of the prostaglandin E_1 analogue misoprostol. Misoprostol is primarily used for gastrointestinal disorders but can also be used for medically induced abortion, although it is teratogenic. In

[7] Garcia AM, Fletcher T. Maternal occupation in the leather industry and selected congenital malformations. Occup Environ Med 1998;55:284-6.

[8] Lindbohm ML. Effects of parental exposure to solvents on pregnancy outcome. J Occup Environ Med 1995;37:908-14.

[9] Hooiveld M, Haveman W, Roskes K, Bretveld R, Burstyn I, Roeleveld N. Adverse reproductive outcomes among male painters with occupational exposure to organic solvents. Occup Environ Med 2006;63:538-44.

[10] Shirangi A, Fritschi L, Holman CD, Bower C. Birth defects in offspring of female veterinarians. J Occup Environ Med 2009;51:525-33.

[11] Brender J, Suarez L, Hendricks K, Baetz RA, Larsen R. Parental occupation and neural tube defect-affected pregnancies among Mexican Americans. J Occup Environ Med 2002;44:650-6.

[12] Matte TD, Mulinare J, Erickson JD. Case-control study of congenital defects and parental employment in health care. Am J Ind Med 1993;24:11-23.

[13] Lerman Y, Jacubovich R, Green MS. Pregnancy outcome following exposure to shortwaves among female physiotherapists in Israel. Am J Ind Med 2001;39:499-504.

many LMICs there is a high rate of self-induced abortion with misoprostol and therefore an increased risk of congenital disorders when abortion is unsuccessful[14].

Due to concern over the safety of medicines during pregnancy, many women look to complementary and alternative medicine as 'natural' and therefore it is assumed 'safe'. Unfortunately very few high quality studies are conducted into the efficacy and safety of these therapies, and practitioners in many places may not be regulated, making the use of such products and treatments during pregnancy unwise[15].

Owing to the uncertainty that surrounds drug safety during pregnancy (see Appendix 1), experts advise taking the lowest drug dose necessary, and where possible, limiting usage altogether. In cases where total avoidance of the drug would cause substantial harm, the risk/benefit balance should be assessed; for example, certain antimalarials and antiretrovirals are contraindicated in pregnancy, but infection could lead to severe consequences for both mother and baby and so taking the drug is often the best choice. Decisions to prescribe any medicine to a pregnant woman should be a joint decision between the patient and the doctor, based on the evidence available and following a discussion regarding the risk and benefits of therapy for the mother and child.

Global epidemiology

Prevalence of environmental teratogen-induced congenital disorders

It is difficult to determine the prevalence of environmental teratogen-induced congenital disorders due to under-reporting and difficulties in establishing a definite link between environmental exposure and adverse pregnancy outcome. An estimated 2% of congenital disorders are thought to be attributed to chemical or radiation exposure, but this proportion may be much higher, as the cause of 70% of cases remains unknown[16].

The low availability of public health measures and poor environmental protection policies and legislation in many low- and middle-income countries may be a contributing factor to the high rate of environmental teratogen-induced congenital disorders. Inadequate education about environmental teratogen risks and poor healthcare before conception, during pregnancy and after birth all contribute to a higher rate of congenital disorders.

The risk of specific teratogen exposure depends on geographical location and occupation. People living in regions of high agricultural activity are more likely to be exposed to teratogenic and mutagenic pesticides and herbicides, either through environmental or occupational exposure. Those who live in industrial centres will have a higher risk of exposure to chemical teratogens and radiation.

Disability and quality of life

Teratogenic exposure can cause a wide variety of congenital disorders that may present with physical and/or mental manifestations. For example, Thalidomide syndrome is characterised by limb abnormalities ranging from absence of limbs to shortened limbs whereas nicotine is not associated with congenital malformations but intrauterine growth retardation. Consequently, the level of disability and the resulting quality of life experienced by a child

[14] Costa SH, Vessey MP. Lancet. 1993;341(8855):1258-61

[15] Drugs in Pregnancy and Lactation. 2011. Briggs et al. Published by Lippincott Williams & Wilkins.

[16] Rubin R, et al. (2008) Rubin's Pathology: clinicopathologic foundations of medicine. Lippincott Williams & Wilkins

born with a congenital disorder caused by teratogen exposure can vary greatly depending on the type and severity of the disorder.

