Drug Induced Birth Defects –
the dangers of every-day pills

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Abstract

The potential for drug induced birth defects is significantly increased during early pregnancy, in particular during the period of embryonic development. This early phase of pregnancy may often go undetected. Therefore, every menstruating female and her treating practitioner should be aware of the possibility of pregnancy and associated risk of birth defects attributed to some substances. A 2004 study found that pregnant women are regularly taking an average of 13 medications. Commonly used drugs include alcohol, antibiotics, antacids, analgesics, antimicrobials, tranquilizers, and diuretics supporting the call for a greater awareness of teratogenic actions of these, and other, substances.

Health professionals meet a great challenge in providing care and education about drug induced birth defects for women of child bearing age. Early pregnancy often goes undetected leaving the embryo vulnerable to drug damage. The purpose of this article is to raise consciousness about the susceptibility of the embryo to teratogenic effects of many commonly used substances. The liberal use of alcohol and other drugs is supported in a study by Moore and Persaud (2003, p. 175) who report that an average of 40% to 90% of pregnant women consume at least one drug during pregnancy. The use of prescription and non-prescription drugs throughout pregnancy is surprisingly high. Several studies have indicated that pregnant women take an average of four drugs with about half of these consumed during the first trimester. Drug consumption also tends to be higher during the critical period of development among heavy smokers and drinkers (Moore & Persaud, 2003, p. 176). Widespread and accepted use of these substances is fuelled by clever marketing which often limits the effectiveness of health care advice provided by professionals.

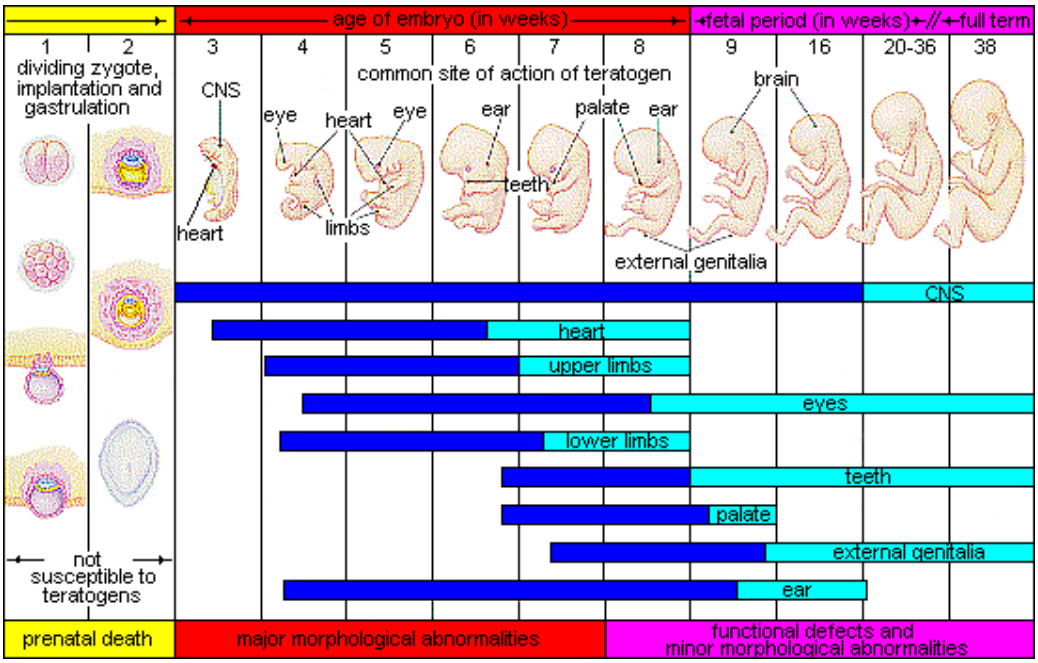
The importance of timing

During the first two weeks following fertilisation rapid mitotic division within the fertilised ovum results in formation of the blastocyst which implants into the posterior wall of the uterus around days seven to ten. Major anomalies in development during the first two weeks often result in embryonic death and spontaneous abortion (Moore & Persaud, 2003, p. 50). Early spontaneous abortion

may be passed off as menstruation. Once securely implanted, and by the end of the second week, parts of the inner cell mass differentiate into three germ layers: ectoderm, mesoderm and endoderm (Jones & Lopez, 2006, pp. 257-263). It is these cells that become the embryo, differentiating into the main structures as follows:

- Ectoderm layer forms the nervous system as well as the epidermis of the skin, hair, nails and tooth enamel;
- Mesodermal layer forms many of the internal structures including the skeleton, muscles and circulatory system, deep layers of skin, kidneys, gonads and notochord which is later replaced by the vertebral column;
- Endodermal layer forms the lining of two tubes – the digestive tract including liver, gall bladder and pancreas – and respiratory tract including the lungs.

