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Research Article

The Impact of Pre-Pregnancy Maternal Obesity on Nuchal Translucency Measurement at Time of First-Trimester Screening: A Single Center Retrospective Analysis

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Abstract

Objective: To evaluate the impact of pre-pregnancy maternal obesity on Nuchal Translucency (NT) measurement during a first trimester screen ultrasonographic examination.

Methods: Using the Magee-Women's Hospital Ultrasound Database, a retrospective cohort study of women with singleton pregnancies undergoing successful NT screening from January 2008 to October 2013 was performed. Body Mass Index (BMI) was calculated from available pre-pregnancy height and weight data. The relationship among obesity, gravidity, parity, diabetes status, maternal age, ethnicity, pre-pregnancy weight and NT measurement was analyzed via multivariable linear regression. BMI categories and NT thresholds for consideration of invasive fetal testing for aneuploidy were examined via χ^2 test and t-test, when appropriate. A P-value <0.05 was considered statistically significant.

Results: Among 24, 862 women with singleton pregnancies, 7,408 (29.8%) cases were identified. After adjustment for confounders, increasing pre-pregnancy maternal BMI was significantly associated with a larger NT measurement (P<0.0001). Those with a BMI ≥40kg/m^2 had a significant association with a NT measurement of 3.5mm or greater (P=0.028). Mean NT measurements between BMI <30kg/m^2 and BMI ≥ 30kg/m^2 were not statistically significant but trended toward an increased NT in the BMI ≥ 30kg/m^2 cohort (1.62mm vs. 1.67mm: p=0.31).

Conclusion: Pre-pregnancy BMI greater than or equal to 40kg/m^2 is significantly associated with a NT measurement of 3.5mm or greater at time of first trimester screen.

Keywords: Maternal Obesity; Body Mass Index; First-Trimester Screen; Nuchal Translucency

Abbreviations

NT: Nuchal Translucency; BMI: Body Mass Index; CDC: Centers For Disease Control; FMF: Fetal Medicine Foundation; WHO: World Health Organization

Introduction

Obesity has become an increasingly prevalent public health problem in the United States of America, reaching epidemic proportions. According to 2009 Centers for Disease Control and Prevention (CDC) epidemiologic data on obesity in the United States, 35.7% of the American population is considered overweight or obese [1]. Currently, on the review of the literature, over 20% of American pregnancies are complicated by maternal obesity [1]. Obesity has been well correlated with numerous adverse maternal pregnancy outcomes such as hypertensive disorders of pregnancy, gestational diabetes, and increased rates of operative delivery [2]. Moreover, a recent meta-analysis demonstrated that, for obese mothers, the odds of having a fetus with a neural tube defect is 1.87 times higher compared to a mother of normal weight [3]. Thus, obesity can portend the possibility of detrimental consequences for both mother and fetus.

First trimester screening is employed for the detection of fetal aneuploidy with use of Nuchal Translucency (NT) measurement and assessment of maternal serum markers. Its use has been validated in the First-Trimester or Second-Trimester, or Both for Down syndrome (FASTER) Trial in 2005 [4]. However, this study did not include any data relating Body Mass Index (BMI) to the components of first trimester screening [4]. An increased NT has also been associated with adverse outcomes including spina bifida, skeletal dysplasia, congenital heart disease, congenital diaphragmatic hernia or intrauterine fetal demise [3,5,6]. With nearly 29.7% of adults in the state of Pennsylvania being classified as obese, the implications of obesity on adverse pregnancy outcomes in our population become even more essential to recognize and define [7]. There are insufficient data to suggest whether or not pre-pregnancy maternal

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Table 1: Demographics of women presenting for first-trimester screening. The table demonstrates data for three strata: all women in cohort, those with a body mass index greater than or equal to 30kg/m^2 and those with a body mass index greater than or equal to 40kg/m^2. Variables presented with mean values with standard deviations or percentages of their respective cohort size, when appropriate.

Variable	All Women	Women with BMI ≥ 30 kg/m^2	Women with BMI ≥ 40kg/m^2
Total Number (n)	24, 862	7, 408 (29.5%)	870 (3.5%)
Nuchal Translucency (mm)	1.64 +/- 1.01	1.67 +/- 0.97	1.67 +/- 0.87
Body Mass Index (kg/m^2)	25.94 +/- 6.39	35.75 +/- 5.49	44.74 +/- 4.33
Patient Age (years)	29.55 +/- 6.03	29.33 +/- 6.26	29.21 +/- 6.36
Ethnicity Caucasian	18,887 (75.97%)	5, 185 (69.99%)	548 (62.99%)
African-American	4,605 (18.52%)	1,990 (26.86%)	312 (35.86%)
Asian/Pacific Islander	647 (2.60%)	87 (1.17%)	1 (0.11%)
Hispanic	94 (0.38%)	22 (0.30%)	2 (0.23%)
Native American	10 (0.04%)	1 (0.01%)	0 (0%)
Unknown	321 (1.29%)	70 (0.94%)	0 (0%)
Bi-Racial	88 (0.35%)	24 (0.32%)	3 (0.34%)
Other	210 (0.84%)	29 (0.39%)	4 (0.46%)
Maternal Diabetes (n)	294 (1.18%)	159 (2.15%)	58 (6.67%)
Maternal Smoking (n)	1,191 (4.79%)	370 (4.99%)	70 (8.05%)