Having a child with a congenital disorder can also be a great burden for the parents, both in terms of the additional care that the child may need and also the psychological burden that is associated with the condition.

Reducing prevalence, morbidity and mortality

The identification of teratogenic sources through monitoring systems and the provision of intervention programmes to minimise exposure to teratogens are the key strategies to reduce the prevalence of teratogen-induced congenital disorders.

Interventions before pregnancy including population-wide interventions

Screening and monitoring

Several organisations publish maximum safe levels of exposure for teratogenic or suspected teratogenic substances (e.g. German technical rules, EUROCAT, Registry of Toxic Effects of Chemical Substances). This allows levels of these substances to be monitored regularly. Industries that utilise such substances should be obliged to regularly measure the levels; inspection and audit should be required to ensure that this is carried out.

Regular occupational health meetings for women working in particularly at-risk occupations can help to prevent e.g. by change of activity in preparation for a planned pregnancy and detect incidences of exposure to potentially dangerous teratogens before conception occurs. Meetings with a trained health professional would then allow education and family planning advice. Tighter regulation on the availability and access to agricultural and pharmaceutical products would enable the exposure to these teratogens to be better controlled, and risks discussed and minimised.

Public education campaigns

One of the central issues in preventing congenital disorders in is the frequent lack of awareness surrounding the impact of chemicals on the human body and in particular on the risk of congenital disorders. Educational programmes to raise awareness may take a number of different forms:

Education of healthcare professionals

Public campaigns incorporating posters, TV/radio programmes and newspaper articles to raise the awareness of the dangers of chemicals to reproductive health

Incorporation of short classes on the long-term effects of chemicals in the primary and secondary science curricula (in units on the environment, pollution or human health)

Preconception care counselling in primary care settings or as part of family planning and reproductive health care services that examines potential exposures to teratogens and is tailored to the woman and her partner's circumstances. Preconception care visits represent additional and important opportunity to identify and mitigate individual risks in those planning pregnancies.

Reduction in exposure to teratogens

Both male and female employees should be protected from unnecessary exposure to teratogenic chemicals. Most high-income countries have well-developed legislation in place to ensure that the health and safety of employees is not compromised for the sake of higher

profits for the company. Across all areas of employment, there is a role for occupational health professionals to identify the potential hazards for employees, devise solutions with management to minimise these hazards and evaluate the success of these solutions in protecting employees.

In the agricultural sector, workers may be exposed to teratogenic chemicals through the skin during handling; through the nose, eyes and mouth during spraying; and through the mouth during consumption of contaminated food and drink. Exposure can be reduced by wearing protective clothing such as gloves and facemasks during handling and spraying. Proper storage of chemicals is also necessary, as is the control of concentrations of chemicals throughout the food chain and particularly at consumer level..

Hospital staff who regularly work with radiological sources (e.g. radiologists and radiological nurses) can be protected by a number of measures that reduce exposure (e.g. lead aprons), or through the monitoring of environmental levels and alerting of managers if safe levels are breached.

A number of other occupations place employees at increased risk of exposure to teratogens (e.g. sawmill workers, painters, dye workers, agrochemical production workers, employees in general manufacturing etc.). In such industries, any legislation enacted to reduce the exposure of employees to hazardous, teratogenic chemicals will help to reduce the rates of congenital disorders.

Interventions during pregnancy

Monitoring for congenital disorders

While exposure to teratogens should be considered and acted upon prior to conception, where this has not been possible prenatal care provides an opportunity to discuss and minimise exposure to teratogens. Ultrasound provides an opportunity for detection of congenital disorders. Detection of severe conditions during pregnancy can allow parents and clinicians the option to terminate a pregnancy if such a decision is legal and acceptable to the parents. Where legislation does not permit termination, or when termination would be unacceptable to parents, prenatal diagnosis of the congenital disorder allows both parents and the medical team to be prepared to care for the child at birth and beyond. Whilst monitoring of all women may not be possible in some LMIC, there is a case for monitoring women who are at higher risk of having a child with a congenital disorder (i.e. those who have previously had a child with a congenital disorder, or those in higher risk occupations).

Maternal protection laws

Many countries have maternal protection laws to protect the rights of the mother and to reduce any occupational exposure to teratogens. The effectiveness of occupational health meetings and education on reducing exposure to teratogens depends on women not fearing job loss if they present themselves as pregnant at work.

