Short and Long-Term Outcome of Pregnant Women with Preexisting Dilated Cardiomypathy: an NTproBNP and Echocardiography-Guided Study

Alex Blatt MD MSc[1], Ran Svirski MD[2], Gil Morawsky MD[1], Nir Uriel MD[1], Ortal Neeman MD[2], Dan Sherman MD[2], Zvi Vered MD[1] and Ricardo Krakover MD[1]

Departments of [1]Cardiology and [2]Obstetrics and Gynecology, Assaf Harofeh Medical Center, Zerifin, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

ABSTRACT: **Background:** Little is known of the outcome of pregnant patients with previously diagnosed dilated cardiomyopathy. These patients are usually firmly advised against continuation of the pregnancy.

Objectives: To examine the usefulness of serial echocardiographic follow-up and plasma N-terminal pro-B type natriuretic peptide levels in the management of pregnant women with preexisting DCM.

Methods: We prospectively enrolled pregnant women with DCM either known or diagnosed in the first trimester. Clinical examination and serial echocardiography studies were performed at baseline, at 30 weeks gestation, peripartum, and 3 and 18 months postpartum. Blinded NTproBNP levels were obtained at 30 weeks, at delivery and 3 months postpartum.

Results: Between June 2005 and October 2006 we enrolled seven women who fulfilled the study criteria. Delivery and postpartum were complicated in 3 patients (42%): 2 with acute heart failure, which resolved conservatively, and 1 with major pulmonary embolism. The left ventricular ejection fraction was stable throughout the pregnancy (35% ± 2.8 at baseline, 33% ± 2.9 at 30 weeks) and postpartum (35% ± 2.8 at 1 day, 34% ± 3.1 at 90 days). Similar stable behavior was observed regarding left ventricular dimensions: LV end-systolic diameters 43.3 ± 2.7 mm and LV end-diastolic diameters 57.3 ± 3.3 mm at baseline compared with 44.1 ± 3.1 mm and 58.7 ± 3.1 mm postpartum, respectively. The NTproBNP levels rose significantly peripartum in all three patients with complications.

Conclusions: Serial NTproBNP levels, as compared to echocardiography, may be a better clinical tool in monitoring and management of pregnant women with preexisting DCM. An early rise in NTproBNP level appears to predict the occurrence of adverse events.

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KEY WORDS: pregnancy, preexisting dilated cardiomyopthy, N-terminal pro-B type natriuretic peptide (NTproBNP), echocardiography

Pregnancy in women with known (preexisting) dilated cardiomyopthy has been rarely described, and the clinical management and prenatal care of this patient population are unclear. While some studies reported a good pregnancy outcome and stable cardiac function in patients with DCM, others noted poor clinical outcome including maternal death or heart transplantation [1,2]. The physiologic cardiovascular adaptations during pregnancy are well characterized [3]. The observed increase in cardiac output is primarily due to increases in both heart rate and stroke volume, as demonstrated in several echocardiographic studies [4,5]. B-type natriuretic peptide is an emergent and relatively new clinical tool with diagnostic [6] and prognostic value [7]. In healthy pregnant women BNP levels are in the normal range throughout gestation but may increase to pathologic levels during alterations in hemodynamic homeostasis, such as preeclampsia [8].

We conducted a prospective observational study to examine the usefulness of blinded serial BNP levels and echocardiographic studies as non-invasive tools in the monitoring and management of pregnant women with preexisting or newly developed DCM.

PATIENTS AND METHODS

STUDY DESIGN AND PATIENT POPULATION

The study protocol was approved by the Assaf Harofeh Medical Center Institutional Review Board. We prospectively enrolled all pregnant women with known DCM or those diagnosed in the first trimester. DCM was defined as depressed left ventricular ejection fraction ≤ 45% as determined by transthoracic echocardiography. All women fulfilling this inclusion criterion underwent a comprehensive evaluation by obstetricians and cardiologists, and the possible deleterious effects of pregnancy and/or delivery on their cardiac performance were discussed. Women who elected

DCM = dilated cardiomyopathy
NTproBNP = N-terminal pro-B type natriuretic peptide
LV = left ventricular

to continue their pregnancy and agreed to participate in a prospective follow-up study were enrolled and followed in our high risk pregnancy unit and the cardiology department. Written informed consent was obtained from all patients.

Demographic and clinical characteristics were obtained using questionnaires. Clinical follow-up continued in the outpatient cardiac clinic 3, 6, 12 and 18 months after delivery. Echocardiographic studies were performed at enrollment (baseline), at 30 weeks gestation, immediately after delivery and 3, 6 and 18 months postpartum. All studies were conducted with the VIVID 3, GE Health Care system using a 3.25 MHz transducer. The left ventricle was divided into 16 segments and left ventricular dimensions were measured according to the recommendations of the American Society of Echocardiography, based on a 16 segment model. Ejection fraction was determinated by the modified method of Quinones et al. [9].

