REVIEW

Review of recent epidemiological studies on paternal occupations and birth defects

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The main findings reported by recent epidemiological studies on paternal occupations and birth defects are reviewed, and the main limitations associated with these studies discussed. Epidemiological studies on paternal occupations and birth defects were reviewed for the period 1989 to 1999 inclusive. Systematic searches were made with search engines with related keywords. There were several common paternal occupations that were repeatedly reported to be associated with birth defects. These paternal occupations were janitors, painters, printers, and occupations exposed to solvents; fire fighters or firemen; and occupations related to agriculture. The common weaknesses in most of these studies include inaccurate assessment of exposures, different classification systems, different inclusion criteria of birth defects, and low statistical power. It is concluded that epidemiological studies, reported in the past decade, suggest that several common paternal occupations are associated with birth defects. Future studies could be focused on these specific, rather than general, occupational groups so that causative agents may be confirmed and thus enable appropriate preventive measures to be taken.

Occupational and environmental agents are the suspected causes for about 60% of birth defects with unknown aetiology.[1]

The existence of hazards in the workplace has raised concerns about the potential of these substances for adverse reproductive effects.

Historically, studies assessing the role of occupational exposure as aetiological agents for birth defects focused on maternal exposures during pregnancy. The role of paternal exposure received less attention despite animal evidence showing that exposures of males to toxic agents may result in congenital malformations in offspring.[2–9] With increasing concern about male reproductive function in the past decade, epidemiological studies are being published considering the role of paternal exposures by evaluating paternal occupations and risk of birth defects.

In this review, the epidemiological evidence about the relation between paternal occupations and risk of birth defects is summarised, and the limitations associated with the studies discussed.

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METHODS

Epidemiological studies on paternal occupations and birth defects were reviewed for the period 1989 to 1999 inclusive. These dates were chosen as we wanted to reflect on the findings over the past decade. Studies before 1989 were not included as there were earlier review papers that would have covered those periods. Systematic searches were made with search engines and related keywords. Only articles that detailed the reproductive effects on birth defects based on human epidemiological studies are presented in this paper. Where relevant we try to give a critique of the paper, but we have also attempted to provide sufficient information for the readers to evaluate the quality of the evidence.

RESULTS

Suggested pathway and relevant periods for male mediated teratogenesis

Table 1 summarises the possible pathways that have been suggested by several studies, which might explain associations between paternal exposures and congenital anomalies in offspring. Most congenital malformations are thought to be due to the interaction of both environmental and genetic influences.[10] They can be a consequence of genetic damage before conception or of the direct action of an agent on the embryo or fetus. Both processes can operate as a result of male or female exposure at different periods related to conception and pregnancy.[11]

There are some interesting findings from experimental research about the male mediated teratogenetic and mutagenetic effects on germ cells covering various stages of spermatogenesis.[2–6] Multiple mechanisms seem to be involved, including cytogenetic damage, proliferation arrest or delay, and fertilisation failure.[2] Extrapolations from results of experimental studies to humans are complicated because there are structural and functional differences between species, and the mechanisms of harmful effects are seldom known. Some possible mechanism include mutagenic damage to paternal germ cells or sperm DNA,[8 12 13] transmission of teratogenic agents through the seminal fluid and sperm,[12 14–16] and household contamination by substances brought home by the father.[12 17 18]

If toxin is presence in the seminal fluids, intercourse during pregnancy can lead to maternal systemic absorption of the toxin and eventual effects on the fetus.[19–21] High concentrations of some chemicals have been measured in the houses of workers exposed in their workplaces, and different diseases and health effects have been reported in their families.[12]

Table 1 Possible pathways relating to paternal occupation exposures

Classification	Relevant period	Postulated mechanisms
Acute	3 Months before conception First and second trimester of pregnancy	Mutagenesis of germ cells Toxin in seminal fluids, and mothers' contamination after intercourse Home contamination (working clothes, equipment) leading to exposure of mother during pregnancy
Non-acute	Lifelong before conception	Potential storage of chemicals Stem cell damage

Epidemiological studies

Table 2 summarises the main information about recent epidemiological studies on paternal occupations and birth defects. Although conclusive evidence is not available, interesting findings are emerging.

