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IN-DEPTH REVIEW

Occupational risk factors and reproductive health of women

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Background This in-depth review summarizes and interprets the available recent epidemiologic evidence on the relationship between occupational exposures and negative reproductive outcome among women workers.

Methods The studies examined by the review include those published in the international scientific literature since 1990, and were identified through the search of relevant data banks using selected keywords.

Results From the examination of studies dealing with exposures of women to chemical agents, pesticides, physical agents, ergonomic factors and stress, it appears that at present the evidence is sufficient to warrant the maximum protection of pregnant women to several well-documented occupational risk factors. These include exposures to anaesthetic gases, antineoplastic drugs, heavy metals, solvents, heavy physical work and irregular work schedules. For other work risks, such as exposure to non-ionizing radiation and psychosocial work stress, the evidence is often suggestive but not conclusive.

Conclusions Policy makers and health professionals should advise women and employers to avoid exposure to the well-known occupational risk factors, while epidemiologic research should pursue methodological improvements and provide more insight into the magnitude of exposures responsible for detrimental effects.

Key words Chemical exposures; ergonomic factors; female reproduction; infertility; occupation; pesticides; physical agents; pregnancy; spontaneous abortion; stress.

Introduction

Research into occupational exposures and effects on reproductive systems has made important scientific contributions in the past few decades. Early studies focused on possible effects on the foetus rather than the reproductive health of the woman. Later, it was realized that reproductive toxins may also induce hormonal alterations affecting other aspects of reproductive health such as the menstrual cycle, ovulation and fertility. Attention is now shifting from concern for the pregnant woman and the foetus, to the entire spectrum of occupational health hazards among women and the reproductive health of both genders.

Methodology

The review that follows attempts to summarize and interpret the available recent evidence on the role of occupational risk factors on the reproductive health of women. For practical reasons, the epidemiologic evidence is reviewed by examining the studies dealing with specific occupational exposure agents or conditions including chemical agents such as metals, solvents, pesticides and chemical exposures in the health care sector, physical agents including radiation and noise and ergonomic factors such as heavy workload, shift work and psychosocial stress. Whenever possible, the review focuses attention on the evidence obtained from the more rigorous and reliable epidemiological studies. The studies included in this review were identified in the databases of the scientific literature (PubMed) searched with the keywords: occupation, work, female reproduction, pregnancy, spontaneous abortion, infertility, subfecundity, stillbirth, low birth weight (LBW). Specific risk factors were also searched, using keywords such as pesticides, radiation and stress. The review is based primarily on the studies conducted in the past 15 years, while older studies are sometimes mentioned along with previously published reviews.

Chemical agents in the workplace affecting reproductive health

Metals

Lead, mercury, nickel and manganese have been known to be toxic to reproduction for many years. Systematic

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studies in the last few decades have shown that reproductive effects may be observed at exposure levels which were previously considered safe. These effects include increased risk of spontaneous abortion, developmental toxicity in the offspring, stillbirth and delay in conception. Metal production employees are predominantly males, so most studies concern male effects, in particular on spermatogenesis [1]. In a review of all methodologically sound epidemiologic studies up to 1994, Anttila and Sallmen [2] found five studies dealing with negative reproductive effects (specifically spontaneous abortion), among women exposed to metals. Increased risks were observed for women in a copper smelter (exposed to lead, arsenic, mercury and cadmium), among women exposed to lead (B-Pb $>$ 1.4 umol/l), nickel (in a nickel refinery) and mercury (Table 1).

Negative reproductive effects of relatively low doses of heavy metals have also been shown in studies of lead as a contaminant of urban air. Prenatal lead exposure increased the risk of pre-term delivery and LBW [3], while a large clinical study of infertile women showed that treatment to reduce the heavy metal body burden improved the chances of conception [4]. A recent study in Mexico City also found a dose–response relationship between the risk of spontaneous abortion and the blood–lead level of the women [5].

Mercury exposure among female dental assistants preparing amalgams has identified mercury in hair samples. Both spontaneous abortion and reduced fertility were found to be associated with exposure to mercury, especially among dental assistants working without appropriate protective measures [6]. Heavy metals such as lead and mercury have been shown to interfere with the endocrine system and this might explain why exposed women present menstrual disorders, delayed conception rates [7] and other reproductive effects such as LBW and neural tube defects [8].

