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Determinants of stillbirth mortality in Greece

Summary

A population-based case-control study of the determinants of stillbirths was conducted in Greece from 1989 to 1991. All reported stillbirths after 28 weeks of pregnancy (N=2,006) during the three year study period comprised the case group. The control group derived from random sampling of 10% of all livebirths in Greece, during the same period (N=30,705). The data were analysed by modelling through multiple logistic regression. The adjusted relative risk of stillbirth was significantly higher for males compared to females. A statistically significant monotonic increase in relative risk was observed with shorter gestational age, low maternal education, and older maternal age. Birthweight and parity showed a statistically significant U-shaped association with stillbirth risk, with a higher risk being observed among both low and high birthweight deliveries, as well as among primiparous or multiparous (4+) mothers. Positive associations of stillbirth with multiple births, out-of-wedlock marriage and non-Greek-orthodox maternal religion were noted in crude analyses, but these associations almost disappeared in the logistic regression model. Maternal urban or rural residence showed no relation to risk. Overall, the prospective risk of stillbirth after the 24th week of gestation in Greece has been estimated to be higher than that in Japan (a more developed country) with more than 40% of stillbirths occurring after the 36th week of pregnancy.

fetal mortality rates, since that time the relation has been reversed, with stillbirth rates exceeding those of neonatal deaths². Fetal deaths are part of a continuum of reproductive casualty, and differ from neonatal deaths in that death occurs in utero or during labor and delivery. Given that reproductive rates are steadily decreasing in most European countries, it is of great importance to study factors that influence reproductive hazards in general and fetal mortality in particular, in order to pursue methods to prevent or minimise adverse pregnancy outcomes.

Thus, we undertook a population-based case-control study in order to investigate the risk factors for fetal death in the Greek population, using routinely collected data from birth and death certificates. In 1991, approximately 700 late fetal deaths were recorded in Greece, giving a late fetal mortality of 6.9 per thousand liveborn. Table 1 presents the late fetal mortality in Greece in comparison to that of other selected European and North American countries and Japan. The rates vary greatly among different countries, but late fetal mortality in Greece is among the highest in the European Union³.

Perinatal mortality has decreased markedly in most developed countries during the recent decades. According to European and North American reports, published since 1950, the overall perinatal mortality rate has steadily improved, decreasing by 65–80%¹. Stillbirth rates in the United States dropped from 15.8 per thousand livebirths

in 1968 to 7.6 per thousand in 1989^{2,3}. Despite this decrease, among pregnancies of at least 20 gestational weeks, approximately one out of 100 infants is born dead. The decline in fetal mortality has not followed the same pattern as that in neonatal mortality; although until the mid-1970s neonatal mortality rates were higher than

Country	Year	Number	Ratio**
Austria	1990	325	3.6
Belgium	1985	764	6.5
Czechoslovakia	1986	1,089	4.9
Germany (Former Dem. Republic)	1988	1,076	5.0
Greece	1991	705	6.9
Ireland	1989	330	6.3
Italy	1990	3,112	5.5
Netherlands	1990	1,139	5.8
Portugal	1987	1,045	8.5
Romania	1990	2,231	7.1
Switzerland	1990	390	4.6
United Kingdom	1990	3,713	4.6
USSR (former)	1989	49,528	9.8
USA	1989	30,649	7.6
Canada	1989	1,626	4.1
Japan	1990	4,664	3.8

* Late fetal deaths are those after 28 or more completed weeks of pregnancy. Late fetal "mortality" is estimated as the ratio of late fetal deaths per thousand livebirths

** Ratios were estimated from the latest available data from the United Nations Demographic Year Books, and the World Health Statistics Annual

Table 1. Late fetal mortality* in selected European and North American countries and Japan.