Some of these studies are large population based studies and others investigated specific birth defects and occupations.

Olshan *et al* studied 20 birth defect categories and 58 paternal occupations.[22–24] After adjusting for potential confounders (parental age, race, outcome of previous pregnancies), some associations between paternal occupations and birth defects were found. This study has several limitations. If a toxic agent only acts to produce fetal death, those associations would have been missed when studied cases simply include live births. The problem of multiple comparison remains unresolved. Potential confounding effects of other factors, such as socioeconomic status and maternal exposures, are not measured in this study. As such, the results must be viewed with caution. None the less, the study provided new leads for further evaluation of the role of father's occupation in the aetiology of birth defects.

Schnitzer *et al*[25] and Matte *et al* [26] compared major birth defects (live and stillbirths), which were retrieved from the Metropolotan Atlanta Congenital Defects Program, with matched controls in the Atlanta area of the United States. Several paternal occupational exposures from 6 months before to 1 month after the estimated date of conception were identified as being associated with birth defects (table 2). Paternal occupation was used as a surrogate for workplace exposure. As this was a case-control study the inherent problem of interviewee and selection bias cannot be eliminated.

What is interesting from both of these studies, based in the United States, is some common occupations reported to be associated with birth defects. Both studies reported increased odds of birth defects for paternal occupations for firemen, painters, janitors, and printers. From both the studies only firemen shared similar birth defects, and had increased odds of having children with cardiac anomalies (table 2).

The Baltimore-Washington infant study investigated the possible associations between paternal exposures (rather than occupation) and cardiovascular malformations.[27] Home interviews of parents of cases and controls elicited information on parental home and occupational exposures. Analysis focused on 12 cardiac diagnostic groups and paternal exposures during the 6 months preceding the pregnancy. Some significant associations were identified among fathers who were exposed to lead, ionising radiation, and solvents (table 2). It is interesting to note that the likelihood of exposure to solvent (paint stripping among painters) is also linked with an increased risk of cardiac anomalies (table 2).

The association between employment as a fire fighter and congenital heart defects among offspring have been reported repeatedly in the studies based in the United States.[22–26] A large Canadian study comprising 9340 fathers of children with at least one of three heart anomalies of interest and the equivalent number of matched controls were analyzed.[28] Paternal occupation of fire fighter was identified by linkage between a cohort of Metropolitan Toronto fire fighters, and live born cardiac congenital anomalies were retrieved from the Canadian Congenital Anomalies Surveillance System. Although the study had sufficient power to detect the level of risk reported in a previous study, the results did not support a hypothesis of increased risk of cardiac congenital anomalies among the offspring of fire fighters.

In Montreal, paternal occupation records within a survey of the occupation of 56 067 women and pregnancy outcome were analyzed for spontaneous abortion in 24 occupational groups adjusting for seven potentially confounding variables.[29] The analysis of congenital defects was based on 47 822 pregnancies. An association of developmental defects was found with processing food and beverages (table 2). However, there was no specificity in type of food, beverage, or congenital defects, and no obvious explanatory mechanism. Some significant findings may have occurred by chance among the many occupations analysed. Despite the fairly large sample size, no specific paternal occupation, other than food and beverage processing, was found to be associated with birth defects in this Canadian study.

The relation between paternal occupational exposure shortly before pregnancy and risk of spina bifida in offspring was studied by Blatter *et al*.[30] A total of 470 live born children with spina bifida aperta (as defined by the ninth revision of the international classification of diseases (ICD-9)) was identified by review of hospitals' medical records in The Netherlands. No associations were identified for other paternal occupational exposures, such as organic solvents.

Lead is a known fetal toxic agent for women. Lead can have a direct toxic effect on sperm or an indirect effect through endocrine dysfunction.[31 32] However, evidence about adverse effects of lead on reproductive outcomes in exposed men remains to be confirmed. Irgens *et al* in a population study investigated the reproductive outcome in offspring of parents who were occupationally exposed to lead in Norway. In that study, offspring of fathers exposed to lead had no increased risks of any of the analysed birth defects, although mothers exposed to lead had a significantly increased risk of neural tube defects.[33] One significant limitation of this study, as was pointed out by the authors, was that job titles were used as a surrogate to measure degree of lead exposure. This type of classification is open to misclassification. Also, some of the job titles used were obtained 10 years before conception of the offspring. This problem arises because registry of birth defects had to be linked to the population census records to obtain the occupational exposure.

