Cardiomyopathy Phenotypes and Pregnancy Outcomes with Left Ventricular Noncompaction Cardiomyopathy
Three Cases and a Literature Review

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Summary
Little is known about pregnancies of left ventricular noncompaction cardiomyopathy (LVNC), much less cases in which LVNC was definitively diagnosed pre-pregnancy. We report the cases of three pregnant Japanese women definitively diagnosed with LVNC pre-pregnancy. Case 1 presented LVNC with restrictive phenotype. Her pregnancy was terminated due to exacerbated pulmonary hypertension and low output status at 30 weeks’ gestation. Case 2 presented isolated LVNC with nonsustained ventricular tachycardia. A cesarean section was performed at 36 weeks’ gestation because of placenta previa. Case 3 presented dilated LVNC. Labor induction was performed because of decreased left ventricular ejection fraction, leading to a vaginal delivery at 37 weeks’ gestation. In all cases, no thromboembolic event was identified during pregnancy; two patients received anticoagulants. We reviewed all English-literature cases of pregnant women definitively diagnosed with LVNC pre-pregnancy to analyze causes of adverse pregnancy outcomes and the necessity of anticoagulation. Four of the six pregnancies identified were terminated due to exacerbated cardiomyopathy phenotypes and not complications due to noncompaction itself, resulting in three cases’ preterm deliveries. No thromboembolic event was identified by maintenance of the anticoagulation strategy determined pre-pregnancy. In pregnancies with LVNC, the possibility of a severe cardiac event and the indications for termination of the pregnancy can depend on the cardiomyopathy phenotypes, not noncompaction itself. Anticoagulation only because of the pregnancy itself may be redundant. In the management of LVNC during pregnancy, close monitoring of the condition of different phenotypes and reassessment of the necessity of anticoagulation can contribute to the pregnancy outcome.

Key words: Heart failure, Thromboembolism, Anticoagulation, Echocardiography

Left ventricular noncompaction cardiomyopathy (LVNC), classified as a distinct form of cardiomyopathy in 2006,1 is a heterogeneous myocardial disorder characterized by prominent trabeculae, intratrabecular recesses, and a left ventricular myocardium with two distinct layers: compacted and noncompacted.2-5 LVNC can lead to life-threatening complications such as heart failure, arrhythmia, and thromboembolic events and to sudden death.2-4 Although LVNC has been deemed rare, the diagnosis is becoming more frequent due to increased awareness and advances in imaging techniques.2,5 The same is true of women of reproductive age.

In recent years, the prognosis of patients with LVNC has improved, as more benign LVNC that has preserved cardiac size and function has been diagnosed and as more cases of LVNC have been identified and treated earlier.2,5 Notably, more women with LVNC will become pregnant. However, little is known about pregnant women with LVNC, much less women with LVNC diagnosed definitively before pregnancy.

Although some investigators have proposed that adequate anticoagulation should be given to pregnant women with LVNC because the deep recesses of endomyocardium have an increased risk of thrombus formation and because pregnancy can induce hypercoagulability,7,8 there are no studies concerning anticoagulation given to women with LVNC all during pregnancy, to the best of our knowledge.

Here we report the cases of three pregnant women definitively diagnosed as having LVNC before pregnancy, all of whose pregnancies were managed without thromboembolic events (by the administration of anticoagulants in two cases). We also review all of the cases in the English-literature of pregnant women diagnosed definitively with LVNC before pregnancy, to identify the causes of adverse pregnancy outcomes and to investigate the necessity of anticoagulation.

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**Case Reports**

**Case 1:** A 31-year-old nulligravida Japanese woman with previously diagnosed LVNC and a strong family history of LVNC was referred to our department at 5 weeks’ gestation. As a 2-year-old, she had acute heart failure due to pulmonary hypertension and was treated with digoxin and diuretics. Her echocardiography at that age showed restrictive dynamics due to endocardial fibroelastosis and impaired left ventricular ejection fraction (LVEF) at 34%. Although she had had recurrent heart failure thereafter, she remained asymptomatic and had experienced no cardiac event including thromboembolic events since she was 11 years old. When the patient was 19 years old, the increased awareness of LVNC and the more prominent trabeculations shown by echocardiography compared with the situation in her childhood helped us diagnose LVNC. No anticoagulation was initiated because a paucity of information was available on LVNC at the time. Only carvedilol (10 mg/day) had been administered since the patient was 28 years old. At 6 weeks’ gestation, her NYHA was class I, and her echocardiography showed distinct features demonstrating LVNC (Figure 1) with the restrictive phenotype as same as prepregnancy findings; the systolic left atrial diameter was 46 mm, the LVEF was 51%, measured by the biplane modified Simpson’s rule, mitral inflow was restrictive pattern (E/A 2.6, DeT 143 ms), and the tricuspid regurgitation pressure gradient (TRPG) was 48 mmHg. Anticoagulation was not initiated only because of the pregnancy itself, and the carvedilol was continued. Follow-up echocardiography was repeated, and the patient’s diastolic dysfunction was exacerbated (E/A 2.5, DeT 108 ms), and TRPG was increased to 63 mmHg with mild dyspnea as early as 26 weeks’ gestation. The plasma levels of B-type natriuretic peptide (BNP) increased to 164 pg/mL, from 107 pg/mL at early gestation.

