PATERNAL SMOKING AND RISK OF BIRTH DEFECTS

SUMMARY OF THE EVIDENCE

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Date: 22nd July 1993

Introduction

A number of studies have investigated the possible effects of maternal smoking during pregnancy on the risks of the child being born with a malformation, with most reviews of the available data concluding that while there is conflicting evidence for birth defects of all types [2,3], for spontaneous abortions there does appear to be some evidence of an association with maternal smoking [2,4]. However, few studies have considered the effects of paternal smoking. The first study to do so was published in 1974, when Mau and Netter [1] suggested that children of fathers who were heavy smokers had about twice the expected incidence of severe malformations than the children of non-smokers. Since then, at least six further studies have been published. A study investigating paternal smoking and spontaneous abortion was also published prior to the study by Mau and Netter, although a copy of it has not yet been received. A recent paper by Ames et al [9] suggested a possible mechanism, through oxidative damage to the sperm, by which paternal smoking may lead to a higher incidence of birth defects. It is their interest in the matter which has inspired this review, the objective of which is to provide a summary of the available epidemiological evidence pertaining to the possible risks of birth defects in the children of fathers who smoke, either during, or just prior to, the relevant pregnancy.

The Studies

Only seven studies were found which investigated the possible association between paternal smoking and birth defects. The main features of the studies are summarized in Table 1. Three were of a case-control design and four were prospective. The study by Seidman looked at all birth defects, without separating the results by diagnostic category,

while Hearey limited his study to neural tube defects, and the studies by Ahlborg and Windham considered only spontaneous abortions. The remaining three studies all looked at several diagnostic categories of birth defects.

None of the studies measured paternal smoking objectively, for instance by measuring nicotine metabolites in body fluids, relying instead on self-reported questionnaire data, gathered usually from the mother of the affected child, although attempts to interview the father were also made in the study by Hearey. The diagnosis of cases was based mainly on hospital records, although information from physicians, paediatricians and pathologists, labour wards, death certificates and autopsy reports were also used in some of the studies. The source of diagnosis was not stated in one study. The case-control studies matched for a variety of factors, with all including some index of the child's age. Levels of non-response were not stated at all in one of the studies, and were only given for the cases (10%) in another. Few differences in non-response were seen in the other two case-control studies. Reported levels of non-response in the prospective studies ranged from 2-28%.

Paternal Smoking and Risk of Birth Defects

The results from the three studies which looked at paternal smoking in relation to all types of birth defects are given in Table 2, which includes the unadjusted relative risks and ninety-five percent confidence intervals. Although all of the studies found raised relative risks, only two were significantly so, and in one of these the significance was marginal. Using a fixed effects model, meta-analysis gave a relative risk estimate of 1.13, which was statistically significant (95% CI 1.03-1.25). As there appeared to be some differences between the results of the studies a random effects model was also used, and this gave a risk estimate of 1.26, which was not significant (0.98-1.61).

All three of the studies considered the risk of birth defects in relation to the number of cigarettes smoked per day by the child's father, and the results are summarized in Table 3. The study by Zhang failed to find a statistically significant dose-response relationship, and although the other two studies appeared to show positive trends, neither reported the significance of their findings.

Analysis was also carried out according to the diagnostic subgroups considered by each of the studies, and the findings for each type are summarized in Table 4, which gives the number of studies investigating each defect category, and indicates the direction and significance of the results. Meta-analysis produced only one significantly raised relative risk, for multiple deformities (1.55, 95% CI 1.14-2.09) (Mau, Zhang). A significantly negative relative risk, of 0.20 (95% CI 0.10-0.60) was also produced for pyloric stenosis (Savitz). However, it should be borne in mind that no correction was made for multiple testing, and also that by chance one or two significantly positive or negative results would be expected from this number of tests. Table 5 summarizes the results for those studies which attempted to relate the risk of particular deformities with the number of cigarettes smoked per day by the father. Although several apparent dose-response trends were found, no estimates of the significance of these findings were given. No negative dose-response relationships were found.

Separation of Potential Effects of Maternal and Paternal Smoking

If both the parents of a child are smokers, separating out the effects of smoking by either the father or the mother is very difficult. However, only one study (Hearey) made no attempt to do this. The study by Zhang was limited to women who were non-smokers, and while the studies by Ahlborg, Savitz, Seidman and Windham included women who were themselves active smokers, they were separated out during the analysis, although Ahlborg and Seidman did not adjust for the amount smoked. The study by Mau analysed perinatal mortality excluding women who smoked, but did not make it clear whether the analyses concerning birth defects were similarly restricted.