Solvents

Many of the early occupational studies examined 'solvents', in general, specifying neither the specific product nor the level of exposure. Later studies examined individual solvent exposures, showing statistically significant increases in the risk of spontaneous abortion among women exposed to tetrachloroethylene (dry cleaners), toluene and aliphatic hydrocarbons (in several industrial settings monitored for exposure). One Finnish study with documented exposure by biological monitoring found an increased risk for reduced fertility among primiparous women with higher exposures to toluene, aromatic and aliphatic hydrocarbons and especially to trichloroethylene and tetrachloroethylene. Among those exposed to organic solvents (compared with those not exposed), the probability of conceiving was reduced by half [10].

Table 1. Selected occupational exposures of women to chemical agents with negative effects on pregnancy (studies conducted after 1990)

Chemical agent (type of work)	Effects observed	References
Metals (Pb, Hg, Cd, Ni) (industrial work)	Spontaneous abortion	Anttila and Sallmen [2] (review)
Lead (urban populations)	Spontaneous abortion and pre-term delivery, LBW, reduced fertility	Herz-Picciotto [5], Andrews *et al.* [3], Gerhard *et al.* [4]
Lead (occupational exposures)	Reduced fertility, LBW	Sallmen *et al.* [7], Irgens *et al.* [8]
Mercury (dental assistants)	Spontaneous abortion, reduced fertility	Rowland *et al.* [6]
Solvents		
Organic solvents (laboratories, industry, dry cleaning, etc.)	Spontaneous abortion	Lindbohm [9] (review)
Specific solvents (toluene, aromatic and aliphatic hydrocarbons, trichloroethylene, tetrachloroethylene)	Reduced fertility	Sallmen *et al.* [10]
Tetrachloroethylene (dry cleaners)	Spontaneous abortion	Olsen *et al.* [11], Doyle *et al.* [12]
Glycol ethers (semiconductor industry)	Spontaneous abortion and reduced fertility	Figà-Talamanca *et al.* [13] (review), Elliot *et al.* [14], Chen *et al.* [15]
2-Bromopropane (electronics industry)	Haematological effects, menstrual disturbances, spontaneous abortion	Takeuchi *et al.* [16] (review)
Petrochemicals (petrochemical industry)	Spontaneous abortion, reduced birth weight	Xu *et al.* [18], Ha *et al.* [19]
Chemical exposures in the health care sector		
Ethylene oxide (dental assistants)	Spontaneous abortion, pre-term birth	Rowland *et al.* [21]
Anaesthetic gases (operating room staff)	Spontaneous abortion, reduced fertility	Figà-Talamanca [22] (review)
Antineoplastic drugs (oncology hospital staff)	Spontaneous abortion	Figà-Talamanca [22] (review)
Other chemicals		
Formaldehyde (wood processing)	Reduced fertility	Taskinen *et al.* [23]
Solvents used in biochemical research laboratories	Pre-term births	Wennborg *et al.* [20]

Particular attention was focused on tetrachloroethylene (also known as perchloroethylene or PER) which is primarily used in dry cleaning. Work in dry cleaning has been associated with menstrual disorders, infertility, delayed conception and spontaneous abortion in several different studies. In a multi-centre Scandinavian study, the levels of exposure to PER were estimated indirectly and an increased risk for spontaneous abortion was observed in the Finnish sample. No other negative reproductive outcomes were found in this investigation [11]. More recently, the association of tetrachloroethylene with increased risk of spontaneous abortion was also observed in the UK among the women operating dry-cleaning machines [12].

An increased risk of spontaneous abortion among the women exposed to glycol ethers was found in several studies in the semiconductor industry [13], although the role of other solvents present in this industry could not be excluded [14]. A Chinese study [15] confirmed that exposure to glycol ethers is associated with both decreased fertility and increased risk of spontaneous abortion.

Other solvents suspected of toxicity to female reproductive function with possible negative effects on the menstrual cycle and on pregnancy outcome include carbon disulfide (through interference with hormonal equilibrium), styrene and 2-bromopropane [16].

Working with petrochemicals is known to increase the risk of cytogenetic alterations and mutagenic effects, in both somatic cells and in embryonic tissues [17]. In a Chinese petrochemical plant employing 3000 women, a study found increased risk of spontaneous abortion among those exposed to benzene (OR = 2.5; 95% CI 1.7–3.7), gasoline (OR = 1.8; 95% CI 1.1–2.9) and hydrogen sulphide (OR = 2.3; 95% CI 1.2–4.4) [18]. In the same setting, maternal exposure to organic solvents was associated with reduced birth weight [19].