obesity plays any role on the value of the NT measurement obtained at the time of first trimester screening and what is both the extent and clinical implications of such an increase [8,9]. Therefore, given the ever-increasing rate of pre-pregnancy maternal obesity, we aim to determine if pre-pregnancy maternal obesity, as defined by BMI, increases the value of the NT measurement obtained on a first trimester screening ultrasonographic examination among a diverse obstetric population in western Pennsylvania. Our hypothesis is that women with pre-pregnancy obesity have a higher incidence of having an abnormal nuchal translucency on first trimester screening.

Materials and Methods

We reviewed a retrospective cohort study utilizing the Magee-Women's Hospital Obstetric Ultrasound Database for all women with singleton pregnancies between January 2008 and October 2013 who presented for first trimester screening. Magee-Women's Hospital is a tertiary care center in western Pennsylvania whose obstetric service delivers over 11,000 babies per year and performs over 100,000 ultrasound examinations per year. Pregnancy dating was determined by the crown-rump length, as measured on the day of the NT measurement. All women with singleton gestations were included in our analysis if they had a successful NT measurement obtained between 11 weeks 0 days and 13 weeks 6 days and had a crown rump length between 41mm and 84mm. The following cases were excluded from analysis: those with a cystic hygroma, a fetal anomaly diagnosed at the time of NT measurement, fetal demise or those who declined testing. All NT measurements were performed at Magee-Women's Hospital, an obstetric tertiary care center performing over 100,000 ultrasounds per year.

In our ultrasound unit, both sonographers and maternal-fetal medicine physicians are able to obtain NT measurements in accordance with previously published criteria established by the Fetal Medicine Foundation (FMF) only if they are certified to do so [10]. All NT measurements were taken with the fetus in a neutral, sagittal position with the widest part of the nuchal translucency being measured. Calipers were placed on the inner border of the horizontal lines defining the nuchal measurement. Each fetus had 3 measurements of the NT taken, with the image fulfilling FMF criteria being accepted as the NT measurement for that respective fetus. All NT measurements were obtained using a Philips IU22 ultrasound system using a C5-1 MHz trans-abdominal probe (Philips Healthcare, Andover, Massachusetts). All images were automatically stored into the picture archiving and communications systems software for any future review. We hypothesize that pre-pregnancy maternal obesity does influence the fetal NT measurement, with a larger BMI leading to a larger NT. We used the previously accepted World Health Organization (WHO) criteria to define obesity as having a BMI greater than or equal to 30kg/m^2 [11,12]. BMI was calculated using available pre-pregnancy height and weight data, which were obtained from both the electronic medical record and, if not immediately available, patient self-report at presentation for nuchal translucency measurement.

The primary outcome of our study was an abnormal NT measurement. We examined the association between the NT measurement and maternal BMI, as calculated from the recorded height and weight at the time of the examination, via multivariable linear regression. Measurements of both NT and of maternal obesity were transformed into categorical variables in order to observe the association of increased NT measurements with maternal obesity, defining 3.0mm and 3.5mm as an increased NT measurement and using WHO definition of obesity as previously described, via a chi-square test. Pearson's correlation coefficient was used to examine the correlation between pre-pregnancy weight and NT measurement.

Furthermore, we planned subgroup analyses a priori using a two-step approach. Firstly, we investigated the relationship of maternal obesity class (i.e. BMI ≥ 30kg/m^2 and BMI ≥ 40kg/m^2) on having an increased NT measurement, as compared to non-obese controls (BMI < 30kg/m^2), via an analysis of variance with Bonferroni correction for multiple comparisons. Secondly, we analyzed the association between maternal obesity and an increased NT measurement by

ethnicity classification, while controlling for maternal age. Other covariates controlled for in the analysis included gravidity, parity, ethnicity, gestational age at NT measurement, smoking history and maternal diabetes status. Definitions of a NT measurement threshold at which to consider further testing for fetal aneuploidy (i.e. chorionic villus sampling, amniocentesis or non-invasive prenatal testing) vary by gestational age and institution; however, current literature does support using either 95th percentile or 99th percentile as cut-offs for an abnormal measurement [13]. Nicolaides and associates provided two different recommendations for a NT threshold for invasive testing: one study suggesting 3.0mm, given its correlation with aneuploidy, while a second study suggested a threshold of 3.5mm since it represents the 99th percentile irrespective of gestational age or crown rump length [13,14]. Therefore, a priori, we considered an abnormal nuchal translucency measurement as both 3.0mm and 3.5mm in separate analyses. The statistical significance of the associations was analyzed by the means of a two-sample Student's t test.