Recording of Data on Smoking

Although all of the studies were concerned with paternal smoking, only one (Hearey) appeared to have collected smoking data directly from the father of the index child, with the other relying on information gathered from the mother. It is clearly possible that misclassification may occur due to inaccuracies in this information, as the mother may not have complete knowledge of the father's smoking habits, particularly in couples who are not actually living together. Additionally, all of the

case-control studies suffer from the problem that the smoking data was collected after the outcome of the birth was known. This may have affected parents' recall, with some over-estimating the amount smoked in an attempt to rationalize their child's illness.

Effect of Adjustment for Confounding Variables on Estimates of Relative Risk

Table 8 compares the available adjusted relative risks with the unadjusted ones, giving the factors adjusted for. It can be seen that, on the whole, the effects of adjustment appear to be quite minor, with no overall pattern of increase or reduction in risk for any diagnostic category. However, in the study by Savitz, the relative risk estimates increase or decrease by quite a large amount after adjustment, but the direction is not consistent. The failure of two of the studies to present the results separately for each factor adjusted for made the effect of any one particular variable impossible to estimate. Additionally, three of the studies did not appear to have carried out any form of adjustment at all. On the whole, although information on a large number of potentially confounding factors was collected by the studies, most had not adjusted for more than a few of them. Risk factors which have been suggested for birth defects in children include maternal smoking during pregnancy [1-11]; epidemic illnesses [5]; genetic factors [6,10]; parental age [6,8]; and environmental exposures, particularly alcohol intake, by both the mother [10,11] and the father [1,8,11]. It is therefore possible that one or more of these factors may be confounding any observed associations seen between paternal smoking and birth defects.

Difficulties in Interpretation of Meta-Analysis

The differing methodology used by the studies makes it difficult to ascertain the relative weight which should be given to each study. There may also be a failure to publish studies which do not find a positive result. As so few studies were found which looked at paternal smoking and birth defects in offspring it is difficult to reach any firm conclusions regarding this point.

Conclusions

At first glance the epidemiological evidence suggests a weak positive association between paternal smoking and birth defects of any type. All three of the studies which considered the risks for all types of birth defects found raised relative risks, two of which were significant. For birth defects of specific types, just over half of the relative risks presented were raised, although only two were significantly so. One significantly negative association was also found. However, the risk factors found were nearly all below 2.0, and at this level it would take only a small bias to produce a spuriously positive association, or to mask a true association. This is particularly true of studies based on small numbers of cases, as several of these were. Additionally, examination of the evidence suggests that important sources of bias may have been introduced from misclassification of paternal smoking habits and a lack of adjustment for confounding variables. Other study weaknesses may also have contributed to the observed associations.

Overall, when these factors are taken into account, the conclusion can be drawn that the epidemiological data provide little convincing evidence of a true association between paternal smoking and the risk of birth defects in the offspring.

References

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Table 1 Details of the studies

Study	Ref.	Location	Study design	No of cases	Control type	Matching factors
Mau	1	Germany	PR	68		
Hearey	2	USA	C-C	9	Population	DB,R,S
Seidman	3	Israel	PR	1295*		
Ahlborg	4	Sweden	PR	323		
Savitz	5	USA	PR	1437*		
Windham	6	USA	C-C	626	Population	DP,H
Zhang	7	China	C-C	1012	Population	DR,TB

* Estimated from data given

C-C = Case-control; DB = Date of birth; DP = Date of last menstrual period; DR = Delivery room; H = Hospital; PR = Prospective; R = County of residence; S = Sex of child; TB = Time of birth

Table 2 Risk of birth defects for paternal smoking during pregnancy: all types

Study	Unadjusted relative risk (95% limits)
Mau	2.23 (1.33-3.74)
Seidman	1.07 (0.95-1.20)
Zhang	1.21 (1.01-1.45)

All relative risks estimated from data given

Table 3 Risk of birth defects in relation to number of cigarettes smoked per day by father during pregnancy: all types

Study	Groupings of cigarettes per day				Relative risk by grouping				Significance of trend
Mau	0	1-10	11+		1.0	1.69	2.62		Not given
Seidman	0	<1 pack	≥1 pack		1.0	1.05	1.17		Not given
Zhang	0	1-9	10-19	20+	1.0	1.20	1.19	1.26	NS

NS = Not significant

Table 4 Summary of results by type of defect for paternal smoking during pregnancy