Results from studies on male workers in a nuclear power plant[34] and medical practitioners (orthopaedic surgeons[35] and medical radiographers[36]) suggested that exposures to low levels of ionising radiation before conception may not be associated with birth defects. However, it must be noted that the statistical power in these studies was limited. Birth outcome in the offspring of fathers who were exposed to electric and magnetic fields at the time of sperm production were studied in two Swedish cohorts. No clear cut effects on infants

Table 2 Reported findings in recent epidemiological studies regarding the paternal occupations and birth defects

Type of study	Assessment of exposure	Assessment of birth defects	Main results		
			Occupation/exposure	Birth defect	OR (95% CI) or p value
Population registry based case-control study[22–24]	Birth certificate	Health surveillance registry	Janitors	Hydrocephalus	5.04 (1.23 to 20.64)*
				Ventricular septal defect	2.45 (1.10 to 5.45)*
				Other heart defects	2.35 (1.07 to 5.13)*
				Down's syndrome	3.26 (1.02 to 10.44)*
			Painters	Spina bifida	3.21 (0.91 to 11.36)
				Patent ductus arteriosus	2.34 (1.00 to 5.45)*
				Cleft palate	3.36 (1.19 to 9.46)*
			Forestry and logging workers	Cataract	2.28 (1.29 to 4.02)*
				Atrial septal defect	2.03 (1.35 to 3.05)*
				Hypospadias	1.83 (1.24 to 2.71)*
			Plywood mill workers	Patent ductus arteriosus	2.52 (1.08 to 5.87)*
				Pyloric stenosis	4.12 (1.41 to 12.07)*
				Dislocation of lip	2.71 (1.08 to 6.81)*
			Sawmill workers	Down's syndrome	1.43 (0.90 –2.66)
			Printers	Atresia of urethra	4.50 (0.97 to 20.81)
				Clubfoot	2.18 (1.17 to 4.05)*
			Fire fighters	Ventricular septal defects	2.70 (1.02 to 7.18)*
				Atrial septal defect	5.91 (1.60 to 21.83)*
			Mechanics	Down's syndrome	3.27 (1.57 to 6.80)*
			Farm managers or workers	Down's syndrome	2.03 (1.25 to 3.03)*
			Material moving equipment operators	Down's syndrome	1.88 (0.93 to 3.82)
			Food processors	Down's syndrome	1.79 (0.96 to 3.31)
			Sheet metal workers, iron workers, and other metal workers	Down's syndrome	1.57 (0.92 to 2.69)
Population based case-control study[25 26]	Interview	Congenital malformation programme	Firemen	Cleft lip	13.3 (4.0 to 44.4)*
				Other heart anomalies	4.7 (1.2 to 17.8)*
				Hypospadias	2.6 (1.1 to 6.2)*
				Clubfoot	2.9 (1.4 to 6.0)*
			Painters	Atrial septal defect	2.7 (1.0 to 7.4)*
			Farmers	Cleft lip and palate	3.3 (0.9 to 11.9)
			Janitors	Reduction defects upper limb	3.6 (1.0 to 13.5)*
			Carpenters, wood workers	Atrial septal defects	3.6 (1.3 to 9.8)*
			Electricians, electrical workers	Coarctation of aorta	3.0 (1.2 to 7.5)*
			Sheet metal, other metal workers	Cleft lip and palate	2.5 (1.1 to 5.7)*
				Patent ductus arteriosus	1.8 (1.0 to 3.5)*
				Gall bladder, liver anomalies	3.5 (1.0 to 12.6)*
			Motor vehicle operators	Small intestine atresia/stenosis	2.5 (1.0 to 6.4)*
			Printers	Cleft palate	2.1 (0.9 to 4.7)
				Gall bladder, live anomalies	9.0 (2.2 to 37.9)*
				Hip dislocation	6.7 (2.1 to 21.5)*
			Electronic equipment operators	Reduction defects upper limb	4.2 (1.3 to 13.7)*
			Food processors	Hydrocephalus	3.3 (1.2 to 8.8)*
				Down's syndrome	3.1 (1.3 to 7.6)*
			Policemen, guards	Transposition of great vessels	3.3 (1.1 to 9.8)*
				Hypospadias	2.3 (1.2 to 4.5)*
				Hip dislocation	3.8 (1.3 to 11.8)*
			Vehicle manufacturers	Anencephalus	4.6 (1.9 to 11.1)*
				Spina bifida	2.5 (1.0 to 6.3)*
				Cleft lip	4.7 (1.4 to 15.7)*
				Rectum, anus atresia/stenosis	5.1 (1.3 to 19.2)*
				Hypospadias	2.1 (1.0 to 4.4)*
				Down's syndrome	3.0 (1.1 to 8.6)*
				Other heart anomalies	3.3 (0.9 to 12.5)
			Anaesthetic gases exposure	Decreased risk for birth defects	0.4 (0.21 to 0.98)
Population based case-control investigation[27]	Interview		Jewelry marking	Atrial septal defect	12.6 (2.3 to 68.6)*
				Membranous ventricular septal defect	8.1 (2.0 to 33.3)*
			Welders	Endocardial cushion defect with Down's syndrome	1.8 (1.1 to 3.0)*
			Lead soldering	Pulmonary atresia	2.3 (1.1 to 4.9)*
			Ionising radiation exposure	Endocardial cushion defect without Down's syndrome	4.7 (1.7 to 12.6)*
				Endocardial cushion defect with Down's syndrome	5.6 (1.7 to 17.9)*
				Coarctation of the aorta	3.5 (1.5 to 8.0)*
			Paint stripping	Muscular ventricular septal defect	3.5 (1.5 to 8.5)*
				Hypoplastic left heart	11.9 (2.4 to 60.0)*
Matched case-control study[28]	Linkage with another cohort study	Congenital Anomalies Surveillance System	Fire fighters	Selected cardiac congenital anomalies	1.22 (0.46 to 3.33)

