TOBACCO USE IN THE THIRD-TRIMESTER OF PREGNANCY AND ITS RELATIONSHIP TO BIRTH WEIGHT.
A prospective study in Spain.

INTRODUCTION

Optimal foetal growth is dependant on a variety of physiological and pathological determinants[1]. Amongst the physiological factors, pre-gestational body mass index (BMI) is directly related to birth weight, with higher BMI associated with higher birth weight[2]. On the contrary, the misuse of toxic substances during pregnancy, including tobacco, can lead to foetal growth retardation and low birth weight[3,4]. Nicotine reduces the blood flow to the placenta, whilst carbon monoxide present in smoke reduces oxygenation of the fetus[5].

Different authors have analysed tobacco use during pregnancy using different methods including self-reported questionnaires, measurements of nicotine concentration in urine or expired carbon monoxide[6-8]. In Europe, the prevalence of tobacco use during pregnancy is approximately 20%[9]. In Spain, figures are higher and around 30–43% of expectant mothers are smokers at the start of their pregnancy[6]. Although about 40% of them quit in the first trimester[10], about 13–25% continue smoking up to delivery[11]. Spanish studies, however, are affected by methodological weaknesses. For example, the majority of studies assessed tobacco use through self-reported instruments, which may facilitate socially desirable responses and thus underestimate smoking status by 11–26%[6,10].

However, the combined effect of BMI and tobacco on birth weight remains unclear[12] and few studies on tobacco prevalence have examined the effect of quitting smoking in the third-trimester of pregnancy and birth weight. Some authors have suggested that early cessation of smoking in pregnancy has a greater impact on birth weight improvement[13,14] with a relatively small impact if quitting takes place during the third-trimester of pregnancy[15]. However, other researchers have claimed that third-trimester maternal cigarette consumption had the strongest association with birth weight, regardless of pre-pregnancy consumption levels[16].Our study evaluated the association of prenatal exposure to maternal smoking with birth weight in different stages of pregnancy.

Additionally, we aimed to identify the trimester of pregnancy in which tobacco use produced the greatest reduction in neonatal birth weight.

SUBJECTS AND METHODS

Design: Prospective observational study. Participating expectant mothers were classified into two groups according to their use of tobacco during gestation. A sample of 159 women was obtained from April 2011 to March 2012.

A two-stage sampling approach was used. In the first stage, we selected health centers in Carlet and Benimodo (Spain) from all primary care centers of La Ribera health district using simple random probability sampling (probability= 2/13). In the second stage, we selected pregnant women using a similar probability sampling with systematic monitoring of the number of pregnancies per year on each health center (N'). The ratio's value (k) for the calculated sample size (n) was 2 (k = N'/ n). We estimated that for 180 pregnant women per year attending the health centers, a minimum sample of 123 women was required (95% confidence interval (95% CI), 5% precision error). The attending midwives recruited the women at clinic and obtained their informed consent to participate. Overall, one of every two pregnant women was selected until the required sample size was obtained.

The inclusion criteria were: a maternal age of 18-36 years, first prenatal visit between 5-12 weeks of gestation, and single foetus with no malformations. Exclusion criteria included: patient declined to participate in the study, language barrier, and expectant mothers with pathologies that significantly modified foetal growth, such as pre-gestational diabetes, essential hypertension prior to pregnancy, maternal infection or other chronic maternal pathologies.

Ethics: The Committee of Ethics and Research of the University Hospital of La Ribera (UHLR) approved the study proposal in January 2011 (#11-415). Written informed consent was obtained from all women. The participants were free to decline their participation and withdraw from the research at any time.

Study variables: The questionnaire was purposely designed with agreement from the research team. Birth weight was considered the dependent variable, and was recorded in the delivery room following the clamping and separation of the umbilical cord, using a digital scale (SECA®, Vogel & Halke GmbH & Co, Hamburg, Germany), to an accuracy of 10 g.

The independent variables included socio-demographic characteristics (maternal age, country of origin, marital status, educational level, occupational state), anthropometric measurements (pre-gestational BMI, as calculated from self-reported body weight at 2–3 months prior to pregnancy and recorded at the first prenatal visit; absolute gestational weight gain; and difference between final weight on the day of delivery and pre-gestational weight), and obstetric-neonatal features (newborn gender and gestational age at birth expressed in days of gestation from the end of the mother's last menstrual cycle). Women selected for inclusion in our study provided an estimate of their pre-pregnancy day cigarette consumption. Self-reported average tobacco consumption was used to estimate pre-gestational tobacco misuse. Equally, women were asked to report the mean number of cigarettes consumed per day in the 7 days prior to the enrolment in the study, and again for each trimester on appointment with the midwife.

Data collection also included the frequency of smoking cessation attempts and relapses during pregnancy and for a period of 30 days postpartum.

