ORIGINAL ARTICLE

Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies

James

ABSTRACT

Peripartum cardiomyopathy is marked by the development of maternal systolic heart failure late in pregnancy or early in the postpartum period.[1,2] The incidence varies from 1 in 100 to 1 in 300 in geographic hot spots, including Nigeria and Haiti, to 1 in 1000 to 1 in 4000 in Europe and the United States. The strongest known risk factors are the presence of preeclampsia, twin gestation, and advanced maternal age. Among patients with peripartum cardiomyopathy, heart failure can resolve but often does not: rates of death of 5 to 10% are common, and 4% of cardiac transplantations in the United States among women are performed for the treatment of peripartum cardiomyopathy.

The cause of peripartum cardiomyopathy remains unknown. Hypotheses include fetal autoimmunity or microchimerism, myocarditis, and dietary excess of salt or deficiency of selenium.[1-3] Previous studies have suggested that peripartum cardiomyopathy is largely a vascular disease, triggered by the hormonal milieu of late gestation and the early postpartum period.[3-5] There are no clear explanations for why heart failure develops in only a small subgroup of women in these contexts.

Peripartum cardiomyopathy shares some clinical features with idiopathic dilated cardiomyopathy, including decreased systolic function, enlarged cardiac dimensions, and nonspecific histologic findings on biopsy. Mutations in a number of genes have been shown to cause idiopathic dilated cardiomyopathy. These genes include *TTN*, which encodes the sarcomere protein titin. Up to 25% of patients with familial dilated cardiomyopathy and 18% of those with sporadic dilated cardiomyopathy harbor deleterious truncating variants (i.e., variants that are predicted to result in the truncation of translation) in *TTN*.[6]

Some evidence supports the hypothesis that peripartum cardiomyopathy may have a hereditary or genetic component. Geographic hot spots of incidence, including Nigeria and Haiti, may reflect genetic factors, and a genomewide association study identified a locus near the gene encoding parathyroid hormone–like hormone (*PTHLH*).[7] Although hot spots could be environmental, familial clustering of peripartum cardiomyopathy has been noted,[8-11] and 15% of patients in a German cohort had a family history of cardiomyopathy (defined as the presence of peripartum cardiomyopathy, dilated cardiomyopathy, sudden death, or arrhythmias in a first-degree relative).[12] Two groups of investigators who have studied rare pedigrees affected by these two types of cardiomyopathies have identified variants in genes encoding myofibrillar proteins, including *TTN*.[13,14] However, very few cases of peripartum cardiomyopathy are clearly familial or associated with dilated cardiomyopathy. A genetic underpinning to the great majority of cases of peripartum cardiomyopathy remains uncertain.

We therefore sequenced DNA from 172 women with peripartum cardiomyopathy to determine the contribution of variants in 43 genes that have been previously associated with dilated cardiomyopathy.

PATIENTS

Patients with peripartum cardiomyopathy were recruited from six independent groups. Group A was recruited from a cohort of patients who underwent either cardiac transplantation or placement of a left ventricular assist device (LVAD) at Temple University in Philadelphia. Group B was recruited from a cohort of patients that included some who had been referred for cardiac transplantation and who were being treated in a clinic at the University of Pennsylvania in Philadelphia. Group C was recruited from a cohort of patients who had been referred to a peripartum cardiomyopathy clinic at the University of Hannover in Hannover, Germany. Group D consisted of a subgroup of 9 women from a cohort of 100 Japanese women with peripartum cardiomyopathy from whom samples were obtained.[15] Group E consisted of patients in the multicenter, prospective Intervention in Myocarditis and Acute Cardiomyopathy 2 (IMAC-2) study,[16] which enrolled patients with acute nonischemic cardiomyopathy, including a subgroup with peripartum cardiomyopathy. Group F consisted of patients who were enrolled in the Investigations in Pregnancy Associated Cardiomyopathy (IPAC) trial, a multicenter, prospective study involving women with peripartum cardiomyopathy.[17,18] The study was approved by the institutional review board at each study center. All the patients provided written informed consent.

Reference groups were taken from the Exome

Aggregation Consortium (ExAC) in Cambridge, Massachusetts (http://exac.broadinstitute.org), which contains more than 60,000 exomes, and the Exome Variant Server (data release, ESP6500SI-V2; evs.gs.washington.edu/EVS), which contains exomic sequences from 6503 persons. For comparison, patients with dilated cardiomyopathy were recruited at the Royal Brompton and Harefield NHS Foundation Trust in London, as described previously.[19]

DNA SEQUENCING AND ANALYSES

We constructed bar-coded sequencing libraries from genomic DNA obtained from 172 patients with peripartum cardiomyopathy and 332 patients with dilated cardiomyopathy. The libraries were enriched for protein-coding portions of 43 genes that when mutated cause dilated cardiomyopathy and were then sequenced (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The 43 genes comprise the great majority of genes known to be associated with dilated cardiomyopathy and were present on the two platforms that were used to sequence patients with peripartum cardiomyopathy and those with dilated cardiomyopathy.

For the peripartum-cardiomyopathy libraries, genes were captured with the use of SureSelect Target Enrichment (Agilent Technologies) and sequenced on the HiSeq 2500 sequencing system (Illumina). Reads were aligned to hg19 (GRCh37) with the use of NovoAlign, version 3.02.04 (Novocraft), with measurements set for full Needleman–Wunsch alignments and a gap penalty of 10. Variants were identified with the use of the Genome Analysis Tool Kit (GATK) HaplotypeCaller tool on the basis of GATK Best Practices.[20] Variants were annotated with the use of SnpEff and GRCh37.68.[21] In samples obtained from patients with dilated cardiomyopathy, genes were captured with the use of in-solution hybridization and sequenced on the SOLiD 5500XL (Applied Biosystems). Reads were demultiplexed, optimized with the use of the SOLiD Accuracy Enhancement Tool, and aligned to hg19 with the use of the SOLiD targeted resequencing pipeline. Variants were identified with the use of LifeScope genomic analysis software, version 2.5.1, with default measurements, and annotated with the use of the Ensembl Variant Effect Predictor (API version 75 on GRCh37).[22]

STATISTICAL ANALYSIS

We used either Fisher's exact test (for two-tailed analyses) or Pearson's chi-square test of association for cross-cohort and cross-group analyses. The frequency of truncating variations was compared between cohorts with the use of the binomial test. Analyses were performed with the use of the R statistical package.