Figure 1 – Critical periods in human development (Hill, 2006)



Morphological development is very precise with certain tissues being laid down within very narrow time frames as depicted in Figure 1. Particularly sensitive phases are during neural tube development from week three and rapid brain development from week five. These organs continue to develop through to week 16 highlighting the need for caution during the first trimester. The digestive tube starts to form during weeks seven and eight. After week eight, the embryo is known as a foetus and continues to undergo cell differentiation and organ development. It is during this rapid period of growth that teratogenicity has its greatest affect on the unborn child (Jones & Lopez, 2006, pp. 277-283).

Dangers of socially accepted drugs

Marketing strategies targeting fast relief from pain often result in the promiscuous use of drugs. One only has to watch television briefly to be exposed to advertisers promoting pain relief which, it is inferred, "belongs in every woman's handbag." It

is not only analgesics that give rise for concern. Adverse effects of alcohol consumption as well as incorrect dosages or poor quality supplements are often overlooked by the unknowing mother-to-be. Complementary health medicine training constantly highlights the importance of teratogenic effects of some substances. Prior to prescribing herbal remedies, the naturopath will ensure that a female patient is not pregnant. Perhaps similar measures to protect the unborn should be adopted throughout all areas of health care. In order to properly cater for the health and well-being of an unborn child, it is important to understand the mechanism of how commonly prescribed and over the counter substances consumed during pregnancy can induce birth defects.

- **Antibiotic and anticoagulant medication**

Some antibiotic medications are able to cross the placental membrane and be deposited in the embryo's bones and teeth at sites of active calcification. As little as one gram per day of tetracycline administered during the third trimester of pregnancy can produce yellow staining of both primary and secondary teeth. When used from as early as the fourth month it may cause tooth defects and diminished growth of long bones. Moore and Persaud (2003, p. 177) report of deafness in infants whose mothers have been treated with high doses of streptomycin and dihydrostreptomycin. These antibiotics cause damage to the eighth cranial nerve, Vestibulocochlear, which innervates the balance organs and organs of hearing. Moore and Persaud further note that the popular anticoagulant *Warfarin* is a definite teratogen. They report of mothers who took this anticoagulant during the critical period of embryonic development (between weeks six and 12) whose children suffered hypoplasia of the nasal cartilage, stippled epiphyses and various central nervous system defects.

- **Analgesic, decongestant and anti-inflammatory drugs**

Analgesics are readily available over the counter from the chemist as well as the supermarket. As a result of easy access, the wide ranging effects of analgesics are often forgotten and not put into context of being potentially dangerous to the defenceless unborn. Some of the more common non-steroidal anti-inflammatory drugs (NSAIDs) contain ibuprofen, acetylsalicylic acid and paracetamol. A study by Burdan and Belzek (2001) involved ingestion of ibuprofen during pregnancy and found the substance caused embryonic implantation disturbances, inhibition of parturition and contraction of the ductus arteriosus leading to maternal pulmonary hypertension. Gastroschisis is a congenital ibuprofen-related malformation in which foetal organs develop outside the abdominal wall. Other drug-related cases of gastroschisis have been linked to maternal use of other NSAIDs including *Aspirin* and the decongestants pseudoephedrine and phenylpropanolamine (Torfs, Katz, Bateson, Lam & Curry, 1996).

Aspirin enjoys a reputation of being generally safe to use during pregnancy except during the latter months as its inhibition of prostaglandins may affect parturition. Despite being considered safe to use, Burdan (2001) reports that human trials have shown high doses of acetylsalicylic acid may produce a variety of congenital malformations. The current literature suggests that acetylsalicylic acid should be given in pregnancy only if the potential benefit justifies the potential risk to the foetus, thereby acknowledging the existence of *Aspirin*-related defects. Due to the emotionally charged aspect of conducting human trials on pregnant women, results of research on animals including rats and rabbits provide much of the data. Use of NSAIDs during the first trimester of pregnancy in human trials by Ofori, Oraichi,

Blais, Rey and Bérard (2006) has been shown to cause ventricular septal defects, midline defects, diaphragmatic hernias and hydrocephalus in the foetus. Most defects occurred when administered during days six to 17 following fertilisation (Gupta, Cook, Tassinari & Hurt, 2003) again highlighting the importance of early stage pregnancy abstinence from drugs.

