OBSTETRICS

Risk of selected structural abnormalities in infants after increased nuchal translucency measurement

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OBJECTIVE: We sought to examine the association between increased first-trimester fetal nuchal translucency (NT) measurement and major noncardiac structural birth defects in euploid infants.

STUDY DESIGN: Included were 75,899 singleton infants without aneuploidy or critical congenital heart defects born in California in 2009 through 2010 with NT measured between 11-14 weeks of gestation. Logistic binomial regression was employed to estimate relative risks (RRs) and 95% confidence intervals (CIs) for occurrence of birth defects in infants with an increased NT measurement (by percentile at crown-rump length [CRL] and by ≥3.5 mm compared to those with measurements <90th percentile for CRL).

RESULTS: When considered by CRL adjusted percentile and by measurement ≥3.5 mm, infants with a NT ≥95th percentile were at risk of having ≥1 major structural birth defects (any defect, RR, 1.6; 95% CI, 1.3—1.9; multiple defects, RR, 2.1; 95% CI, 1.3—3.4). Infants with a NT measurement ≥95th percentile were at particularly high risk for pulmonary, gastrointestinal, genitourinary, and musculoskeletal anomalies (RR, 1.6-2.7; 95% CI, 1.1—5.4).

CONCLUSION: Our findings demonstrate that risks of major pulmonary, gastrointestinal, genitourinary, and musculoskeletal structural birth defects exist for NT measurements ≥95th percentile. The ≥3-fold risks were observed for congenital hydrocephalus; agenesis, hypoplasia, and dysplasia of the lung; atresia and stenosis of the small intestine; osteodystrophies; and diaphragm anomalies.

Key words: congenital birth defects, increased nuchal translucency, normal karyotype, prenatal screening

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Fetuses with increased fetal nuchal translucency (NT) measurement are at elevated risk of chromosomal and cardiac abnormalities.[1,2] However, the relationship between increased NT and major noncardiac structural birth defects in the absence of chromosomal abnormalities is less documented.

Many have reported frequencies of anomalies such as congenital diaphragmatic hernia, skeletal dysplasia, and genitourinary defects in populations of euploid fetuses with increased fetal NT measurements, but have not used a comparison group and therefore did not measure risk.[3-5] Studies calculating risk of birth defects associated with increased fetal NT measurement tend to lack power to investigate infants without critical congenital heart defects (CCHDs) or to examine specific birth phenotypes.[6-8]

In addition, varied use of the definition of "increased" NT measurement in the literature adds to uncertainty about delineation of risk. Knowledge of the association between anatomic anomalies by NT percentile and by the commonly applied 3.5-mm cutoff in chromosomally normal liveborn infants would be helpful for clinicians counseling pregnant women in whom an increased fetal NT measurement is identified.[9,10]

This study examines the risk of major noncardiac structural birth defects in a population of 75,899 liveborn euploid infants in California following a first-trimester fetal NT measurement ≥90th, ≥95th, and ≥99th percentile for crown-rump length (CRL) and ≥3.5 mm compared with those with NT measurement <90th percentile.

Materials and Methods

All infants included in the study had mothers who were participants in the California Prenatal Screening Program administered by the Genetic Disease Screening Program (GDSP) within the California Department of Public Health, and had NT measured when fetal CRL was 45-84 mm. NT practitioners who submit measurements to the GDSP are credentialed by the Nuchal Translucency Quality Review Program[11] or Fetal Medicine

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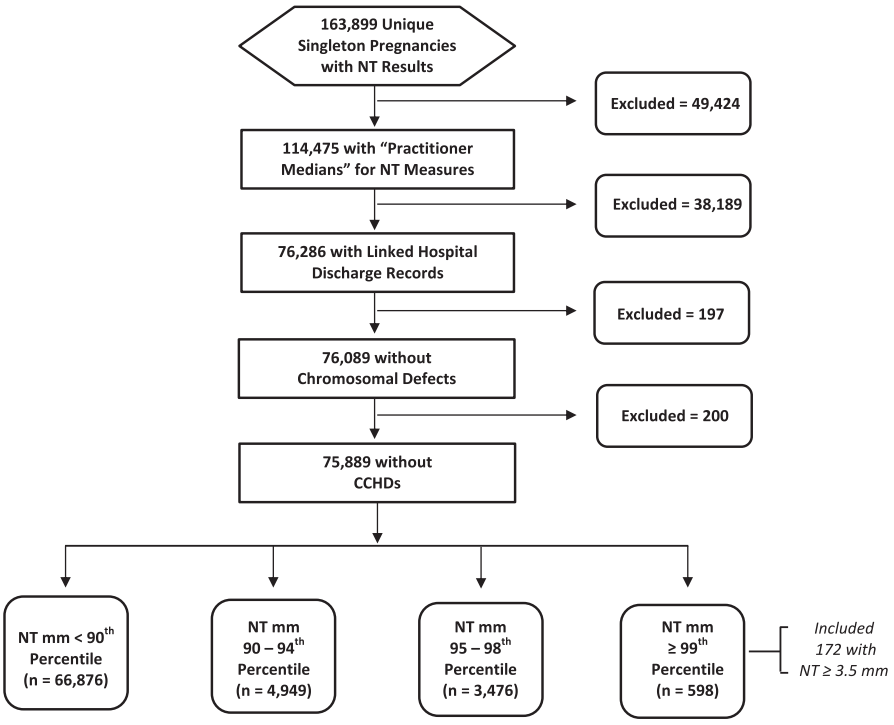
FIGURE
Included singleton pregnancies with first-trimester NT measurement