RESULTS

STUDY PATIENTS

A total of 172 women with peripartum cardiomyopathy were recruited from the six cohorts (Table 1). Approximately one third of the patients were of African descent, consistent with the known increased prevalence of peripartum cardiomyopathy in this group. Ancestry was defined genetically by means of principle-component analysis of all common variants that were sequenced (Fig. S1 in the Supplementary Appendix). The ejection fraction was lowest in group A, which consisted of patients who were under evaluation for cardiac transplantation.

DNA SEQUENCING

Next-generation sequencing was performed on 43 genes, including *TTN* (Table S1 in the Supplementary Appendix). More than 95% of targeted bases were sequenced to a read depth of more than 20 times (data not shown). Rare variants (ExAC frequency, <0.1%) were chosen for further analysis. We focused on truncating variants that included nonsense, frameshift, and splicing variants, because they are predicted to have a strong effect on protein structure and function. All truncating variants were confirmed by means of traditional Sanger sequencing.

GENETIC VARIATION IN PERIPARTUM CARDIOMYOPATHY

Among the 172 women with peripartum cardiomyopathy, we identified 26 who carried 26 distinct rare heterozygous truncating variants in eight different genes (Table S2 in the Supplementary Appendix). No homozygous or compound heterozygous truncating variants were observed. Eleven variants were nonsense, seven were frameshift, and eight affected canonical splicing sites. The prevalence of truncating variants did not differ significantly among the six

Table 1. **Demographic Characteristics of the Patients in Each Cohort and the Prevalence of Truncating Variants at Baseline.***

Characteristic	Group A (N=10)	Group B (N=26)	Group C (N=10)	Group D (N=9)	Group E (N=34)	Group F (N=83)	All Patients (N=172)
	Temple University	University of Pennsylvania	University of Hannover, Germany	Japan	IMAC-2	IPAC	
Age — yr	34.2±7.6	34.1±7.4	34.3±6.7	30.8±3.4	31.2±6.8	29.8±6.3	31.3±6.7
African descent — no. (%)†	5 (50)	16 (62)	5 (50)	0	11 (32)	24 (29)	61 (35)
Left ventricular ejection fraction — %	10.0±3.9	30.1±13.5	27.6±10.8	29.1±10.1	27.2±7.4	29.8±9.7	28.6±10.4
Patients with truncating variants — no. (%)							
Any	2 (20)	1 (4)	1 (10)	1 (11)	6 (18)	15 (18)	26 (15)
TTN	0	0	1 (10)	1 (11)	4 (12)	11 (13)	17 (10)

* Plus–minus values are means ±SD. IMAC-2 denotes Intervention in Myocarditis and Acute Cardiomyopathy 2, and IPAC Investigations in Pregnancy Associated Cardiomyopathy.
† Ancestry was defined genetically by means of principle-component analysis of all common variants that were sequenced.

cohorts (Table 1). The overall prevalence of truncating variants in 26 of 172 women with peripartum cardiomyopathy (15%) was significantly higher than that in the ExAC reference population of more than 60,000 samples (4.7%, $P=1.3\times10^{-7}$) and similar to that in a cohort of patients with dilated cardiomyopathy (55 of 332 patients [17%], P=0.81).

Of the 26 truncating variants, 17 (65%) affected *TTN* (in 10% of the cohort; $P=2.7\times10^{-10}$ for the comparison with the reference population). *TTN* truncating variants were seen in 8 of 61 women of African descent (13%) and 8 of 102 women of European descent (8%). In the reference ExAC population, such variants were found in 2.1% of persons of African descent ($P=3.8\times10^{-5}$) and in 1.1% of those of European descent ($P=1.4\times10^{-5}$). Four of the *TTN* truncating variants (two nonsense and two splice-site donors) were identical to variants previously identified in 26 patients with dilated cardiomyopathy who were studied at Brigham and Women's Hospital in Boston (Table S3 in the Supplementary Appendix). Three of these variants were absent from the more than 60,000 exomes in the ExAC database, and one was identified only once. Five of the *TTN* truncating variants (in 3% of the 172 women) are also identical to variants annotated as probably pathogenic for dilated cardiomyopathy in the ClinVar database (www.ncbi.nlm.nih.gov/clinvar), as compared with a frequency of 0.1% found in ExAC ($P=1.1\times10^{-5}$).

Of 17 truncating variants in *TTN*, 14 were located in a region that encodes the A-band portion of the protein (Fig. 1, and Table S3 in the Supplementary Appendix), as compared with 21 of 56 in a reference population[19] (P=0.002). (The A-band, named for its anisotropic properties on polarized microscopy, is the portion of the sarcomere that contains the myosin thick filament.) Truncating variants in patients with dilated cardiomyopathy cluster similarly in the region encoding the A-band.[6,19] Sixteen of the 17 *TTN* truncating variants were in exons that are constitutively expressed in the heart (i.e., that appear in every messenger RNA isoform that is transcribed from the gene) (Fig. 1, and Table S3 in the Supplementary Appendix), as compared with 83 of 168 variants in the Exome Sequencing Project ($P=1.1\times10^{-4}$). This finding again reflects the pattern seen in patients with dilated cardiomyopathy.[19] Truncating variants were more likely to be positioned in the region of the gene encoding the C-terminal regions of the protein (Fig. 1). In persons with dilated cardiomyopathy, truncating variants that are found near the C-terminus are associated with more severe disease than are N-terminal truncating variants.[19]

The prevalence of missense variants among the 172 women with peripartum cardiomyopathy was high (1.06 per person among women of African descent and 1.25 per person among those of European descent) and was not significantly different from the burden found in the

