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Peripartum cardiomyopathy is associated with increased uric acid concentrations: A population based study

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ABSTRACT

Background: Peri-partum cardiomyopathy (PPCM) is a clinical heart failure that usually develops during the final stage of pregnancy or the first months following delivery. High maternal serum uric acid concentrations have been previous associated with heart failure and preeclampsia.
Objectives: 1) To explored the clinical characteristics of PPCM patients; and 2) to determine the association between maternal serum uric acid concentrations and PPCM.
Methods: This is a retrospective population based case control study. Cases and controls were matched 1:4 (for gestational age, medical history of cardiac conditions and creatinine); conditional logistic regression was used to identify clinical parameters that were associated with PPCM.
Results: The prevalence of peripartum cardiomyopathy at our institution was 1−3832 deliveries (42/160,964). In a matched multivariate analysis high maternal serum uric acid concentrations were associated with PPCM (O.R 1.336, 95% C.I 1.003−1.778). Uric acid concentrations were higher within the Non-Jewish patients and mothers of male infant with PPCM in compare to those without PPCM (p value 0.003 and 0.01 respectively).
Conclusion: PPCM patients had increased maternal serum uric acid concentrations. This observation aligns with previous report regarding the increased uric acid concentration in women with preeclampsia and congestive heart failure, suggestive of a common underlying mechanism that mediates the myocardial damage.

Introduction

Peripartum cardiomyopathy (PPCM), first described in the 1930's, is a clinical heart failure with a reduced LV systolic ejection fraction, usually manifested as a dilated cardiomyopathy, that develops during the last month of pregnancy or the first months following delivery.[1] PPCM is a diagnosis of exclusion. It commonly develops in the absence of an identifiable etiology of cardiomyopathy.[2,3] The incidence of PPCM varies worldwide, from 1:4000 births in the USA to 1:300 in Haiti and 1:100 in Zaria, Nigeria.[4–6]

Several explanations have been proposed in the past to clarify the patho-physiology of PPCM, but the specific cause remains unclear. However, recently two hypotheses have emerged: the increasing understanding of the genetic component, and the role of prolactin in the vasculo-hormonal hypothesis.[7] The genetic hypothesis has not been considered seriously in the setting of PPCM, since most of the cohorts were sporadic and unrelated. Even the same patient has a good chance to return to normal LV function following the next pregnancy. Lately, 26 truncating variants of 8 genes associated with dilated cardiomyopathy, were identified in 15% of 172 PPCM patients, compared to a prevalence of 1.3×10^{-7} in the control group. The sequencing of these variants may shed light on the genetic predisposition of PPCM.[8] The vasculo-hormonal hypothesis was first described in 2007 on knockout mice in the cardiac tissue-specific signal transduction and activator of transcription 3 (STAT3) gene. Decreased STATS3 leads to increased cleavage of prolactin, a late pregnancy hormone, into a 16-kDa fragment that promotes apoptosis in endothelial cells. This process may lead to myocardial dysfunction, in addition to the well known anti-angiogenic effect of 16-kDA.[9,10] The latter may also explain the association of PPCM with preeclampsia and multiple gestation pregnancies. These conditions are associated with

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increased secretion of VEGF inhibitors and angiogenic imbalance, which may lead to vascular end-organ damage (cardiac, renal and placental).[11]

Hyperuricemia is an established key factor for preeclampsia and hypertensive pregnancy disorders, but its role in the pathogenesis of PPCM was unknown for decades. Uric acid is produced by the enzyme xanthine oxidase (XO) as the end product of purines catabolism. It is predominantly excreted by the kidney. Consequently, uric acid levels fall as the glomerular filtration rate inclines during the progress of a normal pregnancy. During the metabolism of purines by XO, the generation of free radicals is enhanced. This may increase cellular oxidative stress and nitric oxide imbalance, and lead to over production of pro-inflammatory cytokines.[12–14]

In this study we explored some of the unique characteristics of PPCM to identify clinical parameters that correlate with PPCM and specifically uric acid in the light of the previously proposed pathophysiology hypothesis.

Methods

Study population

Women in the PPCM group were identified through our computerized medical records system that includes information regarding all patients who were admitted to Soroka University Medical Center (SUMC) or visited its outpatient clinics during the years 2004–2014. The SUMC is a tertiary medical center serving a population of approximately 700,000 as the only primary hospital, and nearly 1.2 million as a tertiary hospital, as well as attending all the deliveries in this region. Thus, the information presented herein can be regarded as a population based study. The study was approved by SUMC ethics committee.

