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Prepregnancy maternal obesity and fetal-perinatal death in a Mediterranean country

Abstract

Objective: Pre- or early-pregnancy obesity carries significant health implications. This retrospective cohort study investigates the association between pre- or early-pregnancy body mass index (BMI) and the risk of fetal and neonatal death in pregnancies implicated by obesity in a Mediterranean country.

Study design: Data on pregnancies delivered during 2003–2008 at a University hospital was linked to data from regional registry. Logistic regression models were used to determine the odds ratios of a spontaneous fetal death and perinatal death among overweight, obese, and morbid obese women.

Results: Independent predictors of fetal death were maternal prepregnancy BMI over 25, maternal age, maternal co-morbidities, and maternal residence in an island. Perinatal mortality was independently correlated to neonatal birthweight, maternal age, maternal residence in towns and villages, and maternal BMI over 40. Overall, maternal residence in an island, maternal autoimmune disease, and maternal prepregnancy BMI (over 25) were independent risk factors predicting offspring death (both intrauterine and perinatal).

Conclusions: Maternal obesity is correlated to offspring's mortality during fetal and/or perinatal period. This is one of the very few studies in a Mediterranean country. This study underlines the need for public health interventions to prevent obesity in young women.

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Introduction

During the last decades, there is a steady decline in fetal demise and perinatal mortality rates due to improved healthcare services [34]. In Greece, these rates in 2011 came up to 4.6‰ for perinatal mortality, 3.2‰ for late fetal mortality, and 2.2‰ for neonatal deaths [25]. Obesity trends seem to increase over the last years [16]. To be more specific, obesity rates have more than doubled since 1980. It is estimated that 500 million adults were obese, in 2008, worldwide [8], while Greek rates of obesity in males secure the first place among European countries [8]. Moreover Greek women (over 20 years) face obesity in 10–19.9% [35].

Obesity is strongly correlated to cardiovascular diseases (hypertension, coronary heart disease, venous thrombosis, stroke), endocrinological disorders (diabetes mellitus type 2, insulin resistance, dislipidemia) [27], musculoskeletal disorders (osteoarthritis, degenerative disease of joints), and cancer [21]. Obesity's complications seem to affect directly the patient but also may put an indirect risk for the offspring, as well [12]. Mother's obesity is an inflammatory process with elevated levels of circulating cytokines such as tumor necrosis factor, interleukin-1, and leptin [7]. These cytokines can modify the insulin signaling pathway and can lead to insulin resistance [2]. Moreover obesity-induced oxidative stress and possible endothelial dysfunction-lower endothelium vasodilation, dysfunction of fibrinolytic mechanism and coagulation [28] seem to influence trophoblast function and result in implications in pregnancy [22]. Thus, neonates of obese mothers who tend to be macrosomic, have lower Apgar scores, be admitted to neonatal intensive

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care unit (NICU), and have congenital malformations. Numerous studies have linked prepregnancy obesity to increased maternal and perinatal morbidity and mortality rates [5, 27]. However, these studies focus mainly on either intrauterine or neonatal death, and they do not explore sufficiently the association of prepregnancy obesity with second trimester loss as well.

Our study aimed to investigate the association between maternal prepregnancy obesity and offspring's demise, both intrauterine and perinatal, taking into account a number of potential confounding factors. To our knowledge, there are very few studies focusing on Mediterranean population and pregnancy outcome concerning offspring's death in obese pregnant women [12, 30].

Materials and methods

Study population

The study was conducted in Western Greece region, a geographically distinct area containing Patras City as a capital and many surrounding rural communities with a permanent living population of 500,000 habitats and 39,648 deliveries during 2003–2008 [23]. In 2005, the average total population of women aged 15–44 years old in the region of Achaia was 72,190 with recorded 3315 live births [23]. We used data from University Hospital of Patras, which is the largest hospital in Western Greece, having more than 50% of the births in that area. Data used for this analysis included the Western Greece region resident birth records from 1st January 2003 to 31st December 2008. The deliveries, either planned or urgent, took place in the Obstetrical Department of University General Hospital of Patras.

