ORIGINAL ARTICLE

Paternal exposure to agricultural pesticides and cause specific fetal death

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Aims: To study the association between fetal death and paternal agricultural occupation in areas and time periods with different levels of use of agricultural pesticides.
Methods: A total of 1 473 146 stillbirths and births occurring in Spain between 1995 and 1999 were analysed.
Results: The offspring of agricultural workers had the highest risk of fetal death from congenital anomalies in the southern and eastern area (where pesticide use is greatest) and the lowest risk in the rest of Spain. In both areas the offspring of agricultural workers had a similar excess risk of fetal death from the remaining causes of death. The relative risk of fetal death from congenital anomalies in infants conceived between April and September (the months of greater use of pesticides) in the southern and eastern area was 0.90 in manual workers and 1.62 in agricultural workers, compared to non-manual workers; in individuals who were conceived during the rest of the year, the relative risk was 0.87 and 0.85, respectively. In both periods the offspring of agricultural workers had an excess risk of fetal death from the remaining causes of death.
Conclusions: Paternal agricultural work in the areas where pesticides are massively used increases the risk of fetal death from congenital anomalies. The risk is also increased for fetuses conceived during the time periods of maximum use of pesticides The higher risk of fetal death from the remaining causes of death in the offspring of agricultural workers seems unrelated to pesticide exposure.

The results obtained in different studies about the relation between adverse reproductive outcomes and parental agricultural occupation are not consistent. Whereas some studies show that the children of agricultural workers have a higher rate of fetal death and/or perinatal mortality than the children of non-agricultural workers,[1 2] probably due to exposure to pesticides,[2 3] other studies do not find differences between agricultural and non-agricultural workers in these adverse reproductive outcomes,[4–6] nor do they find convincing evidence that perinatal death is associated with the use of pesticides.[7]

One possible explanation for these inconsistent results is that leading causes of fetal death and perinatal death are different from one place to another. It has been observed that the offspring of agricultural workers have a higher risk of congenital anomalies,[1 7–10] but whereas congenital anomalies in the mid-1990s represented around 20% of deaths during the first year of life in some countries, in others that percentage was almost 40%.[11]

One methodological approach to the measurement of the risk of fetal death among agricultural workers compared to other occupations would be to study both fetal deaths from congenital anomalies and fetal deaths from other causes of death. Thus, the objective of this study is to analyse data on stillbirths and births occurring in Spain in 1995–99 in order to measure the association between fetal death from specific causes and father's occupation in two areas of the country and at two times periods with different use of agricultural pesticides.

MATERIALS AND METHODS

Source of data

The data consist of individual records from the Stillbirth and Birth National Register of Spain for the period 1995–99. This register contains information on all pregnancies in Spain ending in live birth or late fetal death—stillbirth at 26 weeks or more of gestation. For legal reasons, the register also includes infant deaths within 24 hours of birth. Underreporting of late fetal death and infant death within 24 hours of birth to the Registry is about 30%.[12 13] The information obtained from the Stillbirth and Birth National Register for the present study includes the year and month of birth, weeks of gestation, sex and weight of the product of conception in grams, cause of late fetal death or of death in the first 24 hours of life (in accordance with the International Classification of Diseases), and parental information (age, marital status, mother's economic activity, and father's occupation). The total number of observations included in the study was 1 473 146, which represents 80% of all the stillbirths and live births occurring in Spain between 1995 and 1999. The remaining 20% were not included in the analysis due to lack of information on birth weight (4%), father's occupation (14%), or both variables (2%).

Variables

Fetal deaths are defined as stillbirths at 26 weeks or more of gestation plus deaths in the first day of life. The population at risk was composed of all live births and stillbirths. The causes of death studied were congenital anomalies and all other causes except congenital anomalies. We have also examined four specific causes of death included in the latter group that are responsible for the largest number of fetal deaths.

The father's occupational group was determined by the classification in the Stillbirth and Birth National Register of Spain, which uses the first digit of the 1968 International Standard Classification of Occupations.[14] For the purposes of the present study, individuals were classified into the following three groups: non-manual workers, including professionals, managerial, clerical, sales, and service workers; manual workers, including production, transport, labour, and related workers; and agricultural workers, including agriculture, forestry, and fish workers.

