The Influence of the Environment and Other Exogenous Agents on Spontaneous Abortion Risk

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Abstract

It has been estimated that close to 30% of all pregnancies end in spontaneous abortion. Although about 60% of spontaneous abortions are thought to be due to genetic, infectious, hormonal and immunological factors, the role of the environment remains poorly understood. Pregnancy involves a delicate balance of hormonal and immunological functions, which can be affected by environmental substances. Many toxic substances which are persistent in the environment and accumulate in the fatty tissues may disrupt this equilibrium. This overview addresses known risk factors for spontaneous abortion, and examines the role, if any, that environmental factors (chemical and physical) may play in the etiology of this adverse health outcome.

1. Introduction

Pregnancy involves a complex interaction between genetic, anatomic, endocrine, immune and neurological systems. When any of these are disturbed, the pregnancy may be lost. Approximately 60% of spontaneous abortions are thought to be related to genetic, infectious, hormonal and immunological factors (Giacomucci et al. 1994a;Bulletti et al. 1996). However, the role of the environment in the etiology of spontaneous abortion remains poorly understood.

A variety of environmental agents are present in umbilical cord blood (Rhainds et al. 1999), amniotic fluid (Foster et al. 2000), and seminal fluid (Garcia 1998;Friedler 1996;Chia and Shi 2002;Stachel et al. 1989). At the same time a number of environmental chemicals possess estrogenic (Palmiter and Mulvihill 1978;Soto et al. 1994;Kojima et al. 2004), anti-androgenic (Sonnenschein and Soto 1998;Kojima et al. 2004), carcinogenic (Zahm et al. 1997), and immunotoxic (Vial et al. 1996) properties. In this article we will critically review the literature on the association between environmental contaminants and spontaneous abortion.

2. Epidemiology of Spontaneous Abortion

The World Health Organization (World Health Organization. 1977) has defined spontaneous abortion as "the expulsion or extraction from its mother of an embryo or fetus weighing 500 g or less". Early spontaneous abortions are defined as those that occur before the 12^{th} week of gestation, with late spontaneous abortions being those that occur from 12-20 weeks of pregnancy, and 500g or less (Källén 1988;Statistics Canada 2004). Embryologic deaths, that is those less than or equal to 12 weeks gestation, tend to be related to gross chromosomal anomalies, while late fetal deaths are attributed to an array of other factors (Strom et al. 1992;Garcia-Enguidanos et al. 2002;Strom et al. 1992). Prospective studies in which urine specimens are monitored on a daily basis have estimated the rate of early pregnancy loss to be between 22 and 31% (Zinaman et al. 1996;Ellish et al. 1996;Wilcox et al. 1988). Other investigators have suggested

that up to 70% of pregnancies end in spontaneous abortion, if unrecognized pregnancies which abort during the first month of gestation, are taken into account (Bulletti et al. 1996). The frequency of recurrent spontaneous abortions is close to 0.4 to 0.8% but the risk increases with the number of past abortions; 24% after one abortion, 26% after two consecutive abortions, and 32 % after the third abortion (Giacomucci et al. 1994b).

3. Etiology of Spontaneous Abortion

3.1 Physiological Factors & Biological Mechanisms

3.1.1 Genetic Risk Factors

The majority of spontaneous abortions are due to chromosomal abnormalities, particularly trisomies (Eiben et al. 1990;Ohno et al. 1991;Zhou 1990). Cytogenetic studies have identified chromosomal abnormalities in between 21 and 50% of first trimester spontaneous abortions (Chua et al. 1989;Eiben et al. 1990;Boue et al. 1975), with more than half containing no embryonic parts for examination (Kalousek et al. 1993). Another study confirmed that 70% of missed abortions, defined as an embryo without cardiac activity, had chromosomal abnormalities, most of which represented non-viable genetic defects (Philipp and Kalousek 2002).

Male-Mediated Genotoxicity

The development of mature sperm from spermatogonia occurs in an approximately 74 day cycle in man (Friedler 1996). Sperm aneuploidy (missing or extra chromosomes) occurs due to non-disjunction (the failure of homologous pairs of chromosomes to separate) (O'Rahilly and Muller 2001), and has been suggested as the leading cause of spontaneous abortions (Hassold et al. 1996). Occupational or residential exposure to pesticides among males can result in an increased risk of sperm aneuploidy (Padungtod et al. 1999;Recio et al. 2001). In addition, male pesticide applicators have demonstrated significant increases in the frequency of chromosome breakage and rearrangement in G-banded lymphocytes, representing long-lived chromosomal aberrations associated with phenotypic changes in gene expression (Garry et al. 1989;Garry et al. 1992).

Experimental studies have indicated that spermatozoa that have experienced DNA damage are still able to fertilize the oocyte, thereby providing a possible mechanism for male-mediated reproductive effects (Aitken et al. 1998).

3.1.2 Anatomical Risk Factors

Uterine anomalies include congenital malformations (unicornuate uterus, uterus didelphys, bicornuate uterus, and septate uterus), acquired uterine defects (Astherman's syndrome (uterine scaring) and defects secondary to diethylestilbestrol), leiomyomata (fibroids), and cervical incompetence (Garcia-Enguidanos et al. 2002). Although these anomalies are commonly considered to be associated with spontaneous abortion, their incidence, classification, and etiologic role remain uncertain (Bulletti et al. 1996). Uterine abnormalities are thought to occur in 1.9% of the female population, and in 13 to 30% of women with repetitive or recurrent spontaneous abortions (Bulletti et al. 1996;Garcia-Enguidanos et al. 2002). Without treatment, fetal survival rates have been documented to range from as high as 64% with uterus didelphys to as low as 15-28% with septate uterus (Garcia-Enguidanos et al. 2002). Other studies have shown that women with acquired anomalies such as Asherman syndrome, uterine adhesions, and anomalies acquired through diethylstilbestrol exposure have both lowered fetal survival rates (Garcia-Enguidanos et al. 2002) and increased spontaneous abortion rates (Herbst et al. 1981).