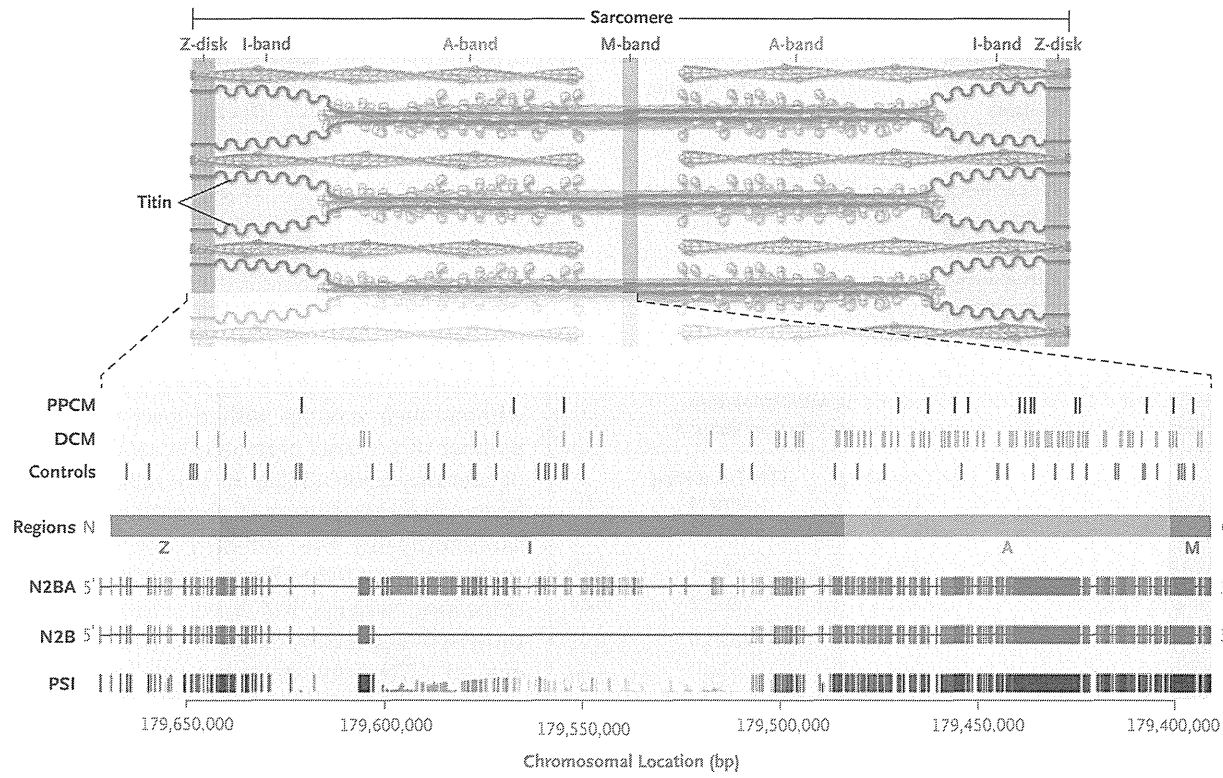

Figure 1. Titin Protein and Spatial Distribution of Variants in the Protein.

Titin, a protein encoded by *TTN*, makes up one of the three major filaments of the cardiac sarcomere, the basic unit of striated muscle tissue. Regions of the sarcomere are designated as the Z-disk (red), I-band (named for its isotropic properties under a polarizing microscope, shown in blue), A-band (named for its anisotropic properties, shown in green), and M-band (from the German *mittelscheibe*, the disk in the middle of the sarcomere, shown in purple). The spatial distributions of the truncating variants that were found in samples obtained from patients with peripartum cardiomyopathy (PPCM) and dilated cardiomyopathy (DCM) are indicated, along with the distributions of such variants in healthy controls. At the bottom of the diagram, the genomic locus of *TTN* is shown. N2BA and N2B denote the exons (vertical lines) encoding the two main cardiac transcripts. For PSI (i.e., the proportion spliced in), the height of the vertical line indicates the proportion of cardiac transcripts obtained from patients with dilated cardiomyopathy that contain the exon. Images are adapted from Herman et al.[6] and Roberts et al.[19]

ExAc cohort (1.26 per person among women of African descent [P=0.21] and 1.19 per person among those of European descent [P=0.59]). No missense variants that were annotated in ClinVar as pathogenic or probably pathogenic for dilated cardiomyopathy were identified among the women with peripartum cardiomyopathy. Three missense variants that are associated in ClinVar with hypertrophic cardiomyopathy were identified in *MYH7* (encoding a myosin heavy-chain isoform expressed mainly in the heart) in the 172 women with peripartum cardiomyopathy (P=0.10 for the comparison with the reference population), and seven missense variants reported in association with the long-QT syndrome were identified in *SCN5A* (encoding a voltage-gated sodium-channel isoform) in these women (P=0.02 for the comparison with the reference population).

CLINICAL CHARACTERISTICS

At baseline, there were no significant differences with respect to age, ancestry, or ejection fraction between the women with truncating variants and those without such variants (Table 2). In the IPAC study,[17,18] enrollment took place within 13 weeks after delivery, which was followed by comprehensive clinical evaluation during 1-year follow-up. Of 83 women in the IPAC study, 15 (18%) carried truncating variants, including 11 (13%) who had such variants in *TTN*. During the index pregnancy, there were no significant differences between

Table 2. **Age, Ancestry, and Ejection Fraction among 172 Patients with Peripartum Cardiomyopathy, According to Variant Status at Baseline.***

Variable	No Variant (N=146)	*TTN* Variant (N=17)	P Value	Any Variant (N=26)	P Value
Age — yr	31±7	29±6	0.23	30±7	0.42
African descent — no. (%)	48 (33)	8 (47)	0.28	13 (50)	0.12
Ejection fraction — %	29±10	26±9	0.25	25±10	0.12

* Plus–minus values are means ±SD.

Table 3. **Clinical Characteristics of the Patients with Peripartum Cardiomyopathy in the IPAC Study, According to Variant Status.***

Characteristic	No Truncating Variant (N=68)	*TTN* Truncating Variant (N=11)	P Value
Age — yr	30±6	28±6	0.25
No. of pregnancies	2.8±1.9	2.9±2.3	0.84
No. of births	2.1±1.2	2.1±1.5	0.92
Family history of cardiomyopathy — no. (%)	7 (10)	1 (9)	1.00
Hypertension — no. (%)	35 (51)	1 (9)	0.009
Twin gestation — no. (%)	15 (22)	1 (9)	0.45
Ejection fraction — %			
At enrollment	35±9	30±12	0.14
At 1 yr	54±8	44±17	0.005†

* Plus–minus values are means ±SD.
† P=0.04 by the Wilcoxon rank-sum test.