Main messages

- Evidence about the association between paternal exposure to pesticides and fetal deaths from congenital anomalies in offspring is incomplete.
- It is possible that agricultural pesticide exposure increases the risk of fetal deaths from causes other than congenital anomalies.
- Results suggest that paternal exposure to agricultural pesticides during the first months of gestation increases the risk of fetal death from congenital anomalies.
- Results do not support as a plausible pathogenic mechanism the mutation of germ cells due to pesticide exposure in the three months preceding conception.
- The higher risk of fetal death from the remaining causes of death in the offspring of agricultural workers seems unrelated to pesticide exposure.

Policy implications

- Pregnant women living with men who are involved in agricultural work should be protected during the first trimester of pregnancy from indirect exposure to pesticides.
- Further research is required to ascertain why the offspring of men who work in agriculture have an excess risk of fetal death from causes other than congenital anomalies.

Other variables included in the analysis because of their potential confounding effect were birth weight (<2500, 2500–2999, 3000–3500, >3500 g); weeks of gestation (unknown, <37, 37–42, >42 weeks); infant's sex; mother's age (<20, 20–24, 25–29, 30–34, >34 years); mother's marital status (married, not married); and mother's economic activity (unknown, works outside the home, housewife).

Analysis

We divided Spain into two areas depending on both geographical location and the mean annual amount of pesticides used in each one of the 50 provinces during the period 1995–99: southern and eastern Spain and the rest of Spain. The 16 provinces of the southern and eastern area were included between the 20 Spanish provinces with the greater mean annual amount of pesticides use. During the period of study, pesticide use in the southern and eastern area represented two thirds of all pesticides used in Spain, whereas the mean annual area of cultivation in this area was 37% of the area cultivated in the entire country (table 1). The greater pesticide use in the southern and eastern area is due to the fact that most crops in this area are grown on land requiring irrigation.

Cause specific relative risks of fetal death were calculated by paternal occupation and geographical area. Statistical analyses were based on the Poisson regression model with cause specific mortality as the dependent variable. Crude and adjusted relative risk were estimated. Of the 1 473 146 observations, 11% had no information on weeks of gestation and 8% had no information on mother's economic activity, but they were included as an additional category for these variables. Non-manual workers were the reference group for all the analyses.

Indirect exposure of the mother during the first trimester of pregnancy can affect the association between male pesticide exposure and congenital defects in offspring.[9 10 15] Because of this, the risk of fetal death from specific causes in fetuses conceived during the months of greater pesticide use and in fetuses conceived during the rest of the year were also compared in these groups of workers in the southern and eastern area. The estimated month of conception was based on the data available on weeks of gestation and month of birth, thus we could not include stillbirths and live births in which the number of weeks of gestation was unknown. Due to humidity and environmental temperatures, the highest use of pesticides in agriculture in the southern and eastern of Spain takes place between April and September. According to the National Institute of Toxicology, 70% of acute poisonings from the use of agricultural pesticides in this area during 1995–99 were produced during those months (table 2). Therefore, the risk for fetuses conceived during April to September in the southern and eastern area of Spain was estimated as compared to fetuses conceived during the rest of the year.

RESULTS

Table 3 shows the distribution of births—stillbirths and live births—included in each paternal occupational group, by the rest of the independent variables in the two areas analysed. The offspring of agricultural workers in both areas were more likely to have unknown weeks of gestation, mother's age lower than 20 years, and less likely to have an employed mother. The offspring of agricultural workers had the highest relative risk of fetal death from congenital anomalies in the southern and eastern area, but the lowest relative risk in the rest of Spain (table 4). The adjusted relative risk of death from congenital anomalies in manual workers and agricultural workers compared to non-manual workers was respectively 0.91 (95% CI 0.72 to 1.14) and 1.20 (95% CI 0.85 to 1.69) in the southern and eastern area and 0.94 (95% CI 0.73 to 1.22) and 0.64 (95% CI 0.30 to 1.38) in the rest of Spain. In fetal deaths from the remaining causes of death, the magnitude of the adjusted relative risk in manual workers and agricultural workers compared to non-manual workers was 0.91 (95% CI 0.83 to 1.00) and 1.20 (95% CI 1.05 to 1.38) in the southern and eastern area, and 1.08 (95% CI 0.98 to 1.19) and 1.26 (95% CI 1.01 to 1.57) in the rest of Spain (table 4).