3.1.3 Endocrine Risk Factors

Both estrogen and progesterone play essential roles in pregnancy. During the menstrual cycle the first half is estrogen-dominated while the second half is progesterone-dominated. Estrogen and progesterone initially prepare the endometrium for implantation by initiating a cascade of local morphological and physiological events via their respective receptors (Critchley 1999). Progesterone acts on the reproductive tract in preparation for the initiation and maintenance of pregnancy by inhibiting contraction of the uterus and the development of new follicles (Niswender et al. 2000). Following fertilization of the oocyte, the developing embryo secretes

human chorionic gonadotropin (HCG) which sustains progesterone levels. During pregnancy, fetoplacental estrogens, progestogens and adrenocorticoids are secreted into both fetal and maternal circulation (Gabbe et al. 2002). Estrogen production is mainly under the control of the fetus and is the primary signaling method by which the fetus directs essential physiologic processes that affect fetal well-being. By the 20th week of pregnancy, approximately 90% of maternal estriol excretion can be accounted for by dehydroepiandrosterone sulfate (DHEA-S) production by the fetal adrenal gland. Estrogens affect progesterone production, uterine blood flow, mammary gland development and fetal adrenal gland function (Speroff et al. 1999).

A number of endocrine disorders have been implicated in recurrent spontaneous abortion, including poorly controlled diabetes mellitus (Mestman 2002), hypo- and hyperthyroidism (Lazarus and Kokandi 2000;Fedele and Bianchi 1995), oligomenorrhea (Hasegawa et al. 1996), luteinizing hormone hypersecretion, corpus luteum insufficiency or luteal phase dysfunction (Fritz 1988;Dlugi 1998), and polycystic ovarian disease (Regan et al. 1990;Homburg et al. 1988). More recently, attention has been given to the role of hyperandrogenaemia (Okon et al. 1998;Tulppala et al. 1993) and hyperprolactinaemia (Hirahara et al. 1998) in recurrent pregnancy loss.

Endocrine Toxicants

Given the important role that estrogen and progesterone play in pregnancy, it is plausible that chemicals in the environment that affect these hormones could induce spontaneous abortion. Several exogenous chemicals, including certain polychlorinated biphenyls (PCBs), bisphenol A, pesticides (specifically DDT and its metabolites, methoxychlor, lindane, endosulfan, toxaphene, and dieldrin) (National Research Council 1999;Soto et al. 1994), chemicals in cigarette smoke (Key et al. 1996), and possibly lead (Ronis et al. 1998a;Ronis et al. 1998b) have been shown to exhibit estrogenic and anti-estrogenic activity. Furthermore, many of these chemicals are persistent in the environment and accumulate in the fatty tissues of animals and humans where, because of their long half-lives, they remain for several years (Dewailly et al. 1999). However, because the general population is exposed to very low levels of these chemicals, their impact on spontaneous abortion is not clear.

3.1.4 Immunological Risk Factors

The immunological interaction between the mother and the fetus remains a scientific enigma. In normal pregnancies, the maternal immune system does not react to spermatozoa or the embryo, even though they express antigens that are exogenous to the maternal system. Maternal-fetal tolerance has been compared to that of a semi-allogenic fetal "graft", and may be the result of a complex array of mechanisms (including HLA-G expression of trophoblast; the leukemia inhibitory factor and its receptor, indoleamine 2,3-dioxygenase; the Th1/Th2 balance; suppressor macrophages; and hormones such as progesterone, or the placental growth hormone, CD95, and its ligand and annexin II) that may be pregnancy-specific and interconnected (Thellin and Heinen 2003;Thellin et al. 2000).

It is estimated that the fetus is immunologically rejected in approximately 40% of recurrent abortions (Giacomucci et al. 1994b). Immune responses can be triggered by a variety of endogenous and exogenous factors, including the production of anti-paternal antibodies,

autoimmune disorders leading to the production of autoimmune antibodies (antiphospholipid antibodies, antinuclear antibodies, polyclonal B cell activiation), infection, toxic agents, and stress (Thellin and Heinen 2003;Giacomucci et al. 1994b).

Immunotoxicty

Immunotoxicity may occur when the immune system acts as a passive target to chemicals, or when the immune system responds to the antigenic properties of a chemical as part of a specific immune response (WHO 2002). Toxic substances that alter metabolism or vascularization can disturb placental development and thus impeding or blocking mechanisms of tolerance, and increasing the chance of rejection (Thellin and Heinen 2003). Experimental and epidemiological studies have reported alterations in immune response after exposure to some PCBs (Chao et al. 1997;Tryphonas 1995), dioxins (Kerkvliet 1995) and pesticides (Vial et al. 1996). However, the effect on fetal loss, if any, remains unknown at this time.

Teratogens

A teratogen has been defined as "any substance that produces abnormalities in the embryo or fetus by disturbing maternal homeostasis or by acting directly on the fetus in utero" (Last 2001). Exposure to teratogenic agents may lead to minor or major birth defects. A teratogenic effect early on in pregnancy may lead to maternal rejection of the embryo.

