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Maternal Hormone Levels and Perinatal Characteristics: Implications for Testicular Cancer

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PURPOSE: It was hypothesized that the risk for testicular germ cell tumors (TGCTs) is associated with maternal hormone levels. To examine the hypothesis, some studies used perinatal factors as surrogates for hormone levels. To determine the validity of this assumption, hormone–perinatal factor relationships were examined in the Collaborative Perinatal Project.

METHODS: Maternal estradiol, estriol, and testosterone levels in first- and third-trimester serum samples were correlated with perinatal factors in 300 mothers representative of populations at high (white Americans) or low (black Americans) risk for TGCT.

RESULTS: For white participants, testosterone levels were associated negatively with maternal height ($p < 0.01$) and age ($p = 0.02$) and positively with maternal weight ($p = 0.02$) and body mass index (BMI; $p < 0.01$), whereas estradiol levels were associated negatively with height ($p = 0.03$) and positively with son's birth weight ($p = 0.04$). For black participants, estriol levels were associated negatively with maternal weight ($p = 0.01$), BMI ($p = 0.02$), and gestational age $p < 0.01$) and positively with son's birth weight ($p < 0.01$), length ($p = 0.04$), and head circumference ($p = 0.03$).

CONCLUSIONS: These findings indicate that use of perinatal characteristics as surrogates for hormone levels should be limited to a specific ethnic group. For white men, previously reported associations of TGCT with maternal weight and age may be caused by lower maternal testosterone levels.

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KEY WORDS: Testicular Cancer, Maternal Hormones, Perinatal Factors.

INTRODUCTION

There is increasing evidence that testicular germ cell tumors (TGCTs) originate in utero (1). Although the mechanism that increases risk is unknown, it was suggested that an imbalanced intrauterine hormonal milieu may be important (2–4). However, it is very difficult to study the association between a fetal exposure that is not routinely measured, such as hormone levels, and a disease that occurs decades later. To overcome this problem, some studies examined the relationship between perinatal variables and TGCT under the assumption that perinatal variables are good surrogate measures of in utero hormonal conditions.

To test the validity of this assumption, several studies examined relationships between perinatal factors and maternal hormone levels (5–11). However, some of these studies included hormone samples from only one time in pregnancy or studied members of only one ethnic group. In addition, almost all studies to date included mothers pregnant with both male and female fetuses. Because relationships between perinatal factors and maternal hormones may vary by sex of the fetus or by ethnic group, further scrutiny of these relationships was indicated.

With the goal of informing future studies of TGCTs, relationships between perinatal factors and maternal hormone levels were examined in mothers pregnant with male fetuses. The mothers were selected to represent populations at differing risks for TGCT, white Americans (high risk) and black Americans (low risk), to determine whether perinatal factor–hormone relationships vary by ethnicity. In addition, relationships were examined in samples drawn in the first and third trimesters because these are critical periods for testicular descent, the failure of which is associated strongly with risk for TGCTs (12).

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Selected Abbreviations and Acronyms

TGCT = testicular germ cell tumor
BMI = body mass index
CPP = Collaborative Perinatal Project
DHEAS = dehydroepiandrosterone sulfate

METHODS

Study Population

A detailed description of the study population was reported previously (13). Briefly, 150 pairs of black and white mothers were selected from participants of the Collaborative Perinatal Project (CPP). The CPP cohort study was designed to examine perinatal risk factors for neurologic disorders in offspring (14). Pregnant women were enrolled at 12 medical centers in 11 US cities (Baltimore, Boston, Buffalo, Memphis, Minneapolis, New Orleans, New York (two centers), Philadelphia, Portland, Providence, and Richmond) between 1959 and 1965. At 11 study centers, patients were recruited from the participating university hospital's prenatal care clinic, and in one study center (Buffalo), patients were recruited from 13 participating private medical practices. Methods of participant selection varied across study centers. For example, at Columbia-Presbyterian Medical Center, every sixth woman who potentially was eligible was invited to participate; at Charity Hospital in New Orleans, potentially eligible women were selected if their patient identification number ended in zero; and in Boston, all potentially eligible women were invited to participate. Women were ineligible if they were incarcerated, planning to leave the area or give up the child for adoption, or gave birth on the day they were recruited into the study. Records of the number of women who refused to participate at baseline were not kept, but participation rates were assumed to be high (e.g., the rate was >99% at the Johns Hopkins Center in Baltimore; Janet Hardy, Johns Hopkins University, personal communication, November 2001). Characteristics of women in the sample at registration were essentially the same as those in the sampling frame (14). Four percent of subjects who enrolled were lost to follow-up before delivery.

Mothers donated nonfasting blood samples at approximately 8-week intervals throughout their pregnancies, as well as at delivery and 6 weeks postpartum. All serum samples subsequently have been stored in glass vials at −20°C, with no recorded thaws. Details of all clinic visits were recorded in the study records. Maternal characteristics of interest to the current analysis (age, height, prepregnancy weight, smoking, and socioeconomic index) were obtained from the women at the time of enrollment in the study. Neonatal characteristics (length of gestation, birth weight, birth length, and head circumference) were obtained in the delivery room. Approximately 42,000 women were enrolled in the study, and 55,000 children were born into the study. The children were assessed systematically at regular intervals for the presence of birth defects and other outcomes through the age of 7 years. Follow-up to age 7 years was completed for approximately 75% of subjects born into the study.

Mothers were selected for the current study based on the following criteria: pregnant for the first time, gave birth to a singleton male infant who lived at least 1 year, length of gestation between 26 and 48 weeks, blood samples available from both first and third trimesters, baby's birth weight at least 500 g, and baby had no diagnosis of undescended testes, late descending testes, retractile testes, or other malformations possibly related to maternal hormone levels (i.e., central nervous system and related musculoskeletal, genitourinary, inguinal hernia, hydrocele, and supernumerous nipples). The study was limited to mothers pregnant for the first time because estrogen levels were reported to be greater in first pregnancies (10, 15) and some studies linked TGCT risk to birth order (16, 17).

A total of 162 black and 652 white mothers satisfied the study inclusion criteria. The principal limiting criterion was the availability of first-trimester samples because the median entry time into the study for the entire CPP population was 20 weeks' gestation. In addition, the nulliparity criterion restricted the study group to approximately one third of the entire population. Each of the 162 black mothers was matched to a white mother on the closest blood draw gestational age dates. Matches then were reordered to select the 150 pairs best matched on draw dates. For the 300 mothers selected, gestational ages ranged between 30 and 43 weeks.

Laboratory Assays

Serum hormone levels were assessed at the Reproductive Endocrine Research Laboratory of the University of Southern California Keck School of Medicine (13). Unconjugated estriol, unconjugated estradiol, and testosterone were determined by using well-established validated radioimmunoassay methods that are carried out routinely in the laboratory (18, 19).

Study samples, labeled with unique random identification numbers, were analyzed in 17 batches. Each batch contained four quality-control samples aliquotted from a single blood pool. Intraassay coefficients of variation ranged between 3.7% and 12.6%, whereas interassay coefficients of variation ranged between 4.8% and 13.3%.

Statistical Analysis

Distributions of perinatal characteristics were compared by using chi-square tests. Small-for-gestational age was determined by comparing birth weights for each gestational age in weeks in the CPP with the 10th percentile of birth weight