Teratology information services

Public education programmes can provide information on the risk of environmental and pharmaceutical teratogenic exposure, particularly during the early stages of pregnancy. In addition, it is important to have organisations that can provide reliable advice on specific cases on request, both during pregnancy and before conception. Teratology Information Services (TIS) are available in some countries that provide reliable information and advice

on teratogens primarily to medical professionals, but also to lay people[17]. Where possible, the advice given is tailored to individual cases. TIS have been shown to reduce rates of congenital malformations and occupational risks. [18]

Occupational health meetings

If regular occupational health meetings are not possible, it would still be beneficial to have occupational health meetings available for women who are planning a pregnancy or become pregnant so that their occupational tasks can be evaluated and, if necessary, adapted to reduce teratogenic risk.

Pregnancy management

For those women who are currently taking medication, the health benefits of the treatment to the mother must be weighed against the risks to the fetus. For example, phenobarbital, which is recommended by the WHO as the first-line therapy for partial and generalized tonic-clonic seizures, has been linked to various congenital defects when used during pregnancy, including cardiovascular, urinary tract defects, and oral clefts. However, in circumstances where a woman who is being successfully treated with phenobarbital becomes pregnant the general medical advice is that treatment should be continued, as the maternal risk is greater if the drug is withheld during pregnancy[19]. There should be a focus on educating women who are taking medication for chronic conditions, such as epilepsy and HIV, on the potential risks associated with conceiving whilst taking these drugs and an assessment of whether safer drug options are available. In addition, identification and management of pregnant women with chronic illnesses can help mitigate adverse outcomes.

Furthermore, when non-pregnant women of child-bearing age are prescribed medicines that are potentially teratogenic, they should be informed of adequate contraceptive measures to prevent conception, and also what action should be taken if they do become pregnant.

Interventions after birth

Newborn screening

Newborn screening is a crucial part of the long-term plan aimed at reducing congenital disorders. Diagnosing congenital disorders at birth will help to evaluate the success of interventional programmes aimed at reducing the number of congenital disorders. In the cases where a congenital disorder is diagnosed, a further system should ideally be in place to investigate the risk factors during the pregnancy that may have contributed to the development of the disorder. The implementation of such a monitoring system will allow health systems to identify trends in congenital disorders (for example mothers in a specific occupation or parents living near a particular industrial site) and investigate these further. Within industry, companies should have a duty to ensure that any case where a baby with a congenital disorder is born to a worker is investigated and appropriate action taken to reduce further risks where appropriate, independent of whether that worker is the mother or father. The results of these investigations would feed back into a national or regional Teratology Information Service, if available, or to another responsible agency.

[17] Major Teratology Information Services include: http://www.entis-org.com (Europe); http://www.otispregnancy.org (USA) and http://www.siat.ufba.br (Brazil).

[18] Major Teratology Information Services include: http://www.entis-org.com (Europe); http://www.otispregnancy.org (USA) and http://www.siat.ufba.br (Brazil).

[19] Drugs in Pregnancy and Lactation. 2011. Briggs et al.

Epidemiological monitoring and research

A Congenital Abnormality Monitoring Service involves a team with a number of responsibilities:

Receiving case reports from physicians of newborns with congenital disorders, inputting this into a monitoring database and investigating further the potential risk factors.

Continually monitoring cases and identifying any trends, with a view to establishing possible clusters and causal links.

When an industrial accident occurs whereby large numbers of the population are exposed to chemicals, conducting robust prospective epidemiological studies starting immediately after the accident to investigate whether the chemicals released are linked to congenital disorders in the exposed population.

Care and support

For many congenital disorders, particularly in the case of physical malformations, surgery may be the best therapeutic option. However, other forms of care, including from education, health and social services, such as financial support to families and rehabilitation services are extremely relevant and the best or only option available.

Gaps in current research and knowledge of environmental teratogen exposure

There are many problems associated with the completeness of reporting of congenital disorders and links with possible environmental teratogens. This is particularly the case in LMIC where the prevalence of congenital disorders is likely to be greatly underestimated due to deficiencies in diagnostic capabilities, and the lack of reliable medical records and health statistics. The currently reported rates of congenital disorders in many LMIC should therefore be taken as a minimum estimate of the true burden.