Table 2 continued

Type of study	Assessment of exposure	Assessment of birth defects	Main results: Occupation/exposure	Main results: Birth defect	OR (95% CI) or p value
Survey[29]	Interview	Interview	Food and beverage processing	Developmental defects	8.02 (O/E), p<0.05
Multicentre case-referent study[30]	Postal questionnaire, telephone interview	Review of medical records	Low exposure to welding fumes	Spina bifida	1.6 (1.0 to 2.6)*
			Low exposure to UV radiation during welding	Spina bifida	2.6 (1.2 to 5.6)*
			Moderate or high pesticide exposure	Spina bifida	1.7 (0.7 to 4.0)
			Stainless steel dust exposure	Spina bifida	2.0 (0.8 to 5.2)
Cohort?[35]	Interview	Interview	Orthopaedic surgeons, obstetricians, and gynaecologists	Birth defects	p<0.01
Nested case-control study[38]	Expert raters' estimation	Multiple linkage	Exposure to chlorophenate wood preservatives in the sawmill industry	Developing congenital anomalies of eye/genital organs Anencephaly/spina bifida	>1, p<0.05
Cohort?[40]	Minnesota Department of agriculture (MDA)	Birth registry	Private pesticide appliers	Circulatory/respiratory anomalies Urogenital anomalies Musculoskeletal/integumental anomalies	p=0.05 p=0.02 p=0.02
Prevalence survey[42]	Interview, Company records	Medical registers	Pesticide exposure	General birth defects	1.53 (1.04 to 2.25)*

*p≤0.05.

fathered by men who were exposed to electric and magnetic fields around the time of sperm production could be found in these two studies.[37]

Dimich-Ward *et al* conducted a nested case-referent study within a cohort of 9512 fathers, who had worked for at least 1 year in sawmills. Expert raters were asked to estimate the hours of exposure, applied to specific time windows before birth, in which chlorophenate (a wood preservative) had been used. They reported that offspring of fathers with cumulative exposures were at increased risks of developing congenital anomalies of the eyes and genital organs.[38] Fathers with higher cumulative exposures in the 3 month period before conception, had a 5.7 times greater risk of having infants with congenital cataracts.

