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Effects of parental occupational exposures on spontaneous abortion and congenital malformation

by Helena K Taskinen, MD¹

TASKINEN HK. Effects of parental occupational exposures on spontaneous abortion and congenital malformation. *Scand J Work Environ Health* 1990;16:297-314. Human reproduction is a complex process and can be disturbed in many phases by both host and environmental factors. Therefore, it has been difficult to distinguish the occupational causes of spontaneous abortion and congenital malformations from other factors related to the parents' characteristics and their living environment. The extrapolation of results of animal studies to humans is often complicated because there are structural and functional differences between the species and the mechanisms of harmful effects are seldom known. There is also a lack of conclusive epidemiologic studies on the topic. At present knowledge on the potential reproductive toxicity of even rather common occupational exposures is limited and in many cases only suggestive. Paternal exposure to organic solvents before conception and maternal exposure during pregnancy may have adverse effects on the pregnancy and offspring. Heavy physical work during pregnancy may increase the risk of spontaneous abortion.

Key terms: ionizing radiation, lead, metals, mercury, organic solvents, physical strain, review, shortwaves, ultrasound.

Various reproductive problems, for example, infertility, spontaneous abortion, stillbirth, neonatal death, macrocephaly, and neurological symptoms in the offspring, were reported in excess in the families of lead workers already in the 19th century (1). Ionizing radiation was shown to be teratogenic in the 1920s, and rubella virus infection in the 1940s. The first experimental findings of teratogenesis in animals were reported in the late 1940s. The thalidomide catastrophe in the 1960s increased interest in the investigation of the role of prenatal exposures in human teratology. In the 1970s it was found that methyl mercury (2) and polychlorinated biphenyls (3) from contaminated food had harmful effects on the fetus, although the pregnant woman did not necessarily have symptoms of poisoning. These findings warranted further studies on the effects of industrial chemicals on pregnancy.

Spontaneous abortions were reported in excess among anesthetists first in the Soviet Union (Vaisman 1967, cited in reference 4), and thereafter many studies corroborated the findings. In most of the early studies the information on abortion was collected with postal questionnaires. Later studies in which the pregnancy outcome was confirmed from hospital records or medical registers did not, however, reveal any increased risk for spontaneous abortion (5-8). Thereafter, the

potential effects of other occupational exposures on spontaneous abortion have been sought in many investigations. (For a review see references 9 and 10.)

Interest focused on potential male reproductive toxicants once nematocide dibromochloropropane was found to cause sterility in male production workers (11). Male exposure to dibromochloropropane, anesthetic gases, vinyl chloride, and work in metallurgical factories has also been reported to be associated with adverse pregnancy outcome of the wife (For a review see reference 12.)

Recently, comprehensive reviews of the external causes of spontaneous abortion and congenital malformations have been published (9, 10, 13-15). In the present review studies on the potential effects of maternal or paternal occupational exposure to organic solvents and maternal exposure to pharmaceutical chemicals, lead, and some physical agents on pregnancy outcome are discussed. In addition a variety of nonoccupational effects are included. As examples of sources of pregnancy outcome data, the relevant Finnish medical registers are described.

Frequency of spontaneous abortion

In Finland the rate of spontaneous abortion calculated from the data base of hospitalized or polyclinically treated spontaneous abortions was 8.9 % in 1973-1983 (16). The rate was defined as the proportion of spontaneous abortions among all recognized pregnancies (spontaneous abortions plus induced abortions plus births). The rate of spontaneous abortion in-

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creased from 7.8 % in 1973 to 10.2 % in 1983. The increase was seen in all age groups, but it was the most pronounced among women over 30 years of age. The mean age of women giving birth to their first child increased from 23 to 25 years in 1961–1981 (M Makkonen, personal communication). The mean age of all women having given birth to a child was 26.4 years in 1970–1979 (17). According to the Medical Birth Registry (started in 1987 and maintained by the Finnish National Board of Health) the mean age of women giving birth to their first child in 1987 was 26.5 years, and the mean age of all women giving birth to a child in the same year was 28.9 years. The increase in the age of women having children may also have contributed to the increase in the occurrence of spontaneous abortion.

Induced abortions may affect the miscarriage rates since some of the interrupted pregnancies would nevertheless end in a spontaneous abortion. When abortions are induced early, the spontaneous abortion rate should decrease, as pregnancies which would otherwise have aborted spontaneously are interrupted before the abortion occurs. (For a review see reference 18.) In Finland the proportion of induced abortions in 1973–1983 decreased from 26.6 to 14.5 %, and the decrease was the most prominent in the older age groups. In the same age groups also the increase in the rate of spontaneous abortion was the clearest (16). If abortions are induced rather late, they do not greatly affect the spontaneous abortion rate since most of the potential abortions would have occurred before the interruption of the pregnancy.

The frequency of clinically unrecognizable early abortions has been estimated in a few prospective studies, in which chorionic gonadotropin has been measured in the urine or blood of women trying to become pregnant. The proportion of early pregnancies not becoming clinically apparent varied from 8 % (19) to 57 % (20). In a later study, in which a very sensitive assay was used, the rate of early pregnancy loss was 22 % when the total pregnancy loss, including clinically recognized spontaneous abortions, was 31 % (21). According to the preliminary results of a Finnish study in which 332 women were followed monthly with urinary analyses of chorionic gonadotropin for six months, 48 % of the women experienced at least one early abortion. The rate of early abortions among all pregnancies was 58 %, and the total pregnancy loss, including clinical abortions, was 62 % (22).

Some of the variation in the rate of very early abortion may be due to the different sensitivity and specificity of the used laboratory assays (19, 21). For example, cross-reactivity with urinary human luteinizing hormone or its degraded fragments may have caused false positive results in earlier studies (21). In the latest work (22) a fluoroimmunoassay was used for the detection of urinary chorionic gonadotropin in humans, and the possibility of cross-reactions was excluded.

Prevalence of congenital malformations

According to the Finnish Register of Congenital Malformations the prevalence of congenital malformations among newborns varied from 1.3 to 2.0 % in 1963–1980, and the mean for the period 1963–1981 was 1.4 %. According to several hospital studies, the true frequency of structural malformations in the Finnish population is on the order of 3 %, of which two-thirds are detected at birth. (For a review see reference 23.)

Worldwide surveys show that the frequency of congenital malformations varies greatly from country to country. The figures range from 2 to 6 % of all living children (24). The frequency depends on the time of observation after birth, the types of malformations included, and the differences in reporting and statistical procedures. There is also marked geographic variation in the frequencies of some malformations, for example, anencephaly and spina bifida were more common (3- to 10-fold) in the United Kingdom than in most of Europe in the 1970s and at the beginning of the 1980s (25). In the past few years the frequencies in European countries have evened out, but differences still exist.

Fetuses with neural tube defects are estimated to abort at a rate of 60 to 90 % (24). Chromosome anomalies are also more frequent in spontaneous abortions than in live births (26). Thus some of the figures on spontaneous abortions and malformations may overlap so that malformations leading to death of the fetus in early pregnancy are included in the statistics on spontaneous abortion.