Materials and Methods

Individual data for the 2,176 stillbirths during the 3-year period 1989–1991 in Greece were retrieved from the National Statistical Service of Greece, through a special search. Data were collected on gender, gestational age (in weeks), birthweight (in gm), type of pregnancy (singleton, multiple), parity (number of full-term pregnancies), maternal education (in years of schooling), maternal age, maternal religion (Greek orthodox or other), maternal permanent residence (urban, i.e. cities or towns with more than 10,000 inhabitants; non urban) and status of pregnancy (in our out of wedlock). Stillborn babies were used as cases in a case control (case referent) study. Controls (referent group) were chosen through random sampling of 10% of all liveborn babies in Greece during the same time

period (N=30,769). Stillbirths after a pregnancy of less than 28 weeks were excluded from the case control analysis, because there are indications that stillbirths are underreported during that period, particularly before the 24th gestational week. Livebirths before the 28th week of pregnancy were also excluded in order to satisfy the study's basic requirements. Thus the case control analysis was based on 2,006 stillborn and 30,705 liveborn children.

The design of the study allows the calculation of either the odds ratio or the risk ratio linking stillbirth to a particular exposure characteristic. Statistical procedures for the odds ratio are much more flexible compared to those focusing on the risk ratio^{4–6}. Furthermore, when the risk of the outcome under investigation is small, as in this instance, the odds ratio is a good approximation to the risk ratio.

The statistical analysis was done initially through univariate frequency distributions, allowing the calculation of crude odds ratios, and through multiple logistic regression that allows the calculation of mutually adjusted odds ratios and 95% confidence intervals. It should be noted that in this instance crude odds ratios are useful descriptors of associations, frequently reported in the demographic literature and used in clinical practice. In the logistic regression, most polytomous variables were used categorically (split into categories), since many of the relations are not log linear as postulated by the logistic model and some are not even monotonic. Additionally, we also used the data by gestational age of all stillborn and liveborn children in Greece in 1989 to 1991 after a gestation period of more than 24 weeks in order to calculate the prospective risk of stillbirth at any particular gestational week subsequent to the 24th. Prospective risk of stillbirth is a newly-proposed statistic, calculated as the number of stillbirths at or beyond a particular gestational week divided by the total number of births at or beyond this week, expressed per thousand⁷. This statistic represents in essence the changing risk of a stillbirth as the pregnancy progresses.

Results

Figure 1 shows the prospective risk of stillbirth from the 24th until the 40th gestational week in Greece during the 3-year period 1989 to 1991. For comparative purposes, published data for Japan are also presented⁷. The Figure also shows the cumulative percentage of stillbirths by gestational age in Greece. The Greek curve of prospective risk of stillbirth is systematically higher than that for Japan, but the difference is particularly striking between 26 and 34 weeks, whereas