CCHDs, critical congenital heart defects; *NT*, nuchal translucency.

Baer. Structural birth defects in infants with increased nuchal translucency. Am J Obstet Gynecol 2014.

Foundation.[12] The GDSP works with both credentialing agencies to monitor NT data and maintain quality assurance for all accredited practitioners.[13] All NT measurements are submitted to the California Prenatal Screening Program as part of routine first- and second-trimester screening for aneuploidies.

Study participants were drawn from a sample of all singleton infants with NT results who had estimated dates of delivery from July 2009 through December 2010 based on CRL (n = 163,899). The sample was restricted to pregnancies for which NT measurements were done by clinicians who had practitioner-specific NT medians (n = 114,475). Clinicians who had practitioner-specific medians are those who had a minimum of 75 examinations and for whom the slope of their NT measurements increased by at least 11% across gestational weeks. In California, practitioner-specific medians have been shown to help control for less-experienced practitioners tending towards smaller NT measurements.[13] The sample was further restricted to infants born in 2009 through 2010 who had linked newborn screening records maintained by GDSP, birth certificates, and hospital discharge records from the birth cohort files maintained by the Office of Statewide Health Planning and Development (n = 76,286). Given that our study was focused on euploid infants without CCHDs, we also excluded all infants with chromosomal defects (n = 197) and CCHDs (n = 200) resulting in a final sample of 75,899 infants (Figure).

The GDSP Chromosome Registry personnel collect abnormality information on all California births.[14,15] Registry ascertainment sources include physicians, laboratories, hospitals, and prenatal diagnostic centers; California law mandates that these sources report chromosomal abnormalities to the GDSP. Information about structural birth defects was acquired from hospital discharge records from the birth cohort files maintained by the Office of Statewide Health Planning and Development, which collects outcomes through 1 year of age for each study infant. Structural birth defects for the study were considered "major" if determined by clinical review as causing major morbidity and mortality that would likely be identified in the hospital at birth or lead to hospitalization during the first year of life. Study protocols also required that major structural birth defects be identified by their 4-digit *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*)[16] codes given that while all hospitals in the state reported diagnoses to 4-digit *ICD-9-CM* code, not all reported to 5- or 6-digit *ICD-9-CM* codes. Supplementary Table 1 includes all major birth defect diagnoses included under the specific *ICD-9-CM* 4-digit codes used in most comparisons. Information on maternal race/ethnicity, weight at first screen, smoking status, and self-reported presence of pregestational diabetes was obtained from prenatal screening records.

Analyses utilized logistic binomial regression methods (relative risks [RR]) and their associated 95% confidence intervals (CIs) (2-tailed, significance threshold $P < .05$) to measure whether maternal characteristics were associated with having an increased NT measurement (grouped by 90th-94th, 95th-98th, or ≥99th percentile, and/or ≥3.5 mm) compared with <90th percentile. NT percentile was based on CRL at measurement among all fetuses evaluated (ie, not solely the measurements of the liveborn infants) and the distribution used in comparisons was for all singleton pregnancies screened with NT measurement where CRL was between 45.0-84.0 mm and had practitioner-specific NT medians (n = 114,475) (Supplementary Table 2). The frequency of increased NT was calculated for self-reported Hispanic, black, Asian, and "other" race/ethnicity relative to white non-Hispanic race/ethnicity, for maternal age <18 years or >34 years relative to maternal age 18-34 years, maternal weight ≤5th or ≥95th weight percentiles relative to the weight between the 6th-94th percentile (based on weight for gestational age by race/ethnicity at the time of NT measurement), smoking status, and pregestational diabetes (yes relative to no). The association between increased NT and major structural birth defects was measured by