Known teratogens include some pharmaceutical and recreational drugs, heavy metals, radiation, and infections (Gardella and Hill, III 2000). All prescription drugs have risk factors (A, B, C, D and X) assigned to them based on the level of risk the drug poses to the fetus. Class X drugs such as accutane and methotrexate have evidence suggesting that the teratogenic risk to the fetus outweighs the benefits of using the drug in pregnant women (Briggs et al. 2002). Teratogenic agents have been measured in umbilical cord blood (Rhainds et al. 1999), and seminal fluid (Stachel et al. 1989).

3.1.5 Thrombophilias

Thrombophilias are hyper-coaguable states associated with a predisposition to thrombolitic events. Pregnancy itself initiates a hyper-coagulable state and involves a balance between procoagulant and anticoagulant pathways (Kujovich 2004). Thrombophilias can be both inherited and acquired. There is a well established link between acquired antiphospholipid antibodies and recurrent pregnancy loss (Rand 1998;Branch 1998;Vinatier et al. 2001) and a variety of therapies and combination therapies that include heparin and aspirin have been recommended to support the maintenance of pregnancy until birth (Empson et al. 2002). In the antiphospholipid syndrome (APS), antiphospholipid antibodies occur in association with venous thrombosis, arterial thrombosis, pregnancy loss or thrombocytopenia. However, the exact mechanism by which antiphospholipid antibodies lead to thrombosis is unknown. More recently, several other inherited and acquired thrombophilic disorders have been linked with recurrent pregnancy loss including: Factor V Leiden, deficiencies of natural anticoagulant proteins C, S and antithrombin, hyperhomocystinemia, prothrombin gene mutation, and homozygous point mutation (C677T) in the methyleneterhydrofolate reductase (MTHFR) gene (Kujovich 2004).

3.2 Exogenous Risk Factors

3.2.1 Chemical Agents

Anesthetic Gas

Nitrous oxide and other anesthetic gases have been described as risk factors for spontaneous abortion (Aldridge and Tunstall 1986). In a review by Tannenbaum et al. (Tannenbaum and Goldberg 1985), women working in operating room theaters prior to and during pregnancy were 1.5 to 2.0 times more likely to have a spontaneous abortion in comparison with unexposed medical personnel. However, the authors described significant flaws in the design and conduct of many of these studies, including lack of exposure information or well-defined outcome criteria, poor response rates, selection and recall bias, and lack of control for potential confounding variables. In a more recent meta-analysis of the association between maternal occupational exposure to

anesthetic gases and the risk of spontaneous abortion (Boivin 1997), the overall relative risk was 1.48 (95% CI: 1.4 - 1.58). However, the authors suggested that the studies included in the meta-analysis suffered from several problems, including differences in comparability among the study groups, inadequate control for confounding, and potential biases arising from imperfect response rates. .

Drinking Water Contaminants

A number of studies have assessed spontaneous abortion rates in relation to drinking water source. In China, women using pond water as a source of drinking water exhibited an increased risk of spontaneous abortion (OR=1.63, 95% CI: 1.11-2.39) compared to women using well or river water (Cho et al. 1999). Studies conducted in California have found a higher prevalence of spontaneous abortion among women who drank tap water as compared to those who drank bottled water (Hertz-Picciotto et al. 1989;Wrensch et al. 1992;Deane et al. 1992); however, it is possible that these results may be attributed to recall bias (Petitti 1992).

When chlorine is added to drinking water it reacts with residual organic matter to form chlorination disinfection by-products , including trihalomethanes (THMs), haloacetic acids, and 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furoanone (also known as MX), of which all have been shown to be teratogenic or mutagenic in animal studies (Bove et al. 2002). Several epidemiologic investigations have utilized data from municipal water treatment facilities to characterize environmental exposures (Bove et al. 2002). A prospective study in California (Waller et al. 1998) found a significant association between spontaneous abortion risk in women who were exposed to high levels of total trihalomethanes TTHM (OR=1.8, 95% CI: 1.1-3.0), and to one of its constituents, bromodichloromethane (OR=3.0, 95% CI: 1.4-6.6). As well, women living in the Santa Clara county, the region with the highest bromine content in surface water, had over 4 times the odds of a spontaneous abortion (OR=4.3, 95% CI=1.8-10.6). In contrast, Savitz et al. (1995) only found an increased risk for the highest sextile of TTHM exposure (OR=2.8, 95% CI=1.1-2.7)

among mothers from parts of North Carolina, with no dose response gradient. In Boston, women who drank surface water had an elevated risk of spontaneous abortion as compared to women who drank ground water (OR=2.2, 95% CI: 1.3-3.6), although no excess risk was seen in relation to the type of treatment used (chlorination vs. chloroamination).

Dioxins

Dioxins have been shown to cause cancer in both humans and animals, and to cause reproductive anomalies in animals (IARC 1997;McNulty 1985). These chemicals are produced through the incomplete combustion of a variety of natural and industrial processes, and are ubiquitous in the environment. Once in the body, dioxins tend to accumulate in adipose tissue, where they remain for several years. Pirkle et al. (Pirkle et al. 1989) found the median half-life of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in Vietnam veterans involved in operation Ranch Hand was over 7 years.