Data sources for pregnancy outcome

Personal interviews and postal questionnaires have been used to obtain information on pregnancy outcome. The reliability of questionnaire data may be weakened by a low response rate and uncertainty in the recognition and recalling of an abortion or malformation. Socioeconomic status and educational level may influence a person's ability and willingness to participate in interview and questionnaire studies. Furthermore, selection by exposure or pregnancy outcome between the respondents and nonrespondents may cause bias. For example, exposed women who have experienced a spontaneous abortion are usually more eager to participate in postal questionnaire studies than unexposed women (7, 27).

Medical records or nationwide registers are more reliable than questionnaire data, since the information is based on medical diagnoses and is recorded at the time of the event. The recorded data are not very sensitive, however, as far as early abortions and occasional exposures are concerned. In addition different types of care-seeking behavior may weaken the validity of the data. Educational level, economic factors, and the

availability of medical services may influence the use of medical services (28). These background factors must be taken into account when comparison groups are selected in occupational reproductive studies.

National data base on pregnancy outcome

In Finland the Hospital Discharge Register, maintained by the Finnish National Board of Health, contains information on spontaneous abortions, induced abortions, and deliveries recorded by hospitals. The structure, data content, reliability, and coverage of the Register has been described recently (16). The register covers 94 % of all births and 85 % of all induced abortions recorded officially by the Statistical Office of Finland. The diagnoses of spontaneous abortions in the Register were in agreement with the hospital records in 91 % (N = 245) of the cases treated in a large Helsinki hospital (29).

In 1973–1983, 10–17 % of the spontaneous abortions occurring in Finland were treated in polyclinics (16). Information on the spontaneous abortion patients treated in this manner has been collected in questionnaires from the hospitals and linked with the Register data. Information on a few spontaneous abortions treated polyclinically in a few municipal health care centers are not included in this data base. The diagnosis of spontaneous abortion seems to be rather reliable since, in the polyclinic of a large Helsinki hospital, the diagnosis was confirmed in 86 % of the cases in the pathological-anatomic examination alone or supported by a positive pregnancy test (30).

A comparison of registered and self-reported pregnancies showed that 17–20 % of the reported abortions were not found in the national data base (16). About half of the deficit can be explained by erroneous personal identification codes in the Register. It is estimated that about 10 % of the recognized spontaneous abortions are not treated in hospitals or polyclinics in Finland. They are presumably earlier abortions than those found in the data base (16).

Finnish Register of Congenital Malformations

The Finnish Register of Congenital Malformations was established in 1963. It is based on compulsory notification of all malformations detected during the first year of life. The malformations of stillborn infants weighing over 600 g during 1963–1985 (over 500 g after the year 1985) are registered from compulsory death certificates and completed from the pathologist's autopsy records (23). The notification lists the names and dates of birth of the mother and child and the type of malformation of the child. From the year 1986 on, information has been registered on the type of work of the parents at the beginning of the pregnancy.

The structure of the Register and surveillance studies based on it have been reviewed earlier (23). When registered data have been compared with hospital infor-

mation, a reporting failure of about 15–30 % has been found. The failure rate in detection should be added to this value; according to the hospital comparisons it is on the order of 30 %. Hence the underreporting to the Register has been estimated to be 45–60 % (23). The deficiency is thought to be mainly due to minor malformations and those not detectable during early childhood. However, although gastrointestinal atresias are rather severe and are noticed early, 55 % of them were not found in the Register (17).

Selective reporting may cause bias in the questionnaire studies and selection due to different care-seeking behavior in the register studies. Therefore, in occupational reproductive studies it would be preferable to use both questionnaire information and registers as sources of pregnancy outcome data.

Analyses and control of confounding

Many of the studies conducted in reproductive epidemiology recently have been so-called nested case-referent studies. They have been preferred over retrospective cohort studies because they seem to be economical and effective (30). Prospective studies (22, 31) have also been introduced.

Logistic regression models (32) used in the analyses of case-referent studies assume that the risk factors affect the occurrence of the disease multiplicatively (ie, the occurrence of the disease among the exposed persons equals the rate of the unexposed ones, multiplied by the relative risk). The relative risk, expressed as an odds ratio in case-referent studies, is an indirect estimation of the risk of adverse pregnancy outcome among the exposed persons in relation to the unexposed ones.

A confounder is a factor which is causally associated with the disease of interest, and it is associated with the exposure of interest in a given study. The woman's age at pregnancy, previous adverse pregnancy outcome, life-style factors like smoking, alcohol consumption, and use of drugs may be considered potential confounders.

Matching can be used to control for confounding. Matching the cases and referents for multiple factors diminishes the availability of suitable referents and thus decreases the number of case-referent combinations in the study. Matching by many factors may also lead to overmatching (ie, if the matching has been carried too far, the cases and referents are similar even with respect to the exposure studied) (32). Matching has also been criticized because it may cause some inefficiency in case-referent studies (33). The inefficiency is due to the diminishing of the study population; for example, if the case of the fixed case-referent triplet, quadruplet, and so forth does not respond, the data of the referents cannot be used either. Stratification is also recommended for use instead of matching in case-referent studies.

Etiology of spontaneous abortion

Chromosomal abnormality is a common cause of spontaneous abortion. In various studies chromosomal anomalies have been reported in 31–54 % of abortions with a gestation time of ≤ 28 weeks. Anomalies are the most common, 39–56 %, in abortuses at the 8th–15th weeks of gestation, and the number decreases with increasing gestation time (26).

Some aborted fetuses lack chromosome anomalies but may have morphological abnormalities. In some abortuses only little or no embryonic development has occurred; in such cases the damage can be presumed to have happened either prior to conception or very early during pregnancy (4). In animals such phenomena may be caused by lethal genes, either dominant mutants or homozygotes of recessive genes (18).

The embryo may be damaged so badly by a teratogenic effect that it dies and is aborted. In cases in which the fetus is present (ie, the developmental age of the conceptus is at least nine weeks) the causes of abortion may have operated later during the pregnancy (4).

Embryotoxicity and fetotoxicity refer to any toxic effect on the conceptus during pregnancy. A toxic agent may affect the conceptus transplacentally (chemicals, drugs) or directly (ionizing radiation). If the toxic effect is strong enough to cause in-utero death, an abortion will follow.

The human embryo is the most sensitive to ionizing radiation during the first 5 d after conception. The dose of 10 rad (100 mSv) has been estimated to be lethal during that period and would consequently lead to an abortion (34). During the 18–28 embryonic days the lethal dose is estimated to be 25–50 rad, the corresponding figure for later during pregnancy being 50–100 rad. According to animal and human data no increase in the incidence of spontaneous abortion should occur with exposures of < 5 rad (34).

Maternal causes of spontaneous abortion may be physiological-anatomic (eg, anomalous or small uterus, uterine tumors, cervical insufficiency, premature contractions), hormonal (imbalance in the excretion of sex hormones), immunologic (eg, Rh incompatibility), infection (general or genital infections), or some general diseases (eg, diabetes mellitus, disturbed function of thyroid gland). Conditions related to pregnancy (eg, toxemia) also increase the risk of an adverse outcome of pregnancy. (For a review see reference 18.) Mechanical (blunt) trauma in the abdominal region during pregnancy rarely increases the risk of abortion before the second trimester since the embryo/fetus is well protected within the bony pelvis during the first trimester (35).