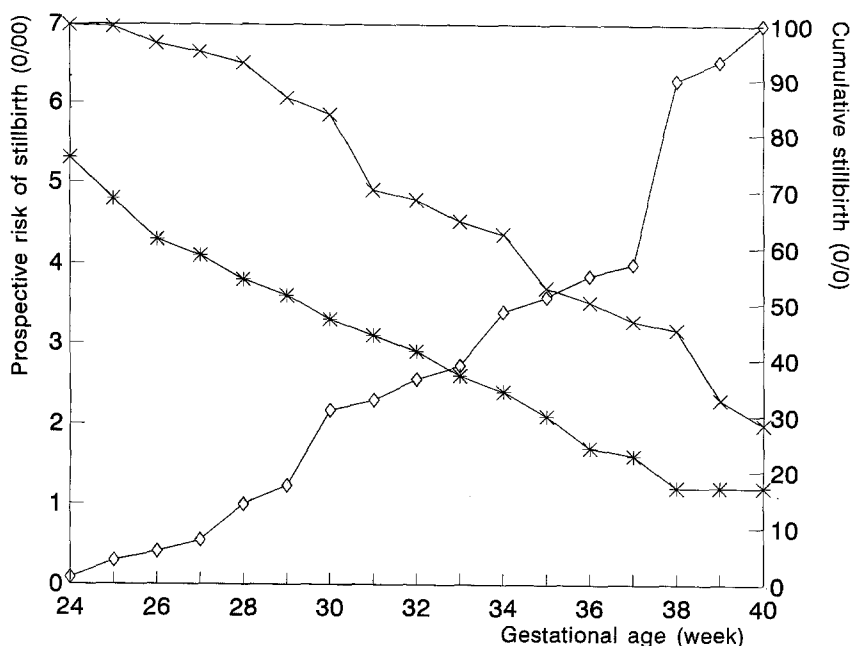


Figure 1. Prospective risk of stillbirth by gestational age in Greece (X) compared to Japan (*) calculated from all births reported during 1989–1991; and cumulative percentage of stillbirths (◇) by gestational age in Greece calculated from stillbirths after 24 weeks of pregnancy during the same time period.

it is less evident before the 26th week and after the 34th week. The cumulative percentage of stillbirths indicates that more than 40% of stillbirths in Greece occur after the 36th week of pregnancy, even though the individual risk is lower during this period than in earlier intrauterine life.

Tables 2–5 present data based on all stillbirths after 28 weeks of pregnancy, and a 10% random sample of all liveborn babies in the same country during the 3-year period 1989–1991. Tables 2 and 3 show univariate distributions by pregnancy characteristics and maternal demographic variables, whereas Tables 4 and 5 present mutually adjusted odds ratios as relative risk estimates (and 95% confidence intervals) of a stillbirth rather than a livebirth, by pregnancy or maternal characteristics. In Tables 2 and 3, confidence intervals of odds ratios are not present-

ed, because these are not directly interpretable on account of mutual confounding. Point estimates of odds ratios are also confounded, but their presentation serves a useful purpose, since they reflect the perceptions derived from clinical experience, such as the increased risk of stillbirth in multiple pregnancies and premature or low birthweight births.

Gender: the crude risk of stillbirth is 8% higher among male embryos in comparison to female ones. After adjustment for confounding – mostly by birth weight – the relative risk increases to a highly significant 1.26.

Gestational age: gestational age and birth weight are both independently and strongly related to stillbirth risk, but they are also strongly correlated. Therefore, low birthweight confounds the effect of

short gestational age. Controlling for birthweight reduces the effect of prematurity, but the latter remains a powerful predictor of stillbirth. Indeed, the almost nine-fold relative risk of stillbirth until the 31st week is only slightly reduced during the subsequent four weeks of pregnancy, although some underreporting during the earlier period may be responsible for the lack of a stronger trend. Even after controlling for birthweight the risk of stillbirth is approximately 70% higher in children born during the gestational period from 36–39 weeks.

Birthweight: as indicated, gestational age and birthweight are strongly correlated and the crude association of low birth weight with risk of stillbirth is strongly confounded by prematurity. Nevertheless, birthweight, which is more amenable to exogenous influences, is in itself a powerful predictor of stillbirth. The odds ratio for a stillbirth declines substantially for birthweights in excess of 2,500 gm (from 11.46 to 2.97) and the risk is minimised in the birthweight bracket 3,500–3,999 gm. The risk increases again for heavier embryos, and those over 5,000 gm have a risk of stillbirth as high as those weighing 2,000–2,499 gm at birth.

Multiple births: the risk of stillbirth is almost five times higher in multiple births compared to singleton pregnancies. The excess risk is accounted for by the low birthweight, frequent prematurity and high maternal age of multiple pregnancies. Controlling for these factors through multiple logistic regression wholly explains the elevated risk of stillbirth for embryos in multiple pregnancies.