For this analysis, 8293 total resident birth records were linked to 208 offspring death records. The 30.58% (2.536) linked records were excluded as there were no medical records found. Additionally there were 63 linked records excluded (Group A) as they referred to induced abortions (Figure 1).

Definitions

Fetal deaths or prenatal mortality include, in our analysis, miscarriages which are the spontaneous loss of a fetus ≥14 weeks of gestation but <23 weeks of gestation. Early fetal deaths included losses between 14 and 16 weeks of gestation and late fetal deaths included losses between 17 and 22 weeks of gestation. Missed miscarriages ≥14 weeks of gestation were included. Perinatal deaths include stillbirths and neonatal deaths. Stillbirths are deliveries of a fetus showing no signs of life at 23 or more completed weeks of gestation. Neonatal deaths are deaths, following live birth, of babies before aged 28 days. Early neonatal deaths are neonatal deaths occurring before aged 7 days.

According to the World Health Organization, maternal body mass index (BMI) was categorized into three groups: <18.5 kg/m^2 as Underweight, 18.5–<25 kg/m^2 Normal Weight, 25–<30 kg/m^2 Overweight, and ≥30 kg/m^2 Obese. The last group was subcategorized in three subgroups: 30–<35 kg/m^2 Obesity class I, 35–<40 kg/m^2 Obesity class II, and ≥40 Obesity class III-morbid obesity [24].

Data collection

The hospital data were collected and evaluated directly from the clinical records. Data were linked by fuzzy matching on five key variables: mother's surname, mother's name at booking, infant date of birth, infant sex, and birthweight. Fuzzy matching is an interactive procedure that matches on progressively less data, perfect matches being matched first (four variables), followed by matches on three variables. According to the medical records, all mothers were measured in the first visit (between 4 and 12 weeks of gestation) for their weight and height. Additionally, all pregnant women underwent a glucose tolerance test; their blood pressure was measured during every visit and also a urine stick was induced in order to diagnose albuminuria. The age of the mother was based in self-reported records. Gestational age was measured according to ultrasound findings. Co-morbidities of the mother were derived from medical history.

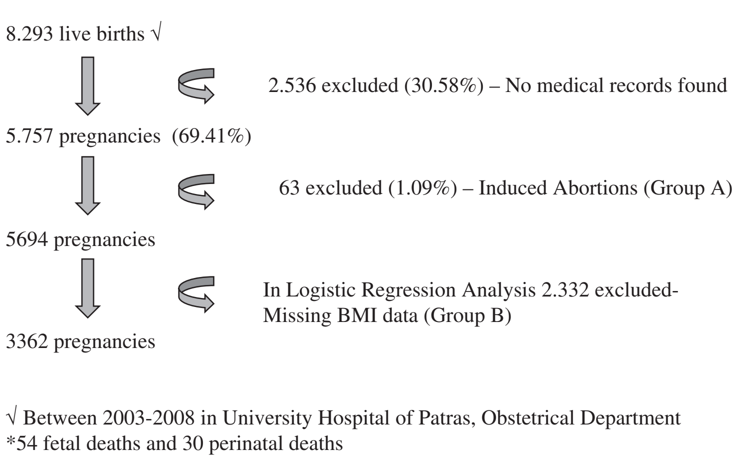

Figure 1 Population selection criteria.

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A standardized questionnaire of 32 questions was completed through an interview by an experienced obstetrician. The questionnaire consisted of four parts. The first two parts were completed during the history taking from the obstetrician and the data were recorded in an Excel file. The first part included demographic data – maternal age, race, address. The second part included obstetric data weight before pregnancy, height, prepregnancy BMI, method of conception, method of delivery, indication for cesarean section, date of delivery, and gestational age. The third and the fourth parts were completed after the delivery in the same Excel file, by the same obstetrician. The third part included data of the outcome of pregnancy (intrauterine death, perinatal death, delivery of a live infant), birthweight of the newborn, sex of the newborn, NICU admission; finally the last part included maternal co-morbidities (diabetes mellitus, high blood pressure including preeclampsia and eclampsia – renal, respiratory, liver, and gastrointestinal pathologies, epilepsy, autoimmunity, infection, and others). The geographic areas, where pregnant women were living during pregnancy, were categorized into four groups: (a) cities – capitals ≥100,000 population; (b) cities with population between 100,000 and 5000; (c) towns and villages ≤5000 population; and (d) islands.