Although the administration of oxygen and diuretics improved the TRPG (38 mmHg) temporarily, at 30 weeks’ gestation, the pregnancy was terminated due to exacerbated pulmonary hypertension (TRPG 54 mmHg) and low output status. The BNP levels were 107 pg/mL. The newborn was delivered with a birth weight of 1,444 g and Apgar score of 8/9 at the first and fifth minutes. The baby showed somehow delayed psychomotor development at 1 year. The patient was given warfarin after the delivery. No thromboembolic event was identified during the pregnancy or postpartum.

**Case 2:** A 40-year-old nulliparous Japanese woman with previously diagnosed LVNC was referred to our department at 5 weeks’ gestation. She had no family history of LVNC other than the sudden death of her father. One year prior to the current pregnancy, the echocardiography to investigate the cause of occasional abnormal electrocardiograms showed distinct features demonstrating LVNC with the LVEF of 57%. She had had one syncope episode, and nonsustained ventriclre tachycardia was also pointed out. Warfarin (3 mg/day) and carvedilol (2.5 mg/day) were initiated for the prevention of thrombus formation, arrhythm-

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**Figure 1.** Echocardiographic images at 6 weeks’ gestation in case 1. Trabeculae at apical view (A), M-mode of parasternal long axis view (B), and trans mitral flow (C). Left ventricular contraction was preserved (LVd/Lv 41/24 mm), but images indicated its restrictive pattern and elevated intraventricular pressure (E/A = 2.6, E/e’ 12).
Figure 2. Echocardiographic images at 6 months before pregnancy in case 2. Trabeculae at apical view (A), M-mode of parasternal long axis view (B), and trans mitral flow (C). Left ventricular contraction was preserved (LVDD/LVDS 55/37 mm), but images showed its abnormal relaxation pattern (E/A = 1.8, E/e' 5.7).

mia, and the deterioration of cardiac function. She was NYHA class I, and her echocardiography showed isolated LVNC at 6 months before the current pregnancy (Figure 2).

At 6 weeks’ gestation, the warfarin was replaced by therapeutic intravenous unfractionated heparin (20,000 U/day) to avoid the potential complications of fatal embryopathy. She presented slight and intermittent painless vaginal bleeding due to placenta previa beginning at 23 weeks’ gestation although she had neither fatal arrhythmia nor thromboembolic events during pregnancy. Echocardiographic findings and plasma BNPs were not significantly changed through her pregnancy. A scheduled cesarean section was performed at 36 weeks’ gestation due to an increase in the frequency of painless vaginal bleeding. The newborn was a healthy male with a birth weight of 2,912 g and Apgar score of 8/8 at the first and fifth minutes. She received warfarin after the delivery, and no thromboembolic event was identified postpartum.

Case 3: A 36-year-old nulliparous Japanese woman with previously diagnosed LVNC was referred to our department at 9 weeks’ gestation. She had no family history of LVNC. Six years prior to the current pregnancy, she had had acute heart failure, which was treated with an ACE inhibitor, digoxin, carvedilol, and warfarin, and her echocardiography revealed LVNC with the dilated cardiomyopathy phenotype; decreased LVEF (30%) and dilated diastolic left ventricle diameter (62 mm). She remained asymptomatic thereafter and defaulted on all medications including warfarin.

Her echocardiography of early gestation was shown in Figure 3. Her LVEF was 35%-40% visually. Therapeutic subcutaneous unfractionated heparin (18,000 U/day), instead of Warfarin, was initiated for the prevention of the thromboembolic events at 8 weeks’ gestation. Carvedilol (15 mg/day) was given due to additional nonsustained ventricle tachycardia at 16 weeks. Although she remained asymptomatic during the pregnancy, her visual LVEF in echocardiography at 35 weeks decreased to 30%-35%. The BNP levels were 6.7 pg/mL. At 37 weeks, the induction of labor was carried out to avoid complications associated with exacerbated systolic function of the left ventricle, leading to a vaginal delivery. A small-for-gestational-age, healthy female baby was delivered (weight 1,962 g) and Apgar score of 8/9 at the first and fifth minutes. No thrombohemorrhagic event was identified during the pregnancy or postpartum.