The rates of spontaneous abortion have been found to be associated with maternal age. Both in pregnancies in which the embryo or fetus is euploid (ie, has a normal number of chromosomes) or aneuploid (ie, has an abnormal number of chromosomes) the risk of spontaneous abortion has been higher after the age of

35 years (36). The rates of spontaneous abortion have also been found to be associated with the number of previous pregnancies (37). Paternal age, maternal age, and birth order have been reported to have separate, equal, and significant effects on the risk of fetal death (38).

Etiology and pathogenesis of congenital malformations

The pathogenesis of developmental defects has been described to occur in successive stages (39). For example, gene mutations, chromosome aberrations, mitotic interference, lack of precursors or energy, enzyme inhibition, or osmolar imbalance may be the initial changes after teratogenic insult. They may lead to such occurrences as abnormal cell death, failed cell interactions, reduced biosynthesis, abnormal morphogenetic movement, or mechanical disruption of tissues. Abnormal embryogenesis may be the result of damage in one or more phases of development.

Malformations are divided into those of simple genic origin caused by single major mutant genes (about 7.5 % of all congenital malformations in the live born); those due to interactions between hereditary tendencies and usually undefined nongenetic factors (about 20 % of malformations); those associated with chromosome aberrations (about 6 % of malformations); those attributed to discrete environmental factors (about 6.5 % of malformations); and those with no identified cause (about 60 % of malformations) (40). Figure 1 illustrates the distribution.

Of the environmental causes, maternal infections due to rubella virus, cytomegalovirus and *Toxoplasma gondii* have been thought to be responsible for about 3 % of congenital malformations (40). Other microbes (varicella, hepatitis B, herpes simplex Type 2, Group B coxsackie virus, etc) have been suspected, but their role is not fully confirmed.

Ionizing radiation is known to be teratogenic in animal tests, and to the human embryo and fetus (34). Ionizing radiation and congenital malformations seem to have a dose-response relation. The lowest doses with adverse effects have varied between 1 and 5 rad (10 and 50 mSv).

In the pregnancies of diabetics, malformations are about three times more common than in the pregnancies of others. It has been estimated that maternal diabetes mellitus would be the cause of malformation in 1.4 % of the live born malformed children (40). Less than 1 % of congenital malformations are estimated to be due to other noninfectious maternal illnesses.

Maternal age beyond 35 years has been found to be associated with an elevated risk of Down's syndrome, other trisomies, central nervous system defects, oral clefts, and malformations of the circulatory system. (For a review see references 23 and 41.) For some malformations, for example, hypospadias and neural tube

defects, the associations with maternal age have been contradictory in various countries. (For a review see reference 18.) Parental ethnicity (ie, Irish versus non-Irish) has been suggested to be a risk factor for neural tube defects. (For a review see reference 41.)

Effects of socioeconomic factors

Spontaneous abortions

Socioeconomic status has been found to influence the spontaneous abortion rate in some studies, but not in others. (For a review see reference 13.) In one Finnish study the rate of spontaneous abortion was 5.9 % in the highest social group (higher-level officials, employers) and 8.5 % in the lowest social group (unskilled workers) when the social group was classified according to that of the woman (42). In a Danish study, however, no association with the woman's social class, education, or net family income was found (43).

Among Italian women spontaneous abortion was more common among women with schooling beyond the eighth grade than among those with less schooling (44). The authors suggested that more-educated women recognize and recall their spontaneous abortion experiences better than others. Thus the found effect would be due to more complete information received from the more-educated women.

Working women in Finland have had slightly more spontaneous abortions than housewives; the age-standardized rates are 7.4 and 6.9 %, respectively (42). In another study spontaneous abortion rates among women working in industry were higher than those of homemakers, but the differences were statistically significant only for the second and third pregnancies (45).

Industrial, construction, and agricultural workers have had higher rates of spontaneous abortion than other occupational groups (42). In a prospective study

on working women in one county of Sweden, there were no significant differences in the incidence of adverse pregnancy outcome (including spontaneous abortions) between nine occupational categories, when the nonoccupational factors age, previous spontaneous abortion, educational level, and personal habits were accounted for (31). In Finland, however, a mother's lack of knowledge on pregnancy and childbirth before and during the pregnancy was associated with poorer pregnancy outcome. The women with a small amount of knowledge on childbirth were less educated, more often unemployed, and used more drugs, cigarettes and alcohol during their pregnancy than the other clients of the maternity clinics (46).

It is possible that the social class of the husband determines the social class of the wife more than the wife's own occupation. This possibility might partly explain the contradictory findings in the studies in which the social class was assessed according to the wife's occupation.

For cultural and social reasons women's participation in the work force varies from country to country. In countries where employed women are common, working women may be healthier as a group than those outside worklife. In countries where the career of a housewife reflects a high socioeconomic status, unemployed women may be better off than employed ones. Thus the comparison between working women and housewives may also reflect the effects of factors other than occupational exposure.

In cross-sectional studies the rate of spontaneous abortion may be biased because women with a successful pregnancy and childbirth tend to stay at home to care for the child, whereas women whose pregnancy ended in an abortion usually continue to work. Thus the spontaneous abortion rate may be overestimated because only women who are employed at the time of the study are included. The findings of a Swedish study support such a hypothesis (47). On the other hand, in

Figure 1. Causes of congenital malformations as proposed by Kalter & Warkany (40).

a cross-sectional study conducted in France, women who had two or more deliveries with a history of spontaneous abortion were more likely to have left their jobs than women without such a history (48). A longitudinal approach, in which women who have left their jobs are also included, is preferable so that this kind of bias can be avoided.

Congenital malformations

Low socioeconomic status has been found to be associated with congenital malformations. (For a review see references 10 and 24.) In Finland, there were differences in malformations in four social classes formed according to parental occupations. The odds ratio for musculoskeletal malformations was increased among the children of women in social class 3 (skilled workers), and the odds ratio for oral clefts among the children of men in social class 4 (unskilled workers) (49). A contradictory result has been found in a register-based study in Sweden, where no differences in congenital malformations between three socioeconomic groups (most privileged, middle and less privileged) were found (50). The social group classification was formed according to the socioeconomic background of the mothers.

Employment during pregnancy has been suspected to increase the risk for an adverse pregnancy outcome. In a Finnish investigation all types of malformations were less common among the children born to housewives than among employed women and students (49). In another study, however, no differences in the frequency of malformations were found when the pregnancy outcome of 7155 employed and 4018 unemployed women was studied (51).