Patients were included in the PPCM group only if they had two consecutive echocardiogram examinations. The first, performed during the last trimester of pregnancy or in the first four weeks postpartum, showing reduced LV systolic function without any significant valvular or congenital abnormality, and after excluding other etiologies of heart failure. The second follow up echo was performed at least more than 30 days after the initial echo. The exclusion criteria were any previous valvular or congenital heart diseases and presence of other severe conditions that coupled with reduced ejection fraction (EF).

Data extraction

We identify all patients in SUMC electronic database in a retrospective approach, with the diagnosis of Peripartum Cardiomyopathy (ICD 9 code 674.5) or other cardiovascular diseases complicating pregnancy, childbirth or puerperium (ICD 9 code 678.6). Two independent clinicians examined each patient's records to determine those to be included in our analysis with the final diagnosis of PPCM according to the 2010 European Society of Cardiology (ESC) Working Group on Peripartum Cardiology[3]: 1) Development of clinical heart failure (HF) toward the end of pregnancy or in the months following delivery. 2) Absence of another identifiable cause for the HF; and 3) Left ventricular (LV) systolic dysfunction with an LV ejection fraction less than 45%. The left ventricle may or may not be dilated.

The obstetrical information of the patients in the PPCM group and that of the rest of our obstetrical population who served as the comparison group was extracted from the computerized dataset of the Division of Obstetrics and Gynecology. This dataset includes all the information of the delivery records of all patients who delivered at our medical center. The diagnoses are coded by trained secretaries according to the ICD-9 coding system. Laboratory tests were included in a range of 7 days from delivery.

Statistical analysis

Descriptive statistics were used (prevalence and standard deviations) to describe the demographic, clinical and obstetric characteristics of the study cohort. We performed independent t tests and chi square tests to compare continuous and categorical variables between groups of patients diagnosed with or without PPCM. To estimate the effects of parameters that were found significant in the univariate analysis ($p < 0.05$) we used a multivariate logistic regression to predict PPCM. In addition, we matched our PPCM patients to the entire cohort, with gestational age, medical history of cardiac conditions (other than heart failure) and creatinine in a ratio of 1:4. We used caliper widths of 0.1 of the pooled standard deviation of the model logit predicted values.[15] Then we conducted a conditional regression to evaluate the effect of the same predictors to develop PPCM versus matched controls. Data analysis was performed using SPSS version 22 (SPSS Inc. Chicago, Illinois).

Results

We Identified 160,964 live births of 65,442 different women during the study period (2004–2014). We identified 523 patients with the aforementioned ICD diagnosis. After careful review of echocardiogram results, only 42 met all the eligibility criteria and were included in the statistical analysis. The prevalence of peripartum cardiomyopathy at our institution was 1–3832 births. There were no deaths reported among PPCM patients during the study period. The majority of the patients were diagnosed with PPCM post partum (31 patients, 73.8%) compared to pre-partum. Table 1 presents the baseline maternal and gestational characteristics according to the diagnosis of PPCM vs. the non-PPCM patients. Women at the PPCM group had a higher rate of advance maternal age (p value 0.027), Bedouin ethnicity (p-value 0.045), and prior preeclampsia, as well as maternal cardiac conditions rather than heart failure (p value < 0.001 for both).

Women in the PPCM group delivered earlier ($p < 0.001$), had a higher rate of low 1 and 5 min Apgar scores ($p < 0.01$, $p = 0.001$), as well as male neonates ($p = 0.03$) than women in the comparison group (Table 1).

Maternal laboratory characteristics are presented in Table 2. PPCM patients had a higher mean creatinine concentrations as well as a higher rate of elevated creatinine $\geq$0.7 mg/dL (p value 0.034 and $<$0.001 respectively) than the comparison group. PPCM patients had higher maternal serum concentrations of urea and uric acid, and lower concentration of albumin (p value 0.036, 0.002 and $<$0.001 respectively) than the comparison group. PPCM group had higher concentrations of detectable troponin T, while other markers of inflammation and cardiac damage (such as d-dimer, creatine phosphokinase and c-reactive protein) were not showed statistically significance (Table 2).

In order to examine the parameters associated with PPCM, we preformed univariate analysis followed by standard and matched multi-variate analysis with the same parameters in order to test their impact on PPCM (Table 3). When tested separately, non-Jewish ethnicity, male infant, history of preeclampsia in the current pregnancy and uric acid levels were associated with increased risk to develop PPCM. When constructed a logistic regression comprising these parameters, Non Jewish origin (O.R 2.714, 95% C.I 1.312–5.612), preeclampsia (O.R 2.376, 95% C.I 1.188–4.753), and maternal uric acid concentrations (O.R 1.301, 95% C.I 1.049–1.614) were independently associated with PPCM. Additionally, we conducted 1:4 matched model according to gestational age at delivery, prior maternal cardiac