- **Anti-viral & anti-fungal medication**

The anti-viral group of drugs varies in its application by being administered either topically or ingested with duration of treatment depending on the specific condition involved. With the increase in viral herpes infections, Stahlmann and Klug (1997, p. 231) report that acyclovir is among the most often prescribed chemotherapeutic agents. While limited treatment is prescribed for herpes zoster, continuous administration of acyclovir is frequently the preferred treatment for suppression of recurrent genital herpes. Although the causative action remains obscure, Stahlmann and Klug (1997, p. 231) report that foetal structural malformations have been noted in human studies involving pregnant women.

The mode of action of virustatic agents is to alter DNA metabolism which may explain their teratogenic action, particularly during the embryological development phase but also throughout pregnancy. Embryological development involves precise DNA replication and rapid cell division, a process which continues throughout pregnancy as the foetus develops. Published trials of foetal defects attributed to virustatic agents include skull bone abnormalities including malformation of the tympanic membrane, impaired immune function due to reduced thymus and increased spleen sizes (Stahlmann & Klug, pp. 258-259). Experimental doses were low at 1000 mg per day whereas doses prescribed for the treatment of shingles are in the vicinity of up to 4000mg per day (Stahlmann & Klug, pp. 258-259). According to the Australian Food & Drug Administration (FDA), repeated doses of fluconazole, used to treat vaginal thrush, have been associated with a "consistent pattern of birth defects" (TGA, 2006) similar to those seen in animal studies. Apgar (1997) reports on fluconazole causing Trisomy which is a chromosomal abnormality often seen in Down Syndrome.

- **Mood stabilisers, anti-depressants, tranquilisers and hypnotics**

Although this category of drugs usually requires a prescription, it may often be taken for longer periods of time and commenced well before the woman conceives. The Australian Bureau of Statistics (2006) reports that over 16,000 women aged between 18 and 44 years had taken antidepressant medication during the two weeks preceding the 2004-05 survey. It is acknowledged that benzodiazepines are the most commonly used drugs in the United States for the treatment of anxiety, phobias and tension (Iqbal, Sobhan, & Ryals, 2002). Human trials have revealed that *diazepam*, a benzodiazepine, passes into the placenta from week six of gestation transferring the drug into both amniotic fluid and foetal tissues during organogenesis (Jauniaux, Jurkovic, Lees, Campbell & Gulbis, 1996). Iqbal, Sobhan and Ryals (2002) reveal that the effects of taking benzodiazepine drugs during pregnancy may lead to foetal abortion, malformation, intrauterine growth retardation, functional deficits, carcinogenesis and mutagenesis with greatest risks occurring between two and eight weeks after conception. When the drug is used near term, foetal dependence and withdrawal have been known to occur.

A recent study conducted at the University of Montreal, Canada, revealed that taking more than 25mg/day of paroxetine during the first trimester of pregnancy

may cause major congenital and cardiac malformations (Bérard et al, 2007). Paroxetine is one of many selective serotonin reuptake inhibitors (SSRIs) frequently prescribed in cases of mild depression or anxiety. In 2005, the drug manufacturers, GlaxoSmithKline, and the American FDA warned of congenital malformations in infants born to women taking *Paxil* (brand name for paroxetine) (Consumer Affairs, 2005).

Another drug commonly prescribed as a mood stabiliser is the carboxamide, carbamazepine. Although traditionally associated with the treatment of more severe psychiatric conditions including bipolar disorder and schizophrenia as well as an anticonvulsant and for trigeminal neuralgia, it has become widely used by many women coming into my clinic who have been prescribed carbamazepine as a muscle relaxant. Related defects when taken during pregnancy include cleft palate, clubfoot, neural tube defects, growth retardation and sub-normal intelligence quotient (Iqbal, Gundlapalli, Ryan, Ryals & Passman, 2001). Manish and his colleagues (2007) found that maternal use of carbamazepine was linked to foetal arteriovenous malformations, cardiovascular teratogenicity and anticonvulsant syndrome.