Table 4. **Clinical Characteristics of the Patients with Peripartum Cardiomyopathy in the IMAC-2 Study, According to Variant Status.***

Characteristic	No Truncating Variant (N=26)	*TTN* Truncating Variant (N=4)	P Value
Age — yr	31±7	31±5	0.94
No. of pregnancies	2.5±1.5	1.5±0.6	0.20
No. of births	2.0±0.9	1.5±0.6	0.31
Family history of cardiomyopathy — no. (%)	3 (12)	2 (50)	0.12
Ejection fraction — %			
At enrollment	27±8	27±3	0.95
At 6 mo	45±14	51±11	0.51

* Plus–minus values are means ±SD.

the women with truncating variants and those without such variants with respect to age, the number of previous pregnancies, or the number of previous births (Table 3). The reported prevalence of a family history of peripartum or dilated cardiomyopathy was similarly low in the two study groups (10%). Fewer patients with *TTN* truncating variants had hypertension than did those without such variants (P=0.009). The burden of *TTN* truncating variants among the women without hypertension (10 of 43 [23%]) was significantly higher than that among those with hypertension (1 of 40 [2%]) (P=0.005).

In the IPAC study, cardiac function at presentation was not significantly different between the women with *TTN* truncating variants and those without such variants (mean [±SD] left ventricular ejection fraction, 30±12% and 35±9%, respectively; P=0.14). However, a year after enrollment, the ejection fraction was significantly lower in the group with *TTN* truncating variants than in those without such variants (44±17 and 54±8%, P=0.005). The majority of *TTN* truncating variants in the IPAC cohort (7 of 11) were found among women of African descent. At the 1-year follow-up, significant differences in the ejection fraction were observed within this subgroup of women (38±16% with *TTN* variants vs. 52±12% without *TTN* variants, P=0.04) but not in the smaller number of women of European descent (56±17% vs. 55±10%, P=0.75). There were no significant between-group differences in the incidence of LVAD placement, cardiac transplantation, or death, although the total number of such events was small (data not shown).

In the IMAC-2 study,[16] 4 of the women (3 of European descent) carried *TTN* truncating variants (Table 4). Within this smaller cohort, no

significant differences were seen in the ejection fraction at enrollment or at 6-month follow-up. Follow-up echocardiography at 12 months was not available.

DISCUSSION

We identified truncating variants in eight genes among 26 of 172 women with peripartum cardiomyopathy. The prevalence of truncating variants in these genes was significantly higher among these women (15%) than in the reference group ($P=1.3\times10^{-7}$), and most of the variants occurred in *TTN*. We conclude that many of these truncating variants lead to a strong genetic predisposition to peripartum cardiomyopathy. However, the presence of the more common variants probably is not a risk factor for penetrant peripartum cardiomyopathy in isolation, although such variants may be risk alleles for the disease.

The burden of genetic variants that were found in the women with peripartum cardiomyopathy resembled that found in patients with dilated cardiomyopathy. Most notably, 65% of variants occurred in TTN (in 10% of the patients, $P=2.7\times10^{-10}$ for the comparison with the reference population). The great majority of these variants occurred in constitutively expressed exons and in the region encoding the A-band, akin to the distribution seen in patients with dilated cardiomyopathy.[6,23] Seven of these variants have been found previously in association with dilated cardiomyopathy. Approximately 15% of patients with dilated cardiomyopathy and peripartum cardiomyopathy share the same types of truncating variants, so we propose that a shared mechanism is responsible for these cardiomyopathies. Since a gene-based diagnosis is clinically available for dilated cardiomyopathy, it is plausible that the same genetic diagnosis could be used for peripartum cardiomyopathy with similar sensitivity and specificity. However, further study is needed to understand the penetrance of variants identified in the context of peripartum cardiomyopathy.

Reliable prognostic indicators for peripartum cardiomyopathy are currently lacking. In a predefined, prospectively followed, and well-characterized subgroup of 83 women in the IPAC study, we found that the ejection fraction at 1-year follow-up was significantly lower among women with *TTN* truncating variants than among those without such truncating variants ($P=0.005$). Dilated cardiomyopathy similarly carries a worse prognosis in the presence of truncating *TTN* variants.[19] On the other hand, at 6-month follow-up of the 34 women in the IMAC-2 cohort, the ejection fraction was not significantly different among the 3 women with *TTN* truncating variants than among those without such variants. Although these data are suggestive, the value of genetic information in determining the prognosis for patients with peripartum cardiomyopathy will require further studies.

Truncating variants occurred equally among patients who did not report a family history of cardiomyopathy and among those who did. Similarly, dilated cardiomyopathy with causative *TTN* variants is frequently not familial.[6] Of the 26 truncating variants, 13 (including 8 in *TTN*) were found in women of African heritage, which indicates that a genetic cause of peripartum cardiomyopathy is not exclusive to one ancestry. Peripartum cardiomyopathy occurs more frequently and has a poorer prognosis among women of African descent than among those of European descent,[24] which may be due in part to the higher prevalence of *TTN* truncating variants among those of African descent.

Preeclampsia and gestational hypertension are strong risk factors for peripartum cardiomyopathy, but there has been controversy as to whether cardiomyopathy that is associated with hypertension may represent a separate disease from cardiomyopathy in the absence of hypertensive disorders. Among 15 women with truncating variants in the well-characterized IPAC cohort, only 4 had any form of hypertension (chronic or gestational), and among the 11 women with *TTN* truncating variants, only 1 had hypertension. This finding contrasts sharply with the overall 47% prevalence of hypertension in the IPAC cohort and most other cohorts.[25] The prevalences of preeclampsia and hypertension are higher among women of African descent, and yet none of the 7 women of African descent with a *TTN* truncating variant had a hypertensive disorder, whereas 15 of the 17 women of African descent with peripartum cardiomyopathy who did not carry *TTN* variants had hypertension ($P<0.001$). Overall, the burden of truncating *TTN*

variants among women without hypertension was 10 times as high as that among women with hypertension (23% vs. 2%, P=0.005), a burden that approximates that found in familial dilated cardiomyopathy (25%).[6] These post hoc analyses suggest that peripartum cardiomyopathy that is associated with hypertension may reflect a different pathophysiologic process than that in the absence of hypertension and that peripartum cardiomyopathy in the absence of risk factors such as hypertension may be of genetic origin.