Few human studies have shown associations between dioxins and spontaneous abortion. No significant increase in risk was found among the offspring of male workers exposed to dioxins in manufacturing plants in the United States (Schnorr et al. 2001), Vietnam veterans exposed to dioxins in Agent Orange (Wolfe et al. 1995), or residents near Seveso, Italy after the 1976 ICMESA chemical plant explosion (Fara and Del Corno 1985;Eskenazi et al. 2003). In the late 1990's, dioxins were found in air, soil, drinking water, as well as human milk and blood in the town of Chapaevsk, Russia. Drinking water levels of dioxins from the city center were the highest ever found in Russia, and the mean frequency of spontaneous abortions was found to be significantly higher in Chapaevsk relative to other towns (Revich et al. 2001).

Pesticides

Since 1970, it has been estimated that approximately 28 billion kilograms of pesticide active ingredients have been sold worldwide, representing 900 active ingredients and 50,000 commercial pesticide formulations (Pan American Health Organization 2002). Along with agricultural applications, pesticides have found use in public health, highway weed control, dry cleaning processes, shelf papers, paints, and chemical mixtures used to treat water in swimming pools (Al-Saleh 1994;Murphy 1986). Some pesticides have been shown to be estrogenic (Kojima et al. 2004), as well as genotoxic in exposed male workers (Zeljezic and Garaj-Vrhovac 2002;Garaj-Vrhovac and Zeljezic 2002).

The risk of spontaneous abortion has been examined in a number of occupational groups in which pesticides were used. An increased prevalence of spontaneous abortion has been seen in the wives of male pesticide applicators in Italy (Petrelli et al. 2000), India (Rupa et al. 1991) and the U.S. (Garry et al. 2002), greenhouse workers in Columbia (Restrepo et al. 1990) and Spain (Parron et al. 1996), ornamental plant growers in Argentina (Matos et al. 1987), sugar beet growers from the Ukraine (Kundiev 1994), and women involved in agriculture in the United States (Engel et al. 1995) and Finland (Hemminki et al. 1980). An increase in the prevalence of late fetal abortions has been observed among women living on grain farms in Norway (Kristensen et al. 1997), and Canadian women employed in agriculture or horticulture (McDonald et al. 1988). Other studies have demonstrated an increased risk in fetal death or spontaneous abortion when either parent worked with fur-bearing animals (Lindbohm et al. 1984), or when mothers worked in a pet store, or as a veterinarian (Vaughan et al. 1984).

Uncertainties in exposure characterization based on job title makes it difficult to elucidate these positive findings. Without specifying the pesticide class, family, or active ingredient, as well as the frequency, method or time window of application, few conclusions can be drawn. As well, agricultural workers are exposed to a variety of other exposures such as dust, molds, mycotoxins,

zoonoses which may have had an impact on the outcome. Other studies have shown no significant increase in the risk of spontaneous abortion in families where the fathers worked in occupations involving the use of pesticides (Smith et al. 1982;Roan et al. 1984;Steele and Wilkins, III 1996;Schenker et al. 1990;Heidam 1984).

Several studies have specifically defined exposure to the use of pesticides in the home or at work. One study in the Philippines compared households that use integrated pest management (IPM), spot spraying done only as a last resort, to households who used pesticides conventionally and applied pesticides beyond the spot spraying method in the period 3 months prior to conception and 3 months after conception (Crisostomo and Molina 2002). Approximately 1,400 different brands of pesticides were used in the 341 conventional use households, compared to only 399 brands amongst the 331 IPM households. The risk of spontaneous abortion was over 6 times greater in households that used pesticides conventionally (RR=6.17, 95% CI: 1.37-27.86), relative to the IPM households. Garry et al. (2002) found an increased risk of pregnancy loss among women who reported personal use of pesticides, including mixing, loading, and pesticide applications (OR=1.81, 95 %CI: 1.04-3.12). In this study, spouses of male pesticide applicators who applied a combination of herbicides, insecticides and fungicides (OR=1.64, 95% CI: 1.01-2.67), or specifically the fungicide organotin (OR=1.55, 95% CI: 1.01-2.37) or EBDC (ethylene bisdithiocarbamate) (OR=1.77, 95% CI: 1.11-2.83) had the afformention odds of spontaneous abortion. Among 5,674 women from a rural area of China, a significant increasing risk of spontaneous abortion was found in relation to the number of pesticides used by the family during pregnancy (Pan 1994). In this investigation, the relative risk ranged from 0.2 for the use of one pesticide product to 3.28 when families used five pesticide products.

Herbicides

A number of studies have explored the effects of herbicides on spontaneous abortions. The Ontario Farm Family Health Study examined the risk of spontaneous abortion from direct and