Statistical analysis

The SPSS version 21.0 (SPSS, Chicago, IL, USA) software was used for data analyses. Categorical variables were analyzed by using the Fisher's exact test or chi-square and continuous variables with Mann-Whitney *U*-test, as appropriate. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any association. Univariate analysis was used to determine the predictors of prenatal or perinatal mortality. Backward stepwise multiple logistic regression analysis used all those variables from the univariate analysis with a $P<0.08$ in order to determine which were independently associated with the prenatal or perinatal mortality, respectively. All statistical tests were two-tailed and $P<0.05$ was considered statistically significant.

After preliminary exploration of the data, we used multivariable logistic regression to investigate the association between maternal BMI category and offspring's death. Covariates included in the model were maternal age, urban and rural residence, and mortality during summer months, neonatal birthweight and maternal co-morbidities as diabetes, autoimmune disease, and high blood pressure. We analyzed the association between maternal prepregnancy BMI and infant death, using the same controls. We classified maternal prepregnancy BMI, according to the World Health Organization definition, into four categories: underweight, normal weight, overweight, and obese.

For each study, separate 2×2 tables were constructed to calculate the ORs and 95% CIs of three different cases of mortality (fetal, perinatal, and all deaths) for each BMI/weight category analyzed (i.e., overweight, obese, and morbid obese). The ORs for different causes of neonatal death were calculated in separate logistic regression models with the same control group.

Ethical approval

The study was given approval by the hospital's ethics committee (Number 2/19-02-2013 signed form).

Results

Epidemiological characteristics

The study sample consisted of 5757 pregnancies. Some 63 pregnancies were excluded as induced abortions, and finally 5694 pregnancies were included in the statistical analysis. In our study sample, maternal characteristics as well as neonatal outcomes are shown in Table 1. Overall, 347 women (10.3%) were classified as obese, 842 (25%) as overweight, 112 (3.3%) as underweight, and 2.061 (61.3%) as having normal weight. The prevalence of maternal obesity and overweight tendencies through the years 2003–2008 are shown in Figure 2.

According to our data there were 5.549 (97.4%) live births and 145 (2.5%) offspring's losses. Of those losses, 99 (68.3%) occurred intrauterine or during second trimester and 46 (31.7%) occurred during perinatal period [38 (82.6%) fetal deaths, 6 early neonatal deaths (13.04%), and 2 late neonatal deaths (4.35%)]. The offspring losses, according to maternal BMI, maternal residency, and offspring's gestational age at loss are shown in Tables 2 and 3, and Figure 3, respectively. The total BMI and death distributions are shown in Table 4.

Table 1 Demographic statistics of maternal and neonatal characteristics.

Maternal characteristics	
Age	36.43±5.69
BMI	24.29±4.39
Race	
Greek	94.1%
Albanian	3.9%
Roma	1%
Other	1%
Conception	
Natural	97.5%
Assisted conception, etc.	2.5%
Delivery	
Vaginal	51.7%
Cesarean section	46.3%
Co-morbidities	
Diabetes	1.3%
High blood pressure	1.2%
Neonatal characteristics	
Birthweight	3123.19±642.82
Gestational age (weeks)	37.52±3.74
NICU admission	7.4%
Sex	
Boys	50.7%
Girls	48%

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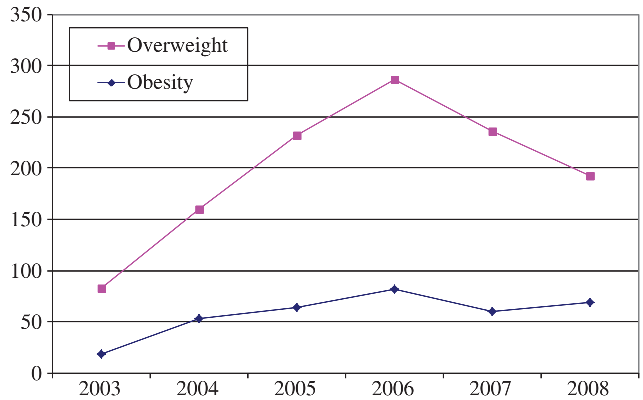

Figure 2 Prevalence of maternal overweight and obesity in the years 2003–2008.