Evidence for the teratogenicity of environmental factors in humans typically derives from observational studies, in which it is difficult to infer causality for any identified association between an environmental factor and congenital disorder. Even harder is the establishment of associations between outcomes and exposures at low doses or over prolonged periods at time as opposed to acutely. Compared with observational studies, experimental trials can provide more definitive evidence for a causal relationship but, for obvious reasons, all experimental evidence for such a relationship is limited to the use of animal models.

The degree of passive exposure to an environmental factor is far more difficult to define or quantify than exposure to an agent which is actively undertaken, such as the consumption of alcohol or pharmaceuticals. Much of the literature considering the teratogenicity of environmental factors relies on proxy measures of exposure such as parental occupations associated with a higher likelihood of exposure, or residential proximity to the source of a potential teratogen. Although these are often the only feasible measures of exposure, the reliability of data from such studies is likely to suffer from poor estimations of actual levels of exposure.

The teratogenicity of more difficult-to-define environmental factors may be masked or overshadowed by the effects of agents for which the teratogenic effect has been more clearly demonstrated (such as rubella infection or alcohol). The teratogenic effects of an environmental agent may therefore be wrongly attributed to a factor for which there is

stronger evidence for causality, thus playing down the true teratogenic contribution of the environmental factor.

More research is required to assess the benefits and cost-effectiveness of interventions that have been put in place to determine if they warrant further expansion or application.

What are the main ethical, legal and social issues (ELSI) to consider?

Equity of access to preconception care and education

Occupational health reviews, preconception counselling and education are not systematically offered in most countries and there may be variations in access to these services. Instead, this type of support is often performed on an opportunistic level by primary healthcare providers or is targeted at particularly high risk women who are planning a future pregnancy. Barriers to appropriate preconception counselling may include: unplanned pregnancies; lack of community or professional knowledge about the reproductive risks associated with specific occupations, locations or substances; and lack of access to quality free health services, health insurance or ability to afford preconception education or risk modification.

Employment legislation

Where there is a lack of legal job protection for pregnant women, or where such laws are not strongly enforced, women would be fearful of losing their employment if they reveal they are pregnant or if they ask to change their occupational tasks. The implications of this would be that pregnant women, or those trying to conceive, are not given the provision that they require in order to protect themselves and the fetus from teratogenic exposure at work.

Legislation to protect health and safety and the environment

Some high-income countries have legal frameworks that acknowledge strict liability for workplace exposures or pollution (to make it easier to bring a successful criminal conviction). Other countries have statutory authorities that can intervene promptly to monitor and police environmental exposures, or laws that state that vulnerable groups (such as pregnant women) can be excluded from a pool of possible employees without contravening anti-discrimination legislation. Without these protections as is the case in many LMIC, the responsibility of minimising exposure to teratogens falls on the individual, who may not be educated sufficiently or willing to sacrifice their job prospects in order to do so.

A woman's autonomy over her own body versus her unborn child's rights

The concept of a pregnant woman's autonomy over her own body when participating in high risk occupations or activities is a source of contention in legal and medical communities worldwide. Respecting a woman's right to freedom of choice versus the right of her child to be born healthy is a delicate balance to achieve. Preconception paternal exposure to dangerous substances can also have a detrimental impact on the development of the fetus, and thus there are also issues of the paternal right to freedom of choice.

Equity of access to prenatal services

Around 98% of women utilise prenatal care services in high-income countries, compared with only 68% women in low- and middle-income countries, where quality of these services

is often poor. In many countries, knowledge and education about safe motherhood are lacking, and there is poor access to healthcare facilities due to factors such as long distances, lack of transport and lack of legislation enabling women to take paid leave from work to attend prenatal appointments.

Attitudes to termination of pregnancy

In many countries, legal termination of pregnancy is unavailable or severely restricted to cases where it is necessary to protect the woman's life. In some countries access to procedures to terminate a pregnancy may also depend upon parental or spousal consent. In practice, in many countries procedures are often offered illegally, and these tend to lead to higher maternal morbidity and mortality than legal termination, especially for women who cannot afford to pay for treatment by qualified medical professionals. In countries where termination of pregnancy is legal in cases of fetal abnormality, opinions may vary on the ethical justification of termination for conditions that are not lethal.