Parity: the crude data on parity indicate a higher risk of stillbirth in primiparae, that is reduced in women in their second pregnancy

Variable	Categories	Stillborn (%)	Liveborn (%)	Crude Odds Ratios
Gender	female	46.8	48.6	baseline
	male	53.2	51.4	1.08
Gestational age (weeks)	28-31	27.1	0.7	140.53
	32-35	19.9	1.3	53.48
	36-39	45.8	73.1	2.18
	40+	7.2	24.9	baseline
Birthweight (grams)	≤1,499	29.8	0.5	225.78
	1,500-1,999	14.2	1.0	59.21
	2,000-2,499	15.4	3.3	19.14
	2,500-2,999	12.3	15.1	3.35
	3,000-3,499	17.0	40.5	1.73
	3,500-3,999	7.3	30.2	baseline
	4,000-4,499	3.0	8.0	1.54
	4,500-4,999	0.6	1.2	2.31
Multiple birth	no	89.1	97.5	baseline
	yes	10.9	2.5	4.78
Parity	1	48.7	44.1	1.39
	2	30.7	38.5	baseline
	3	12.1	12.3	1.23
	4+	8.5	5.1	2.06

Table 2. Univariate frequency distributions, in percentages, of all stillborn after 28 pregnancy weeks ($N=2,006$) and a 10% random sample of all liveborn ($N=30,705$) in Greece in 1989-1991, by pregnancy characteristics, with corresponding crude odds ratios.

and increases by 50% in women with four or more pregnancies after controlling for confounding. Primiparity is associated with young maternal age, which could be expected to introduce some negative confounding, whereas multiparity is associated with old maternal age, which would be expected to introduce positive confounding. Indeed, after adjustment for maternal age and other variables, the odds ratio of stillbirth for babies of primiparous mothers increases slightly from 1.39 to 1.47, whereas the odds ratio for multiparity (4+) is reduced from 2.06 to 1.51. Even after adjustment, the excess risk of stillbirth among children of both primiparae and multiparae remains significantly

higher than the corresponding risk among children born after a second or third pregnancy.

Maternal education: maternal education is weakly associated with stillbirth risk. However, after controlling for mutual confounding influences, women with less than seven years of schooling had a significant elevation of stillbirth risk.

Maternal age: after adjustment, there appears to be a monotonic relation of stillbirth risk with maternal age. Among women less than 20 years old the adjusted risk of stillbirth is relatively low, although the frequent correlation of young maternal age with primiparity elevates the crude risk to base-

line levels in the crude analysis. Statistically significant and modest elevations of stillbirth risk are noted among women 30-39 years old, whereas a more than two-fold elevation is found in the small group of women who give birth after the age of 40.

Maternal religion: less than 3% of children are born to women whose religion is not Greek orthodox. In this group, the risk of stillbirth is elevated, although the elevation is modest and of marginal statistical significance.

Maternal residence: there is no significant difference with respect to stillbirth risk between urban and non-urban areas. It is worth noting that the inverse crude association becomes positive after adjustment - a more plausible result.

Legal status: about 3% of children are born out of wedlock, and among these pregnancies the crude risk of stillbirth is 64% higher. The excess risk is accounted for by maternal education, parity, gestational age and birthweight.

Discussion

In the present all study all cases in the primary base were ascertained from death certificates from 1989-1991 and controls were randomly chosen from live birth certificates of the population that satisfied the study base principle⁶. The study explored maternal and fetal correlates of stillbirth, since the odds ratios for individual risk factors represent relative increases in the risk of fetal death. Use of routinely collected data limited the possibility of exploring the role of other environmental factors such as maternal nutritional intake, coffee and alcohol consumption as well as smoking habits. Nevertheless, the analysis of routinely ascertained sociodemographic and

Variable	Categories	Stillborn (%)	Liveborn (%)	Crude Odds Ratios
Maternal education	–6 years	39.1	32.3	1.25
	7–9	12.1	14.3	0.88
	10–12	36.5	40.6	0.93
	13+	12.3	12.8	baseline
Maternal age	–19 years	6.7	7.6	1.01
	20–24	27.9	32.0	baseline
	25–29	30.2	33.8	1.02
	30–34	22.8	18.7	1.40
	35–39	9.4	6.3	1.69
	40+	3.0	1.6	2.35
Maternal religion	Greek orthodox	96.5	97.7	baseline
	other	3.5	2.3	1.51
Maternal residence	urban	65.9	63.2	baseline
	non-urban	34.1	36.8	0.89
Wedlock	in	95.5	97.2	baseline
	out	4.5	2.8	1.64