Exposure to solvents continues to be an important risk for women of reproductive age, because new technologies introduce new chemical risks. It was recently found that laboratory technicians using recombinant DNA techniques (where different solvents are used) had an increased risk for pre-term births [20].

Chemical exposures in the health care sector

Women working in the health care sector are exposed to many different potentially harmful chemical agents including disinfectants, anaesthetic gases and drugs. Exposure to ethylene oxide, for example, was associated with spontaneous abortion and pre-term birth in dental assistants [21].

Practically, all anaesthetic gases (nitrous oxide, cyclopropane, methoxyflurane, halothane and ether) induce embryonic and foetal loss and congenital defects to experimental animals. Many epidemiologic studies conducted between 1980 and 1990 have shown human reproductive toxicity with increased risk for delayed pregnancy and especially spontaneous abortion. Recent studies conducted in the Western countries, where appropriate preventive measures were taken, are often negative, indicating that such measures can indeed reduce the risk [22].

The reproductive toxicity of antineoplastic drugs is known from clinical evidence. Effects on nurses, or among women working in pharmaceutical companies producing them, have been studied in many epidemiological studies. From the evidence available, there is little doubt that occupational exposure to antineoplastic drugs as it occurred in the past might constitute a risk factor for spontaneous abortion and might also be related to infertility [22].

Other chemical agents

There is evidence of negative effects on pregnancy for many other chemical agents which cannot be described in detail. Formaldehyde exposure was associated with LBW in several studies [23,24]. Dioxin, pesticides, as well as several other environmental contaminants present in industrial waste (e.g. polychlorinated biphenyls and phthalates) have oestrogenic and androgenic properties which have been shown to interfere with the reproduction of wildlife through the disruption of the endocrine balance. At present, human evidence of such effects due to environmental pollution by endocrine disrupting chemicals is not conclusive and deals mostly with possible male effects [25–27].

Pesticides

The hypothesis that exposure to pesticides may interfere with the human reproductive function was first documented among men more than 20 years ago [28–30]. Investigations among women are not numerous, but here too, negative reproductive effects such as spontaneous abortions, congenital defects and pre-maturity have been confirmed by a number of studies [31–34]. Infertility and delay in conception is another reproductive health effect observed in association with pesticide exposure of women in a number of different studies [35–37].

Greenhouse workers have repeatedly been shown to be more likely to suffer adverse reproductive effects, probably because exposure to pesticides is higher and more continuous than in other occupations. A study among members of the Danish Gardeners Trade Union showed women greenhouse workers handling cultures and spraying pesticides without protection experiencing a significant reduction in fecundity [38]. This was also observed in the wives of male greenhouse workers in Italy [39] and Finland [40,41].

Since the evidence was reviewed ~10 years ago, Table 2 summarizes a few of the more recent studies focusing only on the possible association between occupational pesticide exposure of women and spontaneous abortion and reduced fertility.

Studies on the effects of pesticide exposure in residential settings show reproductive effects (in particular spontaneous

Table 2. Selected epidemiological studies on the reproductive effects of occupational exposure of women to pesticides (studies conducted after 1990)