Excluded data

Some 63 pregnancies (Group A) were excluded, as they were induced abortions. In this population the median maternal age was 39 and the median maternal BMI was 24.02±4.08, while the conception was natural in 100% of these. Some 98.41% of the mothers were Greeks, while 1.58% belonged to other ethnicities. Some 42 (66.67%) pregnancies were terminated due to fetal congenital or chromosomal anomalies (Trisomy 21, Trisomy 18, etc). The median maternal BMI in these pregnancies – complicated by congenital or chromosomal anomalies – was 24.20±4.51.

In logistic regression analysis, there were 2332 (Group B) pregnancies excluded because of missing BMI data. The median age of the mothers was 35 years. Some 98.11% (2.288) were Greeks, 0.81% (19) were Roma, 0.73% were Albanians, and 0.34% (8) belonged to other ethnicities. The conception was natural in 99.6% (2.323) of the pregnancies and *in vitro* fertilization (IVF) occurred in 0.4% (9) subjects. Some 97.4% (2.271) of the infants were delivered alive; there were 1.9% (45) intrauterine deaths, and 0.7% (16) perinatal deaths. The median gestational age at delivery was 38±3.80 weeks. Some 1156 (49.6%) of labors were boys. Some 1.195 (51.2%) of labors were vaginal. The median birthweight of the infants was 3.170±665.69. Some 213 (9.1%) of the infants were admitted to NICU. Of those the median gestational age was 33±4.22 weeks and 114 (53.5%) were boys. The median birthweight of the NICU-admitted infants was 1980±897.1 while 154 (72.3%) of them were delivered by cesarean section.

Table 2 Offspring death and maternal BMI categories.

Maternal prepregnancy BMI	Fetal death	Perinatal death
Underweight <18.5 kg/m^2	1 (1.9%)	3 (10%)
Normal weight 18.5–24.9 kg/m ^{2}	42 (77.8%)	14 (46.7%)
Overweight 25.0–29.9 kg/m^2	9 (16.7%)	6 (20%)
Total obesity ≥30	2 (3.7%)	7 (23.3%)
Class I Obese 30.0–34.9 kg/m^2	2	5
Class II Obese 35.0–39.9 kg/m^2	–	–
Class III or morbidly Obese ≥40 kg/m^2	–	2
Total data	54 (54.5%)	30 (65.2%)
Missing data	45 (45.5%)	16 (34.8%)

Table 3 Maternal residency categories in total offspring's death.

Maternal residency	
A (Cities – capitals ≥100,000)	56 (40.3%)
B (Cities with population between 100,000 and 5000)	43 (30.9%)
C (Towns and villages ≤5000)	25 (18%)
D (Islands)	15 (10.8%)
Total	145 (100%)
Missing	6 (4.1%)

Fetal death

Fetal death occurred in 99 subjects. The median age of mothers was 38±5.4. Median maternal BMI before pregnancy was 22.9±3.06. Greek ethnicity dominated with rates up to 99% (99) compared to Albanian ethnicity (1%). Conception was natural in 98% (97) of pregnancies, while 2% (2) of them were IVF pregnancies. Concerning maternal co-morbidities, the prevalence of diabetes mellitus was 3% (3), hypertension was 0.0%, and other maternal health problems was 5.1%. Fetal loss during summer months was 32.3% (33) compared to 67.7% (67) for all the other months.

Multivariable analysis revealed maternal BMI before pregnancy over 25, maternal age, maternal residency in geographic area type d (Islands), maternal diabetes and autoimmune disease, as independent risk factors influencing intrauterine death (Table 5).

In contrast, maternal residency in towns and villages (population ≤5000), maternal high blood pressure, and delivery during summer months did not reach statistical significance for fetal death.