NTProBNP LEVELS

Peripheral venous blood samples were obtained at 30 weeks gestation and during the first stage of delivery. The samples were centrifuged and the serum was stored at -70ºC. The NTproBNP analysis was performed on serum using a standard core laboratory assay (Roche Diagnostic, Basel, Switzerland). The medical management team was blinded to the BNP results.

STATISTICAL ANALYSIS

Values are expressed as the median and interquartile range.

RESULTS

Between June 2005 and October 2006 we enrolled seven women fulfilling the study criteria. The mean age was 33.5 ± 3.3 years; six women were Caucasian and one was Ethiopian. DCM had been diagnosed in five patients before the current pregnancy and in two during the first trimester in the course of workup for effort dyspnea. New York Heart Association functional class before the pregnancy was good in all women: NYHA I-II. Medical history revealed hypothyroidism in four patients (57%), pregestational diabetes type 2 in one, and chronic hypertension in another [Table 1]. Four patients (57%) were primagravidas; two of them conceived following infertility treatments. Six patients had singleton gestation and one patient had a twin gestation.

All the women underwent fetal echocardiography during pregnancy, which was normal. None had pregnancy-induced hypertension or any deterioration in their functional class according to the NYHA during the pregnancy. During delivery all women were given epidural analgesia without any complication; four had vaginal delivery and three had cesarean section. All neonates were born at term, had normal Apgar score and pH level, and their weight was appropriate for their gestationl age.

Table 1. Characteristics of patients with preexisting dilated cardiomyopthy

Age (yrs)	33.5 ± 3.3
Ethnicity	
Caucasian	6
Black	1
Risk factors	
Hypertension	1
Diabetes mellitus	1
Gestation-induced	
Hypertension	0
Diabetes mellitus	0
Hypothyroidism	4
NYHA Functional class	
I	4
II	3
Prior heart failure acute decompensation	2
Medication	
None	3
Beta-blocker	2
ACE/ARB	4
Diuretic	1

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker

The delivery and postpartum were complicated in three patients (42%): two (patients 2 and 5) developed acute heart failure several hours after the delivery and were transferred to the intensive cardiac care unit. These cardiac events resolved following conservative medical therapy. One patient (# 3) developed massive acute pulmonary embolism 3 days after delivery. The patient was treated with tissue plasminogen activator acutely and an inferior vena cava filter was inserted due to recurrent pulmonary embolism despite adequate anticoagulation therapy.

Six patients, including the two with acute heart failure, returned rapidly to the baseline NYHA functional class. The woman with pulmonary embolism became asymptomatic 3 months after delivery.

Left ventricular ejection fraction was stable throughout gestation (35 ± 2.8% at enrollment, 33 ± 2.9% at 30 weeks) and in the early and late postpartum periods (35 ± 2.8% on first postpartum day, 34 ± 3.1% at 90 days, and 33 ± 2.7% at 18 months) [Figure 1]. Similar stable findings were observed in left ventricular dimensions: LVESD 43.3 ± 2.7 mm and LVEDD 57.3 ± 3.3 mm at baseline and 30 weeks gestation, respectively. At 3 and 18 months after delivery echocardiographic measurements did not change significantly: 44.1 ± 3.1 mm, 58.7 ± 3.1 mm and 57.8 ± 2.9 mm.

Figure 2 represents the NTproBNP levels during the study. The NTproBNP levels were above a cutoff of 300 pg/ml before

NYHA = New York Heart Association

LVESD = left ventricular end-systolic diameter
LVEDD = left ventricular end-diastolic diameter

delivery in all patients with complications. These patients presented a "step up" in their 30 week pregnancy NTproBNP levels. In the remaining, event-free four patients, NTproBNP levels remained stable throughout gestation, before delivery and in the immediate postpartum period. One uncomplicated delivery (patient 7, twins pregnancy) showed values above 300 pg/ml, without a significant elevation between samples.

DISCUSSION

Our prospective study found relative safety and good pregnancy and neonatal outcome in this high risk population due to close obstetric and cardiology supervision. The present study demonstrates the potential additional clinical value of serial NTproBNP levels to predict cardiovascular complications in the management of these high risk pregnant women. Serial echocardiography failed to predict adverse outcome in this small study group.

This is no doubt a high risk population. The theoretic estimated risk in this patient group according to the Canadian risk index [10] is > 27% (one or more predictors). Fortunately, this is an infrequent clinical situation, since most women with DCM avoid pregnancy, and some will choose pregnancy termination to avoid the reportedly adverse outcomes. In our relatively large series of women we observed the occurrence of major cardiovascular events in 3 patients (42%). There was, however, no fatal event in the short and long-term follow-up, an observation in concordance with the low mortality rate among patients with peripartum cardiomyopathy [11-13].