indirect chemical exposures in the pre-conception and post-conception periods of nearly 4,000 pregnancies (Arbuckle et al. 1999;Arbuckle et al. 2001;Savitz et al. 1997). Moderate increases in risk of early abortions were seen for preconception exposures to phenoxy acetic acid herbicides (OR = 1.5; 95% CI: 1.1-2.1), triazines (OR = 1.4; 95% CI: 1.0-2.0), and any herbicide (OR = 1.4; 95% CI: 1.1-1.9) (Arbuckle et al. 2001). Families in which fathers were involved in chemical activities in the preconception period and living on farms that had reported use of herbicides and thiocarbamates (OR=1.9, 95 % CI: 1.1-3.3), herbicides and carbaryl (OR=1.9, 95% CI: 1.1-3.1) or insecticide and carbaryl (OR=2.1, 95% CI: 1.1-4.1) were associated with a significant increase in spontaneous abortions (Savitz et al. 1997). In Minnesota spring miscarriages were elevated among the spouses of pesticide applicators that had applied one or more of the following classes of herbicides: sulfonylurea (OR=2.11, 95% CI: 1.09-4.09), imidizolinone (OR=2.56, 95% CI: 1.11-5.87), or a mixture consisting of chlorophenoxy pesticides, sulfonylurea, and benzothiodiazole (OR=2.94, 95% CI: 1.4-6.16) (Garry et al. 2002). Studies published on residents and veterans from Vietnam have shown relative risks ranging from 0.87 to 1.61 for spontaneous abortion or fetal loss in relation to Agent Orange exposure. However, the use of an ecological design, possible recall bias, small sample size, and weak exposure assessments limit the findings of most of these studies (Arbuckle and Sever 1998). Other studies of chemical factory workers exposed to 2,4,5-T and dioxin have found no increase in the risk of spontaneous abortion (Suskind and Hertzberg 1984).

Organochlorine Pesticides

In India, a small case-control study found that families in which the mothers or fathers worked in grape gardens where organochlorine pesticides were used experienced a nearly 6-fold increase in the risk of spontaneous abortion (RR=5.83, $p<0.05$) (Rita et al. 1987). Other studies in India (Saxena et al. 1981;Saxena et al. 1980), the Ukraine (Mazorchuk et al. 1974), Israel (Bercovici et al. 1983), and China (Korrick et al. 2001) have found elevated serum levels of DDT, or its metabolite DDE, in women who have had a spontaneous or missed abortion. Some studies

have also shown significant associations between serum lindane (Saxena et al. 1981), aldrin (Saxena et al. 1981), and HCB (Jarrell et al. 1998) levels and spontaneous abortion. However, other studies have shown no increase in serum HCB, DDT, DDE, DDD, or HCH levels in women following spontaneous abortions (Leoni et al. 1986;Lembrych et al. 1986;O'Leary et al. 1970).

Miscellaneous Pesticides

In California, Thomas et al. (Thomas et al. 1992) found a non-significant increase in the prevalence of spontaneous abortion among residents of areas subject to aerial spraying with malathion (RR=1.20, 95% CI: 0.94-1.52). However, there was no information on the amount of time that the mothers spent at home during the spraying period or on other possible sources of pesticide exposure. In China, Li et al. (Li et al. 1986) found no significant increase in spontaneous abortion among 1,600 women who ingested N, N'-Methylene-bis-(2-Amino-1,3,4-Thiadiazole) (MATDA) in contaminated rice between 1977 and 1983 in comparison with unexposed pregnancies. Two studies of fathers exposed to dibromochlorpropane in Israeli chemical plants or banana fields have shown some evidence of an elevation in risk of spontaneous abortion (Potashnik and Yanai-Inbar 1987;Kharrazi et al. 1980), but both studies were limited by their design, having small sample sizes or paternal rather than maternal reporting of reproductive histories.

PCBs

Polychlorinated Biphenyls (PCBs) are a group of synthetic compounds that are a complex mixture of up to 209 different individual chlorinated congeners. Because of their inflammability and insulating properties, they were used in electrical, heat transfer and hydraulic equipment from the 1930s through to the mid-1970's. Non-human primates exposed to PCBs via concrete sealant in their cages or ingestion of 2.5 to 5ppm of PCBs in their diet have shown an increased incidence of spontaneous abortions and stillbirths (Barsotti et al. 1976;Altman et al. 1979).

No convincing evidence has been seen for an association between spontaneous abortion and relatively high exposures to PCBs among the following human populations: capacitor factory workers in New York, insulation workers in Japan, and Japanese and Taiwanese families exposed to PCB contaminated heat exchange fluid in their cooking oil (Rogan et al. 1985). The consumption of contaminated fish has been shown to be an important source of human exposure to PCBs and other organochlorine compounds (Fiore et al. 1989;Muckle et al. 2001). However, no increase in risk was found among high consumers of fatty fish in Sweden (Axmon et al. 2000;Axmon et al. 2002), New York anglers (Mendola et al. 1995) or women with high fish consumption from Wisconsin (Dar et al. 1992). In contrast, Bercovici et al. (Bercovici et al. 1983) found significantly higher serum PCB levels in women with former missed abortions (n=7) than in women with normal 2nd trimester pregnancies (n=7). Another study found that women with a history of at least 4 miscarriages had significantly greater concentrations of total PCBs than women with less than 4 miscarriages (p=0.0386) (Gerhard et al. 1998).

Lifestyle Factors

Smoking

Cigarette smoke contains hundreds of toxic components that may have an adverse effect on reproductive outcomes, including nicotine, cotinine (major metabolite of nicotine), cyanide, carbon monoxide, cadmium, lead, and polycyclic aromatic hydrocarbons (Werler 1997). Epidemiologic studies of cigarette smoking and spontaneous abortion suggest that cigarette smoke may only

slightly, if at all, increase the risk of spontaneous abortion. However, the association between smoking and spontaneous abortion depends on other factors, including alcohol consumption, reproductive history, gestational timing of spontaneous abortion, fetal karyotype, and indicators of socioeconomic status (Werler 1997).