Table 5 shows the relative risk of fetal death by period of conception in the southern and eastern area. In both periods the offspring of agricultural workers had an excess risk of fetal death from the remaining causes of death. After adjusting for all the variables, the relative risk of fetal death from congenital anomalies among births conceived between April and September was 0.90 (95% CI 0.64 to 1.28) in manual workers and 1.62 (95% CI 1.01 to 2.60) in agricultural workers compared to non-manual workers. In individuals who were conceived during the rest of the year, the relative risk in manual workers and agricultural workers was 0.87 (95% CI 0.62 to 1.23) and 0.85 (95% CI 0.47 to 1.52), respectively. Relative risks of fetal death from the remaining causes of death in manual workers and agricultural workers, after adjusting for all the variables were, respectively, 0.91 (95% CI 0.79 to 1.04) and 1.35 (95% CI 1.11 to 1.65) for births conceived between April and September, and 0.94 (95% CI 0.83 to 1.07) and 1.22 (95% CI 0.99 to 1.49) for those conceived during the rest of the year. When specific causes of fetal death were analysed, there were no statistically significant differences in the relative risks after adjusting for all the variables (table 6).

The relative risks of fetal death by trimester of conception in the offspring of agricultural workers in the southern and

Table 1 Mean annual amount of agricultural pesticides used and mean area (in hectares) cultivated annually in two areas of Spain*, 1995–99

Areas	Mean number of tons of pesticides used annually		Mean number of hectares cultivated annually	
	Number	%	Number	%
Total	8830401	100.0	18829403	100.0
Southern and eastern Spain†	6022333	68.2	6891561	36.6
Rest of Spain	2808068	31.8	11937842	63.4

*Estimates based on information provided by the Professional Association for Plant Protection and by the Ministry of Agriculture.
†Includes the following provinces: Alicante, Almería, Barcelona, Badajoz, Cádiz, Córdoba, Castellón, Granada, Huelva, Jaén, Lleida, Málaga, Murcia, Sevilla, Tarragona, and Valencia.

eastern area were also estimated and the results are shown is table 7. The highest adjusted relative risk of fetal death from congenital anomalies was for births conceived in the third and second quarter; in contrast, little difference was seen in the magnitude of the adjusted relative risk of fetal death from the remaining causes of death among births conceived in the four quarters.

DISCUSSION

Fetal death from congenital anomalies

After adjusting for potential confounding variables, no significant differences were seen in the risk of fetal death from congenital anomalies among the three occupational groups in the two areas of study. Nevertheless, the occupational group composed of fathers who worked in agriculture had the highest risk of fetal death from congenital anomalies in the southern and eastern area and the lowest risk in the rest of Spain. When we analysed births and stillbirths in the southern and eastern area, we found a statistically significant excess risk of fetal death from congenital anomalies in the offspring of agricultural workers who were conceived during the period of greater pesticide use. This phenomenon was not observed, however, in the pregnancies that were conceived in the rest of the year. Likewise, when we analysed only the offspring of agricultural workers in the southern and eastern area, we found that the highest risk of fetal death was observed in offspring conceived in the two quarters of the year with maximum pesticide exposure.

Different studies have found an association between exposure of women to pesticides in the first trimester of pregnancy and the occurrence of congenital anomalies,[9 10 16–18] but there is little, and less conclusive, evidence of the association between paternal exposure to pesticides in the first trimester of pregnancy and the development of congenital anomalies.[9 19] The findings of this study support the existence of an association between pesticide exposure in fathers who work in agriculture during the first trimester of pregnancy and the risk of fetal deaths from congenital anomalies in offspring. The routes of exposure to pesticides include inhalation, absorption through the skin, contamination of water, ingestion of residues present in food, or some combination of all of these.[6 20] Indirect maternal exposure to pesticides can occur in relation to father's occupation in agricultural work through contamination of work clothing and work materials or equipment stored at home.

