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IN-DEPTH REVIEWS

Effects of occupational exposure on the reproductive system: core evidence and practical implications

Alex Burdorf[1], Irene Figà-Talamanca[2], Tina Kold Jensen[3] and Ane Marie Thulstrup[4]

Introduction

With the increasing labour force participation among women in Western countries, many women will work during their reproductive years. This will increase the likelihood that women during pregnancy will be exposed to a variety of chemical, physical and psychosocial factors at work. The presence of hazardous conditions in workplaces has raised concerns about their potential effects on pregnancy outcomes and birth defects in offspring. Occupational exposure may directly affect the outcome of pregnancy, such as spontaneous abortion, stillbirth, pre-term birth, small-for-gestational age and birth weight. Occupational exposure may also interact with foetal development, resulting in health effects in the offspring that range from congenital birth defects, neurobehavioral disorders at young age and even cancer in older age. To complicate matters further, occupational exposure among men may result in direct effects on the male reproductive system as well as contribute to negative pregnancy outcomes and birth defects. Thus, the reproductive system of both women and men can be affected by occupational exposure and for most health effects both maternal and paternal exposure may be a relevant route. A timely recognition of the impact of hazardous agents on this broad array of reproductive effects will provide insight into the necessary precautions to be taken for the protection of reproductive health of both women and men.

In the scientific literature, there are many publications on adverse reproductive outcomes. Since the reproductive system is a complex, interconnected set of organs, tissues and hormones, there is a large variety of reported adverse effects of environmental agents on the reproductive system. However, the interpretation of an association between an occupational exposure and a reproductive health effect is almost always hampered by the fact that many adverse outcomes may be caused by multiple (work-related) factors, making it extremely difficult to attribute a particular outcome to a specific occupational exposure. In addition, negative outcomes may be due to adverse effects of occupational exposure on both the female and male reproductive system. A third critical issue is that occupational exposure may only be relevant during specific time windows, for example shortly before conception or during early pregnancy.

This issue of *Occupational Medicine* contains three extensive reviews on the epidemiological evidence of occupational hazards to human reproduction. The first comprehensive review focuses on the female reproductive system by addressing the influence of maternal exposure on fertility and pregnancy outcomes [1]. In the second review, the focus is the impact of maternal exposure on the adverse effects in the offspring, as characterized by a variety of birth defects [2]. The third review shifts emphasis towards the contribution of occupational exposure among men to male reproductive dysfunction, primarily measured by semen quality and fecundity [3]. Together these reviews present a comprehensive picture of the role of occupational risk factors in reproductive health. The main aims of this accompanying article are to present a summary of the core findings in the three reviews, to discuss important constraints in the interpretation of these results and then derive practical implications for research and practice in occupational health.

Evidence for effects of occupational exposure on the reproductive system

Table 1 presents the core findings in the epidemiological literature on the effects of maternal occupational exposure

[1]Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands.

[2]Department of Human Biology, University of Rome 'La Sapienza', Rome, Italy.

[3]Department of Environmental Medicine, University of Southern Demark, Odense, Denmark.

[4]Department of Occupational Medicine, Aarhus University Hospital, Aarhus, Denmark.

Correspondence to: Alex Burdorf, Department of Public Health, Erasmus MC, University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, The Netherlands. e-mail: a.burdorf@erasmusmc.nl

Table 1. Qualitative summary of the potentially adverse effects of occupational exposure on the female and male reproductive system

Occupational risk factor	Pregnancy outcomes (maternal exposure)	Birth defects (maternal exposure)	Semen quality (paternal exposure)
Physical factors			
Ionizing radiation	Spontaneous abortion	Congenital defects	Reduced sperm count Azoospermia
Noise (>90 dBA)	Spontaneous abortion, low birth weight, pre-term birth		
Heat			Reduced sperm count
Chemical agents			
Lead	Low birth weight	Neural tube defects	Reduced sperm count
Mercury	Spontaneous abortion		
Organic solvents	Spontaneous abortion		
Tetrachloroethylene	Spontaneous abortion	Cleft lip/palate	
Glycol ethers	Spontaneous abortion		Reduced semen quality
Dibromopropane	Menstrual disturbances, spontaneous abortion	Neural tube defects	Reduced semen quality
Ethylene oxide	Pre-term birth, spontaneous abortion	Cleft lip/palate	
Anaesthetic gases	Spontaneous abortion		
Antineoplastic drugs	Spontaneous abortion		
Pesticides			Reduced sperm count Azoospermia
Ethylenedibromide		Neural tube defects, cleft lip/palate	Reduced quantity and quality
Carbon sulfide			Reduced quantity and quality
Specific types of welding			Reduced quantity and quality
Psychosocial factors			
Irregular work hours	Spontaneous abortion, menstrual disturbances		
Stress	Spontaneous abortion, pre-term birth		
Physical load			
Heavy physical work (high energy expenditure)	Spontaneous abortion, low birth weight		
Frequent heavy lifting	Pre-term birth, spontaneous abortion		
Prolonged standing	Low birth weight, pre-term birth, spontaneous abortion		