Caffeine

Caffeine is known to cross the placenta and has been found in amniotic fluid and umbilical cord blood, as well as the urine and plasma of neonates (Soyka et al. 1981;Sommer et al. 1975). During pregnancy, caffeine metabolism remains largely unchanged in 1st trimester. In the 3rd trimester, the average half-life of caffeine in the body increases to about 10 hours as compared to 3 hours in non-pregnant women (Knutti et al. 1982). A meta-analysis conducted by Fernandes et al. (1998) found evidence of an increased risk of spontaneous abortion in relation to moderate to heavy caffeine consumption (OR=1.36, 95% CI: 1.29-1.45). Sensitivity analyses indicated that no individual study or group of studies unduly influenced the overall summary odds ratio. However, in a more recent review, Leviton & Cowan (2002) suggested that studies of the association between spontaneous abortion and caffeine consumption may simply reflect the Stein & Susser (1991) postulate that a healthy placenta produces a surge of one or more hormones that, in some women, produces a reduced desire for aromatic and strongly flavored beverages. Under this hypothesis, pregnant women consuming caffeine during their first trimester may demonstrate diminished placental hormone synthesis, and thus constitute a vulnerable implantation.

Alcohol and Illicit Drugs

Pregnant women with substance abuse problems often abuse multiple substances, making it difficult to attribute a specific effect to a particular substance (Fischer et al. 1999). Animal studies suggest that blood alcohol levels exceeding 200 mg/dL can induce spontaneous abortions, although the elevated rates of spontaneous abortion seen in alcoholic women may be due to indirect effects of

alcoholism-related disorders, or higher rates of pregnancy (Abel 1997). Studies of moderate alcohol consumption are somewhat inconsistent, with investigations in North America tending to show positive associations, and those conducted in Europe or Australia often showing no significant associations. Abel (1997) suggests that these differences may not be related to alcohol consumption, but rather due to socioeconomic status or study design.

Cocaine use has been associated with several adverse pregnancy outcomes, including placental abruption, pre-term labor and delivery, intrauterine growth retardation, and meconium stained aminiotic fluid (Fischer et al. 1999). Although suggestive, less evidence exists for an association between spontaneous abortion and cocaine use (Slutsker 1992). The evidence for effects of other drugs such as heroin, and marijuana on spontaneous abortion is even more limited (Garcia-Enguidanos et al. 2002).

Antineoplastic Drugs

Antineoplastic agents used to treat cancers are both teratogenic and mutagenic (Arnon et al. 2001), and represent a potential threat to health professionals such as nurses and pharmacists who handle these substances. Some studies have indicated an increase in spontaneous abortion among women who handle antineoplastic drugs (Valanis et al. 1999;Stucker et al. 1990;Selevan et al. 1985). However, other investigators have failed to find such associations (Hemminki et al. 1985;Skov et al. 1992).

Other Chemicals

Paternal employment in industries using vinyl chloride, organic solvents, aromatic hydrocarbons, xylene, petroleum refinery solvents (gasoline, benzene), and rubber chemicals has been associated with an increased risk of spontaneous abortion (Savitz et al. 1994). Xu et al. (1998) observed an association among mothers exposed to petrochemicals including benzene (OR=1.8, 95% CI: 1.1-2.9), gasoline (OR=1.8, 95% CI: 1.1-2.9), and hydrogen sulphide (OR=2.3, 95% CI: 1.2-4.4). Other studies have found increases in the risk of spontaneous abortion among

female dental assistants exposed to ethylene oxide during pregnancy (OR=2.5, 95% CI: 1.0-6.3) (Rowland et al. 1996), and female cosmetologists who applied 13 or more chemical services per week (OR=1.9, 95% CI: 1.0-3.5), 2 or more bleaches per week (OR=1.9, 95% CI: 1.0-3.6), or used formaldehyde-based disinfectants (OR=1.7, 95% CI: 1.0-3.0) during the first trimester of pregnancy, as compared to women who worked full-time in other jobs during this same time period (John et al. 1994).

3.2.2 Heavy Metals

Arsenic

Arsenic has frequently been reported as a carcinogen, mutagen and teratogen (IARC 2002;IPCS 1981) in animal studies. It has also been shown to readily cross the placenta (Golub et al. 1998). Studies in India, Bangladesh and Hungary have shown excess risks for spontaneous abortion among women exposed to high levels of arsenic in drinking water (Borzsonyi et al. 1992;Milton et al. 2005;Chakraborti et al. 2003;Ahmad et al. 2001). Arsenic levels in well water were often = 50 ug/L (Chakraborti et al. 2003;Milton et al. 2005) and women had often been drinking the contaminated water for several years (Ahmad et al. 2001). In Texas, higher spontaneous abortion rates have been associated with higher residential arsenic levels at the time of delivery. Exposures were estimated by linking airborne emission estimates and an atmospheric dispersion model to a geographical information system database (Ihrig et al. 1998). However, weak or non-significant associations were seen among women exposed to arsenic through drinking water (Aschengrau et al. 1989) or while working in a smelter (Wulff et al. 2002). As well, in a review article Golub et al. (1998) propose that human data on arsenic exposure and pregnancy outcomes is limited given that many of the studies have been complicated by multiple exposures to the study populations.

Lead

There is consistent evidence to suggest that high levels of lead exposure (>30 µg /dL) increases the risk of spontaneous abortion (Hertz-Picciotto 2000). However, results for low to moderate lead levels (0-30 µg /dL) are less consistent, and often limited by uncertainties in exposure assessment or ascertainment of outcomes, as well as low response rates or statistical power (Hertz-Picciotto 2000). One study in Mexico City (Borja-Aburto et al. 1999) which examined 668 women with medically confirmed pregnancies found an association between spontaneous abortion and blood lead levels collected during the first trimester of pregnancy. The odds ratios for spontaneous abortion among women with blood lead levels of 5-9, 10-14, and =15 µg /dL were 2.3, 5.4, and 12.2 respectively, compared to the referent category of <5 µg/dL, demonstrating a significant trend (p = 0.03). Wives of men with blood lead levels exceeding 1.4 µmol/L during spermatogenesis were found to have an elevated but imprecise risk of spontaneous abortion (RR=3.8, 95% CI: 1.2-12.0) (Lindbohm et al. 1991).