We defined statistical significance as a p-value of less than 0.05. STATA 13.1 software was used for the conduct of all analyses (StataCorp, College Station, TX). This study was approved by the University of Pittsburgh Institutional Review Board #PRO13100433.

Results

A total of 24, 862 women were included in our analysis with mean pre-pregnancy weight and BMI of 70.0kg and 25.9kg/m^2, respectively. 7,408 women were classified as obese, representing approximately 29.8% of our total cohort. NT measurements for all women were obtained at a mean of 12.24 weeks gestation. Gravidity data was available for 23, 317 women (93.8%), with a mean gravidity of 2.39 (SD: 1.604). Parity data was only available for 12,451 women (50.1%). Of these patients, 6336 (50.9%) were considered multiparous, having given birth to one or more living children.

Our data demonstrate that the average NT measurement does increase with increasing BMI category, as noted in (Table 1) [1]. In evaluating our data for non-obese women and the previously delineated classes of obesity, there was significant difference in NT measurements between non-obese women and those with a BMI ≥ 30kg/m^2 (p=0.046). When adjusted for maternal age, ethnicity, gravidity, parity, maternal diabetes and maternal smoking status, BMI had a significant association with NT measurement (p<0.001) in our regression model. For every 1kg/m^2 increase in maternal BMI, there is, however, only a 0.00442 increase in fetal NT measurement (r^2=0.0107). The regression model also showed a significant association of NT measurement with African-American ethnicity (p<0.001), Asian ethnicity (p=0.002), parity (p=0.007) and smoking (p=0.039). There was a slight positive correlation between patient's pre-pregnancy weight and NT measurements obtained (r=0.0223).

In comparison to all other ethnicities in our cohort, African-Americans were more likely to have a NT measurement greater than or equal to 3.0mm on first trimester ultrasound (p<0.0001). Using 3.0 mm as a threshold at which to consider further testing for aneuploidy and a BMI of greater than or equal to 30kg/m^2, there was no demonstrated significant association between having such a NT measurement and being obese (p=0.40). Moreover, in stratifying our data to include only those having a BMI of greater than or equal to 40kg/m^2, we found no significant association with having a NT measurement of greater than or equal to 3.0mm (p=0.12).

Compared to all other ethnicities, African-Americans were more likely to have a NT measurement of greater than or equal to 3.5mm on first trimester ultrasound (p<0.0001). Using 3.5mm as a threshold for an increased NT measurement and BMI of greater than or equal to 30kg/m^2, there was no significant association between this NT measurement threshold and obesity (p=0.31). However, when considering those with a BMI greater than or equal to 40kg/m^2, which represents over 11.7% of our patient population, there was a statistically significant association with having a NT measurement of greater than or equal to 3.5mm (p=0.028). The mean NT measurements of those with a BMI less than 40 compared to those with a BMI greater than 40 were also statistically significantly different (1.62mm *vs.* 1.67mm: p=0.015).

Discussion

The primary objective of our study was to observe whether or not women with pre-pregnancy obesity have abnormal Nuchal Translucency (NT) measurements at the time of first trimester screening. On review of the literature, assuming a 5% screen positive rate (true positives as well as false positives), when used as a single marker of Trisomy 21, the NT has a detection rate of 64-70% [15]. Furthermore, in a cohort study analyzing 118 cases of NT measurements, the specificity of the NT for Trisomy 21 was 95.4% [16]. Our results indicate that as pre-pregnancy maternal obesity increases, the value of the NT measurement increases. The prevalence of obesity among reproductive-aged women has dramatically increased in the last 40 years. With the average patient age of 29.5 years and the proportion of obesity represented, our cohort is highly representative of national trends. The goal of our study was to examine whether or not women with pre-pregnancy maternal obesity have a higher incidence of having an abnormal nuchal translucency measurement. Our study results do indicate that maternal obesity, as measured by BMI, is associated with having a larger NT measurement as obtained on first trimester screening ultrasound, as seen in the continuous analysis. Furthermore, in the categorical analysis, there was a significant association between women with a pre-pregnancy BMI of greater than or equal to 40kg/m^2 and having a fetal NT measurement of 3.5mm or greater on first trimester ultrasonography. Our study shows obesity itself to be independently associated with NT measurement and, to our knowledge, is the first to employ such a large cohort. Nevertheless, although statistically significant, pre-pregnancy maternal obesity does not appear to be a major contributor to elevated NT measurements.