A total of 261 matched pairs were studied for direct paternal involvement in the handling of pesticides during a defined period relative to conception and pregnancy in Spain.[39] A significantly increased risk of all selected congenital malformations for paternal exposure to pyridils was found (adjusted OR 2.77, 95% CI 1.19 to 6.44). However, this study had a limited statistical power in the analyses of exposure, or outcome, or subgroups. The problem of lumping congenital malformations was unresolved. It was impossible to assess the risk of specific defects or grouped defects properly. The cases were exposed to different types of pesticide. The effects of interaction among the different pesticides were not considered.

The 935 births to 34 772 state licensed private pesticide appliers in Minnesota (women <1%) were linked to the Minnesota state birth registry that contained 210 723 live births in the study time frame.[40] The birth defect rate for all birth anomalies was significantly increased in children born to male private appliers. The birth anomaly rate also differed by crop growing region. The pattern of excess frequency of birth anomalies by pesticide use, season, and alteration of sex ratio suggested exposure-related effects in pesticide appliers and the general population of the crop growing region of western Minnesota. Although this study has sufficient power to make meaningful associations between exposure to pesticides and birth defects, it is not known which specific type of pesticide may be implicated.

The reproductive histories of 1016 couples in which the men were directly exposed to pesticides were compared with 1020 couples who were not exposed to pesticides and belonged to the same socioeconomic group and age range.[41] Statistical analysis showed a significant decrease in fertile men and a significant increase in abortions among the wives of these exposed men. When compared with the offspring of the control group the frequency of live births decreased significantly; stillbirths, neonatal deaths, and congenital defects showed a significant increase in the offspring of exposed men. Smokers exposed to pesticides showed a higher effect than non-smokers exposed to pesticides.[41]

A survey of the flower growing industry assessed the possible association between adverse events and exposure to pesticides in a population occupationally exposed to heterogeneous groups of pesticides reported a moderate increased risk of malformed infants for pregnancies which occurred after work in the floriculture among the wives of the male workers.[42]

Although there are studies which reported the association between exposure to pesticide and birth defects, there are some reports of no association. Negative findings have been reported by some studies on relation between paternal agricultural work, exposures to pesticides, and selected birth defects (nervous system anomalies, cardiovascular anomalies, oral clefts, hypospadias, epispadias, musculoskeletal anomalies, and non-specific anomalies).[43 44] But these studies were reporting on specific anomalies. As such, conclusions could only be drawn to suggest that exposure to pesticides were not found to be associated with the specific anomalies studied and not all birth defects.

DISCUSSION

Although positive associations have been found in some of the studies reviewed, several methodological limitations and some controversial findings preclude definite statements on the relation between paternal occupational exposures and birth defects. Future research will benefit from taking the following issues into account.

Sources of information

Most of the studies were from developed countries—for example, the United States, Sweden, Finland, Norway, and Canada—with the United States contributing to a sizable proportion of all the studies. The exposure levels would be lower

Table 3 Comparison of occupational exposure assessment sources

Assessment sources	Birth certificates	Interview	Company records	Registers
Advantage	Ease of access and low cost Less recall bias The recorded paternal occupation seems more reliable than maternal occupation	Detailed information about occupational exposure can be acquired in standard way Confounder information may be available	Not subject to recall bias and tend to be more complete in recording occupational exposure	Ease of assess and low cost Less recall bias The recorded paternal occupation seems more reliable than maternal occupation Investigator can get the outcome information at any time
Disadvantage	Incompleteness Limited to the title of occupation, information bias is more likely Job changing may introduce the possibility of misclassification of exposure status Limited confounder information related to congenital malformation	Expensive and time consuming Certainty depends on the education level and professional knowledge Easy to contact effect Interview of the spouse may not provide valid and complete information Information bias is more likely	May lack the updating information about changing of exposure status over time for individual or certain job title The completeness and validity of data obtained may be not available Information of potential confounders may be insufficient	Confounding information may be scanty Problem of miscoding and wrong data entry may exist

and the working environment may be very different from that of the developing or third world countries. However, unless a country has a good system to monitor birth defects such studies would be difficult to conduct.

Accuracy of information

Accuracy of risk estimation depends on the accuracy of information on occupational exposures and disease end points.

Exposure assessment

Measurements of exposure during relevant periods and extent of exposures are key issues.