Other Heavy Metals

A number of studies have shown increases in spontaneous abortion rates amongst the wives of smelter, metal-plate, and steel industry workers (Lindbohm et al. 1984), and men with elevated levels of zinc, copper (Lindbohm et al. 1991), and mercury (Alcser et al. 1989;Cordier et al. 1991) . A detailed review by Savitz et al. (1994) concluded that there was strong evidence for a link between paternal exposure to heavy metals, especially mercury, and spontaneous abortion.

Other studies examining workers exposed to lower doses of mercury have shown largely negative results. Schuurs (1999) examined the potential reproductive effects of low level mercury exposure among dentists and dental assistants, and concluded that the handling of amalgam does not increase the risk of adverse reproductive outcomes, provided appropriate hygienic measures are taken. Wulff et al. (2002) found no association between spontaneous abortion and working in or living near a smelter in Sweden. However, the authors suggest these negative results may be attributable to greatly reduced smelter emissions.

3.2.3 Physical Agents

Radiation

Ionizing radiation is known to cause an array of adverse reproductive outcomes, including congenital malformations, intrauterine growth restriction, and embryonic death (UNSCEAR 1993). In 1990, the International Commission on Radiological Protection recommended that the conceptus should not be exposed to more than 5 mSv during pregnancy (Clarke 1990). Studies of radioactive contamination due to fallout from Chernobyl have shown increased spontaneous abortion rates in Finland and Norway (Auvinen et al. 2001;Ulstein et al. 1990). However, no increase was seen among populations in the Ukraine (Buzhievskaya et al. 1995), Sweden (Ericson and Kallen 1994), and China (High Background Radiation Research Group 1980) after the Chernobyl fallout. Studies of women who received abdominal irradiation treatment for cancer prior to pregnancy have rarely shown increases in the risk of spontaneous abortion (Hawkins and Smith 1989), but have revealed significantly increased risks of other adverse pregnancy outcomes, including perinatal death (Li et al. 1987), low birth weight (Green et al. 1982;Green et al. 2002), and congenital malformations (Byrne et al. 1988).

Electromagnetic Fields (EMFs)

Although research on EMFs has focused on their potential carcinogenic effects (Ahlbom 1988;Habash et al. 2003), increasing attention has focused on their possible reproductive effects (Shaw 2001). EMF exposure can occur through a variety of electrical sources including home appliances, electric blankets, and video display terminals (VDTs). Electric fields are present whenever electrical lines are energized, but magnetic fields are present only when power is being used and there is a flow of current (Aldrich and Easterly 1987).

The epidemiologic evidence on the association between residential exposure to EMFs and spontaneous abortion has been inconsistent (Meyer et al. 1989;Shaw 2001;Coleman and Beral 1988). In a detailed review, Shaw (2001) suggested that the evidence for a strong association

between VDTs and spontaneous abortion is deficient, with most increases in risk being around 1.1 to 1.2 fold. A notable exception is the study by Goldhaber et al. (1990), in which a 1.8 fold increase in risk was seen for women who had greater than 20 hours of reported VDT use. When measured field strength was considered, pregnant female workers who used VDTs with high levels of extremely low frequency magnetic fields (>0.9 μT) demonstrated a more than a 3-fold increase in the risk of spontaneous abortion (OR=3.4, 95% CI=1.4-8.6), as compared to women using terminals with lower field strengths (<0.4 μT).

Other studies have shown no significant increase in the risk of spontaneous abortion in relation to heated water bed use (Belanger et al. 1998), cable heat in homes (Wertheimer and Leeper 1989), homes with measured fields above 0.2 μT (Savitz and Ananth 1994), homes with wire codes with the potential for elevated EMF exposure (Savitz and Ananth 1994;Lee et al. 2002;Belanger et al. 1998), or occupational paternal exposure to EMF in switchyards with 400KV substations (Nordstrom et al. 1983).

Two recent studies using personal monitoring devices to measure EMF exposures have found positive associations with spontaneous abortion (Lee et al. 2002;Li et al. 2002). Furthermore, Li et al. (2002) found a greater effect in women with a history of fetal loss or subfertililty (RR=3.1, 95% CI: 1.3-7.7), especially for exposures occurring before 10 weeks of pregnancy (RR=4.7, 95% CI: 1.4-16.0).

Noise

Noise has been suspected of altering normal fetal development either by acting directly as a teratogen, or by eliciting a neural response, causing decreased uteroplacental blood flow, leading to fetal hypoxia and increased secretion of maternal catecholamines (Meyer et al. 1989). Most epidemiologic studies have examined the effect of noise on birth defects and low birth weight, with only a few considering spontaneous abortion. McDonald et al. (1986) reported an association between spontaneous abortion among mothers exposed to noise at work however; this association

disappeared when the potential bias from prior knowledge of the outcome was taken into account. Nurminen et al. (1989) found a more than two-fold increase in threatened abortion when noise exposure was combined with shift work, while Rachootin et al. (1983) found a 2 fold increase hormonal disturbances and idiopathic infertility in relation to self-reported occupational noise exposure.

