OBSTETRICS

Combined elevated midpregnancy tumor necrosis factor alpha and hyperlipidemia in pregnancies resulting in early preterm birth

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OBJECTIVE: The objective of the study was to determine whether pregnancies resulting in early preterm birth (PTB) (<30 weeks) were more likely than term pregnancies to have elevated midtrimester serum tumor necrosis factor alpha (TNF-α) levels combined with lipid patterns suggestive of hyperlipidemia.

STUDY DESIGN: In 2 nested case-control samples drawn from California and Iowa cohorts, we examined the frequency of elevated midpregnancy serum TNF-α levels (in the fourth quartile [4Q]) and lipid patterns suggestive of hyperlipidemia (eg, total cholesterol, low-density-lipoproteins, or triglycerides in the 4Q, high-density lipoproteins in the first quartile) (considered independently and by co-occurrence) in pregnancies resulting in early PTB compared with those resulting in term birth (n = 108 in California and n = 734 in Iowa). Odds ratios (ORs) and 95% confidence intervals (CIs) estimated in logistic regression models were used for comparisons.

RESULTS: Early preterm pregnancies were 2-4 times more likely than term pregnancies to have a TNF-α level in the 4Q co-occurring with indicators of hyperlipidemia (37.5% vs 13.9% in the California sample (adjusted OR, 4.0; 95% CI, 1.1—16.3) and 26.3% vs 14.9% in the Iowa sample (adjusted OR, 2.7; 95% CI, 1.1—6.3). No differences between early preterm and term pregnancies were observed when TNF-α or target lipid abnormalities occurred in isolation. Observed differences were not explicable to any maternal or infant characteristics.

CONCLUSION: Pregnancies resulting in early PTB were more likely than term pregnancies to have elevated midpregnancy TNF-α levels in combination with lipid patterns suggestive of hyperlipidemia.

Key words: early preterm birth, hyperlipidemia, term pregnancy, tumor necrosis factor alpha

Cite this article as: Jelliffe-Pawlowski LL, Ryckman KK, Bedell B, et al. Combined elevated midpregnancy tumor necrosis factor alpha and hyperlipidemia in pregnancies resulting in early preterm birth. Am J Obstet Gynecol 2014;211:141.e1-9.

Studies have reported a link between preterm birth (PTB) and increased midpregnancy levels of tumor necrosis factor alpha (TNF-α)[1-3] as well as PTB and midpregnancy lipid levels[4-6]; the combined influence of these factors on the risk of PTB has not been explored.

Given the established link between TNF-α and lipid release from adipocytes (TNF-α induced lipolysis)[7-9] as well as the association between TNF-α and lipid metabolism,[10,11] we hypothesized that in some instances PTB risk could be associated with the co-occurrence of increased TNF-α levels and lipid levels. Most specifically when elevated TNF-α occurs in combination with hyperlipidemia (eg, suggested by increased total cholesterol [TC], low-density lipoproteins [LDLs], or triglycerides [TGs] or low high-density-lipoproteins [HDLs]).

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Received Nov. 27, 2013; revised Jan. 31, 2014; accepted Feb. 14, 2014.

Financial support was provided by National Institutes of Health/National Heart, Lung, and Blood Institute grants (RC2 HL101748, R01 HD-57192, and R01 HD-52953), the March of Dimes Prematurity Center at Stanford University School of Medicine, Bill and Melinda Gates Millennium grants (OPP52256 and RSDP 5K12 HD-00849-23), and March of Dimes grants (6-FY11-261 and FY10-180).

The authors report no conflict of interest.

Presented at the 34th annual meeting of the Society for Maternal-Fetal Medicine, New Orleans, LA, Feb. 3-8, 2014.

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0002-9378/$36.00 • • http://dx.doi.org/10.1016/j.ajog.2014.02.019

The importance of these combined influences on risk have been investigated in studies focused on gestational diabetes and preeclampsia[12,13] as well as studies focused on obesity, cardiovascular disease, insulin sensitivity, and metabolic syndrome.[11,14-17]

Here we used second-trimester serum samples collected as part of routine second-trimester screening for aneuploidies and neural tube defects to investigate the potential interrelationships between TNF-α and lipid levels for their contribution to the risk in pregnancies resulting in early PTB (<30 weeks) compared with term pregnancies. We examined these associations in 2 nested case-control samples drawn from California and Iowa cohorts.