Statistical analysis: An analysis of the dependent variables was carried out for each of the categories of pre-gestational BMI, using descriptive methods. Afterwards, the normality of the distribution of continuous variables was examined using the Kolmogorov-Smirnov test. Statistical significance was set at the 0.05 level. Bivariate correlation analyses using Pearson correlation coefficient were initially used to explore factors associated with neonatal birth. The comparison of multiple averages was carried out using analysis of variance tests (ANOVA), after assessment of the homogeneity and normality of the data with the Levene test. The magnitude of the effect of first-hand exposure to tobacco on categorised birth weight was estimated using multiple logistic regression, with birth weight (<3000g or >3000g) as the outcome measure and adjusted for pre-gestational maternal BMI (WHO categories: underweight (UW) <18.5 Kg/m^2, normal weight (NW) 18.5-24.9 Kg/m^2, overweight (OW) 25.0-29.9 Kg/m^2, obese (OB) >30 Kg/m^2)[17] as explanatory variable. Additional explanatory variables included gestational age at birth (days).

To analyse the relationship between birth weight (dependent variable) and tobacco use by the expectant mother (independent variable), an adjusted multiple linear regression model was applied using a stepwise method for variables shown to have an effect on birth weight. Smoking indicators examined included the number of cigarettes consumed per day before pregnancy, at the time of registration into the study (first trimester), and in the second and third trimester. Partial correlation coefficients represent the strength of the linear relationship between each independent variable and birth weight, after controlling for other predictors in the regression model. The data was analysed using SPSS Statistics version 22.

RESULTS

Out of a total of 159 expectant mothers initially included in the study, we excluded 22 cases (10 cases of spontaneous miscarriage in the first trimester, 1 case of foetal malformation in the second trimester, 2 cases of loss to follow-up during the pregnancy, and 9 cases of gestational diabetes). Therefore, the final sample included 137 expectant mothers.

Table 1 provides a detailed description of maternal and neonatal characteristics. Smokers were 30-34 years old, less educated, married, employees and more frequently within normal weight than non-smokers at each corresponding point during gestation. The neonatal birth weight of smoking mothers was 235g lower than non-smokers (p= 0.006).

Table 2 presents tobacco statuses. Regarding pre-pregnancy tobacco use, 64.2% (88) did not smoke, 35.8% (49) did, and 0.8% (1) quit prior to becoming pregnant. At the beginning of pregnancy, the proportion of smokers was 35%, of whom 14.6% were underweight, 68.8% were normal weight and 26.7% were overweight. None of the mothers smoking prior to pregnancy were obese. In terms of smoking cessation during pregnancy, cessation rates increased progressively during the three trimesters (8%, 13.1% y 13.9% respectively). We did not find any expectant mothers who relapsed during pregnancy or during 30 days of post-partum. Underweight smokers accounted for the largest proportion of those who stopped smoking (44.5%) when compared to women who either had normal weight (12.6%) or were overweight (10%). Additionally, underweight smokers achieved a greater reduction in the average number of cigarettes smoked compared to women who had normal weight (4.3 fewer daily cigarettes compared to 1.0). Overweight smokers, on the contrary, had increased their daily average consumption by 3.1 cigarettes by the end of their pregnancies.

The results of the bivariate analysis on tobacco status and birth weight for different trimesters of gestation, according to categorised pre-gestational maternal BMI are displayed in Table 3. Maternal smoking was associated with birth weight only at NW pre-gestational BMI. Of the smoking indicators examined, cigarette consumption was significantly and negatively correlated with birth weight before pregnancy (R= -0.243, p= 0.018), as well as the second (R= -0.276, p= 0.007) and third trimester (R= -0.304, p= 0.003). Birth weight in newborns from non-smoking mothers was significantly higher when compared with smoking participants (3297.8g [95% CI: 3187.6–3408.0] compared to 3070.1g [95% CI: 2910.4–3229.8], p= 0.018). Likewise, expectant mothers who did not smoke in the second and third trimesters had babies with higher birth weight than mothers who were smokers during those periods (3284.3g [95% CI: 3179.8–3388.9] vs 2990.6g [95% CI: 2816.7–3164.5] for the second trimester and 3289.0g [3185.5–3392.6] compared to 2960.2g [95% CI: 2789.8–3130.6] for the third), with statistically significant differences (p= 0.007 and p= 0.003, respectively).

Table 4 describes the risk of having a newborn with a weight below 3000g, according to smoking behaviour during pregnancy, and adjusted for pre-gestational maternal BMI and gestational age at birth. Expectant mothers exposed to tobacco during the third trimester were at greater risk of having a lower neonatal weight than their non-smoking counterparts (OR: 5.94 [CI 95%: 1.94-18.16]).

The results of the multiple regression analyses (Table 5 and Figure 1) suggest that of the smoking variables examined, maternal third trimester cigarette consumption was the strongest predictor of birth weight after adjusting for gestational age and pre-gestational maternal BMI (partial R= -0.253, p=

0.003). For each additional cigarette per day smoked in the third-trimester, there was an estimated reduction in birth weight of 32g (CI 95%: -53.08, -11.04). Additional direct independent contributors to birth weight after adjusting for gestational age (partial R= 0.404, p< 0.001) included maternal BMI (partial R= 0.281, p= 0.006). The final model included 3 variables and explained 27% of the variability in newborn birth weight.