Table 2 Number of reported poisonings due to contact with an agricultural pesticide in the southern and eastern area, by quarters, during the period 1995–99*

	No.	%
Total	2209	100
January–March	345	15.6
April–May	719	32.5
June–September	816	36.9
October–December	338	15.3

*Estimates specifically elaborated for the authors by the National Institute of Toxicology.

Another pathogenic mechanism for congenital malformations through pesticide exposure in fathers is the mutation of germ cells.[21 22] Germ cell damage from chemical exposure can occur throughout gametogenesis. A whole spermatogenic cycle in man requires 63–74 days, so meiotic divisions leading to the formation of sperm cells extend to a maximum of 11 weeks before conception.[23] Consequently, roughly three months preceding conception would define the relevant exposure period in relation to this mechanism. However, the results found do not support this mechanism: despite the fact that the third quarter of the year is the period of maximum pesticide use, the offspring of agricultural workers conceived in the fourth quarter of the year have a relatively low risk of fetal death in comparison with offspring conceived in the other quarters. Likewise, although the first quarter was a period of low pesticide use, the offspring of agricultural workers conceived in the second quarter of the year had a relatively high risk of fetal death in comparison to offspring conceived in the other quarters.

Although the observed relative risk may at first sight seem relatively low, its relevance might be potentially high for research and public health. First, because the number of exposed individuals is rather high. Second, because more refined measures of exposure may unveil higher risks. And third, because the findings suggest new paths for research, in order to take into account the fact that pesticide exposures likely exert their effects by interacting with other environmental factors or the need to integrate women's exposure to pesticides.

Fetal death from causes other than congenital anomalies

After adjusting for the potential confounding variables, the offspring of agricultural workers had an excess risk of fetal death from causes other than congenital anomalies in both areas of study. The excess risk was similar in each area. When we analysed births and stillbirths in the southern and eastern area, this excess risk of fetal death among the offspring of agricultural workers was also observed in both periods of study. Although the magnitude of excess risk was higher in the first period than in the second, this difference is probably due to chance, since there were no statistically significant differences in the risk of fetal death from these causes among the offspring of agricultural workers in the southern and eastern area who were conceived in any of the four quarters. These results suggest that exposure to pesticides during the period around conception is not related to the higher risk of fetal death from these causes.

Table 3 Characteristics of births in each area of Spain, by father's occupational group, 1995–99; percentage distribution

	Southern and eastern Spain (*)			Rest of Spain		
	Non-manual workers	Manual workers	Agricultural workers	Non-manual workers	Manual workers	Agricultural workers
Number of births	368190	310538	61543	452239	253352	27284
Characteristics						
Weight <2500 g	5.9	6.5	6.1	6.3	6.9	6.1
Unknown weeks of gestation	13.5	15.0	18.6	7.2	8.7	13.9
<37 weeks of gestation	6.5	7.1	8.5	6.6	6.5	6.6
Male infants	51.7	51.6	51.6	51.5	51.4	51.8
Mother's age <20 years	1.2	3.3	6.5	1.2	3.1	3.3
Mother's age >35 years	18.4	11.9	13.1	20.4	13.1	16.4
Not married mother	9.5	11.4	11.5	10.7	12.8	9.6
Employed mother	63.5	39.2	26.5	65.3	38.9	29.6

It is unlikely that these results can be compared to those of other studies. Very few studies have measured the association between fetal deaths from causes other than congenital anomalies and parental agricultural occupation and/or exposure to pesticides. Two studies that used the same data yielded inconsistent results: one study that looked at self reported maternal occupation and home pesticide use found an association between occupational exposure during the first two trimesters of gestation and all causes of fetal death and fetal deaths due to complications of the placenta, cord, and membranes;[16] in contrast, the other study found no relation between residential proximity to applications of agricultural pesticides and fetal deaths from causes other than congenital anomalies.[15] Some studies have noted that the possible relation between exposure to pesticides and the risk of fetal death from causes other than congenital anomalies is produced in the second trimester of pregnancy.[15 24] In our study, however, it is unlikely that pesticide exposure during the second trimester is associated with an excess risk of fetal death from these causes of death, given the similarity of the results in the offspring of agricultural workers conceived in each of the four quarters of the year.