Two women had truncating variants in *DMD* or *LAMP*, genes that lie on the X chromosome. Mutations in these genes cause Duchenne's muscular dystrophy and Danon's disease, respectively, in male patients and more rarely in female patients. Cardiomyopathy is a prominent feature of the two diseases.[26] Peripartum cardiomyopathy may have occurred in these two women as a consequence of skewed X-chromosome inactivation[27] or stresses of pregnancy superimposed on subclinical cardiac abnormalities. Two previous reports identified a *DMD* or *LAMP2* mutation in a patient with peripartum cardiomyopathy.[28,29]

Previous studies have shown that peripartum hormonal changes can pose a vascular insult to the heart and trigger peripartum cardiomyopathy.[4,5,30,31] What predisposes the development of this disease in only a small subgroup of women in this context remains unclear. We identified a potential genetic predisposition to peripartum cardiomyopathy in approximately 15% of women in our study, owing to truncating variants primarily affecting *TTN*. There must be additional environmental or genetic stimuli that explain why the average age at onset of dilated cardiomyopathy for women with *TTN* truncating variants is 65 years,[6] whereas the age at onset of peripartum cardiomyopathy among women with *TTN* truncating variants is 28 years. In addition, women with peripartum cardiomyopathy recover systolic cardiac function more frequently than do women with dilated cardiomyopathy. Thus, defining the mechanistic interaction between truncations in *TTN* and late gestational antivascular insults will probably lead to further understanding of both peripartum cardiomyopathy and dilated cardiomyopathy.

We conclude that peripartum cardiomyopathy shares a genetic predisposition with both familial and sporadic idiopathic dilated cardiomyopathy. In addition, the presence of truncating variants in *TTN* is the most prevalent genetic predisposition for each of these disorders.

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APPENDIX

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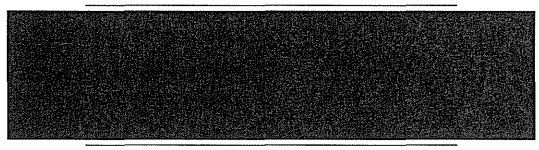

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CORRESPONDENCE

Elevated vasoinhibin derived from prolactin and cathepsin D activities in sera of patients with preeclampsia

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Preeclampsia (PE) is a pregnancy-related disease characterized by high blood pressure and proteinuria. Although the precise pathogenic mechanisms remain unclear, aplasia of the placental helicine artery is considered to be a potential cause of PE. Moreover, several biomarkers, such as soluble fms-like tyrosine kinase and placental growth factor, have been suggested to predict PE.[1,2]

Prolactin, a 23-kDa hypophyseal polypeptide hormone, has an angiogenic function. However, a 16-kDa fragment of N-terminal prolactin, which is cleaved by enzymes, such as cathepsin D (CathD), has anti-angiogenic functions.[3] Cleaved growth hormone and placental lactogen also exert anti-angiogenic effects, and these residues are designated as vasoinhibins.

Recent studies have detected vasoinhibin derived from prolactin (PRL-V) in urine, amniotic fluid, placental and serum samples of patients with PE.[4,5] Placental protein expression of CathD was increased more in PE patients than healthy controls.[6] Thus, PRL-V is suspected as one of the contributing factors to PE. However, PRL-V values and CathD activity in the sera of PE patients remained unknown. The aim of the present study was to quantify PRL-V and to measure CathD activity in the sera of PE patients compared with healthy pregnant women. This study was approved by the Ethical Committee at the National Cerebral and Cardiovascular Center in Osaka, Japan, and was performed with the informed consent of all participants.

Seven healthy pregnant women (control group) and nine patients with PE (PE group) participated in the study. Sera and urine samples were collected from participants in the early morning at three separate time points: antepartum (specifically after the diagnosis of PE in the PE group), soon after delivery and 1 month after delivery. The diagnosis and severity of PE were determined by the physicians' clinical judgments according to the National High Blood Pressure Education Program Working Group Report on high blood pressure in pregnancy.[7]

The quantification method of serum PRL-V was developed in the study on the basis of a previous method.[8] Serum was pretreated with an Albumin/IgG Removal Kit (Merck, Darmstadt, Germany), and immunoprecipitated by the human prolactin polyclonal antibody, anti-hPRL-IC-5, CYTO (National Hormone and Peptide Program, Torrance, CA, USA), according to the protocol recommended by the manufacturer. Immunoprecipitated samples were applied to western blotting with an antibody that detected N-terminal of prolactin (anti-hPRL monoclonal antibody clone 5602, Diagnostics

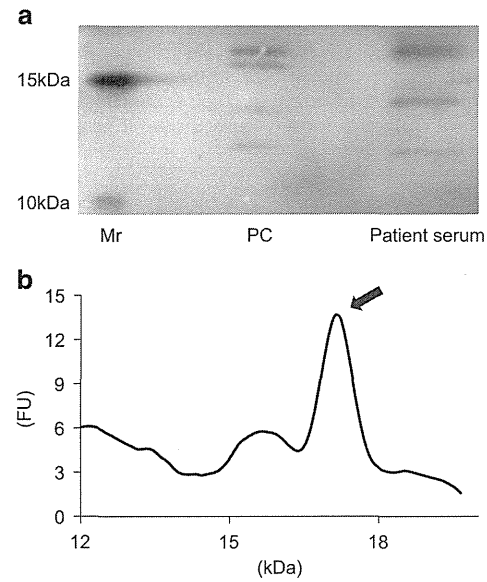

Figure 1 Sample images of vasoinhibin derived from prolactin (PRL-V) measurements. (**a**) Western blot analysis. A western blot analysis of immunoprecipitated serum from a patient with the N-terminal prolactin antibody. Serum bands in the patient serum were detected at ~12, 14.5 and, especially, 17 kDa. Positive control (PC: human prolactin+bovine CathD citrate phosphate buffer, 37 °C, 10 min) bands were detected at 12, 14, 16 and 17 kDa. (Mr, molecular weight marker). (**b**) Electrophoretic waveform by Bioanalyzer. A capillary electrophoresis analysis of the same immunoprecipitated serum in **a**. The vertical axis shows fluorescence units (FU) and the horizontal axis shows the molecular weight of PRL-V. The peak of the electrophoretic waveform was at 17 kDa (arrow). The PRL-V value was quantified with the peak FU. The background FU was subtracted from the peak FU; thus, the PRL-V value was 8.8 FU in this case.