Discussion

We have reported the cases of three pregnant women with LVNC, two of whom were treated by anticoagulants throughout their pregnancies as the first-line prevention of perinatal thromboembolic events. During pregnancy, dramatic changes in the maternal physiological state occur, including increased circulating plasma volume and a hy-
Figure 3. Echocardiographic images at 10 weeks’ gestation in case 3. Trabeculae at apical view (A), M-mode of parasternal long axis view (B), and trans mitral flow (C); left ventricular was dilated, and its contraction was decreased (LVDD/Ds 58/44 mm, visual LVEF 35%~40%, E/A = 1.1, E/e’ 6.9).

percoagulable state. Therefore, two important clinical issues relevant to LVNC arise: the risk of a perinatal cardiac event and the necessity of anticoagulation only because of the pregnancy itself for women with LVNC.

Few reports are available on pregnancy with LVNC, and there have been only three prior case reports on the management of pregnant women definitively diagnosed as having LVNC before pregnancy. We reviewed those case reports together with the present three cases (Table). Four of the total of six pregnancies (67%) were terminated based on exacerbated cardiomyopathy phenotypes (especially in the women with the restrictive type) and not because of complications due to noncompaction itself. Of these four cases, three were preterm deliveries. Although there is no consensus on whether LVNC is a distinct cardiomyopathy or an epiphenomenon of other cardiomyopathies, a recent review suggested that the treatment should be predicated on making the correct phenotypic diagnosis by classifying LVNC into at least eight different phenotypes of LVNC. The specific LVNC-associated cardiomyopathy phenotype predicts the risk of adverse clinical outcomes in nonpregnant patients. Likewise, the pregnancy outcome of LVNC can be related to the phenotypes rather than noncompaction itself. A thorough evaluation and the early initiation of medication for the different phenotypes in pregnant women with LVNC can contribute to the avoidance of life-threatening cardiac events and to the prolongation of pregnancy leading to the improvement of neonatal outcomes.

We have treated pregnant women diagnosed with LVNC before pregnancy with the use of anticoagulants throughout pregnancy. There are no prior studies on therapeutic anticoagulation administered throughout pregnancy. In a Japanese nationwide survey, approximately 3% of the cases of LVNC patients were complicated by thromboembolic events, and all of these patients had decreased cardiac function. In all six cases in the present review, no thromboembolic event was identified when the anticoagulation strategy determined before pregnancy was maintained during the pregnancy. This result suggests that pregnancy itself does not necessitate the initiation of anticoagulation in women with LVNC although a greater number of cases is needed to detect rare complications such as thromboembolism.

There has been controversy over whether the deep recesses themselves due to noncompaction have an increased risk of thromboembolism. When nonpregnant patients with LVNC were matched with controls with a similar degree of left ventricular systolic dysfunction, there was no difference in the rate of systemic thromboembolism. Moreover, the incidence of ischemic-stroke over a mean follow-up period of 7.3 years was only 1.7% in nonpregnant LVNC patients without atrial fibrillation, and 50% of the ischemic-stroke patients had systolic dysfunction. We therefore speculate that anticoagulation therapy for pregnant women with LVNC is justified be-
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mination of the pregnancy can depend on the cardio-
possibility of a severe cardiac event or indications for ter-
throughout the pregnancy. In pregnancies with LVNC, the
out thromboembolic events by giving anticoagulants.

tively diagnosed as having LVNC before pregnancy with-
women without prepregnancy treatment such as warfarin
pregnant women with LVNC: (1) no anticoagulation in
the presence of atrial fibrillation) or previous thromboem-
cause of the cardiomyopathy phenotypes or additional ar-
rhythmia (such as the severity of systolic dysfunction and
the presence of atrial fibrillation) or previous thromboem-
bolic events, rather than pregnancy or noncompaction it-
self. At our hospital, the following are recommended for
pregnant women with LVNC: (1) no anticoagulation in
women without prepregnancy treatment such as warfarin
and (2) a persistent therapeutic heparin throughout preg-
nancy in women with prepregnancy anticoagulation, as
long as the prepregnancy anticoagulation has been appro-
riate. Otherwise, a pregnancy can provide the opportu-
nity for a reassessment of the necessity of anticoagulation.