In a further analysis, fetal death was categorized as early or late. The results are shown in Table 6.

Perinatal death

Perinatal death occurred in 46 subjects. The median age of mothers was 36±7.3. Median maternal BMI before

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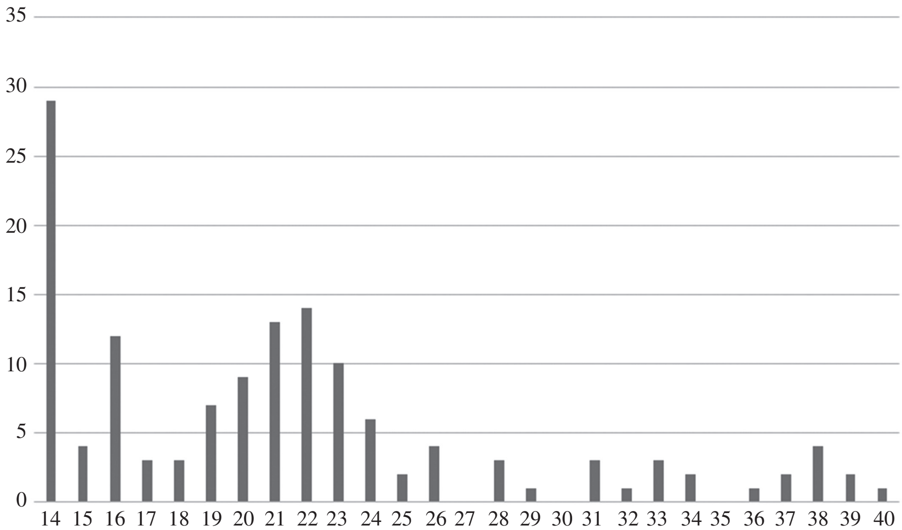

Figure 3 Offspring deaths according to gestational week.

Table 4 Maternal BMI in the years 2003–2008 – total deaths distribution in the years 2003–2008, and maternal BMI categories.

Year	Total sample	Missing sample	Maternal BMI	Total deaths	Missing BMI data	Maternal BMI
2003	215	0	24.09±4.29	7 (3.25%)	0	26.87±7.3
2004	471	1	24.32±4.35	10 (2.1%)	0	24.63±3.36
2005	658	0	24.39±4.43	15 (2.27%)	0	23.21±3.39
2006	1440	711	24.55±4.25	32 (2.2%)	16	24.24±5.14
2007	1399	747	24.27±4.19	34 (2.43%)	19	22.3±3.76
2008	1511	873	23.94±4.74	47 (3.11%)	27	23.47±4.84
Total	5694	2332		145	62	

pregnancy was 22.8±6.58. Some 93.5% (43) of them were Greeks, 4.3% (2) were Albanians, and others were 2.2% (1). There were no cases of IVF. Concerning maternal co-morbidities, hypertension rates were 2.2%, diabetes 0.0%, and others 8.7%. Perinatal death rates during summer months were 21.7% compared to 78.3% for all the other months. The deliveries were performed by cesarean section in 31.3% (10) while 68.8% (22) were vaginal deliveries. Median gestational age of the newborns was 27±5.9. The median birthweight of neonates was 900±1.203. The admission in NICU was 13% (6). Male sex's rates were 65% (26).

Table 5 Multivariable analysis of predictors for fetal and perinatal mortalities.