Increasingly, more women begin pregnancy as obese, which can complicate the course of their pregnancies. While our data do reveal a significant association between increasing BMI and increasing NT measurement size, our results may be limited by the ability to obtain such measurements in super morbidly obese patients. Maternal abdominal adiposity may impact the ability to perform a thorough ultrasonographic examination of the fetus, thus limiting the potential role of prenatal diagnosis [17]. A retrospective analysis of over 2500 patients demonstrated that the median time to obtain a NT measurement in those with a BMI greater than or equal to 40kg/m^2 was twice as long as in those of normal weight (18.7min

vs. 9.7mm: p<0.001) [18]. Moreover, over 12 percent of women with a BMI greater than or equal to 40kg/m^2 were unable to have a NT measurement obtained on repeated attempts [18]. Our data demonstrate that morbidly obese women have first-trimester fetuses with thicker NTs. Just as obese women have a higher incidence of macrosomic fetuses, it is possible that maternal obesity may have some physiologic influence on the fetal neck physiology, even in the first trimester.

Our sample size and its diverse composition do allow our findings to be generalizable to broader obstetric practice. Firstly, the significant proportion of morbidly obese patients does support the generalizability of our results. Recent data show that among euploid singleton pregnancies, BMI does have a small yet unknown clinical significant influence on the NT measurement; however, the authors did not specifically examine the influence of level of obesity on the NT measurement [9]. Our data from representative American cohort do support that of Hildebrand et al, who similarly examined the effect of BMI on NT measurement in Swedish women [19]. Currently, 31.9% of women aged 20-39 years old are classified as obese [1]. Unfortunately, the proportion of class III obesity, defined as a BMI greater than or equal to 40kg/m^2, among similarly aged women is substantial at 7.6%, with African-American and Hispanic women having higher rates as compared to Caucasian women [20]. Secondly, all NT measurements in our study were obtained using the same type of ultrasound machine operated by senior sonographers, which supports the consistency of our data. Thirdly, the final NT measurement established for each patient was adjudicated based on established criteria for NT quality via certified sonologists within our ultrasound division.

Although almost 30% of our cohort was considered obese, those with a BMI ≥40kg/m^2 only represented a minority of total patients. This may be due to our cohort including only those women who actually had a NT measurement obtained. Unfortunately, it is becoming increasingly common to encounter women with BMIs of 60, 70 and 80 in clinical practice, and the obstetric consequences of such obesity remain to be fully elucidated. It is important to consider such a patient in the context of our findings. For example, if a woman with a BMI of 80 presents for NT screening, based on the results of our regression model, her baseline NT value would be increased by 0.35 mm. Therefore, if her normal weight counterpart were to have an NT measured at 2.7mm, our model would predict her to have a NT value of nearly 3.1mm. At our institution, such a NT measurement would warrant a discussion with the patient regarding further testing for fetal aneuploidy. As the obese gravida may be physiologically different from their normal weight counterparts, there may need to be a different normative range of NT values in the morbidly obese women. It is possible that our patients may have underlying medical comorbidities that were either not disclosed at the time of ultrasound examination or were unrecognized by providers, thus confounding our results. While we excluded certain women from our analysis, it is also possible that our cohort studied may be "less at risk" for larger NT measurement than having included these. Nevertheless, our study does still display interplay between obesity and NT measurement, even when adjusted for noted covariates. We fully recognize the importance of correlating our findings with outcome data, such as fetal anomalies and fetal karyotype. However, such data was not available. A follow-up study examining outcomes in obese women with elevated NT results is warranted.

Our study is not without limitations. Patient height and weight data available did come from both the electronic medical record and, if not immediately available, patient self-report at presentation for nuchal translucency measurement. Such ascertainment bias and recall bias may have influenced our results. Moreover, while the amount by which we found the NT measurement to be increased with respect to increasing BMI was statistically significant, the magnitude of this size may argue for its clinical relevance. Outcomes data with respect to antenatal genetic testing or post-natal genetic analysis of those fetuses with thickened NT measurements would support our findings. Future research will need to be undertaken to more closely examine any possible etiology between pre-pregnancy maternal obesity and both aneuploidy risk and congenital malformations and to assess the underlying biological mechanism thereof.

Conclusion

Our findings suggest that maternal pre-pregnancy BMI, particularly if a woman has a pre-pregnancy BMI greater than or equal to 40kg/m^2, does have an association with an abnormal NT measurement but this association is small. Further study, particularly examining fetal/neonatal outcomes, is warranted in order to examine the impact of independent effect of pre-pregnancy maternal obesity on NT measurements.

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