According to estimates obtained in the 1997 Spanish National Health Survey,[25] 84% of the wives of non-manual workers and 80% of the wives of manual workers between 20 and 44 years of age had visited a gynaecologist at least once in their lives. In contrast, this percentage among the wives of agricultural workers was 68%, which suggests the possibility that a smaller percentage of these women's pregnancies were under medical supervision, therefore they had a higher risk of fetal death. However, we found that the results for fetal deaths related with diseases of the mother, with obstetrical complications or with hypoxia and asphyxia at birth were similar to those for fetal deaths from poorly defined conditions in the perinatal period: risk of fetal death was higher in the offspring of agricultural workers than in offspring of non-manual and manual workers, although no statistically significant differences was found due to the scarce number of deaths. Thus, we cannot rule out the possibility that the wives of agricultural workers have a generalised susceptibility to pregnancy terminating in fetal death. The challenge of future investigations in this field is to focus on identifying the causes that increase the risk of fetal death from causes other than congenital anomalies in agricultural workers, especially in places like Spain where they represent 85% of fetal deaths.

Study limitations

In this study exposure assessment was mostly based on paternal job title, and ecological measures of pesticide use were used. However, we lacked specific individual information regarding pesticide exposure, and we have no information on types and levels of pesticides used. The estimate of the results by geographical area and time period partly minimises this limitation, but it is only an indirect indicator of the probable exposure or lack of exposure to pesticides in agricultural workers. In addition, due to the fact that it is impossible to carry out a dose-response analysis to show gradient of risk in agricultural workers with increasing exposure to pesticides, the increased risk for fetal death from

Table 4 Relative risk of fetal death from congenital anomalies and from all other causes of death, by father's occupation, in the two areas of study, 1995–99

	Southern and eastern Spain*				Rest of Spain			
Cause of death and father's occupation	No. of fetal deaths	Rate per 1000	Crude relative risk	Adjusted relative risk†	No. of fetal deaths	Rate per 1000	Crude relative risk	Adjusted relative risk†
Congenital anomalies*								
Non-manual workers	160	0.4	1.00	1.00	164	0.4	1.00	1.00
Manual workers	154	0.5	1.14 (0.91 to 1.42)	0.91 (0.72 to 1.14)	110	0.4	1.07 (0.83 to 1.37)	0.94 (0.73 to 1.22
Agricultural workers	44	0.7	1.65 (1.18 to 2.30)	1.20 (0.85 to 1.69)	7	0.3	0.71 (0.33 to 1.51)	0.64 (0.30 to 1.38)
All other causes of death								
Non-manual workers	1116	3.0	1.00	1.00	1041	2.3	1.00	1.00
Manual workers	1010	3.3	1.07 (0.99 to 1.17)	0.91 (0.83 to 1.00)	702	2.8	1.22 (1.11 to 1.35)	1.08 (0.98 to 1.19)
Agricultural workers	276	4.5	1.48 (1.30 to 1.69)	1.20 (1.05 to 1.38)	89	3.3	1.42 (1.14 to 1.76)	1.26 (1.01 to 1.57)

*Codes 740–759 of the International Classification of Diseases, 9th revision (ICD-9) for 1995–98 and codes Q00–Q99 of the International Classification of Diseases, 10th revision (ICD-10) for 1999.
†Adjusted for birth weight, infant's sex, weeks of gestation, age, marital status, and mother's economic activity.

Table 5 Relative risk of fetal death, by father's occupation, in infants born in the southern and eastern area who were conceived in April–September and in those conceived in the rest of the year, 1995–99

Cause of death and father's occupation	Conceived in April–September				Conceived in rest of year			
	No. of fetal deaths	Rate per 1000	Crude relative risk	Adjusted relative risk*	No. of fetal deaths	Rate per 1000	Crude relative risk	Adjusted relative risk*
Congenital anomalies†								
Non-manual workers	70	0.4	1.00	1.00	115	0.7	1.00	1.00
Manual workers	67	0.5	1.19 (0.85 to 1.66)	0.90 (0.64 to 1.28)	68	0.5	1.07 (0.77 to 1.48)	0.87 (0.62 to 1.23
Agricultural workers	26	1.1	2.40 (1.53 to 3.77)	1.62 (1.01 to 2.60)	15	0.6	1.17 (0.66 to 2.07)	0.85 (0.47 to 1.52)
All other causes of death								
Non-manual workers	494	3.1	1.00	1.00	453	2.8	1.00	1.00
Manual workers	431	3.4	1.08 (0.95 to 1.23)	0.91 (0.79 to 1.04)	470	3.5	1.12 (0.99 to 1.27)	0.94 (0.83 to 1.07)
Agricultural workers	131	5.3	1.72 (1.42 to 2.08)	1.35 (1.11 to 1.65)	122	4.8	1.56 (1.28 to 1.90)	1.22 (0.99 to 1.49)