Paternal exposures before conception could theoretically contribute to the genetic defects in subsequent generations expressed as congenital malformations in the offspring.[11 45] A toxic agent can be retained in the body and gradually released a long time after exposure.[46 47] Paternal occupational exposures are likely to affect congenital malformations through the spermatogenesis cycle. However, development and functional maturation extend beyond organogenesis and even beyond the moment of birth, affording a much wider time span of opportunities for harmful effects than traditionally thought.[48]

Depending on biological consideration and experimental evidence, most studies concentrated on the exposure period of 3 or 6 months before conception and the first trimester of pregnancy.[25 27 39]

Defining exact exposure time relative to postulated mechanisms for male-mediated teratogenesis allows for a greater likelihood of identifying a particular mechanism, but so far it is difficult to know the actual date of conception, which leads to variation in estimation of critical period and misclassification of exposure. Timetables relevant to conception and pregnancy can only be used as crude estimates of periods of sensitivity. As such, caution is needed in interpretation of such information.[49]

In most studies on occupational exposures and congenital malformations, it is difficult to assess the extent of exposures accurately. The validity of reported occupational exposures depends on the sources of ascertainment. Exposure estimates in studies are usually based on a description of occupation or just occupational title, with no detailed information being available. Also, different coding systems made the findings of studies difficult to compare between countries. Some occupational titles may be similar but the nature of work could be very different. Also, the nature of certain occupational exposures may change over time. When this happens, occupation as a surrogate of workplace exposure would result in inconsistency.

Table 3 shows the usual sources from which the information of parental occupational exposures was derived. Direct biological measurements were seldom used.

The combination of interviews and assessment by experts seemed to be attractive in terms of balance between costs (economical) and benefits (statistical power). But the potential problem arose when judgment varied within an individual hygienist, even when the hygienist was blinded to case-control status. Inaccuracy may reduce the power in detecting associations due to non-differential misclassification.[50]

Some strategies should be considered in future research to improve the measurement of occupational exposures. Development of methods for quantitative assessment of exposure is needed. The definition of quantitative patterns of exposure for different tasks and determinants of exposure based on large sets of data on actual air, dermal, and biological measurements in exposed workers would be highly valuable.[39]

End point assessment

There is no unique international classification of birth defects in the world. Worldwide surveys showed that the frequency of congenital malformations varied greatly from country to country. The frequency depended on the time of observation after birth, the types of malformations included, and the differences in reporting and statistical procedures.[10] As such, the differential classification of birth defects and the different methods used across studies posed a challenge for interpretation.

It is important to note that with increasingly complex prenatal diagnostic procedures to detect birth defects earlier in pregnancy and with more accuracy, these birth defects may be electively terminated before birth.[51–55] Future studies would have to take this factor into consideration at the study design stage.

Statistical analysis

Most epidemiological studies could not draw consistent conclusions because data were not large enough to allow classification into specific malformations. The practice of broadly grouping malformations was often undertaken to increase sample size, with concomitant increases in study power.

Defining groups of malformations for analysis is a trade off between the loss of statistical power induced by splitting and the possible increase in misclassification resulting from lumping together unrelated malformations.[56]

Multiple comparisons used in studies increased the number of statistical tests and potential false positives.

Main messages

- Paternal occupations associated with birth defects were janitors, painters, printers, and occupations exposed to solvent; fire fighters or firemen; and occupations related to agriculture.
- Common weaknesses in most of these studies included inaccurate assessment of exposures, different classification systems, different inclusion criteria of birth defects, and low statistical power.
- Future studies could be focused on these specific, rather than general, occupational groups so that causative agents may be confirmed, thus enabling appropriate preventive measures to be taken.

CONCLUSION

Epidemiological studies, reported in the past decade, suggested several common paternal occupations that have been associated with birth defects. These paternal occupations were janitors, painters, printers, and occupations exposed to solvents; fire fighters or firemen; and occupations related to agriculture. The time has come now to move away from generalised studies of birth defects. Rather, future studies should be focused on these specific occupational groups. By studying specific occupational groups, exposure assessment could include not just history taking (with all its potential biases) but also environmental and biological surveillance results (past and present data). Then causative agents could be confirmed and appropriate preventive measures could be taken. In so doing the rate of birth defects associated with occupational exposure could then be minimised.

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