Defect	No. of studies	-ve		RR=1	+ve		Meta-analysis
		S	NS		NS	S	
All deformities	3	0	0	0	1	2	1.13(1.03-1.25)
Craniofacial defects:							
Craniosynostosis	1	0	1	0	0	0	0.60(0.20-1.60)
Refractive errors	1	0	1	0	0	0	0.80(0.70-1.10)
Strabismus	1	0	1	0	0	0	0.70(0.60-1.00)
Ptosis	1	0	0	0	1	0	1.10(0.60-2.10)
Unspec. eye anomalies	1	0	0	0	1	0	1.59(0.49-5.20)
Preauricular cyst	1	0	0	0	1	0	1.20(0.20-6.30)
External ear anomalies	1	0	0	0	1	0	1.41(0.68-2.95)
Microtia/absence of ear	1	0	0	0	1	0	1.55(0.54-4.51)
Branchial cyst	1	0	0	0	1	0	1.60(0.60-4.50)
Nasal aplasia	2	0	1	0	1	0	0.94(0.50-1.78)
Cleft lip ± palate	3	0	0	0	3	0	1.18(0.82-1.68)
Cleft palate	2	0	1	0	1	0	1.27(0.66-2.44)
Central nervous system defects:							
Anencephalus	1	0	0	0	1	0	2.12(0.99-4.55)
Microcephalus	1	0	0	0	1	0	1.41(0.35-5.68)
Hydrocephalus	2	0	0	0	2	0	1.32(0.72-2.45)
Neural tube defects	3	0	1	0	1	1	1.16(0.49-2.72)
Spina bifida	1	0	0	0	1	0	1.88(0.73-4.86)
Limb paralysis	1	0	1	0	0	0	0.50(0.20-1.20)
Cardiovascular system defects:							
Ventricular septal defect	2	0	1	0	1	0	1.28(0.77-2.13)
Pulmonic stenosis	1	0	0	0	1	0	1.30(0.40-4.20)
Atrial septal defect	1	0	1	0	0	0	0.90(0.20-3.10)
Patent ductus arteriosus	1	0	1	0	0	0	0.50(0.10-1.70)
Unspec. heart anomalies	2	0	0	1	1	0	1.10(0.70-1.74)
Lung hypoplasia/aplasia	1	0	1	0	0	0	0.84(0.37-1.88)
Gastrointestinal system defects:							
Diaphragmatic hernia	1	0	0	0	1	0	2.30(0.74-7.09)

Table 4 continued

Inguinal hernia	1	0	0	1	0	0	1.00(0.80-1.30)
Pyloric stenosis	1	1	0	0	0	0	0.20(0.10-0.60)
Unspec. enteral deformities	1	0	1	0	0	0	0.99(0.14-7.01)
Genito-urinary system defects:							
Undescended testes	2	0	1	0	1	0	1.22(0.85-1.76)
Hypospadias	2	0	1	0	1	0	0.92(0.61-1.38)
Urethral stenosis	1	0	0	0	1	0	1.90(0.60-5.70)
Incompetent ureterovesical valves	1	0	1	0	0	0	0.70(0.20-2.00)
Ureter dysplasia/agenesis	1	0	1	0	0	0	0.80(0.20-2.40)
Polycystic kidney	1	0	0	0	1	0	1.59(0.49-5.20)
Unspec. urogenital deformities	1	0	0	0	1	0	1.97(0.36-10.8)
Musculoskeletal defects:							
Clubfoot	2	0	1	0	1	0	0.97(0.64-1.47)
Hip dislocation	1	0	1	0	0	0	0.80(0.40-1.40)
Polydactyly	2	0	2	0	0	0	0.80(0.57-1.13)
Syndactyly	2	0	2	0	0	0	0.84(0.46-1.51)
Brachydactylia/adactylia	1	0	0	0	1	0	1.51(0.61-3.75)
Spine curvature	1	0	1	0	0	0	0.80(0.30-2.20)
Torticollis	1	0	1	0	0	0	0.90(0.30-2.30)
Unspec. musculoskeletal defects	1	0	0	0	1	0	1.98(0.18-21.8)
Dermatologic defects:							
Benign melanoma/dermoid cyst	1	0	1	0	0	0	0.70(0.40-1.20)
Pilonidal cyst	1	0	0	1	0	0	1.00(0.40-2.20)
Haemangioma	2	0	0	0	2	0	1.23(0.81-1.86)
Unspec. pigmentary anomalies	1	0	0	0	1	0	3.30(0.94-11.6)
Chromosomal abnormality:							
Trisomy 21	2	0	2	0	0	0	0.79(0.51-1.22)
Indeterminate sex	1	0	0	0	1	0	1.41(0.42-4.72)
Unspec. chromosomal aberrations	1	0	0	0	1	0	2.64(0.70-9.95)
Defined syndromes	1	0	0	1*	0	0	Not available
Spontaneous abortions	2	0	0	0	2	0	1.09(0.90-1.33)
Miscellaneous abnormalities	1	0	1	0	0	0	0.99(0.06-15.8)
Multiple deformities	2	0	0	0	1	1	1.55(1.14-2.09)