on pregnancy outcomes and birth defects and of paternal occupational exposure on semen quality. In all the four exposure categories, maternal exposure before or during pregnancy may lead to spontaneous abortion and, to a lesser extent, pre-term birth and low birth weight. The latter two outcome measures reflect an effect on intra-uterine growth. The physical factor receiving most attention in the literature is ionizing radiation among health care personnel, both before and during pregnancy, which has been consistently associated with spontaneous abortion and congenital defects. Available evidence suggests that a dose to the unborn child of <1 mSv will protect against unacceptable risks. Chemical risk factors among health care personnel also include anaesthetic gases and antineoplastic drugs. Various other chemical agents may also result in spontaneous abortion and low birth weight, most notably exposure to heavy metals (inorganic lead and mercury), pesticides and organic solvents. Both latter types of exposures encompass a large range of specific chemicals, but most epidemiological studies are not specific enough to identify the particular solvents and pesticides that may lead to adverse pregnancy outcomes. Birth defects seem primarily related to exposure to lead, glycol ethers, organic solvents and pesticides. The same exposures have also been associated with a reduced semen quality, often characterized by a reduced total sperm count, reduced motility or abnormal morphology. Psychosocial factors have received less attention in epidemiological studies, but there is evidence that self-perceived stress particularly has adverse effects on pregnancy outcomes. With regard to physical load, women in jobs with a high energy expenditure and with frequent manual handling are at risk, but it is difficult to distinguish between both risk factors since jobs with heavy physical load are usually also those with frequent lifting of heavy loads, for example among health care personnel.

Table 2 presents the evidence of maternal and paternal exposure on fertility. Since time-to-pregnancy is the result of reproductive problems in a couple, it is difficult to separate the specific contribution of occupational exposures between the woman and her male partner. However, both maternal and paternal occupational exposures to ionizing radiation and heat have been established as

Table 2. Qualitative summary of the potentially adverse effects of maternal and paternal occupational exposure on fertility

Occupational risk factor	Maternal exposure	Paternal exposure
Physical factors		
Ionizing radiation	+	+
Heat	+	+
Chemical agents		
Lead	+	+
Mercury	+	
Toluene	+	
Aliphatic hydrocarbons	+	
Aromatic hydrocarbons	+	
Tetrachloroethylene	+	
Glycol ethers	+	+
Ethylene oxide	+	
Anaesthetic gases	+	
Pesticides	+	+
Psychosocial factors		
Irregular work hours	+	
Stress	+	

risk factors for fertility problems. Most chemical agents that are associated with adverse pregnancy outcomes and birth effects also seem to affect fertility, especially through the female-mediated pathway. The same observation holds true for the effects of stress and irregular work hours among women. The paternal exposures causing reduced fertility (Table 2) have also been identified as occupational risk factors for reduced semen quality (Table 1), indicating that the established effects of paternal exposures on fertility may find their origin in a male-mediated toxicity on semen.

Limitations in interpretation

The epidemiological studies reviewed by the In-Depth Review in this issue of *Occupational Medicine* assess those occupational risk factors most likely to be associated with adverse effects on the reproductive system. Although studies selected for the three reviews were limited to those with reasonably well-defined exposures and health outcomes, many uncertainties still exist as to the interpretation of the evidence presented.

A core issue is, undoubtedly, the exposure assessment in epidemiological studies. In most studies, the exposure assessment relied upon self-reported job titles by means of questionnaires. This assessment strategy is far too crude to establish a meaningful insight into the magnitude and duration of the specific exposure responsible for the observed health effect. Although some occupations have been consistently associated with reproductive effects, for example hairdressers and greenhouse workers, it remains difficult to identify the specific risk factor since in most workplaces these workers are exposed to a mixture of different risk factors and different chemical compounds. This severely limits the evaluation of the exposure–response relationship for single risk factors.

A second issue in the exposure assessment is the appropriate time window of exposure. It is well-established that maternal exposure in the few months before conception is important for fertility and that teratogenic effects may arise during the organogenesis phase during the first 3–8 weeks of pregnancy. Likewise, paternal exposure in the past few months before semen analysis is important, given the spermatogenic cycle span of ~72 days. However, long-term exposure may also be relevant when the exposure of interest causes irreversible changes, for example germ line DNA modifications, or where the agents are biopersistent and accumulate in body fat, such as several pesticides. For most occupational hazards, the appropriate time windows of highest susceptibility are not well-established, which hampers clear advice as to when preventive measures should be undertaken.