Characteristics	Fetal death		Perinatal death		Overall offspring's death	
	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)
BMI ≥25	<0.001	4.995 (2.500–9.981)	0.407	1.508 (0.571–3.985)	<0.001	3.265 (1.962–5.434)
BMI ≥40	–	–	<0.001	0.001 (0.001–0.002)	–	–
Maternal age	0.025	1.067 (1.008–1.130)	0.038	0.913 (0.837–0.995)	0.087	1.041 (0.994–1.090)
Birthweight	–	–	<0.001	0.998 (0.998–0.999)	–	–
Geographic area type D	0.007	3.538 (1.423–8.800)	0.772	0.710 (0.070–7.211)	0.008	3.054 (1.339–6.961)
Geographic area type C	0.065	0.466 (0.207–1.050)	0.040	2.675 (1.047–6.834)	0.862	0.954 (0.558–1.631)
Maternal diabetes	0.28	0.24 (0.067–0.854)	0.999	5.7×10^6 (0.00–∞)	0.130	0.387 (0.113–1.322)
Maternal autoimmune disease	0.007	67.513 (3.108–1466.513)	0.999	0 (0.00–∞)	0.015	38.339 (2.045–718.868)
Maternal high blood pressure	0.999	0 (0.00–∞)	0.999	0 (0.00–∞)	0.998	0 (0.00–∞)
Delivery during summer months	0.989	0 (0.00–∞)	0.989	0 (0.00–∞)	0.988	0 (0.00–∞)

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Table 6 Multivariable analysis of predictors for early and late fetal deaths.

Characteristics	Early fetal death		Late fetal death	
	P-value	OR (95% CI)	P-value	OR (95% CI)
BMI ≥25	0.002	4.253 (1.730–10.455)	0.004	4.695 (1.644–13.405)
BMI ≥40	–	–	–	–
Maternal age	0.205	1.049 (0.974–1.130)	0.071	1.086 (0.993–1.187)
Birthweight	–	–	–	–
Geographic area type D	0.121	2.652 (0.773–9.093)	0.014	4.890 (1.387–17.239)
Geographic area type C	0.026	0.195 (0.046–0.821)	0.585	0.734 (0.241–2.232)
Maternal diabetes	0.436	0.440 (0.056–3.471)	0.019	0.153 (0.032–0.739)
Maternal autoimmune disease	0.999	0.000 (0.0–∞)	0.999	0.000 (0.0–∞)
Maternal high blood pressure	0.998	0.000 (0.0–∞)	0.998	0.000 (0.0–∞)
Delivery during summer months	0.988	0.000 (0.0–∞)	0.989	0.000 (0.0–∞)

Multivariable analysis revealed maternal prepregnancy BMI ≥40, neonatal birthweight, maternal age, and maternal residency in towns and villages, as independent risk factors for predicting perinatal mortality (Table 5).

There was no statistically significant correlation found for maternal BMI <40, maternal co-morbidities (diabetes, high blood pressure, or autoimmune disease), neonatal admission to NICU, gestational week, and summer months.

All death

Overall offspring's mortality – both fetal and perinatal – was correlated to maternal autoimmune disease, maternal residency in islands, and maternal prepregnancy BMI ≥25 (Table 5).

Maternal co-morbidities (diabetes, high blood pressure), maternal residency, maternal age, and delivery during summer months did not reach significance.

Discussion

Greece is a Mediterranean country with a total of 100,371 deliveries in the year 2012 (5504 in Western Greece). This study describes the relationship between prepregnancy maternal BMI and its possible impact on fetal and perinatal deaths from the beginning of second trimester (14th week) until the end of neonatal period (28 days postpartum), in a cohort of singleton pregnancies, drawn from Patras, Western Greece region, over a 6-year period. To our knowledge there are no other studies from Mediterranean countries summarizing the effect of maternal obesity on offspring's mortality.

Mediterranean countries used to follow Mediterranean diet (MD), which is correlated to better health-related quality of life [1], as well as to reduced total mortality rates [33]. This lifestyle probably played an important role in the prevalence of obesity and its impacts. This can be explained as it plays a protective role by reducing metabolic syndrome [26], diabetes mellitus, and cardiovascular disease [13]. Additionally, MD has been referred to as playing a protective role against overweight and obesity during pregnancy [31].

However, during the last years the adherence to MD in Greece is declining [10]. Furthermore, obesity rates in Greece show an increased tendency, with higher rates of obesity and lower rates of adherence to MD in women, especially of younger reproductive age [11]. Evidence supports that more and more Mediterranean countries have abandoned MD principles [29]. For these reasons, during this period, when protective effect of MD is lost, more and more studies from the Mediterranean area will focus on the results of the above-mentioned phenomenon and will demonstrate its impact on public health. As a result of these, in our study population, obesity rates showed an increased median BMI in Greek women compared to the ones recorded in previous years. Furthermore, when compared with other European countries, Greece occupies fifth place for obesity in women after United Kingdom, Latvia, Malta, Hungary, and Czech Republic.