In analyses based on the data of the Finnish Register of Congenital Malformations, a significant association between maternal occupation in industry (industry, construction, transport, and communication) and malformations of the central nervous system, oral clefts, and musculoskeletal malformations was found (49). Malformations of the central nervous system appeared to be particularly common among the children of industrial and construction workers, while oral cleft and musculoskeletal malformations were common among the children of transport and communication workers. The women in technical, scientific, and administrative occupations, compared with other occupational groups, had odds ratios below unity for the offspring's malformation. Confounding factors (maternal illness, medication, obstetric history, smoking, and alcohol consumption) were controlled for in the multivariate analysis (52).

In a prospective study among working women in Örebro County in Sweden, no significant differences were found in the incidence of adverse pregnancy outcome, including congenital malformations, between various occupational groups. In the analysis the age,

educational level, previous spontaneous abortions, and personal habits of the mother were accounted for (31).

In most studies the socioeconomic group has been classified only on the basis of the occupation of the woman, although the socioeconomic group of the family may depend more on the occupation of the husband. Socioeconomic, life-style, and occupational factors are likely to be interrelated, and the differences in them may partly explain the different findings.

Effects of other nonoccupational factors on the occurrence of spontaneous abortion and congenital malformation

Nutrition

The calorie intake of a pregnant woman affects fetal growth especially during the third trimester. Growth retardation is the most marked if the mother is underweight at the beginning of pregnancy (53). Undernourishment has been found to be associated with increased risk of antenatal disorders such as amniotic fluid infections, abruptio placentae, and large placental infarctions. Diminishing of the antimicrobial activity of the amniotic fluid seems to be partly related to zinc deficiency. Zinc deficiency has also been estimated as possibly teratogenic to humans (54). Fasting is dangerous for a pregnancy and the fetus, since a pregnant woman develops metabolic acidosis in a short time (53). Fasting has been teratogenic for some strains of mice. (For a review see reference 55.)

During the famine due to World War II the incidence of adverse pregnancy outcomes, including spontaneous abortion and congenital malformations, was higher in The Netherlands than before the war. An increase in the number of congenital anomalies in general, and cardiovascular malformations and retarded postnatal bone growth in particular, have been reported for infants malnourished before birth. Low birthweight and congenital anomalies correlate with malnutrition. These factors correlate also with low socioeconomic status (55).

Both an excess and a deficiency of vitamin A during pregnancy have been suspected to be teratogenic to humans. Excess dosing in association with malformations has varied from 25 000 to 150 000 IU daily. (For a review see references 15 and 55.) Anomalies of the external ear, skull and brain, urogenital organs, and facial clefts have been reported. (For a review see reference 56.) The recommended daily intake of vitamin A for an adult nonpregnant person is 3000–6000 IU and should not exceed 10 000 IU during or immediately before pregnancy (56).

In animal studies, vitamin A deficiency has caused ocular and urogenital anomalies, diaphragmatic hernias, and congenital heart defects. The data on humans include one case report of an infant born with anophthalmia to a mother with vitamin A deficiency (15).

The association between hypervitaminosis D and supravalvular aortic stenosis syndrome and elfin facies has been suspected although the role of vitamin D in the etiology has not been definitely confirmed (15).

Drugs

Several antineoplastic agents (57) (androgenic hormones, diethylstilbestrol, coumarin anticoagulants, diphenylhydantoin and trimethadione, valproic acid, lithium, methimazole, penicillamine, tetracyclines, thalidomide, trimethadione) have been classified as teratogenic to human offspring (15). In some studies an association between diazepam therapy during pregnancy and oral clefts has been suggested (23). Carbamazepine, primidone, disulfiram, and streptomycin are also suspected to be human teratogens (15).

An increased rate of spontaneous abortion has been reported among women treated with antineoplastic drugs for trophoblastic tumors (58, 59).

Addictive drugs and agents such as lysergic acid diethylamide, marijuana, heroin, methadone, phenylcyclidine, amphetamines, and tranquilizers have been suspected of being associated with congenital malformations, but no firm conclusions have been drawn (18, 54). A condition similar to the fetal alcohol syndrome has been reported to be common among women who have smoked marijuana during pregnancy (18). Cocaine use has been significantly associated with an increase in malformations, stillbirth, and low birthweight among the babies (60).

Coffee

Coffee is a general beverage in many countries, Finns being among the heaviest consumers. Caffeine is ingested also in tea, cola beverages, and in lesser quantities in cocoa and solid milk chocolate. According to a study in the United States 28 % of the pregnant women consumed ≥ 151 mg of caffeine daily. These moderate-to-heavy caffeine users had a significantly increased relative risk for first- or second-trimester spontaneous abortions when demographic characteristics, reproductive history, smoking, and drinking habits were taken into consideration (61).

Reports on the possible association of coffee drinking with congenital malformations are contradictory, but no risk was found for the material of the Finnish Register of Congenital Malformations (23).

Alcohol consumption and smoking

An association between alcohol consumption and spontaneous abortion has been found in many studies; the doses causing such effects have varied greatly. The consumption of one drink 2–6 times a week to 1–2 drinks daily have had an effect in some studies (62–64). In one study a drink once or more than once a week was significantly associated with an excess of

spontaneous abortion, but a drink 1–3 times a month was not (65). Drinking alcohol 1–2 times a week or more was associated significantly with spontaneous abortion in a case-referent study (66), and any alcohol use showed an increased odds ratio for abortion in another study (30).

Heavy alcohol consumption during pregnancy is known to be teratogenic and cause fetal alcohol syndrome in humans. The children with the syndrome are characterized by low birthweight, microcephaly, reduction of the width of palpebral fissures, and maxillary hypoplasia. They also have other malformations often (15). In a Finnish case-referent study alcohol consumption 1–2 times per week or more increased the odds ratio of spontaneous abortion slightly, but the increase was not statistically significant (66).

Smoking during pregnancy is known to lower the birthweight of the child (67). Smoking was shown to have a positive association with spontaneous abortion in several studies (44). In some studies the effects have been found among women smoking 10 cigarettes/d (7) and in others only at higher exposure levels (64). Smoking has been associated negatively with trisomy in abortuses of women under 30 years of age, but positively in abortuses of women over 30 years of age (68).

Smoking has been found to increase the risk of congenital malformation in some studies (69, 70), but in others no significant increase has been found (71). (For a review see reference 67.) Among smoking mothers the risk of having a child with Down's syndrome (trisomy 21) has been low, and significantly below unity in the age group over 30 years (72). This finding, in addition to the found excess of trisomies in abortuses of smoking women (68), may reflect a selective effect of smoking upon the fertilizability of trisomic gametes or the survival of the conceptus.

Reproductive history

Parity has been associated with increased risk for spontaneous abortion (73). Previous spontaneous abortions have been suggested to increase the risk of abortion in subsequent pregnancies (41), and in some recent case-referent studies the same association has been found (30, 73–75).

Previous induced abortions, especially when cervical dilatation is used, have been found to increase the risk of spontaneous abortion in the second trimester of the subsequent pregnancies (76). Some studies have found no increase in the occurrence of spontaneous abortion after an induced abortion (77), but after multiple induced abortions an excess of chromosomally normal spontaneous abortions has been reported (78). The association between induced and spontaneous abortion was strongest when the first abortion was induced before 1973, at a young age, or with the use of a procedure other than suction curettage. However, no risk of abortion in subsequent pregnancies was

found when the induced abortions were conducted with less damaging suction techniques (78).