In the present review, we excluded reported cases of
pregnancy with LVNC when they demonstrated the fol-
lowing: cases diagnosed as LVNC only after the second
trimester of pregnancy, the distinct features of which were
not ascertained in the postpartum period, and cases with-
out medical records sufficient at the time of diagnosis.
Many instances of LVNC detected during pregnancy could
be overdiagnosed or false positive, as increased left ven-
tricular loading due to pregnancy induces reversible left
ventricular trabeculations in a significant proportion of
women.160

In conclusion, we treated pregnant women defini-
tively diagnosed as having LVNC before pregnancy with-
out thromboembolic events by giving anticoagulants
throughout the pregnancy. In pregnancies with LVNC, the
possibility of a severe cardiac event or indications for ter-
momation of the cardiomyopathy can depend on the cardio-
mopathy phenotype of the patient, not noncompaction it-
self. Anticoagulation only because of a pregnancy itself
may be redundant. In the management of LVNC during
pregnancy, close monitoring of the condition of the differ-
ent phenotypes and the reassessment of the necessity of
anticoagulation can contribute to positive pregnancy out-
comes. Further reports should be accumulated to establish
the risk factors of adverse pregnancy outcomes including
thromboembolic events for pregnant women with LVNC.

Disclosures

Conflicts of interest: None.

References

tions and classification of the cardiomyopathies: an American
Heart Association Scientific Statement from the Council on
Clinical Cardiology, Heart Failure and Transplantation Com-
mittee; Quality of Care and Outcomes Research and Functional
Genomics and Translational Biology Interdisciplinary Working
Groups; and Council on Epidemiology and Prevention. Circula-
tion 2006; 113: 1807-16.
2. Towbin JA, Lorts A, Jefferies JL. Left ventricular non-
noncompaction of the left ventricle in adults. J Am Coll Cardiol
4. Zaccarino F, Vollmer I, Sanchez G, Navallas M, Pugliese F,
Gayet A. Left ventricular noncompaction: imaging findings and
5. Thavendiranathan P, Dahiya A, Phelan D, Desai MY, Tang WH.
Isolated left ventricular non-compaction controversies in diag-
nostic criteria, adverse outcomes and management. Heart 2013;
combined with epinephrine-secreted phaeochromocytoma induc-
7. Kral SP, van der Smagt JJ, van den Berg MP, Sollie KM, Pieper
PG, van Spauldonck-Zwarts KY. Systematic review of preg-
nancy in women with inherited cardiomyopathies. Eur J Heart
Fail 2011; 13: 584-94.
8. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA,
Jenni R. Long-term follow-up of 34 adults with isolated left
ventricular noncompaction: a distinct cardiomyopathy with poor

<table>
<thead>
<tr>
<th>Author</th>
<th>Age, years</th>
<th>Phenotype of LVNC</th>
<th>Family history of LVNC</th>
<th>Delivery</th>
<th>Indication for preterm delivery</th>
<th>Prepregnancy</th>
<th>Anticoagulation Antepartum</th>
<th>Postpartum</th>
<th>Cardiovascular</th>
<th>Obstetric</th>
<th>Neonatal</th>
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<tbody>
<tr>
<td>Munehisa</td>
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<td>Restrictive LVNC</td>
<td>Positive</td>
<td>CS at 32 weeks</td>
<td>Cardiac</td>
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<td>Warfarin</td>
<td>Heart failure</td>
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<td>Sawant</td>
<td>37</td>
<td>Isolated LVNC</td>
<td>Positive</td>
<td>CS at 34 weeks</td>
<td>Cardiac</td>
<td>None</td>
<td>None</td>
<td>Temporal UFH at 12 weeks</td>
<td>None</td>
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<tr>
<td>Spitzer</td>
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<td>None</td>
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<td>Cardiac</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Heart failure</td>
<td>None</td>
<td>Not given</td>
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<td>Case 1</td>
<td>31</td>
<td>Restrictive LVNC</td>
<td>Positive</td>
<td>CS at 30 weeks</td>
<td>Cardiac</td>
<td>None</td>
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<td>Heart failure</td>
<td>Postpartum hemorrhage</td>
<td>Development impairment</td>
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<td>Case 2</td>
<td>40</td>
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<td>CS at 36 weeks</td>
<td>Obstetric (placenta previa)</td>
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<td>Therapeutic UFH</td>
<td>Warfarin</td>
<td>None</td>
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<td>Case 3</td>
<td>36</td>
<td>Dilated LVNC</td>
<td>None</td>
<td>VA induced at 37 weeks</td>
<td>Warfarin*</td>
<td>None</td>
<td>None</td>
<td>NSVT</td>
<td>Decreased LVEF (35% → 30%)</td>
<td>None</td>
<td>SGA</td>
</tr>
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</table>

LVNC indicates left ventricular noncompaction; CS, cesarean section; UFH, unfractionated heparin; LVEF, left ventricle ejection fraction; VA, vaginal delivery; NSVT, nonsustained ventricle tachycardia; and SGA, small for gestational age. *This patient, before pregnancy, defaulted on war-
farin initiated at the diagnosis of LVNC.