Authors (reference), country (year)	Study design	Type of population	Results
Restrepo *et al.* [34], Colombia (1990)	Retrospective cohort study. Interviews on reproductive and work history. Comparison between exposed and non-exposed pregnancies.	2900 wives of male, and 5900 female fluoriculture greenhouse workers.	Increased risks for spontaneous abortion for exposed pregnancies. Female exposures: OR = 2.2 (95% CI 1.8–2.7). Male exposures: OR = 1.8 (95% CI 1.2–2.8).
Taskinen *et al.* [41], Finland (1995)	Case–control study. Use of health registry and questionnaire.	186 cases and 470 controls.	No increased risks for spontaneous abortions among clerical works of greenhouses. Increased risk for manual greenhouse workers: OR = 1.4 (95% CI 0.8–2.6). Increased risk for women applying pesticides without protective masks: OR = 5.1 (95% CI 1.2–22.6).
Fuortes *et al.* [35], USA (1997)	Case–control study. Exposure data obtained by interview.	281 females medically confirmed cases of infertility. 216 post-partum women.	Increased risk of infertility for women working in agriculture: OR = 7.0 (95% CI 2.3–20.8).
Curtis *et al.* [37], Ontario, Canada (1999)	Retrospective cohort study. Postal and telephone questionnaires with detailed information on quantities and types of chemicals used.	Farm operators and farm couples in Ontario (a total of 2000 pregnancies).	For women exposed to six of 13 products used, increased time to pregnancy (reduction in the conditional fecundity ratio range = 0.51–0.80).
Abell *et al.* [38], Denmark (2000)	Retrospective cohort study. Data obtained by telephone interview from the Female Gardeners Trade Union.	253 female greenhouse workers, of whom 202 highly exposed, and 239 non-exposed members of the Trade Union.	Reduced fecundity among women never using protective gloves (OR = 0.67, 95% CI 0.46–0.98) and among those highly exposed: OR = 0.64, 95% CI 0.45–0.90).
Greenlee *et al.* [36], USA (2003)	Case–control study in an agricultural region. Interview on occupational exposure to a list of pesticides.	322 cases of female infertility. 322 pregnant women attending a prenatal care clinic.	Increased risk for infertility among women mixing and applying herbicides (OR = 27, 95% CI 1.9–38) or using fungicides (OR = 3.3, 95% CI 0.8–13).

abortion), especially when exposures occurred in the early stages of gestation [42,43]. Two recent studies have tried to define more accurately the degree of exposure by biological monitoring. One found an association between maternal serum concentration of dichlorodiphenyldichloroethane (DDE) and pre-term and small for gestational age babies at birth [44] and the other found an association of dichlorodiphenyltrichloroethane (DDT) with spontaneous abortion [45]. Although these studies were not specifically designed to evaluate occupational exposures, they reinforce the epidemiological literature on the role of occupational pesticide exposure in women and negative reproductive outcomes.

Occupational exposures to physical agents

Radiation

Exposure to ionizing radiation in prenatal life is a known risk factor for foetal death and congenital defects. The probability and type of effect depend on dose and the developmental stage of the embryo or foetus. It is, therefore, widely accepted that women should avoid all exposures to ionizing radiation in the periconceptional period, i.e. before the woman is aware of her pregnancy, as well as during the gestation [46].

The available evidence suggests that exposure of female health care personnel, prior to conception, within the prescribed safe limits, does not constitute a risk factor for reproductive health [47,48]. Since the year 2000, the European Union (EU) directive prescribes that pregnant workers should be protected from doses >1 mSv during the entire period of gestation [49].

Among the physical agents, the one that has drawn most attention in the last two decades is non-ionizing radiation, in particular electromagnetic field waves (EMF). Since EMFs are present in the general environment a large number of studies have been undertaken in recent years in an attempt to define the role of domestic and residential exposures (e.g. electric blankets, heated beds, vicinity to power lines and mobile telephones) in the development of cancer, birth defects and reproductive

effects. Although several of these studies have shown increased risks, most have strong methodological limitations, and the issue is still awaiting a definitive answer [50–52]. The main problem is the determination of the true exposure of women to EMFs in the critical gestational period, a particularly difficult task in epidemiologic studies. In a rare study where this was done by monitoring exposure during the woman's 'typical' day, an increase in risk of spontaneous abortion was observed only in the small group with exposure to >16 mG, especially when this occurred in the first 9 weeks of pregnancy [53].

In the occupational setting, most research concerns male effects. Effects on the reproductive health of women workers have been studied mainly in two areas: the health care sector and in connection with the use of video terminals. Health professionals using diagnostic and therapeutic devices (e.g. magnetic resonance operators and physiotherapists) are potentially exposed to non-ionizing radiation through the use of ultrasound, microwaves, magnetic resonance and other electrical apparatus. These exposures could induce hyperthermia, increasing the risk of embryopathology. However, the epidemiologic studies in health personnel have not shown consistent results [22]. A study conducted among 1915 women magnetic resonance technologists involving exposure to static magnetic fields in the control room provided mixed, but substantially negative results. These women did not experience a delay in conception and their risk for miscarriage in comparison with women in other jobs was only slightly increased (RR = 1.27 95% CI 0.92–1.77) [54]. A more recent Israeli study of physiotherapists found an increased odds ratio (OR) for LBW among women exposed to short waves (OR = 3.37, 95% CI 1.38–8.25) [55]. The authors attributed this to probable hyperthermic effects, in accordance with animal models. Thus, although other risk factors in the work of physiotherapists cannot be excluded (e.g. strenuous physical work, incongruous positions, shift work in the hospital), the possible role of EMFs remains suspected and needs further research.