* Relative risk could not be calculated due to insufficient numbers

NS = not significant; S = significant

Table 5 Risk of birth defects, by type, in relation to number of cigarettes smoked per day by father during pregnancy

Study/ Type	Groupings of cigarettes per day				Relative risk by grouping			
Unspec. eye anomalies								
Zhang	0	1-9	10-19	20+	1.0	1.00	0.90	3.40
External ear anomalies								
Zhang	0	1-9	10-19	20+	1.0	1.70	1.10	1.50
Microtia/absence of ear								
Zhang	0	1-9	10-19	20+	1.0	1.20	2.10	1.10
Nasal aplasia								
Zhang	0	1-9	10-19	20+	1.0	0.70	1.80	2.70
Cleft lip ± palate								
Mau	0	1-10		11+	1.0	1.18		5.97
Savitz[1]	0	1-19		20+	1.0	0.90		1.90
Zhang	0	1-9	10-19	20+	1.0	1.00	1.00	1.20
Cleft palate								
Zhang	0	1-9	10-19	20+	1.0	1.70	1.60	1.40
Anencephalus								
Zhang	0	1-9	10-19	20+	1.0	2.50	2.00	1.80
Microcephalus								
Zhang	0	1-9	10-19	20+	1.0	1.40	1.20	1.80
Hydrocephalus								
Savitz	0	1-19		20+	1.0	3.50		1.50
Zhang	0	1-9	10-19	20+	1.0	0.80	1.60	1.10
Neural tube defects								
Mau	0	1-10		11+	1.0	1.57		1.13
Spina bifida								
Zhang	0	1-9	10-19	20+	1.0	1.40	1.50	3.20
Ventricular septal defect								
Savitz	0	1-19		20+	1.0	2.30		2.00
Zhang	0	1-9	10-19	20+	1.0	0.80	1.10	0.60
Unspec. heart anomalies								
Mau	0	1-10		11+	1.0	1.77		2.13
Zhang	0	1-9	10-19	20+	1.0	0.90	1.00	1.10

Table 5 continued

Lung hypoplasia/aplasia								
Zhang	0	1-9	10-19	20+	1.0	0.40	0.50	2.00
Diaphragmatic hernia								
Zhang	0	1-9	10-19	20+	1.0	1.00	2.60	3.40
Unspec. enteral deformities								
Mau	0	1-10		11+	1.0	∞	1.70	
Undescended testes								
Zhang	0	1-9	10-19	20+	1.0	2.10	1.30	1.20
Hypospadias								
Zhang	0	1-9	10-19	20+	1.0	1.30	0.60	0.30
Urethral stenosis								
Savitz	0	1-19		20+	1.0	1.50		2.40
Polycystic kidney								
Zhang	0	1-9	10-19	20+	1.0	1.60	1.30	2.00
Unspec. urogenital deformities								
Mau	0	1-10		11+	1.0	1.18	2.55	
Clubfoot								
Zhang	0	1-9	10-19	20+	1.0	1.70	1.80	1.90
Polydactyly								
Zhang	0	1-9	10-19	20+	1.0	0.80	0.80	0.80
Syndactyly								
Zhang	0	1-9	10-19	20+	1.0	1.30	0.50	1.20
Brachydactylia/adactylia								
Zhang	0	1-9	10-19	20+	1.0	0.90	2.00	1.60
Unspec. musculoskeletal defects								
Mau	0	1-10		11+	1.0	2.35	1.70	
Haemangioma								
Zhang	0	1-9	10-19	20+	1.0	1.20	1.30	0.80
Unspec. pigmentary anomalies								
Zhang	0	1-9	10-19	20+	1.0	2.10	4.10	3.70
Trisomy 21								
Zhang	0	1-9	10-19	20+	1.0	0.70	0.60	1.20
Indeterminate sex								
Zhang	0	1-9	10-19	20+	1.0	1.60	1.30	1.40
Unspec. chromosomal aberrations								
Mau	0	1-10		11+	1.0	3.15	2.27	

Table 5 continued

Spontaneous abortions							
Windham	0	1-10	11-20	20+	1.0	0.90	1.30	1.30
Miscellaneous abnormalities							
Mau	0	1-10	11+		1.0	2.35	∞	
Multiple deformities							
Mau	0	1-10	11+		1.0	0.78	3.41	
Zhang	0	1-9	10-19	20+	1.0	1.74	1.36	1.45