The risk of congenital malformation is increased if the woman has given birth to a malformed child earlier (41, 79). Malformations of the central nervous system (80) and of the heart (81) have increased the risk of similar malformation in other siblings. Among the parents of children with heart anomalies, similar anomalies are more common than among parents of nonmalformed children (82).

Contraceptive methods

The risk of spontaneous abortion is known to increase if the pregnancy begins while the woman is using an intrauterine contraceptive device; two- to sixfold risks have been reported (65, 83).

The failure of oral contraceptives has been reported to increase first trimester abortions but not later ones. The risk disappears if the pregnancy begins after menstruation since stopping the pill (83). In another study the failure of contraception (intrauterine device, oral contraceptive or spermicide) was associated significantly with spontaneous abortion; for oral contraceptives alone the odds ratio was increased but not statistically significant (75).

The use of spermicides has been suspected to increase the risk of spontaneous abortion, but no clear evidence has been found so far (84).

Occupational associations with spontaneous abortions

Organic chemicals

Among the female members of the union of chemical workers in Finland, the workers in the pharmaceutical industry had an increased frequency of spontaneous abortion for pregnancies occurring during the membership than before or after membership (85, 86). An increased risk of spontaneous abortion has been found also among workers in the pharmaceutical industry in Italy, where women in various fields of industry were interviewed (45).

Reproductive outcome was studied among nurses in intensive care departments, operating rooms, and departments of internal medicine. No association was found between exposure to antineoplastic drugs and the occurrence of spontaneous abortion. However, the odds ratio for congenital malformation was significantly increased (8). These findings initiated another study in hospitals where the usage of antineoplastic drugs was high. In this case-referent investigation a significant association between spontaneous abortion and exposure to antineoplastic drugs during the first trimester of pregnancy was found (65). Occupational exposure to antineoplastic drugs may occur in the pharmaceutical industry, in hospital pharmacies, and among hospital personnel.

In a case-referent study the pregnancy outcome of female workers in the pharmaceutical industry was investigated further (87). The pregnancy outcome data was obtained from medical registers, and the exposure information was gathered through the occupational health personnel. Exposure to organic solvents was associated with the occurrence of spontaneous abortion in a dose-related manner. Of the individual chemicals, estrogens showed a significantly increased odds ratio for spontaneous abortion; for methylene chloride the increase was of borderline significance (table 1). The odds ratios for other solvents (alicyclic and aliphatic hydrocarbons, benzene, xylene, toluene, and chloroform) and for antineoplastic agents were above unity, but because of the few numbers no statistical significance was reached.

In the analysis of hospitalized abortions among the female members of the Finnish union of chemical workers, the union members in general and laundry workers in particular were found to have an excess of spontaneous abortions (85). The study covered the years 1973–1976. In a subsequent study for 1973–1979, no excess of abortions among union members was found (86). The odds ratio for spontaneous abortion was significantly increased among the laundry workers in a study in which the information on the women's occupation was obtained from the Finnish census (88).

A case-referent study conducted among the laundry and dry-cleaning workers in Finland revealed a significant increase in the odds ratio of spontaneous abortion for women who had had high exposure to tetrachloroethylene during the first trimester of their pregnancy (66) (table 1). The exposure information was collected from the workers with the use of questionnaires. For 55 % of the study population the employer's estimation of the exposure was also available, and the results based on either type of information were similar. However, among Swedish laundry and dry-cleaning workers, a high exposure to tetrachloroethylene during pregnancy did not increase the risk of adverse pregnancy outcome (spontaneous abortion, malformations, perinatal death, low birthweight) (89) (table 1). The contradictory findings may reflect different exposure situations, but the effect of change cannot be excluded since the numbers of cases in the high-exposure groups were small in both studies.

The members of the union of chemical workers employed in the plastics industry, particularly in styrene manufacturing, had an increased frequency of spontaneous abortion for pregnancies occurring during the membership compared to that before or after the membership (85). In an interview study among female reinforced plastic lamination workers exposed to styrene, the proportion of spontaneous abortions did not significantly differ between the exposed group and the reference group (90). The small number of pregnancies and the marked difference in the occurrence of induced abortions between the exposed and unexposed

groups make it difficult to interpret the results (table 1). The odds ratio of spontaneous abortion for exposure to styrene was below unity (the confidence interval did not include one) in a case-referent study in which the population was selected from women earlier monitored biologically because of exposure to organic solvents (73) (table 1). The measurement data was used in the exposure assessment together with the questionnaire information received from the workers.

Among the female members of the Finnish union of rubber and leather workers, an increased odds ratio was observed for abortions among the workers in the footwear department, but not for those in the tire department (91) (table 1). The footwear workers were not only exposed to rubber chemicals, but also to organic solvents in the glues. A register-based Swedish study found no difference in the observed and expected numbers of miscarriages among the workers of a rubber factory (92). A study based on a cluster of spontaneous abortions in Sweden revealed an increase in the occurrence of adverse pregnancy outcomes (miscarriages, threatened abortions, and malformations) among tire builders (93). The numbers of various ab-

normalities were small, but the result persisted after age, smoking habits, pregnancy order, and calendar year had been taken into account.

Laboratory work has been studied ever since organic solvents came under suspicion as harmful to pregnancy. In addition laboratory personnel may be exposed to many other toxic chemicals. An increased occurrence of spontaneous abortions has been suggested for women working in hospital laboratories (94, 95) and in chemical laboratories of the pharmaceutical industry (96). A slightly increased odds ratio for spontaneous abortion was observed among laboratory assistants in a study in which information on pregnancy was obtained from medical registers and information on occupation was acquired from the national population and housing census (88). In other studies, in which pregnancy outcome data were obtained both from questionnaires and hospital records, pregnancy outcome was not associated with laboratory work or alleged exposure to organic solvents or other chemicals (27, 97) (table 1).

In a case-referent study in which the study population was selected from women who had earlier been

Table 1. Studies on association between spontaneous abortion and maternal occupational exposure to organic solvents and some other organic chemicals.