The issue of the possible role of video display terminals (VDTs) on pregnancy exploded 20 years ago, with the wide use of terminals by working women and the early reports by North American mass media on the possible role of VDTs in several clusters of miscarriages and birth defects [50]. A large number of studies were then undertaken, most of them aiming to evaluate these two outcomes in occupational settings with heavy use of VDTs. The evidence concerning spontaneous abortion has been recently thoroughly reviewed by Shaw [51], and Figure 1 shows the overall results in terms of the risk ratios (RRs) and associated 95% confidence intervals (CIs) for spontaneous abortion in each study. Of the 13 different studies conducted since 1982, only one found a statistically significant increase in the risk of spontaneous abortion among exposed women (RR = 1.8). In others, the increase in risk was modest (ranging from 1.1 to 1.2) and not statistically significant. Use of VDTs usually leads to exposure to low-frequency EMFs (<60 Hz), which do not have the potential for significantly raising the temperature of the embryo. This might explain why the only epidemiologic study, which was based on measured exposure to EMFs, found an increased risk of miscarriage among women using the early VDTs (emitting high magnetic field levels), compared with women using VDTs with low magnetic field levels, especially if they worked for >10 h/week (RR = 4.3, 95% CI 1.7–11.2) [56].

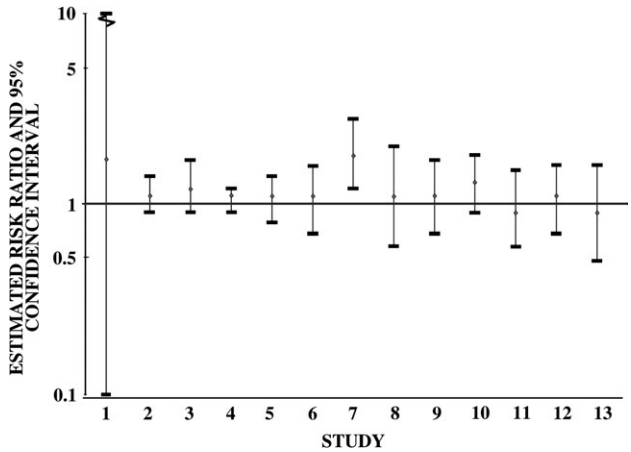

Figure 1. Study results of exposure to VDTs and spontaneous abortions. Source: Shaw [51].

In addition to miscarriage, other reproductive outcomes studied among women using VDTs include LBW, pre-maturity and perinatal mortality. Here, none of the studies conducted so far have found a significantly increased risk for these outcomes, although in most cases, the RR was slightly higher than unity (for a complete review see Shaw [51]).

From the overall review of available evidence, it is now agreed that exposure to contemporary VDTs is suspected to have only a slight association with at best a modest increase in the risk of miscarriage (10–20%). It is unclear whether this is attributable to EMFs or to other work-related conditions such as ergonomic factors, work stress and long working hours.

Noise

Noise-induced stress and its potential interference with the endocrine system have been hypothesized to be a possible risk factor for adverse pregnancy outcomes. The hypothesis has been confirmed in animal studies and in human populations exposed to high levels of environmental noise (e.g. airport noise) [57]. In occupational settings, several studies did find an increased risk in miscarriage, birth defects, pre-term birth and LBW (Nurminen [58]).

Reduction in birth weight and intrauterine growth retardation were also confirmed in the only prospective cohort study of women exposed to measured levels of noise of 90 dB or higher [59]. Although the evidence is not complete, and there are no recent well-designed studies on occupational noise and reproductive outcome in women, the possible negative effect of noise on reproduction is biologically plausible, as well as amenable to prevention.