No tests of significance were carried out by any of the studies

1 Adjusted relative risks

Table 6 Effect of adjustment for confounding variables on estimates of risk of birth defects for paternal smoking

Study	Birth defect	Factors adjusted for	Relative risk (95% limits)
Seidman	All types	None	1.07(0.95-1.20)
		Maternal smoking	1.06(0.95-1.20)
		Severity of malformation	1.07(0.95-1.19)
		Maternal smoking and severity of malformation	1.06(0.94-1.19)
Ahlborg	Spontaneous abortion	None	1.06(0.65-1.73)
		Age, previous spontaneous abortion, education, planning of pregnancy, alcohol use	1.03(0.65-1.64)
Savitz	Craniosynostosis	None	0.60(0.20-1.60)
		Maternal age, race, education and smoking	0.80(0.20-2.40)
	Refractive errors	None	0.80(0.70-1.10)
		As above	0.80(0.60-1.10)
	Strabismus	None	0.70(0.60-1.00)
		As above	0.70(0.50-0.90)
	Ptosis	None	1.10(0.60-2.10)
		As above	1.30(0.60-2.70)
	Preauricular cyst	None	1.20(0.20-6.30)
		As above	1.20(0.20-7.40)
	Branchial cyst	None	1.60(0.60-4.50)
		As above	1.30(0.50-3.90)
	Nasal aplasia	None	0.80(0.40-1.70)
		As above	1.00(0.40-2.20)
	Cleft lip ± palate	None	1.40(0.40-4.60)
		As above	1.70(0.50-6.00)
	Cleft palate	None	0.70(0.20-2.70)
		As above	0.90(0.20-3.60)
	Hydrocephalus	None	1.90(0.50-6.90)
		As above	2.40(0.60-9.30)

Table 6 continued

Neural tube defect	None	0.60(0.20-2.00)
	As above	0.60(0.20-2.50)
Limb paralysis	None	0.50(0.20-1.20)
	As above	0.70(0.30-1.60)
Ventricular septal defect	None	1.80(0.90-3.60)
	As above	2.00(0.90-4.30)
Pulmonic stenosis	None	1.30(0.40-4.20)
	As above	0.90(0.30-3.30)
Atrial septal defect	None	0.90(0.20-3.10)
	As above	0.70(0.20-2.80)
Patent ductus arteriosus	None	0.50(0.10-1.70)
	As above	0.60(0.10-2.30)
Inguinal hernia	None	1.00(0.80-1.30)
	As above	0.90(0.70-1.20)
Pyloric stenosis	None	0.20(0.10-0.60)
	As above	0.20(0.00-0.80)
Undescended testes	None	0.90(0.50-1.50)
	As above	0.90(0.50-1.60)
Hypospadias	None	1.10(0.60-2.00)
	As above	1.20(0.60-2.30)
Urethral stenosis	None	1.90(0.60-5.70)
	As above	2.00(0.60-6.40)
Incompetent ureterovesical valves	None	0.70(0.20-2.00)
	As above	0.50(0.20-1.90)
Ureter dysplasia/ agenesis	None	0.80(0.20-2.40)
	As above	0.70(0.20-2.40)
Clubfoot	None	0.50(0.30-1.00)
	As above	0.50(0.30-1.00)
Hip dislocation	None	0.80(0.40-1.40)
	As above	0.90(0.50-1.70)
Polydactyly	None	0.80(0.40-1.50)
	As above	0.50(0.30-1.00)
Syndactyly	None	0.70(0.30-1.80)
	As above	0.80(0.30-2.10)
Spine curvature	None	0.80(0.30-2.20)
	As above	0.90(0.30-2.80)

Table 6 continued

	Torticollis	None	0.90(0.30-2.30)
		As above	0.80(0.30-2.40)
	Benign melanoma/ dermoid cyst	None	0.70(0.40-1.20)
		As above	0.70(0.30-1.20)
	Pilonidal cyst	None	1.00(0.40-2.20)
		As above	1.10(0.50-2.60)
	Haemangioma	None	1.30(0.80-2.30)
		As above	1.30(0.70-2.40)
	Trisomy 21	None	0.80(0.40-1.80)
		As above	1.10(0.50-2.60)
Windham	Spontaneous abortion	None	1.10(0.89-1.36)
		Maternal smoking	1.18(0.85-1.65)
		Maternal age, race, use of bottled water, caffeine, alcohol and tobacco, prior foetal loss, marital status, insurance coverage, paternal age, race, education and alcohol consumption	1.00(0.79-1.26)