*Adjusted for birth weight, infant's sex, weeks of gestation, age, marital status, and mother's economic activity.
†Codes 740–759 of ICD-9 and Q00–Q99 of the ICD-10.

congenital anomalies in offspring of agricultural workers in the southern and eastern area conceived between April and September, needs further exploration.

The group of agricultural workers includes several different types of workers. All, except for those in the fishing industry, may potentially have been exposed to pesticides. The influence of workers in the fishing industry, however, must have been small, since they represented only 20% of this group in the period studied.[26] In any case, if it is assumed that workers in the fishing industry are probably not exposed to pesticides, the results found for agricultural workers would be underestimated; this underestimate is however probably larger for the period of massive pesticide use as exposure of fishing industry workers does not change throughout the year.

On the other hand, the study hypothesis is based on exposure to pesticides as a potential risk factor for fetal death from congenital anomalies and other causes. However, it is well known that a wide variety of pesticides are used in agriculture, some of which have been shown in experimental studies to have teratogenic effects; for others such evidence does not exist.[27] A more accurate evaluation of risk would require an analysis by exposure to the different families of pesticides or active compounds; this approach is not possible, however, with the data in the present study

Another limitation is the impossibility of controlling for a possible effect of socioeconomic status. However, even if the socioeconomic status of agricultural workers is different from that of other workers, this would not explain why the results for fetal death from congenital anomalies vary, depending on the periods analysed. Furthermore, the evidence from this study suggests that parental socioeconomic status may not influence the risk of fetal death from other causes, given that the results in non-manual and manual workers were very similar.

One factor not included in the analysis that would increase the risk of fetal deaths from causes other than congenital anomalies is smoking.[28] According to the 1997 National

Table 6 Relative risk of fetal death from specific causes other than congenital anomalies, by father's occupation, in infants born in the southern and eastern area who were conceived in April–September and in those conceived in the rest of the year, 1995–99

Cause of death* and father's occupation	Conceived in April–September				Conceived in rest of year			
	No. of fetal deaths	Rate per 1000	Crude relative risk	Adjusted relative risk†	No. of fetal deaths	Rate per 1000	Crude relative risk	Adjusted relative risk†
Diseases of the mother and complications of pregnancy								
Non-manual workers	72	0.4	1.00	1.00	68	0.5	1.00	1.00
Manual workers	70	0.5	1.21 (0.87 to 1.67)	1.16 (0.82 to 1.62)	63	0.5	1.09 (0.78 to 1.54)	0.95 (0.67 to 1.36)
Agricultural workers	18	0.7	1.62 (0.97 to 2.71)	1.62 (0.95 to 2.76)	17	0.7	1.57 (0.92 to 2.67)	1.40 (0.80 to 2.42)
Obstetrical complications								
Non-manual workers	151	1.0	1.00	1.00	156	0.9	1.00	1.00
Manual workers	106	1.0	0.87 (0.68 to 1.12)	0.72 (0.56 to 0.93)	134	0.8	1.01 (0.80 to 1.28)	0.87 (0.68 to 1.10)
Agricultural workers	38	1.3	1.63 (1.14 to 2.32)	1.24 (0.86 to 1.80)	32	1.5	1.29 (0.88 to 1.88)	1.03 (0.70 to 1.53)
Hypoxia and asphyxia at birth								
Non-manual workers	64	0.4	1.00	1.00	67	0.4	1.00	1.00
Manual workers	62	0.5	1.21 (0.86 to 1.71)	0.94 (0.66 to 1.35)	74	0.5	1.30 (0.94 to 1.81)	1.02 (0.72 to 1.44)
Agricultural workers	23	0.7	2.32 (1.46 to 3.75)	1.62 (0.99 to 2.67)	18	0.9	1.68 (1.00 to 2.83)	1.15 (0.68 to 1.97)
Poorly defined								
Non-manual workers	117	0.6	1.00	1.00	102	0.7	1.00	1.00
Manual workers	98	0.9	1.04 (0.80 to 1.36)	0.85 (0.65 to 1.12)	117	0.8	1.35 (1.04 to 1.27)	1.17 (0.89 to 1.55)
Agricultural workers	29	1.1	1.60 (1.07 to 2.40)	1.29 (0.85 to 1.96)	28	1.2	1.72 (1.13 to 2.61)	1.40 (0.91 to 2.17)