Ergonomic risk factors

Heavy workload and awkward postures

Heavy physical work of the woman has long been known to be a risk factor not only for spontaneous abortion but also for LBW and pre-mature birth of the infant. The first large study on the role of workload on pregnancy was conducted in Montreal and was based on data from >30 000 women recruited in prenatal services [60]. Conditions which appeared to contribute most to spontaneous abortion and LBW were long working hours (>40 h/week), physical effort and lifting heavy objects. French researchers found that hospital auxiliaries, who performed the heavier tasks, experienced more negative outcomes, including uterine contractions during pregnancy, pre-term births and LBW infants [61]. Dutch women performing activities requiring high energy expenditure and intensity (more than three times the basal metabolic rate per day) experienced a reduction of fecundity [62], while those with high mechanical load (frequent bending and lifting) had an increased risk for spontaneous abortion (OR = 3.19, 95% CI 1.27–9.78) [63]. Lifting of heavy weights (especially patient transfers) was significantly associated with spontaneous abortion also in a study of Finnish physiotherapists (OR = 3.8, 95% CI 1.1–9.0) [64]. Another prospective study found that standing 7 h/day was associated with an increased risk of spontaneous abortion, especially among those women with a previous history of spontaneous abortion (OR = 4.3, 95% CI 1.6–11.7) [65].

The possible negative effects of heavy workload on the newborn include LBW, pre-term delivery and small-for-gestational-age birth (SGAB). In reviewing the past evidence up to 1992, Marbury [66] stated that although no single ergonomic stressor seems to be strongly associated with birth weight and gestational age, most studies found an effect when several ergonomic stressors were combined. The data from later studies concern various occupational categories. SGABs, for example, were significantly more frequent among women who worked >50 h/week (OR = 1.59), who worked standing for >7 h/day (OR = 1.40), and who took no antenatal leave from work [67]. A case–control study in Spain showed that medium or high intensity physical workload (strenuous postures, load carrying, standing) increased the risk of pre-term birth with an OR of 1.6 and 2.3, respectively [68]. Pregnant sugar cane agricultural labourers in Brazil had a risk for LBW newborns [69]. Standing long hours in textile work was associated with LBW in China [70].

Most studies, especially those conducted in recent years in developing countries, show a negative effect on the foetus from strenuous physical activity. This result is biologically plausible, but the epidemiologic evidence is not unequivocal in all studies [71]. In addition, regular physical exercise in healthy pregnant women does not seem to be a risk factor for pre-term birth or LBW [72,73].

In conclusion, it may be stated that although physical activity itself may not be considered a proven risk factor for pregnancy, some physically strenuous work conditions (e.g. heavy lifting, frequent bending) might increase the risk of negative pregnancy outcome, especially among women with other risk factors (e.g. with previous foetal losses) or in the presence of other work-related risks. The mechanism of action of strenuous physical activity on the foetus is not clear, and it might involve decrease not only in oxygen and nutrient supply but also in the endocrine system. This hypothesis is advanced by a recent prospective study which found that the time window of exposure to physical strain may be important. The risk of spontaneous abortion increased when the physical strain occurred very early in pregnancy, i.e. around the pre-implantation period [74].

Work schedule and pregnancy

The studies examining the role of work schedule on the reproductive health of women, often conducted among health care professionals, have not always reached unequivocal conclusions [75]. In an early Swedish study, hospital workers with irregular hours had a slight increase in the risk of spontaneous abortion (OR = 1.4, 95% CI 0.83–2.51) [76]. No increase in risk, however, was found for night work. Two later case–control studies found an increased risk of spontaneous abortion for shift work and night work [77], and for evening work [78]. Similarly, a study of Swedish midwives, reported an increased risk in connection with night work and three-shift schedules [79]. The latter study involved 3583 pregnancies reported through a questionnaire study of members of the Swedish Midwives Association.

Other negative reproductive outcomes have been associated with inconvenient work schedules. In a study of Swedish midwives, a reduction in fecundity was noted for all irregular work hours: the adjusted fecundity ratio for two shift, three shift and night work were 0.78, 0.77, 0.82, respectively [80]. The same study found an association of night work and pre-term birth (OR = 5.6, 95% CI 1.9–16.4) and to a lesser degree with LBW OR = 1.9, 95% CI 0.6–5.8) [81]. Rotating shift textile workers had a 2-fold increase for LBW and for pre-term birth in

a Chinese study [82]. In a European study of infertility and subfecundity, shift work was associated with subfecundity and longer time to pregnancy [83]. Using the EU data collection instrument in Thailand a study confirmed that long working hours and shift work were associated with increased risk of subfecundity [84]. A slightly reduced fecundity was also found in relation to shift work in the large body of data (nearly 40 000 women) of the Danish National Birth Cohort between 1998 and 2000 [85].