Reference	Type of occupational exposure	Association with exposure ^a
Hemminki et al (85, 86)	Pharmaceutical work by members of the Union of Chemical Workers	(+)
Figà-Talamanca (45)	Pharmaceutical industry	+
Taskinen et al (87)	Pharmaceutical industry Methylene chloride Estrogens	(+) +
Selevan et al (65)	Antineoplastic drugs Nurses in oncological wards	+
Hemminki et al (8)	Nurses in other wards	—
Hemminki et al (85)	Laundry work	+
Hemminki et al (86)	Laundry work	—
Lindbohm et al (88)	Laundry work	+
Ahlborg (89)	Laundry and dry-cleaning work	—
Kyyrönen et al (66)	Dry cleaning (tetrachloroethylene)	+
Härkönen & Holmberg (90)	Styrene (lamination workers)	—
Hemminki et al (85)		+
Lindbohm et al (73)		—
Lindbohm et al (91)	Footwear production by members of the Finnish Union of Rubber and Leather Workers (solvents and rubber chemicals)	(+)
Kestrup & Källén (92)	Rubber work	—
Axelsson et al (93)	Tire building	(+)
Strandberg et al (95)	Hospital laboratories	(+)
Kolmodin-Hedman & Hedström (94)	Hospital laboratories	(+)
Heidam (98)	Hospital laboratories	—
Axelsson et al (97)	University laboratory	—
Heidam (27)	University laboratory	—
Hansson et al (96)	Pharmaceutical laboratory	(+)
Heidam (27)	Industrial laboratories	—
Lindbohm et al (88)	Work of laboratory assistants	+
Heidam (98)	Painting	(+)
Lindbohm et al (88)	Solvent exposure	—
Ahlborg et al (31)	Solvent exposure	—
Lindbohm et al (73)	Organic solvents	+
	Aliphatic hydrocarbons	+
	Toluene	(+)
Pastides et al (99)	Photolithographic process in semiconductor manufacturing (glycol ethers, xylene, toluene)	(+)

^a + = positive association; (+) = positive association, but statistical test revealed only borderline significance; — = no association.

monitored biologically for organic solvent exposure, an association was found between spontaneous abortion and exposure to organic solvents during the first trimester of pregnancy (73) (table 1). The odds ratios were significantly increased for aliphatic hydrocarbons, especially in graphic work, and toluene exposure, especially in shoe work. The odds ratio was increased also for exposure to tetrachloroethylene in dry cleaning, but the result was not statistically significant.

In a prospective study conducted in Örebro County in Sweden, no excess risk of adverse pregnancy outcome, including spontaneous abortion, was found for exposure to organic solvents (31). An adjustment for age, previous spontaneous abortion, educational level, and personal habits was conducted.

There has been an excess of spontaneous abortion also among female painters (98) (table 1). In the semiconductor industry increased relative risk for spontaneous abortion was found for workers in the photolithographic process, but the finding did not reach statistical significance. The used photosensitive materials contain glycol ethers, xylene, toluene and hexamethyldisilazane (99) (table 1).

No association between alleged exposure of men to solvents and spontaneous abortion among their spouses was found in a study in which the informa-

tion on the occupation of the man was retrieved from the population census (88) (table 2). In another study in which the pregnancy history and the occupation of the father were obtained from official birth records (100) the husband's potential exposure to solvents did not increase the risk of spontaneous abortion. The information on the spontaneous abortion was based on the maternal report of the outcome of the most recent pregnancy prior to the current one.

The pregnancy outcome of the spouses of men monitored earlier for organic solvent exposure was determined in a case-referent study (74) (table 2). The pregnancy outcome data came from medical registers and was confirmed by the spouses. Paternal exposure to organic solvents during the estimated time of the spermatogenesis preceding the conception was associated with an increased risk of spontaneous abortion in that pregnancy. The associations were significant for high exposure to toluene and miscellaneous solvents of the thinner type. Painters and wood workers had significantly increased odds ratios for spontaneous abortion among their spouses.

In conclusion, women's exposure to organic solvents during pregnancy seems to be associated with spontaneous abortion, although the association was only suggestive in some studies and also negative results

Table 2. Studies on association between paternal occupational exposure to organic solvents and spontaneous abortion among their wives.

Reference	Type of occupational exposure	Association with exposure ^a
Lindbohm et al (88)	Solvent exposure	—
Daniell & Vaughan (100)	Organic solvents	—
Taskinen et al (74)	Organic solvents	+
	Toluene	+
	"Thinners"	+
Lindbohm et al (88)	Work of service station attendants	—

^a + = positive association; (+) = positive association, but statistical test revealed only borderline significance; — = no association.

Table 3. Studies on association between spontaneous abortion and maternal occupational exposure to lead and metals.

Reference	Type of occupational exposure	Association with exposure ^a
Rom (1) (review)	Lead	(+)
Taskinen (105)	Lead	—
Nordström et al (106)	Smelter work	(+)
Hemminki et al (107)	Soldering in radio and television production by members of the Finnish Union of Metal Workers	(+)
Hemminki et al (108)	Work done by members of the Finnish Union of Metal Workers	—
Lindbohm et al (88)	Occupations involving metal exposure	—
Vaughan et al (111)	Work in the metal industry	+
Pastides et al (99)	Diffusion process in semiconductor manufacturing (arsine, phosphine, diborane)	+
Sikorski et al (109)	Dentistry work (mercury)	+
Ericson & Källén (110)	Dentistry work (mercury)	—

^a + = positive association; (+) = positive association, but statistical test revealed only borderline significance; — = no association.

were reported (table 1). The effects of men's exposure have been studied far less, but in a recent study a significant association was found.

Inorganic compounds

According to historical reports female workers and the wives of male workers in the pottery and lead industries, printing industry, and storage battery plants have an excess of spontaneous abortion and stillbirth (table 3). (For a review see reference 1.) There is also an excess of neonatal deaths and of neurological symptoms in the born children. The exposure levels in those industries have probably been very high during the last century and the beginning of this century.

The effect of lead exposure on the human embryo or fetus during early pregnancy is not well understood. Conflicting results have been obtained about lead transfer in the first trimester of pregnancy. Chaube et al (101) suggested that lead transfer occurs. Borella et al (102) did not find any association between the maternal concentration of lead in blood and the concentration of lead in the abortion material obtained from legal abortions of women not exposed to lead occupationally. About 90 % of the blood lead results of women were below 15 µg/100 ml (0.7 µmol/l). At birth the lead concentration in the umbilical cord of an infant has been found to be near the blood lead level of the mother (103). The gestational time seems to affect the permeability of the placenta to lead.

Recently, Baghurst et al (104) studied the pregnancy outcome of women living in a lead-polluted area. An association was found between the blood lead concentration of the mother and a risk of preterm delivery. There was no detectable association between the blood lead level and spontaneous abortion, but the study design was such that women experiencing early abortion would not have been enrolled as the first blood lead test was taken during the 16th week of pregnancy.

In a Finnish case-referent study based on medical registers and data on workers monitored biologically for exposure to lead, no significant association with spontaneous abortion was found (105) (table 3). Among the few study persons who had been monitored near or during pregnancy, the odds ratio was increased in the group having a blood lead concentration of ≥ 1.4 µmol/l. The increase was not, however, statistically significant.

A significantly increased frequency of spontaneous abortion was found among women working close to the smelting process in a copper smelter when these workers were compared with workers in administration, laboratory, and restaurant work (106) (table 3). Exposure to lead, arsenic, sulfur dioxide, and mercury was possible.

In Finland the age-standardized frequency of spontaneous abortion among the female members of the metal workers' union was significantly higher for pregnancies occurring during the union membership than

for those occurring before the membership (107). Soldering tasks in radio and television production appeared to involve a high risk (table 3). The soldering wire contains tin, lead, and small amounts of colophony. The second analysis, including also the women who had resigned from the union, did not show any significant increase in the rate of spontaneous abortion (108) (table 3).