Table 3. Univariate frequency distributions, in percentages, of all stillborn after 28 pregnancy weeks ($N=2,006$) and a 10% random sample of all liveborn ($N=30,705$) in Greece in 1989–1991, by demographic characteristics of the mother with corresponding crude odds ratios.

pregnancy characteristics of stillbirth provides useful information for the formulation of public health policies. It should also be noted that though there is a theoretical potential for selection or information biases, there is no evidence that any actually operated in the present study.

Some fraction of any cohort of fetuses alive at a given gestational age will ultimately die before birth in any country. However, Greece ranks very high with respect to stillbirth rate among other European countries. Additionally, the prospective risk of stillbirth as a function of gestational age was systematically higher in Greece than in Japan. Observed differences could be attributed, to a certain extent, to different national practices in reporting perinatal deaths, which could bias the comparisons of fetal

mortality rates⁸; this may partly explain the relatively small difference noted between the Greek and Japanese curves of prospective stillbirth risk during the 24–25th week of pregnancy. Thereafter, during the 26–34th week of pregnancy a widening relative difference in prospective risks is noted. This probably reflects differences in the quality of provided obstetric and prenatal care⁹. The high cumulative percentage of stillbirths in Greece after the 36th week of pregnancy may reflect under-ascertainment of early fetal deaths, but it is worrisome, and is in agreement with previous investigations in Greece on perinatal mortality risk factors¹⁰.

The results of the present study indicate that most previously established sociodemographic and gestational risk factors for stillbirth

also operate in the Greek population, but some noteworthy differences do exist. The role of gestational age and of birthweight have been repeatedly examined in relation to stillbirth risk. Gestational age is a powerful predictor of fetal survival, with perinatal mortality being particularly high among preterm births^{10,11,12}. Birthweight, as the end result of the length of time the fetus remains in utero and the velocity of fetal growth, is highly correlated with gestational age. Low birthweight has been related to an increased risk of stillbirth^{11,12}; even after the effects of gestational age had been controlled for, birthweight retained a strong association with survival^{13,14}. In this study, prematurity remained a powerful predictor of stillbirth, after controlling for birthweight. However, the adjusted odds for stillbirth were significantly elevated not only for very low birthweight embryos but for heavier embryos as well. The finding that more than 40% of stillbirths occur after the 36th gestational week, namely when the embryo is big and well developed, is a warning sign showing that further improvement of pregnancy monitoring and of the quality of obstetric care is needed in our country. Gender, parity and multiple pregnancy have less frequently been investigated as correlates of stillbirth risk. Male embryos are consistently found to be at higher risk of stillbirth, but the underlying biological mechanisms have not been adequately explored^{15,16}. Parity has also been associated with perinatal mortality. The lowest mortality is reported among second-born children, whereas the first-born and later than second-born children are found to be at higher risk of fetal death¹⁷. After adjustment for the possible confounding effect of maternal age, the U-shaped association of parity with stillbirth risk also remained unaltered in the present study. Multiple births showed no significant association

Variable	Category or unit	OR	95% CI
Gender	female	baseline	
	male	1.26	1.12–1.41
Gestational age (weeks)	28–31	8.68	6.44–11.69
	32–35	7.74	5.99–9.99
	36–39	1.69	1.41–2.04
	40+	baseline	
Birth weight (grams)	≤1,499	56.96	42.33–76.66
	1,500–1,999	21.26	16.23–27.83
	2,000–2,499	11.46	9.15–14.35
	2,500–2,999	2.97	2.41–3.67
	3,000–3,499	1.69	1.39–2.06
	3,500–3,999	baseline	
	4,000–4,499	1.54	1.14–2.09
	≥5,000+	11.56	5.45–24.53
Multiple birth	no	baseline	
	yes	0.97	0.78–1.22
Parity	1	1.47	1.28–1.68
	2	baseline	
	3	1.00	0.83–1.21
	4+	1.51	1.20–1.91