DISCUSSION

Our prospective observational study included 137 expectant mothers in Spain, who were classified into groups according to their gestational tobacco use. In our results, pre-gestational maternal BMI is positively related to birth weight, independently of all other parameters examined, and in agreement with other studies[2,3,18]. In the Spanish health care system, midwives are the main point of contact for women during pregnancy. National guidelines indicate that midwives should ask about women's smoking status at the first antenatal appointment (usually between 8-12 weeks), and provide smoking cessation advice and referral if warranted. However, there is still a paucity of data regarding the impact of smoking cessation advice on smoking status.

The proportion of smokers decreased progressively from the first to the third trimester, which is also consistent with previous studies[6,7,10,11,13,19]. In our study, we observed statistically significant differences between cigarette consumption and maternal age, educational level and occupational state[20].

Our data suggest that, taking into consideration already known factors that influence on birth weight, a linear relation persists between self-reported consumption of cigarettes in the third trimester and neonatal birth weight, as previously reported[17]. However, other studies have postulated safe levels of tobacco consumption[15,21,22]. The observable effect of maternal smoking later in pregnancy suggests that every additional cigarette consumed per day in the third-trimester results in a reduction of approximately 32g in the birth weight of the newborn. Such effect appears to be greater than the previously reported by Bernstein et al.[16], Mathai et al.[23] or England et al.[15] who noted between 12g-

27g. Overall, our results propose a total weight reduction of 137.6g (32g/cigarette x 4.3 cigarettes/day), within the range determined by other authors[20,24,25] reporting a weight fall between 114-170g among smokers. The greater per-cigarette influence on birth weight in our data can be explained by the continuous linear relationship we observed. Thus, we disagree with the notion of a minimum secure level on cigarette consumption rather than a continuous effect.

A valid estimation of the risks associated with tobacco exposure would depend on accurate measurements. However, some individuals may be more reluctant than others to disclose their smoking status and exposure to tobacco. This can be particularly true for pregnant women, for whom smoking may be regarded as socially unacceptable. Thus, estimates based on self-reported information are likely to underestimate the real proportion of tobacco use. Exposure to tobacco can be analyzed by measuring smoke components in the air, self-reported indicators of exposure through interviews or measuring smoke components concentrations with biomarkers[26]. The first approach is suboptimal as monitors can only be used for short periods of time, which are unlikely to be reflective of overall exposure. In terms of self-reported smoking behaviors, a recent meta-analysis[27] suggested that in most studies it could be an acceptable methodology for estimating tobacco consumption, if validated with biochemical measurements. However, the authors excluded studies which included pregnant women. Other authors have concluded that validation with biomarkers should also be considered in studies with students and intervention studies[28,29]. Despite these advantages, self-reported questionnaires present various concerns related to their validity as tools for data collection, a lack of validation and standardization as well as misclassification of exposure among the most serious drawbacks. These may originate from participants' failure to accurately recall exposure, lack of knowledge, intentional false reporting, biased recall, or memory failure[28]. Bias may be more common whenever social desirability is greater[11]. Furthermore, the quantity of inhaled and absorbed smoking products varies with the manner of smoking, which may be difficult to express and quantify in a questionnaire[25]. Underreporting was found in 4%-12% of pregnant women who demonstrated values inconsistent with their self-report [26].

Other investigators have identified a poor correlation of self-reported maternal cigarette consumption with biomarkers like urinary cotinine. They have reported an inversely proportional relationship of urinary nicotine to birth weight[15,30].

Some methodological considerations should be noted with regard to our study. First, our results rely on the validity of responses to the self-reported questionnaire. Consequently, the prevalence we observed may effectively be an underestimation of the true prevalence, due to the potential for socially desirable responses offered by our participants. The factors most closely related to concealing an individual's smoking status have to do with the timing and the quantity of tobacco consumed [9,12,32]. We acknowledge that in optimal circumstances, midwives caring for participants may not be the ideal recruiters of individuals onto a study. As an additional limitation in our study, we had a reduced number of participants within the underweight and obese categories, although this was due to the nature of the sampling.

The strengths of our study are the use of probability sampling in the selection of the study population. In addition, we were able to draw a valid sample size representative of the total population of expectant mothers in our setting. Unlike other studies, our sample was categorised by pre-gestational maternal BMI, an important independent factor in determining birth weight.

Different studies have tried to determine the relationship between cigarette smoking among expectant mothers and birth weight. Although the studies have produced heterogeneous results, most observe an increased risk of lower birth weight among smokers[1,19-21]. However, the studies are limited by the difficulty in quantifying maternal exposure precisely and in adjusting for the multiplicity of confounding factors that can affect birth weight[32,33].

In conclusion, our results on the association of active smoking during pregnancy with birth weight indicate that smoking in pregnancy increased the risk of having lower weight newborns (<3000g), and that this risk is most pronounced for women who smoke during their third trimester, reinforcing the need to encourage and support women to avoid smoking during pregnancy. Pregnancy offers a strategic opportunity for health professionals to promote smoking cessation and motivate women to give up tobacco use. Such opportunity to encourage smoking cessation interventions should be specially seized by midwives, as first point of contact for women during their pregnancy.

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