*Codes 760–761 of the ICD-9 and P00–P01 of ICD-10 (diseases of the mother and complications of pregnancy), codes 762 of the ICD-9 and P02 of the ICD-10 (obstetrical complications), codes 768 of the ICD-9 and P20–P21 of the ICD-10 (hypoxia and asphyxia at birth) and codes 779 of the ICD-9 and P96.9 of the ICD-10 (poorly defined).
†Adjusted for birth weight, infant's sex, weeks of gestation, age, marital status, and mother's economic activity.

Table 7 Relative risk of fetal death from congenital anomalies and from all other causes of death, by trimester of conception, in children of agricultural workers in the southern and eastern area, 1995–99

Cause of death and trimester of conception	Crude relative risk	Adjusted relative risk*
Congenital anomalies		
January–March	1.00	1.00
April–May	1.83 (0.68 to 4.95)	1.64 (0.60 to 4.43)
June–September	2.61 (1.01 to 6.73)	2.45 (0.95 to 6.32)
October–December	1.37 (0.48 to 3.95)	1.29 (0.45 to 3.74)
All other causes of death		
January–March	1.00	1.00
April–May	1.16 (0.83 to 1.63)	1.05 (0.75 to 1.48)
June–September	1.06 (0.75 to 1.51)	1.00 (0.70 to 1.42)
October–December	0.95 (0.66 to 1.35)	0.90 (0.63 to 1.28)

*Adjusted for birth weight, infant's sex, weeks of gestation, age, marital status, and mother's economic activity.

Health Survey in Spain,[26] the percentage of smokers among the wives of non-manual and manual workers between 20 and 44 years of age ranged between 43% and 46%, while the percentage of smokers among the wives of agricultural workers of this age was 30%. Thus, if it had been possible to control for smoking in the analysis, the excess risk of fetal death in agricultural workers with respect to the other occupational groups would very likely have been higher.

On the other hand, various studies have shown that fetal deaths are underreported in Spain.[12 13] Underreporting does not show variation by sociodemographic variables such as as age or residence of the mother. Although it is not known whether underreporting varies by occupational group of the father, it is unlikely that this phenomenon is different in agricultural workers and the other groups.

In summary, the present study suggests that paternal agricultural work in the areas where pesticides are massively used in Spain increases the risk of fetal death from congenital anomalies, and the risk is also increased for fetuses conceived during the time periods of maximum use of pesticides. The higher risk of fetal death from the remaining causes of death in the offspring of agricultural workers seems unrelated to pesticide exposure.