In reviewing the evidence of shift work, it appears that irregular work hours may be associated with a slight increase in the risk of spontaneous abortion and reduced fertility (Table 3). Regular night work does not seem to have the same effect, suggesting that the regularity of the work schedule may be a more important factor for reproductive outcome. The mechanisms involved in the process may include changes in the circadian rhythm with accompanying changes in hormonal concentrations, affecting both the conception and the normal development of the foetus. This is suggested by several studies examining hormonal effects of shift and night work [86,87]. A recent prospective analysis of two cohorts of the Nurses Health Study showed significantly increased levels of oestradiol and decreased excretion of melatonin after many years of night work [88].

Psychosocial work stress

Stress is known to interfere with the endocrine system of women, often manifested by menstrual disorders. The studies on the effect of work stress on menstrual and ovulatory patterns, and on fecundity and possibly on pre-eclampsia provide some positive evidence, but these studies have not established with certainty the independent role of work stress on female reproduction.

Exposure to stressful work conditions and its effects on the reproductive health of women are studied through the use of standardized instruments measuring stress [89,90]. The main outcomes examined by such studies include: menstrual function, fecundity and spontaneous abortion in occupations such as nurses, manufacturing workers and professional women. One difficulty in the study of work stress-related reproductive outcomes is that the negative reproductive event may be a source of stress in itself, making the direction of the 'cause-effect' relationship uncertain. One rare prospective study which tried to overcome this problem with a prospective design did not show a significant reduction in conception rate or in spontaneous abortion among women with higher work stress compared with other women [91].

Some studies have reported associations between work stress and negative effects on reproduction, especially among women under particular stress or in the presence of other risk factors. A study among nurses in the USA

Table 3. Summary of selected studies of adverse reproductive outcomes and work schedule

Author, reference and location (year)	Study population	Method	Results
McDonald *et al.* [60], Montreal, Canada (1988)	All workers	Large-scale survey of occupation and pregnancy outcome.	No increased risk for spontaneous abortion for shift work, but positive for hospital workers.
Axelsson *et al.* [76], Sweden (1989)	Hospital workers	Mail questionnaire with hospital record validation of spontaneous abortion.	Increased risk for spontaneous abortion for those working irregular hours (but not night work).
Infante-Rivard *et al.* [78], Canada (1993)	All workers	Case–control study of hospitalized spontaneous abortion and controls.	Increased risk for spontaneous abortion for evening work only.
Eskenazi *et al.* [77], California (1994)	All workers	Case–control study of ascertained spontaneous abortion and live births.	Increased risk for spontaneous abortion for shift work and night work.
Xu *et al.* [82], China (1994)	Textile workers	Questionnaire administered by nurse.	Increased risk for pre-term birth and LBW.
Axelsson *et al.* (1996) [79], Ahlborg *et al.* (1996) [80], Bodin *et al.* (1999) [81], Sweden	Midwives	Mail questionnaire to members of the Midwives Association.	Increased risk for spontaneous abortion for night work and three-shift schedule. Reduced fecundity for irregular work hours. LBW and pre-term birth.
Bisanti *et al.* [83], European countries (1996)	All workers	Telephone interview of post-partum women.	Increased time to pregnancy of women in shift work.
Tuntiseranee *et al.* [84], Thailand (1997)	All workers	Interview in prenatal clinics.	Increased time to pregnancy of women in shift work.
Zhu *et al.* [85], Denmark (2003)	All workers	Registry data.	Probable increased time to pregnancy in shift workers.

and Italy found that high stress at work was associated with altered cycle length and anovulatory cycles [92]. A similar study among women followed through a prepaid medical plan in California found that stressful work was related to cycle length [93]. In the same population, but on the basis of a much larger sample (almost 4000 women), the Californian investigators did not find an increased risk of spontaneous abortion among the women with more job stress. When high job stress was combined with other risk factors (older mother, smoking mother, primigravida), stress increased the risk for spontaneous abortion [94].

Several other studies have reported on positive associations between work stress and other reproductive health outcomes. A study among Chinese women in textile mills found that high work stress was associated with dysmenorrhoea [95]. A study of female lawyers found that long working hours (a marker for stress in this profession) was strongly associated with the risk of spontaneous abortion (OR = 3.0, 95% CI 1.5–6.6). Interestingly, self-reported stress was not a significant factor [96].