Living with a disability

Teratogen-induced congenital disorders are associated with ongoing disabilities which can amount to a significant physical, emotional and financial burden. Affected individuals may experience stigmatisation and discrimination, while parents may feel guilt and responsibility if they know or suspect that their actions caused the disability. In high-income countries, both financial support and family counselling may be available to help families to deal with the impact of the congenital disorder, but assistance from the state may be virtually non-existent in LMIC where resources and trained personnel are scarce and the burden of congenital disorders falls entirely on the individual and their immediate and extended family.

KEY REFERENCES

Chia SE, Shi LM. Review of recent epidemiological studies on paternal occupations and birth defects. Occup Environ Med 2002 59(3): 149-155

EUROCAT. Special Report Part III: Environmental Pollution and Congenital Abnormalities. 2003

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Drugs in Pregnancy and Lactation. 2011. Briggs et al.

RELATED TOPICS

Preconception care and screening

Prenatal care and screening

Newborn screening

Neural Tube Defects

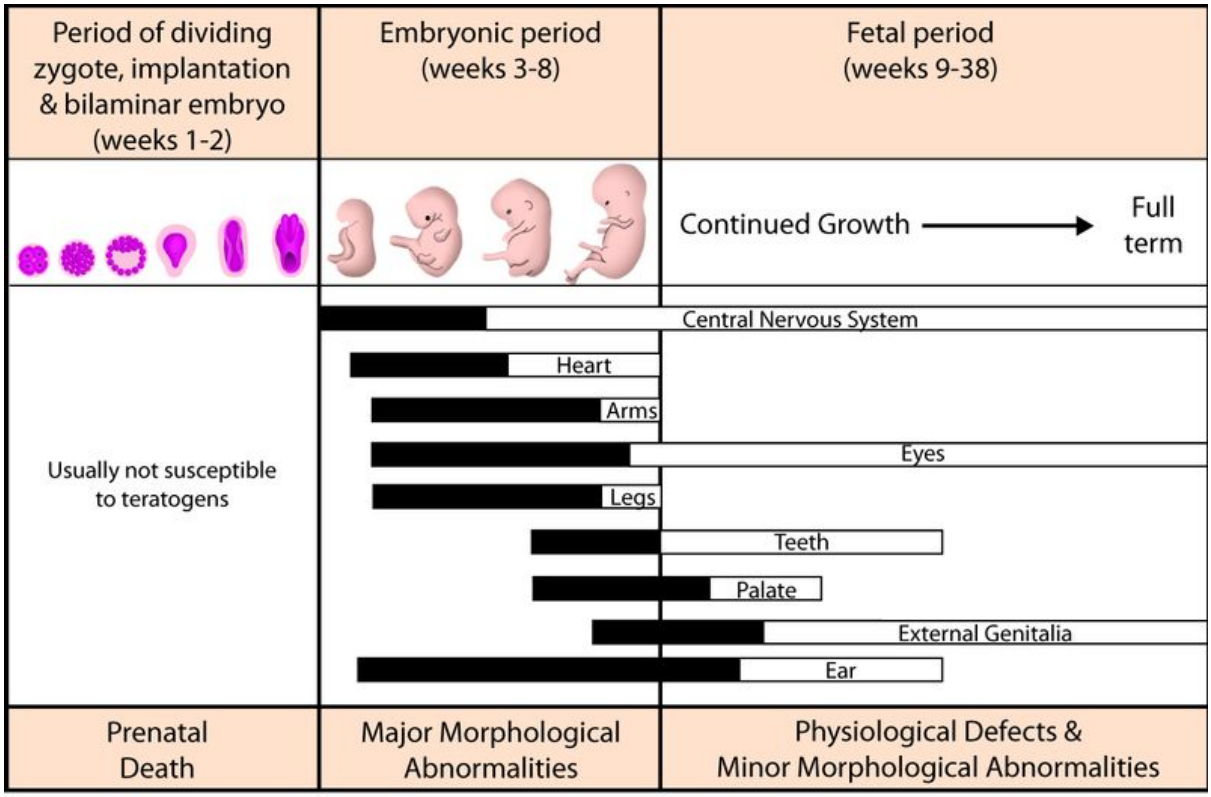
Orofacial Clefts

Congenital Rubella Syndrome

Congenital Syphilis

Fetal Alcohol Spectrum Disorders

Figure 1: Susceptibility to teratogens and the types of congenital disorders caused throughout the gestational period



Source: "Critical periods of human development for teratogen sensitivity" from Public Health Biology. Available at: http://ocw.jhsph.edu.