A specific feature of reproductive health is that the causal pathway of hazardous exposure in occupations may be female- or male-mediated. With regard to pregnancy outcomes and birth defects, the focus in the reviews was on the maternal exposure before and during pregnancy. There is extensive evidence from animal studies for male-mediated developmental effects (i.e. spontaneous abortions, growth retardation, malformations and behavioural abnormalities) of environmental agents [4]. Thus, it cannot be excluded that paternal exposure may have contributed decisively to the adverse health effects reported, especially in those occupations whereby a substantial overlap in work activities between partners is expected (e.g. health care personnel, agricultural workers).

A fourth issue related to the usability of the information on exposure in the epidemiological studies is the presence of long-term trends in exposure levels in Western countries. A comprehensive evaluation of long-term trends in occupational exposure based on almost 700 sets of data showed that most chemical exposures declined at rates between −4% and −14% per year, with a median value of −8% per year. Hence, occupational exposures are generally lower today than they were years or decades ago [5]. Changes in the production process and control measures have had a noticeable impact on exposure levels. In addition, toxic substances may have been replaced by less toxic agents. For example, in the past few decades in dry cleaning operations tetrachloroethylene (PER) has been partly replaced by trichloroethylene (TCE), but due to its classification as a probable carcinogenic substance in 1995 in some operations TCE has been replaced again by PER. Therefore, reproductive health effects observed in a particular industry years ago may no longer be a risk in the current workplace. Although several other studies in different industries have confirmed the downward trend in occupational exposure over time, one has to bear

in mind that industries may have outsourced the most dirty jobs towards less developed countries or less well-protected small enterprises, resulting in hazardous workplaces that are usually not covered by occupational health care. A recent illustration can be found in the European study on occupational hazards of the male reproductive system, whereby blood lead levels dropped considerably during the period 1965–95 in several West-European countries, but not in Poland [6].

In conclusion, the available evidence presented in this issue of the journal does not allow us to derive clear exposure–response relationships. Hence, it remains difficult to arrive at sound conclusions as to the amount of exposure that will require control measures to prevent the occurrence of adverse effects on the reproductive system.

Practical implications for occupational health

The occupational health professional is faced with difficult questions regarding the necessary measures to be taken to ensure that health effects on the reproductive system will not occur. These questions pertain to issues such as when to take action (which exposures constitute an unacceptable risk?) and the timing of the actual action (before or during pregnancy?).

Based on the precautionary principle, the occupational hazards presented in Tables 1 and 2 should be considered to warrant protection of women and men trying to conceive. In general, the precautions to be taken for the protection of the reproductive health of both women and men will not differ from the safeguarding of all workers. Some companies have policies that offer women who intend to become pregnant the option to be withdrawn from activities with exposure to specific chemicals, such as photoresistant solvents in the semiconductor industry or antineoplastic drugs in health care organizations. Given the large uncertainties in the type and level of exposure that constitutes a reproductive risk, it is advisable to limit this approach to those physical and chemical agents for which a formal risk assessment has identified the exposure situation as potentially harmful for the ability to conceive a child. In the European Directive 92/85/EEC, it is obligatory to fully inform women trying to conceive on the reproductive hazards of cytotoxic drugs and to protect women with reproductive capacity against blood lead levels >30 μg/dl [7,8]. In Germany, the latter value has been set at 10 μg/dl.

With respect to pregnant women, the aforementioned document of the European Union presents detailed guidelines on the requirements with respect to physical, chemical and biological agents, and industrial conditions including physical load, mental and physical fatigue, and physical and mental stress [8]. These guidelines contain mandatory provisions for pregnant woman preparing antineoplastic drugs or being exposed to lead. They state pregnant women should not be exposed to prolonged excessive heat or cold or work in a high-pressure atmosphere. Pregnant women should not be exposed to manual materials handling involving risk of injury, work at heights or work in awkward movements and postures, especially in confined spaces. They allow transfer to another job [8].

Conclusion

The evidence on occupational risk factors for adverse effects on the reproductive system is consistent for a limited number of risk factors, most notably exposure to lead, glycol ethers, organic solvents, pesticides and ionizing radiation. It remains difficult to arrive at sound conclusions on the level of exposure and the specific chemicals within the groups of glycol ethers, organic solvents and pesticides that are associated with an increased risk. Precautions to be taken for the protection of the reproductive health of both women and men have traditionally focused on pregnant women in the workplace. The available evidence strongly suggests that exposure in the few months before conception may be of importance too, both among women and men.

Conflicts of interest

None declared.

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