Job strain has been examined as a possible risk factor for pre-term delivery, because it induces a heightened production of catecholamines. This hypothesis was investigated in a case–control study of 421 women delivering a pre-term infant and 612 controls. The results suggest a modest association of chronic strain at work and preterm delivery, mostly observed among full-time workers and black women [97]. The role of catecholamines with possible pregnancy-induced hypertension in women with high job strain was also examined in a case–control study of gestational hypertension (n = 201) and pre-eclampsia (n = 128) and 401 controls. This study confirmed the hypothesis that nulliparous women exposed to job strain had a higher risk of developing pre-eclampsia (OR = 2.1 95% CI 1.1–4.1) and, to a lesser extent, also eclampsia (OR = 1.3 95% CI 0.8–2.2) [98].

Conclusions

As stated in the Introduction, our knowledge of how occupational exposures affect the reproductive health of women is not always conclusive. From the discussion and tables presented, it appears that for a number of exposures at work, the evidence is sufficient to warrant the maximum protection of the pregnant woman. These include exposures to anaesthetic gases, antineoplastic drugs, toxic metals and specific solvents, pesticides, heavy physical load and irregular work schedules. For other work risks, such as exposure to non-ionizing radiation, and psychosocial stress, the evidence is often suggestive but not conclusive.

Recent research has advanced the hypothesis that the risk for a negative pregnancy outcome associated with exogenous or endogenous factors may be modified by the presence of other maternal risk factors, including genetic variation in metabolic detoxification activities [99,100]. This might explain why work-related negative reproductive effects are observed in some women but not in others.

Another reason for the uncertainty of the epidemiologic evidence is related to methodological problems. These refer primarily to difficulties in defining exposures that occur during the more susceptible windows of the gestational period on the one hand, and in detecting negative reproductive outcomes on the other. Several new approaches have been developed in order to overcome these difficulties. Recent studies define exposures with more rigor than in the past and use specific markers of exposure to suspected toxic agents whenever possible. In several recent Scandinavian studies, for example, it has been possible to examine fertility in relation to exposures to lead or solvents recorded in the biological monitoring of workers. This approach is certainly an important step forward in the validity of epidemiological studies. Analogous markers of exposure for physical agents and ergonomic factors are more problematic, especially in retrospective studies. This is why the prospective approach, by defining the levels of exposure to specific risk factors prior to conception and during the gestation, provides more reliable conclusions.

The use of time to pregnancy as a measure of interference with the endocrine system has certainly proved to be a useful tool to detect early reproductive effects in many recent studies. However, several other aspects of female reproductive function are not adequately studied. There is little research on the menstrual function, on very early foetal loss, on age of menopause, on pre-eclampsia and pregnancy-induced hypertension and on post-term birth. In addition, most studies focus on single reproductive outcomes (e.g. delay in pregnancy, spontaneous abortion or LBW), overlooking the chain of events linking these outcomes. Another important aspect not yet sufficiently explored is the effect of work conditions on the endocrine equilibrium of women. In fact, the hormonal effects through the use of hormonal markers of ovarian uterine and menstrual function may be more sensitive indicators of reproductive interference. These may also be more appropriate for purposes of prevention, as they indicate early signs not only of reproductive health problems but also of ill-health of women in general.

It should also be remembered, however, that unreasonable overprotection of women may be both scientifically unsound (men as well as women are often vulnerable to the same hazards), as well as disadvantageous to the economic well-being of women. An example of a 'protective' policy damaging to women was the so-called 'foetal protection' policy adopted by some North American industries in the 1980s, whereby women of reproductive age were given the option of either sterilization or unemployment. The US Supreme Court put an end to this discriminatory practice on the basis of the legal and ethical principle that the workplace should be safe for all workers, including pregnant women.

The EU has recently developed uniform directives for the protection of women workers, and for the labelling of chemicals for reproductive toxicity. The next step is to reach an international agreement on the classification of reproductive hazards, and on the precautions to be taken for the protection of the reproductive health of both women and men. Such an agreement should include rules to safeguard the health of working men and women also in the developing world, similar to those adopted in the Western industrialized countries.

Conflicts of interest

None declared.

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