Appendix 1

The difficulties in determining the teratogenicity of a given drug arise for a number of reasons. Primarily, for ethical reasons, almost all clinical trials exclude pregnant women, and stipulate that participating pre-menopausal women take effective contraceptive precautions. When the teratogenic effects of drugs are instead tested on animals, this still neglects to provide the definitive answer as the relevance of such studies to human pregnancy is debatable. This is exemplified by the now well-known teratogen thalidomide, which despite causing severe malformations in around one third of exposed human fetuses, did not demonstrate teratogenicity in the animals initially tested[20]. Even when malformations should be observed in exposed test animals, the frequency of the malformation occurring is often so low that sample sizes are rarely large enough to detect the risk.

Consequently, it is often not until a drug has entered the market and been used for some time that a large enough sample of women are exposed to it for any teratogenicity to be suspected. With thalidomidee, the disabling effect of the drug on exposed children was immediately apparent; however alterations to the developing fetus can be far more subtle, for example in the case of *in-utero* exposure to diethylstilbestrol, which was only recognised as causing complications of the reproductive system when exposed people tried to conceive[21].

As an illustrative example we have compiled a list of drugs for which research has uncovered evidence of human teratogenic effects. This list is by no means definitive or exhaustive and only includes drugs on the WHO essential medicines list for which human evidence is available. There are other agents not included on this list for which there is strong evidence for teratogenicity, for example thalidomide and isotretinoin.

Approach to the Evidence Review

The WHO Essential Medicines List (2011)[22] was used as a source of medications for review. This list was deemed appropriate as it presents the 'minimum medicine needs for a basic health-care system' and therefore indicates which medications are likely to be widely available in low- and middle-income countries (LMICs). The medicines on this list were cross-referenced with a recently updated reference textbook ('Drugs in Pregnancy and Lactation', Briggs et al, 2011)[23] which provides comprehensive safety summaries for a wide range of pharmaceutical agents in pregnancy. Evidence of teratogenicity from any source (case studies, observational studies and randomised controlled trials) are presented for each agent in the textbook. Items on the Essential Medicines List that were clearly not pharmaceutical agents (such as condoms and in vitro diagnostic reagents) were excluded.

Agents were classified as 'teratogenic' or 'unclear' based on an assessment of the evidence in Briggs et al. Allocation of agents to one of the two risk categories was determined by the following rules:

- An agent could only be classified as 'teratogenic' based on strong human evidence. 'Strong' evidence constituted data from randomised controlled trials and large

[20] Briggs et al Drugs in pregnancy and lactation.
[21] National Cancer Institute. Diethylstilbestrol and Cancer. http://www.cancer.gov/cancertopics/factsheet/Risk/DES
[22] WHO Model List of Essential Medicines. 17th list (March 2011). Available at: http://whqlibdoc.who.int/hq/2011/a95053_eng.pdf
[23] Drugs in Pregnancy and Lactation. 2011. Briggs et al.

observational studies, including data analysis from registries. It was necessary to consider observational studies as strong evidence due to the scarcity of randomised controlled trials in this research area. Individual case studies were not considered as strong evidence.

- If the human evidence for teratogenicity was not strong, the evidence was considered to be 'unclear'.
- Evidence from animal data was excluded.

Which medicines pose the greatest teratogenic risk?

Based on a review of the WHO Essential Medicines List, Table 1 summarises the medications where human evidence indicates there is a risk of teratogenicity. The absence of an agent in the table means that the agent was either not covered in Briggs et al, or the evidence summary for that agent was unclear. The table provides brief details of the indication and details of known human teratogenic effects of each drug. The risk/benefit profile of drug administration during pregnancy is also given in the table (as indicated in Briggs et al.), as for several drugs it is still preferable for the medication to be administered during pregnancy if the benefit to the mother outweighs the potential risk to the fetus. Due to the scarcity of information available, the decision to use medicines during pregnancy should be made between the patient and their healthcare professional, based on the best available evidence and following a discussion of the benefits and risk, to both the mother and the fetus, of using the medicine.