- **Alcohol**

Clinical trials as far back as 1968 have clearly established the link between prenatal ethanol exposure and birth defects, termed Foetal Alcohol Syndrome (FAS) (Rogers & Daston, p. 333). Despite the hundreds of clinical, epidemiological and experimental studies which have been undertaken over the years, alcohol consumption during gestation remains socially acceptable. Abnormalities associated with FAS fall into three major categories: growth retardation; mental retardation and neurological abnormalities; and craniofacial dysmorphism including microcephaly. However, according to research reported by Rogers and Daston (1997, p. 333) abnormalities associated with FAS also extend to organs of the cardiovascular system, liver, kidney, genitals, cutaneous membranes, musculature, skeletal tissue, neural tube and have also been known to cause tumours. Despite the extensive research and findings of FAS, a national drug survey in 2004 found that 55% of women aged between 14 and 39 years consumed alcohol regularly (Statistics on Drug use in Australia, 2004).

Embryonic and foetal nutrient supplies are significantly impaired by drugs inhibiting circulation through the placenta. Delivery of oxygen to the foetus occurs via the umbilical blood flow and hypoxia has been associated in increased foetal mortality, malformations and growth retardation. Impaired blood flow also increases free radical damage to the delicate embryonic tissues by compromising cell membrane integrity (Rogers & Daston, pp. 373-375). Therefore, any drugs inhibiting circulation through the placenta impact on embryonic and foetal nutrient supplies. Impaired placental circulation would not only impact on nutrient flow to the foetus but also delay clearance of waste products leading to toxicity within the developing baby. Adequate nutrition has become the focus of increasing studies which reveal that programming of future health begins long before birth (Newnham, Moss, Nitsos, Sloboda & Challis, 2002, p. 537). Ethanol has been shown to interfere with digestion and absorption of nutrients, in particular zinc, folate and pyridoxine, vitamins A and D, and magnesium while tissue concentrations of iron and manganese are elevated with chronic alcohol intake. Ethanol has further been shown to interfere with essential fatty acid metabolism and prostaglandin synthesis in the embryo (Rogers & Daston, 1997, pp. 368-372).

- **Vitamin A**

Kavlock and Daston (1997, p. 370) refer to Vitamin A as a group of retinoids which are best consumed as compounds rather than isolates. These retinoids are required for normal growth, vision, spermatogenesis, haematopoiesis, immunity, epithelial development, and in particular, mucous membranes as found in the respiratory and digestive tracts (Villamor & Fawzi, 2005). However, hypervitaminosis A has been shown to have teratogenic actions when total consumption exceeds 10,000 IU per day of preformed retinol whereas Vitamin A derived from beta-carotene is not associated with birth defects (Higdon, 2003). Teratogenic response is dependent on the embryonic or foetal developmental stage, quality of retinoid compound consumed and dosage taken. Higher doses, increasing frequency and severity of defects are attributed to embryolethality. Over-exposure during embryonic development has been linked to craniofacial and overt central nervous system defects (Kavlock & Daston, 1997, p. 12).

Just as excess Vitamin A may be teratogenic, insufficient levels of this vitamin impact negatively on the development of foetal mucosa which originated from endodermal tissue. Umesh (2004) found that Vitamin A deficiency during pregnancy increases the baby's susceptibility to infections. Azaïs-Braesco and Pascal (2000, p. 1330) report an association of low Vitamin A status with increased development of eclampsia in the mother and premature rupture of membranes. The effect of Vitamin A on mucosal membranes may be a relevant consideration in light of Australia's high incidence of respiratory ailments, in particular asthma.

Conclusion

A better understanding of the dangers of various substances including alcohol, medications and nutrients may assist in reducing drug related birth defects. A close association between women of child-bearing age and their health care providers may reduce embryonic exposure to teratogenic agents. With nearly 50% of females admitting to taking someone else's prescription drugs including analgesics, antibiotics and anti-depressants, the need for more awareness cannot be stressed enough (Statistics on drug use in Australia 2004). Substances ingested by a woman are of particular relevance during the first weeks of gestation. It is often these fateful first weeks that the woman is oblivious to being pregnant. Therefore, a greater awareness of the possible teratogenic actions associated with many socially accepted substances may limit their use and assist in preventing birth defects.

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