Table 4. Multiple logistic regression derived odds ratios (OR) and 95% Confidence Intervals (CI) of a stillbirth (vs. livebirth) by selected biological characteristics of the pregnancy.

with mortality in the logistic regression model after adjustment for birthweight and gestational age. The five-fold excess risk observed in the crude analysis was accounted for by the low birth weight, small gestational age and high maternal age usually accompanying multiple pregnancies. Rather inconsistent findings have been reported in the literature regarding multiple births, which might be explained by lack of control for possible confounders, or the inclusion of different confounders, in the limited number of existing studies^{17–20}. Maternal and family characteristics have been associated with fetal mortality in several studies, and a significant protective effect of young maternal age is well established^{15,18,21}. A monotonic increase

in risk with increasing maternal age was also observed in our study. The socioeconomic status of the family has been established as a strong predictor of stillbirth rate²². Maternal education and occupation are considered as important components of socioeconomic status²³, and families of professionals have been characterized by lower stillbirth rates compared to families of unskilled workers^{24,25}. In Greece, we used maternal education as the best indicator of socioeconomic status and we found an elevated risk for stillbirths among women with less than secondary education. Although the elevation is relatively small (26%), it is nevertheless of some public health significance, because one third of children in Greece are born to women with no

secondary school education. Status of parental cohabitation did not indicate an independent association with risk of stillbirth after controlling for possible confounding factors. Non-Greek-Orthodox maternal religion showed a modest and marginally significant association with risk of fetal death in the multivariate models. More significantly, the crude risk of stillbirth was 64% higher among out-of-wedlock pregnancies, however, this association disappears after controlling for confounding factors such as maternal education, parity, gestational age and birthweight. Nevertheless, from the public health point of view, an out-of-wedlock pregnancy is always a signal of a high-risk pregnancy on account of its association with several sociodemographic factors that increase the risk. A recent Swedish study has shown no difference in mortality of the newborn in or out of wedlock²⁶, but this may be due to the high quality services universally delivered by the Swedish State to all pregnant women. It is worth noting that 50% of Swedish children are born out of wedlock, whereas by contrast, in Greece the corresponding percentage is around 3%. Lastly, the geographical distribution of stillbirths by maternal residence has also been examined, but no urban-rural difference was found²⁷. It appears that massive improvements in communication and transportation during the recent decades have greatly facilitated identification and follow-up of high risk pregnancies, and may have contributed to the elimination of urban-rural disparities in stillbirth rates.

Stillbirths and perinatal and infant mortality rates have been used for many years as powerful health and socioeconomic indicators. These rates have extensively been used for cross-country and time-trend comparisons as well as for the identification of those groups towards

Variable	Category or unit	OR	95% CI
Maternal education	≤6 year	1.26	1.04–1.54
	7–9	1.07	0.85–1.34
	10–12	0.94	0.79–1.13
	13+	baseline	
Maternal age	≤19 years	0.81	0.64–1.03
	20–24	baseline	
	25–29	1.04	0.89–1.20
	30–34	1.21	1.02–1.43
	35–39	1.32	1.05–1.65
	40+	2.15	1.51–3.06
Maternal religion	Greek orthodox	baseline	
	other	1.43	1.03–1.98
Maternal residence	urban	baseline	
	non-urban	1.07	0.95–1.21
Wedlock	in	baseline	
	out	1.03	0.77–1.37

Table 5. Multiple logistic regression derived odds ratios (OR) and 95% Confidence Intervals (CI) of a stillbirth (vs. livebirth) by selected demographic characteristics of the mother.

which public health policies should be directed. As infant mortality rates rapidly drop, and perinatal survival steadily improves in most developed countries, the stillbirth rate becomes a valuable and sensitive index in assessing the quality of health services to mothers and children. Analysis of routinely collected data provides useful information on risk factors. The information can be further enriched by improvements in specific fetal diagnosis. Chromosomal anomalies, congenital malformations and

congenital infections are currently the most important causes of perinatal mortality²⁸. Complementary information provided by ad hoc studies on environmental and other factors in association with specific causes of death could contribute to a better understanding of stillbirth etiology. Nevertheless, studies such as the present one, utilizing routinely collected data, allow the rationalization of public health priorities with respect to fetal survival.