Materials and Methods

The relationships between midpregnancy TNF-α, lipids patterns, and early PTB (less than 30 weeks) were examined in 2 independent nested case-control samples of pregnancies from California (n = 108) and Iowa (n = 734). Included from California were 72 case pregnancies resulting in early PTB and 36 singleton control pregnancies resulting in term birth (≥37 completed weeks of gestation). Case and control pregnancies were drawn from a larger cohort of more than 1.4 million pregnancies who underwent routine prenatal screening in 2005-2008, of whom 662,889 had no indication of chromosomal or structural defects, smoking, diabetes, or amniotic fluid abnormalities present in prenatal screening, had a birth certificate, or for cases, neonatal intensive care unit (NICU) records.

As described in earlier work,[18] 1928 pregnancies in this cohort delivered before 30 weeks. PTB less than 30 weeks was our focus for the original study, given that in California, there is routine data collection in NICUs for greater than 90% of newborns with birth before 30 weeks.[19] Our focus in the source study was bronchopulmonary dysplasia (BPD) in PTBs less than 30 weeks, which relied on these records.

The present study used data from this source study and associated prenatal screening specimens that had been stored for a portion of these pregnancies as part of regular banking protocols in the state (wherein there is routine banking of specimens in 3 geographic areas [the California Central Valley, Los Angeles and Orange County, and San Diego County]). Thirty-nine of the 246 pregnancies resulting in PTB less than 30 weeks with BPD in the source study had stored midpregnancy samples (18 females and 21 males).

For biomarker testing, we implemented a balanced design wherein 18 of the 21 males with PTB less than 30 weeks and BPD were randomly selected and grouped with the 18 females (n = 36 total). We then randomly selected 18 females and males from stored samples for PTBs less than 30 weeks and no BPD (from a total stored sample of 115 of 1682 in the original set [62 females and 53 males]) and 18 females and males from stored samples from the term births [from a total stored sample of 63,312 of 575,387 in the original set (32,318 females and 30,994 males]).

To best mirror California analyses with respect to PTB less than 30 weeks but without any stratification by BPD or other exclusions, included from Iowa was a complete sample of 57 case pregnancies resulting in PTB less than 30 weeks drawn from a total sample of 12,057 singleton pregnancies with second-trimester screening through the Iowa prenatal screening program in May 2009 through November 2010. Also included were 677 singleton control pregnancies resulting in term birth selected at an approximate 1:1 ratio to all PTBs (<37 weeks, n = 657). Additional details regarding the cohort from which Iowa cases and controls were drawn have been described elsewhere.[6]

Information on maternal characteristics and related data

In both samples, information on maternal characteristics, measurements on routine second-trimester serum screening tests, and information on infant characteristics were abstracted from state prenatal screening program data (the California Prenatal Screening Program within the Genetic Disease Screening Program and the Iowa Prenatal Screening Program) and from state birth certificate records. Included from screening records was maternal race/ethnicity, weight at testing, age at testing, and gestational weeks at the time of second-trimester screening. Other data extracted from birth certificates included parity, birthweight, and gestational age.

For Iowa, information on body mass index (BMI), diabetes, congenital defects (chromosomal or other), information on whether the PTB was spontaneous or medically indicated, and the presence of other factors closely linked with PTB (hypertension, diabetes, previous PTB) were also abstracted from birth certificates. In California, prenatal screening records, hospital discharge records (for cases and controls), and NICU records (for cases) were used along with birth certificates to make exclusions for smoking history, diabetes, structural or chromosomal defects to determine whether the PTB was spontaneous or medically indicated and to determine whether there was any presence of hypertension, diabetes, or previous PTB.

In California, no data on maternal height were present in any record for these birth years. As such, we relied on a diagnostic code for BMI of 30 kg/m^2 or greater to determine obesity. In California, NICU records were also used to identify cases with and without BPD and other indicators of case morbidity including intraventricular hemorrhage and retinopathy of prematurity. In both California and Iowa samples, case pregnancies resulting in spontaneous PTB were considered to be those in which vital statistic birth certificate records (California and Iowa) or hospital discharge records (California) included a flag for premature labor, premature rupture of membranes, or tocolytic administration.

Case pregnancies resulting in medically indicated premature birth were considered to be those without premature labor or premature rupture of membranes for whom there was a flag for medical induction or artificial rupture of membranes or for whom there was a cesarean section given birth less than 37 weeks and none of the aforementioned flags. Case pregnancies