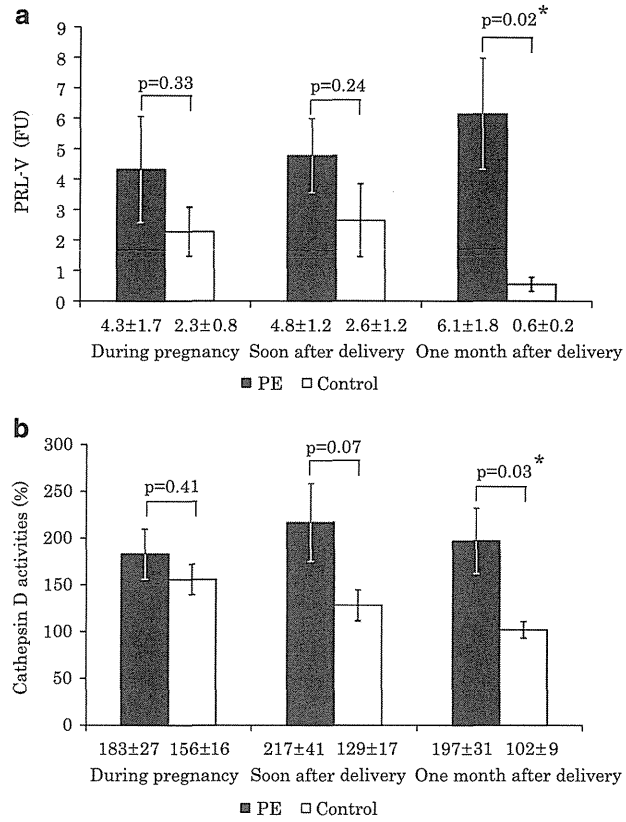

Figure 2 Vasoinhibin derived from prolactin (PRL-V) values and cathepsin D activities in the study participants. (**a**) PRL-V values in the preeclampsia (PE) and control groups. The white bar shows PRL-V values in the control group and the black bar shows those in the PE group. The vertical axis shows the fluorescent unit of PRL-V (mean ± s.e.m., $*P<0.05$ *vs.* control). (**b**) Cathepsin D activity in the PE and control groups. The white bar shows cathepsin D activity in the control group and the black bar shows that in the PE group (mean ± s.e.m., $*P<0.05$ *vs.* control).

Biochem Canada, Dorchester, Ontario, Canada; Figure 1a). Moreover, the same samples were also applied to the Agilent Protein 80 Kit (Agilent Technologies, Santa Clara, CA, USA) and Bioanalyzer (Agilent Technologies) to quantify PRL-V. The peak height of the electrophoretic waveform was indicated as the PRL-V amount (Figure 1b). Each assay was performed in duplicate and the mean values were used for the analysis.

CathD activity was measured by the SensoLyte 520 Cathepsin D Activity Assay Kit (Anaspec, Fremont, CA, USA). The serum of a healthy non-pregnant woman was used as the calibrator in all assays, and CathD activity in participants is presented as a percentage of the calibrator activity. Each assay was performed in triplicate and the mean values were used for the analysis.

Data are expressed as the mean ± s.e.m. Student's *t*-test and the Pearson correlation coefficient were performed.

The average blood pressures of control and PE groups were 108 ± 3/66 ± 3 and 155 ± 4/95 ± 4 mm Hg in antepartum, 113 ± 5/73 ± 5 and 127 ± 4/75 ± 3 mm Hg soon after delivery and 113 ± 4/70 ± 3 and 129 ± 4/81 ± 3 mm Hg 1 month after delivery, respectively (seven patients in the PE group were treated with anti-hypertensive medication soon after delivery; one patient was treated with methyldopa; four patients were treated with nifedipine and two patients were treated with nicardipine). The average proteinuria of control and PE groups were 85 ± 23 and 205 ± 91 mg dl^{-1} in antepartum. The PRL-V values were slightly higher in the PE group than the control group in antepartum and soon after delivery. However, these values were significantly higher in the PE group than the control group 1 month after delivery (Figure 2a).

CathD activities were slightly higher in the PE group than the control group in antepartum and soon after delivery. CathD activity remained significantly higher in the PE group, whereas it had decreased in the control group 1 month after delivery (Figure 2b).

PRL-V values in antepartum were higher in patients with severe PE (5.62 ± 2.61 fluorescence unit (FU), $n=6$) than patients with mild PE (2.15 ± 1.33 FU, $n=3$) but were not significant ($P=0.37$). There were positive correlations between PRL-V and total protein ($r=0.75$, $P=0.05$) and albumin ($r=0.75$, $P=0.05$) in pooled urine. CathD activities correlated with systolic ($r=0.77$, $P=0.07$) and diastolic blood pressures ($r=0.75$, $P=0.16$).

Quantitative detection of PRL-V has been considered to be technically difficult because of the very small amount of PRL-V in serum. This was the first study to quantify serum PRL-V in PE patients, and these results were consistent with previous findings by western blotting analyses.[5,6] Because PRL-V has been investigated in other diseases, such as diabetic retinopathy[8] and peripartum cardiomyopathy,[9] our method may be applicable for elucidating the pathogenic mechanisms for these diseases as well as PE.

PRL-V values and CathD activities were higher in PE patients than healthy controls at all periods, particularly at 1 month after delivery. Although both values 1 month after delivery were decreased in the control group, they remained at a high level in the PE group. PE is usually improved after delivery, whereas vascular dysfunction has been observed late after delivery.[10] Moreover, PE is known as a major risk factor of peripartum cardiomyopathy, which often develops after delivery. Thus, PRL-V may be involved in such vascular disorders or cardiac dysfunction in postpartum women.

As one of the study limitations, the number of samples in this study was small. Further larger studies are required to confirm these results.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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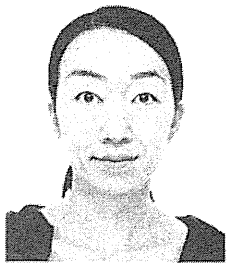
循環器疾患合併妊娠のリスクと診療の実際

Cardiovascular disease in pregnancy



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◎妊娠・出産を通じて，循環動態はダイナミックに変化する．多くの循環器疾患をもつ女性が安全に出産する一方で，一部の病態においては母児の生命も脅かされる高危険性妊娠となる．循環器医療や新生児医療の発展に伴って成人となる先天性心疾患患者が増加していること，遺伝性不整脈や結合織病などあらたな疾患が若年代で診断されることなどにより，わが国における循環器疾患合併妊娠数は増加傾向にある．また，妊婦の高齢化も問題となってきている．心臓病をもっているから妊娠は禁忌とされていた時代は過ぎ，心臓病があってもより安全に出産できるような診療体制の構築が必要とされるが，エビデンスに基づいた標準的診療の確立は不十分である．本稿では，まず周産期における心血管・循環動態の生理的変化について，つぎに周産期リスクの評価法について，最後に妊娠中の検査について述べる．