Table 1: Drugs on the WHO Essential Medicines List (2011) for which strong human evidence of teratogenicity exists, based on our review of the evidence in Briggs et al (2011)

Drug Name	Class of Drug	Details of Teratogenic Effects	Risk/Benefit Profile of Drug in Pregnancy
Carbamazepine	Anticonvulsant	Neural tube defects, cardiovascular and urinary tract defects, and cleft palate. A fetal carbamazepine syndrome has been proposed, consisting of minor craniofacial defects, fingernail hypoplasia and, more controversially, developmental delay	If drug is required during pregnancy it should not be withheld, as the maternal benefit of preventing seizures outweighs potential fetal harm from drug use.
Clomipramine	Antidepressant	Cardiac defects	Not reported
Enalapril	Antihypertensive	Fetal hypocalvaria (underdevelopment or incomplete development of the cranial bones) and renal defects when used in the 2nd and 3rd trimesters	Not reported

Drug Name	Class of Drug	Details of Teratogenic Effects	Risk/Benefit Profile of Drug in Pregnancy
Ethanol	Sedative	Fetal alcohol syndrome, particularly during the first 2 months after conception	Contraindicated
Hydrocortisone	Corticosteroid	Small increase in the incidence of cleft lip with or without cleft palate	Maternal benefit of corticosteroids outweighs the fetal risks; drug should not be withheld if necessary in pregnancy
Lithium carbonate	Mood stabiliser	Cardiovascular defects, particularly when used in the 1st trimester, including Ebstein's anomaly	The risk of abrupt discontinuation of lithium carbonate in bipolar disorder is high. The risks of uncontrolled bipolar disorder during pregnancy outweighs the risks associated with lithium bicarbonate.
Lorazepam	Sedative	Anal atresia	Not reported
Misoprostol	Gastrointestinal agent	Congenital defects, terminal transverse limb defects and Möbius syndrome (an underdevelopment of the cranial nerves controlling eye and facial movement), amongst others	Contraindicated
Nicotine replacement therapy (NRT)	CNS agent (smoking deterrent)	Major musculoskeletal malformations	Maternal benefit may outweigh the fetal risks, but only if non-pharmacologic approaches to smoking cessation have failed
Norethisterone enantate	Progestogenic hormone	Various, including masculisation of the female fetus, cardiovascular defects, oral clefts and hypospadia	Contraindicated
Phenobarbital	Sedative/ anticonvulsant	Various, including cardiovascular, urinary tract defects, and oral clefts	Maternal risk is greater if the drug is withheld during pregnancy; therefore, the drug could continue to be administered at the

Drug Name	Class of Drug	Details of Teratogenic Effects	Risk/Benefit Profile of Drug in Pregnancy
			lowest possible dose to prevent seizures. The use of safer anticonvulsants should be considered (eg. Lamotrigine).
Phenytoin	Anticonvulsant	Significant risk of major and minor congenital abnormalities	The risk/benefit trade-off favours the use of safer anticonvulsants during pregnancy that are now available.
Potassium iodide	Respiratory drug (expectorant)	When used for prolonged periods or close to term, may cause hypothyroidism and congenital iodide goiter in the fetus	Contraindicated during pregnancy by the American Academy of Pediatrics
Tetracycline	Antibiotic	Evidence has been found to suggest a relationship to minor but not major malformations, including hypospadias (1st trimester only), inguinal hernia and hypoplasia of limb	Contraindicated in the 2nd and 3rd trimesters
Trimethoprim	Anti-infective	Cardiovascular defects and neural tube defects, and possibly oral clefts	Not reported
Valproic acid (sodium valproate)	Anticonvulsant	Neural tube defects and a characteristic pattern of minor facial defects	Not reported
Warfarin	Anticoagulant	Exposure in the 6th – 9th weeks of gestation may produce a pattern of defects termed “fetal warfarin syndrome”	Contraindicated in the 1st trimester

It should also be noted that the above list is not exhaustive, and only includes drugs on the WHO essential medicines list for which human evidence is available. There are other agents not included on this list for which there is strong evidence for teratogenicity, for example thalidomide and isotretinoin.

Further information on other medicines can be found through teratogen information services (Table 2).

Table 2: Useful links for international teratology information services

Country	Link
USA	http://www.otispregnancy.org/
Europe	http://www.entis-org.com/
Australia	http://www.sesiahs.health.nsw.gov.au/Mothersafe/
Brazil - Porto Alegre	http://gravidez-segura.org/
Brazil - Bahia	http://www.siat.ufba.br/
Japan	http://www.ncchd.go.jp/kusuri/index.html
Korea	http://www.mothersafe.or.kr/