We propose the use of a new terminology to more precisely characterize patients with heart failure associated with pregnancy:

- Group 1 – preexisting/newly developed DCM according to our inclusion criteria: either known significant systolic dysfunction beforehand or diagnosed in the initial phase of the pregnancy
- Group 2 – gestational DCM: heart failure developing toward the end of pregnancy or several months after delivery (peripartum cardiomyopathy)
- Group 3 – acute heart failure superimposed on preexisting DCM.

This new classification concurs with the presence of hypertension during the pregnancy: chronic hypertension, gestational hypertension, and preeclampsia/eclampsia superimposed on chronic hypertension.

Serial echocardiography in these women showed no significant differences between studies. It is possible that dilated dysfunctional hearts may have responded differently to normal hearts [3-5].

The cutoff of "normal" NTproBNP values depends on the clinical scenario. Based on Resnik et al. [8] the normal value

Figure 1. LVEF during pregnancy and postpartum

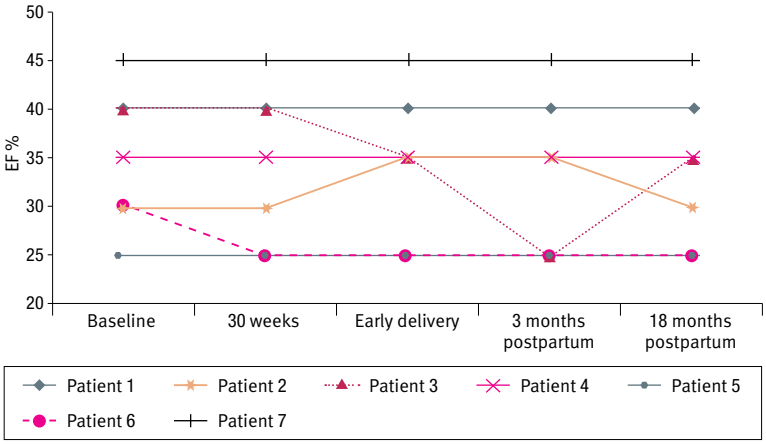
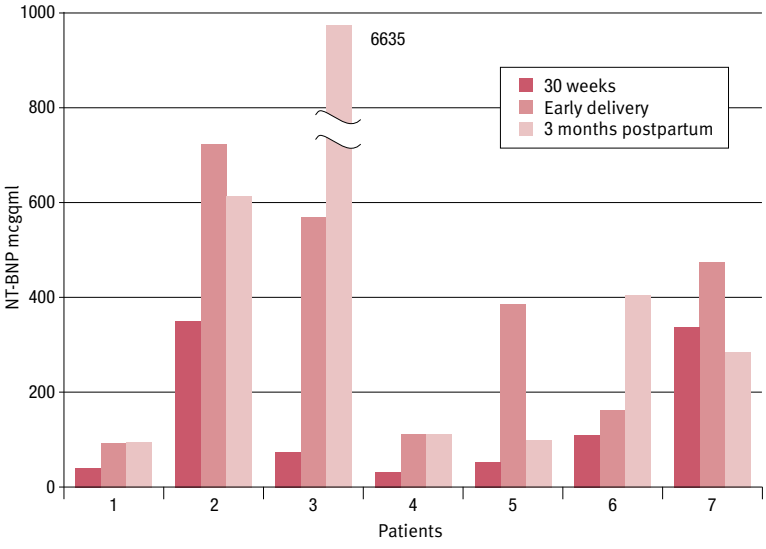


Figure 2. NT-BNP levels during pregnancy and postpartum



of BNP in healthy pregnant wemen (without cardiomyopathy or any other disease) is less than 100 pg/ml. In this sublinical disease – previously asymptomatic women with known depressed systolic function – 300 pg/ml is a reasonable value [14]. Most importantly, the significant increase ("step up") in the peripartum period, compared with the patient's baseline, appears to be a significant clinical value for predicting cardiovascular events.

The present study indicates that in the setting of pregnant women with preexisting, or recently developed DCM during the initial phase of pregnancy, serial NTproBNP levels measurement, as opposed to serial echocardiography studies, may be a useful clinical tool for monitoring and managing these pregnant women. A rise in NTproBNP level (either early, or

particularly during the early delivery stage) appears to predict the occurrence of significant adverse events.

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Corresponding author:

Dr. A. Blatt

Dept. of Cardiology, Assaf Harofeh Medical Center, Zerifin 70300, Israel

Phone: (972-8) 977-9345

Fax: (972-8) 977-9349

email: alexb@asaf.health.gov.il

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