The miscarriage rate in our study was 3% and perinatal mortality rate was 1.4%. According to Greek Birth Records, fetal death rates in 2009 were 4.26‰ and perinatal mortality rates were 5.5‰ [9].

Maternal prepregnancy BMI ≥25 was associated with pregnancy loss (fetal death) and these findings are consistent with previous studies [19]. When categorizing fetal death into two categories, i.e., early and late, maternal BMI ≥25 continues to be a significant factor predicting

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fetal loss in both groups. Furthermore, perinatal mortality was correlated to maternal prepregnancy BMI ≥40. A significant correlation has been previously reported [3, 5]. However, there was an extremely small number of perinatal deaths included (in morbid obese patients) and for this reason these results are weak. There were no morbid obese patients included in the group of fetal death. We could not find any association between overweight and obesity and perinatal deaths as in previous studies [19, 32], although our findings could be due to smaller number of subjects in this group. In a study in Chinese population, increasing maternal BMI was not associated with perinatal death [20].

When summarizing the two categories into one variable – offspring's mortality – which includes both fetal and perinatal death, maternal prepregnancy BMI ≥25 as a continuous variable is an independent risk factor predicting mortality. Overweight, obese, and morbid obese women face in higher rates offspring's death. Same were the results of an American study, where maternal obesity was associated with higher incidence of neonatal death and for overall infant death [33]. Similar were the results of European studies, where maternal obesity increased the risk of both fetal and infant death. In detail, obesity more than doubled the risk of overall offspring's death (stillbirth and neonatal) [19, 32]. Overweight maternal status did not reach significance in predicting offspring's mortality [32]. In a recent study, obesity contributed to fetal and infant mortality, equally to substance abuse [18].

Another factor that proved to have a clear impact on fetal death (late), and on overall infant death, but not on perinatal, was maternal residency in an island. It is the first time that such a finding is reported to influence fetal mortality rate. Taking into consideration suboptimal prenatal care, due to limited access to higher quality healthcare services, this could be the most likely explanation for this finding. An explanation given by studies from developing countries already related delayed transport and reduced accessibility to health services, to increased risk of fetal loss [14].

Moreover, maternal age was correlated to fetal death, perinatal death, and overall infant death. This agrees with previous studies that mention maternal age as a confounding factor for miscarriage [15]. Maternal age >40 years or <18 years seems to play an important role in unexplained intrauterine death [4].

Maternal co-morbidities such as diabetes mellitus and autoimmune disease were significant risk factors for fetal (late) and overall infant death but not for perinatal death. Even though hypertension did not reach significance in our analysis, a positive correlation between hypertension and perinatal mortality has been reported previously [17]. Earlier studies report an increased risk for perinatal mortality in pregnancies implicated by diabetes [6]; however, in our study the rates of diabetes were too small to find any correlation.

Our data suggest that obesity is associated with a marked increased risk in stillbirth and neonatal death. Given the fact that the prevalence of obesity is increasing worldwide, it seems pertinent that there is need for public interventions to prevent obesity in young women. Another point from public health perspective is the link between the limited access to healthcare services (maternal residency) and suboptimal pregnancy outcome. We believe that the goal of preventing antenatal stillbirths in obese women can be achieved by lowering the threshold of referrals for obese women in an obstetric specialist, and a tertiary center.

However strong our results are, the number of subjects studied weaken the reposted association between maternal obesity and pregnancy/neonatal loss. Further investigation with larger numbers is needed to determine how strong this association is. Researchers should be encouraged to conduct analyses for Mediterranean countries that have included maternal height and prepregnancy weight on the birth certificate to assess the consistency and strength of associations between infant mortality and maternal prepregnancy weight. Given the influence of social, economic, and environmental factors on health, future analyses should also consider the role of other important variables, such as Mediterranean diet when assessing risks of poor perinatal outcomes.

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