Zusammenfassung

Risikofaktoren von Totgeburten in Griechenland

In der griechischen Bevölkerung wurde eine Fall-Kontrollstudie über Risikofaktoren von Totgeburten zwischen 1989 und 1991 durchgeführt. Die während der 3 Jahre in ganz Griechenland registrierten Totgeburten innerhalb der ersten 28 Schwangerschaftswochen ($n=2006$) bildeten die Gruppe der Fälle. Im selben Zeitraum wurden 10% der Lebendgeburten des Landes als Kontrollgruppe randomisiert ausgewählt ($n=30705$). Mittels multipler linearer Regression wurden die Daten analysiert. Das angepasste relative Risiko des Todes war bei der männlichen Frucht signifikant höher als bei der weiblichen. Ein statistisch signifikantes und monoton ansteigendes relatives Risiko zeigte sich bei verkürzter Gestationsdauer, tiefer Schulbildung und höherem Alter der Mutter. Geburtsgewicht und Parität verliefen mit intrauterinem Sterberisiko in einer U-förmigen Beziehung. Dabei stieg das Risiko sowohl mit tiefer als auch mit höher werdendem Geburtsgewicht, und es war bei Primiparae und Multiparae (4 und mehr Geburten) höher als bei Müttern mit 2 bis 3 Geburten. Die nach den ersten Berechnungen positive Korrelation zwischen Totgeburt und Multiparität verschwand fast vollständig in der logarithmischen Regression, wenn die Mütter nicht verheiratet und nicht griechisch orthodox waren. Wohnsitz in der Stadt oder auf dem Land hatte keine Beziehung zum Risiko. Insgesamt war das Risiko einer Totgeburt in den ersten 24 Schwangerschaftswochen in Griechenland grösser als im höher entwickelten Japan, wo in den ersten 36 Schwangerschaftswochen mehr als 40% aller Totgeburten auftreten.

Résumé

Facteurs de risque de mort-né en Grèce

Une étude de cas-contrôle a été conduite sur des facteurs de risque de mort-né de la population grecque entre 1989 et 1991. Tous les cas de morts-nés enregistrés après 28 semaines de gestation ($n=2006$) durant les trois années d'étude ont formés la groupe des cas. Parmi tous les nouveaux nés vivants du pays 10% ont été choisis comme groupe de contrôle ($n=30705$) durant la même période. Les données ont été analysés par la régression linéaire multiple. Il se montait que le risque de mort-né fut plus élevé pour le sexe masculin comparé au féminin. Une montée statistiquement significatif et monotone a été observée sur le risque relatif, si la durée de gestation diminuait, si une basse éducation maternelle et un âge maternel plus élevé. Le poids de naissance et la parité suivaient le risque de mort-né par une courbe de forme d'un U. Le risque se réduit si le poids de naissance devenait bas ou haut ainsi que si la mère était une primipara ou multipara (4 naissances ou plus). Selon les premières calculations la corrélation entre mort-né et multiparité était positive mais ce résultat disparaissait presque par la régression logarithmique, si les mères n'étaient ni mariées ni grecque-orthodoxes. Le risque ne dépendait pas du domicile urbain ou rural. Finalement le risque prospectif de mort-né pendant les premières 24 semaines de gestation en Grèce a été estimé plus élevé qu'en Japon, un pays plus développé, avec plus 40% de tous les mort-nés se passent durant les premières 36 semaines de gestation.

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