Key word：循環器疾患，妊娠，心不全，不整脈

妊娠出産による循環動態の変化と心血管疾患合併母体への影響

妊娠出産時には以下のような循環動態の変化がダイナミックに起こる．これらの変化を理解し，個々の症例に応じた診療を行っていくことが重要である．

1．循環血漿量の増大

妊娠成立後，性ホルモンの増加によりナトリウム貯留が起こるため，循環血漿量は徐々に増加する．妊娠28～32週ごろに増加量がほぼピークに達し，平均して非妊時の1.5倍となる．心拍出量も同様の増加を示すが，妊娠前半ではおもに1回心拍出量が，妊娠後半ではおもに心拍数が増加することによって心拍出量の増加が達成される（図1）[1]．分娩時にはさらに心拍出量が増加し，陣痛（子宮収縮）ごとにおよそ200～400 mLの子宮胎盤の血液が体循環へと移行する．分娩中は心拍出量の変化を減少させるために，左側臥位をとることが推奨されているが，これは仰臥位低血圧症候群を予防するためにも有用である．分娩直後には子宮による下大静脈の圧迫が解除され，急激な静脈還流の増大が起こる．また，産後の子宮収縮に伴って子宮動脈にプーリングされていた約1Lの血液が心臓へ灌流する．分娩後も一過性に容量負荷の状態をきたし，正常化するまでには約4～6週間かかる．このような容量負荷の増大に対して狭窄性疾患や肺高血圧症，心機能低下症例では心不全の出現や低心拍出量に注意していく必要がある．

2．血管抵抗の低下

妊娠初期より大動脈圧，全身血管抵抗は低下し，妊娠中期には最低値をとる．このような後負荷軽減により中等度以下の逆流性疾患やシャント疾患では問題なく妊娠出産を終えることが多い．しかし，妊娠後期には血管抵抗は非妊時と同等あるいは増加し，血圧は上昇傾向となる．妊娠高血圧症候群の発症も多くがこの時期である．妊娠高

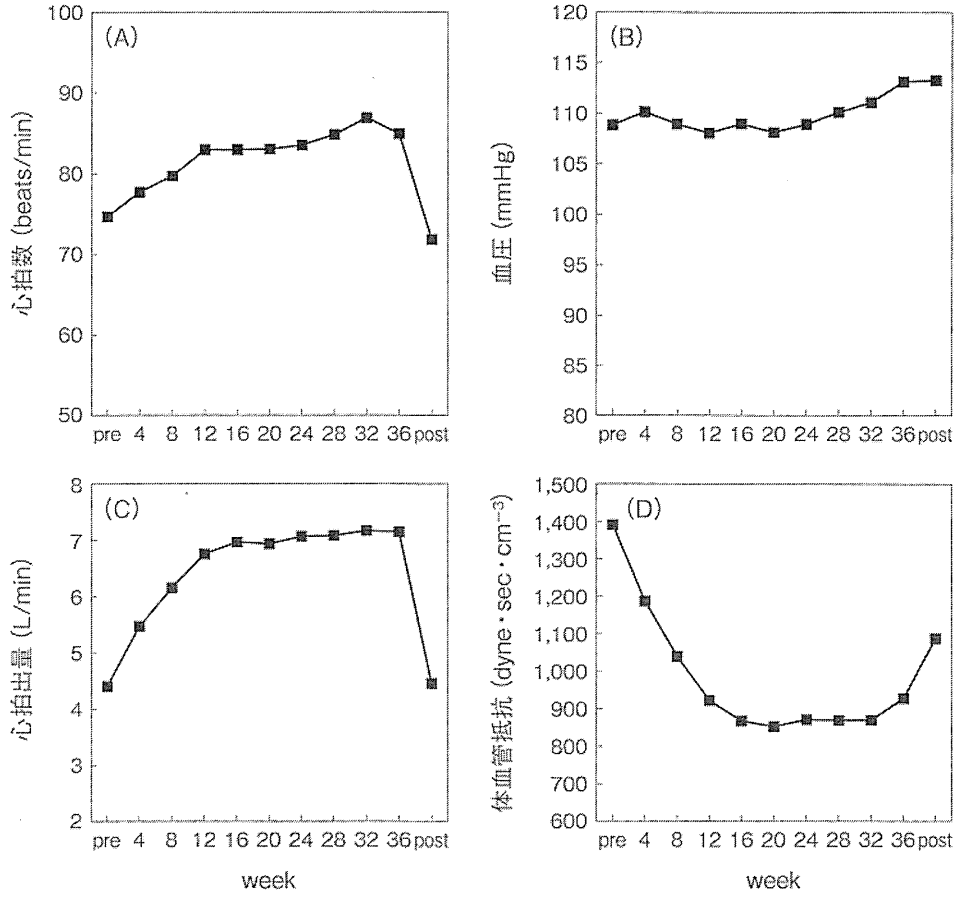

図 1　妊娠に伴う循環動態の変化[1)]
A：心拍数，B：血圧，C：心拍出量，D：体血管抵抗．

血圧症候群は妊娠 20 週以降に血圧上昇や腎障害(蛋白尿)を認める産科合併症であり，大動脈縮窄患者などでは，合併率が高いことが知られている[2)]．妊娠高血圧症候群は周産期(産褥性)心筋症の最大危険因子でもあり，慎重な対応が望まれる．

3. 凝固能の亢進

妊娠中は凝固因子などが増加し活性化されるため，血栓・塞栓のリスクが高まる．深部静脈血栓や肺塞栓の発症，人工機械弁置換術後例では血栓形成による弁機能不全や塞栓症の合併が起こりやすいため，綿密な抗凝固・抗血小板療法が必要である．

4. 心拍数の増加

心拍出量の増加は，妊娠初期～中期にはおもに 1 回心拍出量の増加により，妊娠中期～後期には心拍数の増加により達成される．妊娠後期には妊娠前の約 20%程度まで心拍数は増加する．心拍数の増加や血漿量の増加に伴う心拡大(心筋伸展)に伴い，不整脈の出現も増加する．また，産後は妊娠中の交感神経活性がとれ，徐脈傾向となる．徐脈性不整脈の患者では増悪するリスクがあるので，注意が必要である．QT 延長症候群では妊娠中よりも産後から半年以内の不整脈イベントが多いことが知られている[3)]．