A significantly increased relative risk of spontaneous abortion was found in an interview study among women working in the diffusion process in the semiconductor industry (99) (table 3). Potential exposures in the diffusion process are arsine, phosphine, and diborane gases.

Reproductive failures including spontaneous abortion in the history were significantly related to high total mercury levels in the scalp and pubic hair of women working in dental offices in the Lublin region of Poland (109) (table 3). The number of amalgam fillings in the subjects' teeth was not taken into account. Among Swedish women working in dentistry no significant deviation was seen from the expected values of spontaneous abortion (110) (table 3).

The risk of fetal death among women who have given birth to more than one child was significantly increased among women working in the metal industry when the figures were adjusted for age and pregnancy order (111) (table 3).

Spontaneous abortions in the families of the members of the Finnish metal workers' union were also analyzed by the occupation obtained from the population census. Women employed as smelter workers, foundry workers, or welders did not have higher rates of spontaneous abortion than other industrial workers (108) (table 3).

Women's potential exposure to metals was not associated with spontaneous abortion in a study in which the occupational information was obtained from the national population and housing census in Finland (88) (table 3).

The conclusion drawn on the basis of the reviewed studies on the potential effects of exposure to metals on spontaneous abortion remains uncertain. However, the historical reports on lead workers' families (1) suggest that high exposure to lead during pregnancy may have adverse effects on pregnancy.

Physical exposures

Among female veterinarians and veterinary assistants the use of diagnostic X-rays was significantly associated with spontaneous abortion (112). The increase in risk was significant for veterinary assistants both in the unadjusted analysis and in the analysis adjusted for exposure to waste anesthetic gas. For veterinarians the risk was significant only in the unadjusted analysis. Substantially increased observed-to-expected ratios of late (> 16 weeks) spontaneous abortions were found also among radiology technicians (113).

Among various types of long-wavelength electromagnetic fields or waves, shortwaves have been embryo lethal in animals at intensities producing significant hyperthermia in the dams, and thus a thermal effect has been suggested as the mechanism of the damage. In addition nonthermal effects have been proposed (34).

Ultrasound equipment emit sound waves with a frequency above the audible range. If the energy is very high, ultrasound waves can cause tissue disruption and hyperthermia. Such effects do not occur with the level of energy utilized in medical diagnostic equipment (34).

Women exposed to various forms of electromagnetic fields or ultrasound while working as physiotherapists or in industry have not had an increased risk of spontaneous abortion according to earlier reports (114, 115). In a case-referent study among Finnish physiotherapists an increased odds ratio for spontaneous abortion was associated with long periods of use of shortwave and ultrasound equipment (116). The increase was significant for "late" abortions (ie, abortions occurring during the 10th week of pregnancy or later).

Two randomized trials on routine ultrasound screening in the 16th week of gestation or later have not revealed any significant increase in the occurrence of spontaneous abortion (117, 118).

Physical strain

Physical strain in the form of physical effort or heavy lifting has been found to be associated with spontane-

ous abortion among nursing assistants, cleaners, and janitors (119) and physiotherapists (116). Associations between continuous heavy lifting and spontaneous abortion were found also among personnel in pharmaceutical factories (87), laundry and dry-cleaning workers (66), and among wives of solvent-exposed men (74). In some other studies no associations have been found (73, 97, 105, 120). Work posture was not associated with spontaneous abortion. For shift work and piece work both positive and negative results have been reported (121).

Occupational associations with congenital malformations

Organic chemicals and laboratory work

In a register-based case-referent study among hospital nurses in Finland, the handling of antineoplastic drugs one or more times a week was significantly associated with malformations in the offspring (8) (table 4).

Several studies have suggested an association between maternal use of exogenous sex hormones during early pregnancy and certain types of congenital malformations, but the types of malformations have not been similar in various studies. (For a review see reference 122.) The oral use of progestin-containing medicines for the hormonal pregnancy test has been found to be significantly associated with malformations (122).

Table 4. Studies on association between congenital malformations and maternal occupational exposure to organic chemicals.

Reference	Type of occupational exposure	Association with exposure ^a	Type of malformation
Hemminki et al (8)	Antineoplastic drugs	+	Intestinal atresias
Meirik et al (123)	University laboratory	+	
Hansson et al (96)	Laboratories in the pharmaceutical industry	(+)	Gut atresia
Blomqvist et al (124)	Laboratories in the pulp and paper industry	+	
Ericson et al (125)	Laboratory work	+	Gut atresia
Ericson et al (126)	Laboratory work	+	
Baltzar et al (127)	Hospital laboratory	—	
Olsen (128)	Laboratory occupation	(—)	
Axelsson et al (97)	University laboratories	—	Sacral agenesis
Kucera (130)	Solvents	(+)	
Holmberg (132)	Solvents	+	Central nervous system
Holmberg & Nurminen (133)	Solvents	+	Central nervous system
Holmberg et al (134)	Solvents	+	Oral clefts
Holmberg et al (129)	Solvents	+	All
McDonald et al (136)	Solvents	+	Urinary tract
Tikkanen & Heinonen (135)	Solvents	(+)	Cardiovascular
Tikkanen & Heinonen (135)	Solvents	+	Ventricular defects
Erickson et al (131)	Printing industry	+	Gastroschisis
Holmberg (132)	Styrene	(+)	omphalocele
Hemminki et al (86)	Work done by members of the Finnish Union of Chemical Workers in the pharmaceutical industry	(+)	Central nervous system

^a + = positive association; (+) = positive association, but statistical test revealed only borderline significance; — = no association.

In many studies conducted among laboratory personnel (13) an increased risk of malformation in the offspring has been found (96, 123–126), but also negative findings have been reported (97, 127, 128). No specific types of malformations have been found to be constantly associated with laboratory work, but there seems to be a tendency towards an increase in the malformations of the offspring of laboratory workers (table 4).

Some studies on solvent-exposed workers in other branches of industry have revealed an excess of congenital malformations among the children of solvent-exposed workers (129) (table 4). A study conducted among the female members of the Finnish union of chemical workers suggested an increased risk ratio for malformations in the offspring of workers in the pharmaceutical industry (84). Sacral agenesis (130), gastroschisis (131), malformations of the central nervous system (132, 133), oral clefts (134), and cardiovascular malformations (135) have been reported in excess among children of solvent-exposed women. Maternal exposure to aromatic solvents, including toluene, was associated with a significant excess of malformations in general and urinary tract malformations in particular (136). The odds ratio for congenital malformation was significantly increased for exposure to solvents other than tetrachloroethylene among laundry workers and dry cleaners, but the result was based on only three cases and two referents (66) (table 4).

Paternal exposure to organic solvents has also been associated with congenital malformations (those of the central nervous system or cleft lip or cleft palate). Painters and workers in the printing industry have been among the exposed occupations (128, 130) (table 5).

On the basis of the literature, it may be concluded that exposure to organic solvents during pregnancy seems to be associated with malformations (table 4). The meeting arranged by the World Health Organization on women and occupational health risks (137) concluded that there is evidence of a likely association between laboratory work during pregnancy and malformation of the offspring. The complex and multiple exposures involved in laboratory work may contribute to the hazardous effects, but also organic solvents are commonly used in laboratories, although often in small amounts. On the basis of the results of

only a few studies on paternal effects, the association between exposure to organic solvents and malformations remains possible but uncertain (table 5).