Physical Exertion and Shift Work

The effect of physical effort on pregnancy remains unclear, although it is suspected that physical exertion during pregnancy can affect intra-abdominal pressure and uterine blood flow, hormonal balance, and nutritional status, of which all are important for embryonic and fetal development (Ahlborg, Jr. 1995). Fenster et al. (1997) failed to show an association between physical exertion and spontaneous abortion, although standing at work for more than 7 hours per day increased the risk among women with a previous history of two or more spontaneous abortions (OR=4.3, 95% CI: 1.6-11.7).

There is some evidence that shift work may increase the likelihood of spontaneous abortions. In a review article on shift work and spontaneous abortion, Nurminen (1998) reported that 7 of the 9 studies suggested that some forms of shift work may lead to an increased risk of spontaneous abortion, with risk estimates ranging from 1.3 to 4.2.

Hyperthermia

Animal studies suggest that hyperthermia in pregnancy is potentially associated with resorption of the embryo, fetal death and lethal malformations (Peterka et al. 1996;Edwards 1969). In humans maternal hyperthermia has been found to be associated with neural tube defects (Shaw et al. 1998;Shiota 1982;Lynberg et al. 1994;Miller et al. 1978;Milunsky et al. 1992), and cardiovascular malformations (Tikkanen and Heinonen 1991). For fetal death, Kline et al. (Kline et al. 1985) found that fever was associated with an increase in miscarriage of normal-karyotype

fetuses (OR=2.96, 95% CI=1.99-4.41). However, Andersen et al. (Andersen et al. 2002) failed to find an association between fever in pregnancy and fetal death. In addition, when examining the effect of hyperthermia due to a febrile event, it is difficult to differentiate the effect due to the febrile infection from the effect of the hyperthermia itself (Li et al. 2003). Li et al. (Li et al. 2003) examined the effect of exposure to external heat sources (hot tubs) on the risk of miscarriage. The authors found an increased risk of miscarriage after hot tub use (Hazard Ratio: 2.0, 95 % CI=1.3-3.1); however the study was criticized for it low response rate, recall bias and participation bias (Hertz-Picciotto and Howards 2003).

3.2.4 Biological Agents

Maternal infections demonstrating clear associations with spontaneous abortion include syphilis, parvovirus B19, HIV, and malaria (Garcia-Enguidanos et al. 2002). Brucellosis, a zoonotic disease that is most commonly passed to humans through unpasturized dairy products, may also induce spontaneous abortion. Although brucellosis is known to cause contagious abortion in cattle, sheep, goats, swine and dogs, there is less evidence for such effects in humans (Mandell et al. 2000). A recent retrospective study in Saudi Arabia revealed that nearly half (43%) of pregnant women diagnosed with acute brucellosis early on in their pregnancy had a spontaneous abortion in their first or second trimester (Khan et al. 2001).

Aflatoxins occur in nuts, cereals, and rice under conditions of high humidity, and are known to be acutely toxic, immunosuppressive, mutagenic, teratogenic, and carcinogenic (Peraica et al. 1999). Although they have been detected in maternal and umbilical cord blood (Abdulrazzaq et al. 2002;De Vries et al. 1989), their effect on pregnancy outcomes is unclear at this time. Kristensen et al. (1997) found an increased risk of late-term abortions among Norwegian grain farmers (OR=1.58, 95% CI: 1.19-2.09) as compared to non-grain farmers. This risk was higher after harvest (OR=1.80, 95% CI: 1.14-2.84) and during seasons with poor quality harvest (OR=2.42, 95% CI: 1.54-3.79), suggesting that mycotoxins in grain may be disruptive to the early stage of pregnancy.

4. Limitations of Spontaneous Abortion Studies

A number of methodological problems arise when studying spontaneous abortions. It is difficult to obtain population based data on spontaneous abortion rates because there are no administrative databases for this adverse health outcome, and hospital records are based on admissions, which capture only a subset of spontaneous abortions. An appreciable number of pregnancies end in undetected spontaneous abortions, unless the pregnancy is diagnosed using close hormonal surveillance (Olsen and Torsten 1993). The accuracy of self-reports by women depend on their self-awareness of menstrual cycle, how regular their cycle is, their use of home fertility and pregnancy kits, and their desirability of a pregnancy. Also, spontaneous abortions are a very heterogeneous group as a whole and there is some evidence that risk factors may differ for early versus late spontaneous abortions (Arbuckle et al. 1999;Axelsson et al. 1996;Windham et al. 1997;Windham et al. 1992)

5. Conclusions

Pregnancy involves a delicate balance of hormonal and immunological functions, which can be affected by environmental agents. There is convincing evidence to suggest an association between spontaneous abortion and antineoplastic drugs, ionizing radiation, and high occupation exposure to heavy metals, especially mercury. However, there remain large knowledge gaps concerning many environmental exposures, including substances that may interfere with progesterone and estrogen, hormones essential for the initiation and maintenance of pregnancy. Many of the studies investigating the effects of environmental factors on spontaneous abortion are limited by inadequate exposure assessments, relying on ecological or crude surrogate measures of exposure, and self-reports that are often subject to recall bias. Additional research is needed to elucidate the risk factors for spontaneous abortion, particularly environmental agents. Integration of information from epidemiological, clinical, and toxicological studies may provide useful new information on the etiology of spontaneous abortion (Lasley and Overstreet 1998).

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