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REFERENCES

1 **Mc Donald AD**, Mc Donald JC, Amstrong A, *et al*. Occupation and pregnancy outcome. *Br J Ind Med* 1987;**44**:521–6.
2 **Taha TE**, Gray RH. Agricultural pesticide exposure and perinatal mortality in Central Sudan. *Bull World Health Organ* 1993;**71**:317–21.
3 **Chia S-E**, Shi L-M. Review of recent epidemiological studies on paternal occupations and birth defects. *Occup Environ Med* 2002;**59**:149–55.
4 **Schwartz DA**, Newsum LA, Heifetz RM. Parental occupation and birth outcome in an agricultural community. *Scand J Work Environ Health* 1986;**12**:51–4.
5 **Savitz DA**, Whelan EA, Kleckner RC. Effect of parents' occupational exposures on risk of stillbirth, preterm delivery, and small-for-gestational-age infants. *Am J Epidemiol* 1989;**129**:1201–18.
6 **Kristensen P**, Irgens LM, Andersen A, *et al*. Gestational age, birth weight, and perinatal death among Norwegian farmers, 1967–1991. *Am J Epidemiol* 1997;**146**:329–38.
7 **McDonald AD**, McDonald JC, Armstrong B, *et al*. Fathers' occupation and pregnancy outcome. *Br J Ind Med* 1989;**46**:329–33.
8 **Kristensen P**, Irgens LM, Andersen A, *et al*. Birth defects among offspring of Norwegian farmers. *Epidemiology* 1997;**8**:537–44.
9 **García AM**, Fletcher T, Benavides FG, *et al*. Parental agricultural work and selected congenital malformations. *Am J Epidemiol* 1999;**149**:64–74.
10 **Nurminen T**, Rantala K, Kurppa K, *et al*. Agricultural work during pregnancy and selected malformations in Finland. *Epidemiology* 1995;**6**:23–30.
11 **World Health Organisation**. Mortality database. www.who.int/whosis/mort. Accessed 31 January 2002.
12 **Mosquera C**, González-Rico M. Calidad del registro de muertes perinatales, Asturias, 1986–90. *Gac Sanit* 1994;**8**:112–16.
13 **Rievert M**, Rué M, Moreno C, *et al*. Análisis del infraregistro de mortalidad perinatal y sus factores asociados en una región sanitaria de Cataluña. *Gac Sanit* 1998;**12**:63–70.
14 **International Labor Office**. *International standard classification of occupations*. Geneva: International Standard Classification of Occupations, International Labor Office, 1969.
15 **Bell EM**, Hertz-Piccioto I, Beaumont JJ. Case-cohort analysis of agricultural pesticide applications near maternal residence and selected causes of fetal death. *Am J Epidemiol* 2001;**154**:702–10.
16 **Pastore LM**, Hertz-Piccioto I, Beaumont JJ. Risk of stillbirth from occupational and residential exposures. *Occup Environ Med* 1997;**54**:511–18.
17 **Zang J**, Cai WW, Lee DJ. Occupational hazards and pregnancy outcomes. *Am J Ind Med* 1992;**21**:397–408.
18 **Bell EM**, Hertz-Piccioto I, Beaumont JJ. A case-control study of pesticides and fetal death due to congenital anomalies. *Epidemiology* 2001;**12**:148–56.
19 **García AM**, Benavides FG, Fletcher T, *et al*. Paternal exposure to pesticides and congenital malformations. *Scand J Work Environ Health* 1998;**24**:473–80.
20 **Rowland AS**. Pesticides and birth defects. *Epidemiology* 1995;**6**:6–7.
21 **Hemminki K**, Sorsa M, Vainio H. Genetic risk caused by occupational chemicals. *Scand J Work Environ Health* 1979;**5**:307–27.
22 **World Health Organisation**. *Effects of occupational factors on reproduction*. Copenhagen: Regional Office for Europe, WHO, 1985.
23 **O'Rahilly R**, Müller F. *Human embryology and teratology*. New York: Wiley-Liss Inc, 1992.
24 **White FM**, Cohen FG, Sherman G, *et al*. Chemicals, birth defects and stillbirths in New Brunswick: associations with agricultural activity. *Can Med Assoc J* 1988;**138**:117–24.
25 **Ministerio de Sanidad y Consumo**. *Encuesta Nacional de Salud, 1997*. Madrid: MSC, 1999.
26 **Instituto Nacional de Estadística**. Bases de datos. Encuesta de población activa. www.ine.es\inebase\cgi\um. Accessed 4 December, 2002.
27 **García AM**. Epidemiological evidence of pesticide exposure and adverse reproductive and developmental effects in humans. In: Vergieva T, Kaloyanova-Simeonova F, eds. *Proceedings from the Euroworkshop ''Current epidemiological evidence versus experimental data on reproductive and developmental toxicity of pesticides''*. Sofia: LA PCO, 2001:140–54.
28 **Cnattingous S**, Haglun B, Kramer MS. Differences in late fetal death rates in association with determinants of small for gestational age fetuses: population based cohort study. *BMJ* 1998;**316**:1483–7.