Inorganic compounds

Among the offspring of women who had worked at a copper smelter during pregnancy, a significantly increased frequency of malformations, particularly multiple malformations, was found (138). The emissions from the smelting process included arsenic, lead, mercury, cadmium, and sulfur dioxide.

Macrocephaly has been reported for children of lead-exposed workers (Oliver 1911, cited in 139). Prenatal lead exposure, measured as the concentration of lead in the blood of the umbilical cord of an infant at birth, was found to be associated with an increased risk for minor anomalies (139). The most common anomalies were hemangiomas and lymphangiomas, hydrocele, minor skin anomalies, and undescended testicle. Several potential confounders were controlled for. In another study no association was found between maternal blood lead concentration during pregnancy and congenital malformations in the offspring (104).

Functional disturbance (ie, decreased cognitive capacity at the age of two years) was reported among children whose mean blood lead concentration in the umbilical cord was 0.7 (SD 0.15) $\mu\text{mol/l}$ (140). In another study children with persistently high blood lead levels showed poorer mental development at the age of 24 months than those with low blood lead levels (104).

The data on the transfer of lead from the mother to the fetus during the first trimester of pregnancy are conflicting (101, 102). Lead has, however, been found to cross the placenta during the late phase of gestation. The concentration of lead in the blood of the umbilical cord of an infant at birth is almost at the same level as in the maternal blood (103, 141), but the concentration of lead in the amniotic fluid is significantly higher than in the maternal blood (141).

Significantly increased observed-to-expected ratios for congenital malformations were found among children of women occupied in the manufacture of metal and electrical goods when 60 occupational categories were analyzed (114).

Table 5. Studies on association between congenital malformations and paternal occupational exposure to solvents.

Reference	Type of occupational exposure	Association with exposure ^a	Type of malformation
Kucera (130)	Painters	(+)	Cleft palate
Olsen (128)	Painters	+	Central nervous system
Kucera (130)	Printing industry	(+)	Cleft lip
Olsen (128)	Solvents (painting, typography, linoleum work)	(+)	Central nervous system

^a + = positive association; (+) = positive association, but statistical test revealed only borderline significance.

Table 6. Studies on associations between maternal physical exposure and congenital malformations.

Reference	Type of occupational exposure	Association with exposure ^a
Baltzar (144)	Women in X-ray departments	—
Hemminki et al (8)	X-ray exposure	—
Selevan et al (65)	X-ray exposure	(+)
Harjulehto et al (145)	Radioactive environmental pollution	—
Källén et al (146)	Physiotherapy work	—
Källén et al (146)	Physiotherapy work with shortwave equipment	(+)
Taskinen et al (116)	Physiotherapy work with shortwave equipment	(+)
Larsen et al (115)	Physiotherapy work (cluster)	(+)
Kurppa et al (148)	Shortwaves, microwaves	—
McDonald et al (114)	Shortwaves, microwaves	—
Kolmodin-Hedman et al (149)	Shortwaves, microwaves	—

^a (+) = positive association, but statistical test revealed only borderline significance; — = no association.

The embryotoxicity of methyl mercury has been confirmed in studies examining the effects of poisoning from contaminated food. (For a review see reference 13.) Maternal ingestion of fish contaminated by mercury waste from industrial waste waters in Japan or grain treated with mercury-containing pesticide in Iraq has been linked to microcephaly, brain damage, and neurological disorders in the offspring.

The data on the effect of occupational exposures to metallic mercury on pregnancy comes from dental work. There was no increase in congenital malformations in the offspring of female dentists, dental assistants, or dental technicians in Sweden (110). Contradictory findings are presented in a study from Poland, where six malformations were reported in the children of 57 dental workers. Five of the malformations were spina bifida (109).

Many metals and metalloids (arsenic, cadmium, lead, mercury, nickel, selenium) pass the placenta and are present in the human fetus (9, 142). In animal experiments they have also been teratogenic, some only at high doses. Given in combinations, metals may either augment or cancel the teratogenic effects of each other (143).

In conclusion, the reviewed literature indicates that adverse effects of lead on the offspring seem possible. Despite the reported potential reproductive toxicity of other metals, the data on the effects on pregnancy outcome in humans are scanty and somewhat contradictory.

Physical exposures

In a study on Swedish women in medical occupations working in X-ray departments, 14 malformed children were found, whereas only nine were expected (144) (table 6). The difference was not statistically significant, however.

After the Chernobyl accident, radioactive substances spread also over Finland and caused contamination of the air, waterways, and nature. A study based on the Finnish Register of Congenital Malformations did not reveal any significant increase in the incidence of mal-

formations or perinatal deaths between the referents and the children whose intrauterine life included the period of radioactive pollution (145). The radiation dose from the fallout to an embryo was estimated to have been maximally about 1 mSv.

In a case-referent study within the cohort of registered female physiotherapists in Sweden, an increased risk of adverse pregnancy outcome (malformation or perinatal death) was found among women who often used shortwave equipment (146). In the whole cohort, however, the incidence of serious malformations was slightly below that expected. A cluster of four malformed children among 25 pregnancies of physiotherapists in one hospital has been reported (115). In a Finnish case-referent study the odds ratio for congenital malformation was significantly increased for exposure to shortwaves, but only among those using the equipment 1–4 h/week; among those using such equipment more hours per week the odds ratio was below unity (116). Therefore, the possibility of reporting bias could not be excluded.

Reports of patients treated with shortwaves in the pelvic region during pregnancy have given controversial results. (For a review see reference 147.) Some studies have not revealed any association between exposure to shortwaves or microwaves and malformations (114, 148, 149) (table 6).

In conclusion, ionizing radiation is historically known to be embryotoxic and teratogenic. Harmful effects of electromagnetic waves as shortwaves have been suggested, but not found in all studies. Therefore no firm conclusion can be drawn.

Need for further studies

In addition to present knowledge, information on other possible occupational effects on reproduction is needed. Outcomes other than spontaneous abortion and malformations are of interest. For example, in the future, it might be worthwhile studying infertility, the time needed for a pregnancy to start ("time-to-pregnancy"), and very early abortions. It is also possible that spontaneous abortion is not the most sensitive in-

indicator of the harmful effects of exposure, as is suspected in the case of lead. Some other aspects, for example, course of pregnancy, fetal growth, the child's well-being during the neonatal period, and later mental development, might be important outcomes to study.

Some of the reported associations are only suggestive, and more information is needed before firm conclusions can be drawn. A prospective study design would be ideal to avoid reporting bias and memory bias. Prospective studies are, however, expensive and time-consuming to conduct. Both prospective and retrospective epidemiologic studies on various aspects of reproductive health, and also experimental studies, are needed to shed more light on reproductive toxicity. In addition to suitable study design, reliable outcome, exposure data, and appropriate and comparable study populations are essential for valid results.

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