5. 血管壁の脆弱性増加

妊娠中，エストロゲンなどの影響で大動脈壁は中膜の変性をきたし，脆弱性を増す．大動脈拡大を伴う Marfan 症候群，大動脈炎症候群や大動脈縮窄症患者では，大動脈瘤拡大や大動脈解離のリスクが上昇する．

妊娠出産のリスク評価

妊娠・分娩時の生理的変化による母体や胎児のリスクについて，いくつかの分娩前評価法が報告されている．先天性心疾患合併 599 妊娠における検討では，①NYHA class Ⅲ～Ⅳ，②妊娠前の心血管イベントの既往，③チアノーゼ性心疾患，④左心の狭窄病変(僧帽弁・大動脈弁狭窄や左室流

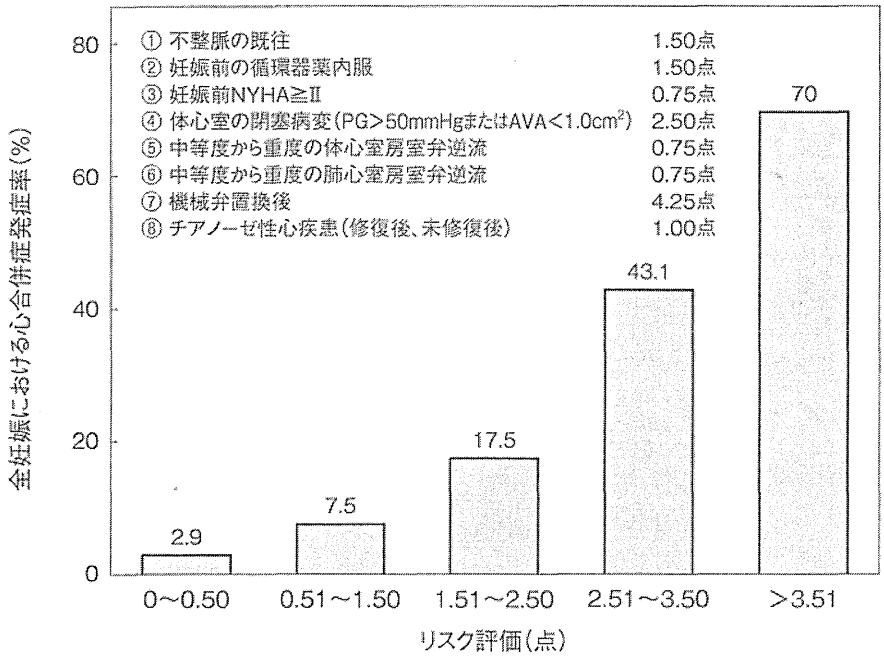

図 2　先天性心疾患女性の周産期心合併症リスク評価[6]

出路狭窄)，⑤体心室機能低下(駆出率40%未満)，を母体危険因子とし，1項目を1点として換算した場合，妊娠中の母体心血管イベントの発症率は0点=5%，1点=27%，2点以上=75%である[4]．また，児の危険因子は，①NYHA classⅢ～Ⅳ，②チアノーゼ性心疾患，③抗凝固薬の使用，④喫煙，⑤複数回妊娠，⑥左心狭窄病変，である．上記に加え，重度の肺動脈逆流と右室不全，喫煙も母体危険因子と報告されている[5]．

オランダ，ベルギーの先天性心疾患合併714人，1,302妊娠の検討では，周産期における母体心血管イベントのリスク因子として，不整脈の既往，妊娠前の循環器薬内服，妊娠前NYHA≧Ⅱ，体心室の閉塞病変(PG>50 mmHg または AVA<1.0 cm^2)，中等度から重度の房室弁逆流，機械弁置換後，チアノーゼ性心疾患をあげ，図2のようにイベント発生率を報告している[6]．

運動耐容能と周産期リスクを検討した報告では，運動時間，最大心拍数，最大収縮期血圧，最高酸素摂取量が妊娠中母体心血管イベントの有無と相関していた[7]．最大心拍数150未満あるいは最高酸素摂取量22.0 mL/kg/min未満であれば，妊娠中母体心血管イベントリスクが高いと予測される．

以上のリスク評価を妊娠前に行い，妊娠出産のリスクを事前に本人・家族に十分説明し，リスクの高さに応じた周産期管理計画を立てておくことが重要である．

表 1　妊娠の際厳重な注意を要するあるいは妊娠を避けるべき心疾患

1．肺高血圧症(Eisenmenger症候群を含む)
⇒母体死亡率：30～70%，胎児死亡率：50%
2．流出路狭窄(大動脈弁高度狭窄，収縮期圧較差>40～50 mmHg)
⇒母体死亡率：17%
3．心不全(NYHAⅢ度以上，LVEF<35～40%)
⇒母体死亡率：7%
4．Marfan症候群(大動脈拡張期径>40 mm)
⇒とくに44 mm以上は絶対禁忌
5．人工機械弁
⇒胎児・新生児死亡率：50%
6．チアノーゼ性疾患(酸素飽和度<85%)
⇒胎児・新生児死亡率：88%

日本循環器学会のガイドラインでは，妊娠の際厳重な注意を要するあるいは妊娠を避けるべき心疾患として，表1の心疾患をあげている[8]．

妊娠中の循環器検査

妊娠・出産に伴う循環動態の変化に対して母体心臓の適応可否を見極めるためには，妊娠産褥を通じ，経過中複数回にわたって血行動態の評価を行うことが望ましい．

表 2　通常の診断手法から受けるおよその胎児線量[9]

	検査	平均(mGy)	最大(mGy)
従来型X線検査	腹部	1.4	4.2
	骨盤	1.1	4
	胸部	<0.01	<0.01
CT	腹部	8.0	49
	骨盤	25	79
	胸部	0.06	0.96
	頭部	<0.005	<0.005

1. 心エコー検査

妊娠母体の血行動態を評価するうえで，非侵襲的かつ情報量の多い心エコー検査は非常に有用である．妊娠による循環動態の変化に伴い，通常の妊娠においても心エコー検査上の各指標は変化する．左室径は拡張末期，収縮末期ともに数mm程度増加し，壁厚も1～2 mm増加するため，左室心筋重量は増加する．また，左室短縮率や駆出率などの左室収縮能が不変あるいは増加する一方，拡張能においては，妊娠後期には僧帽弁通過血流速のE波(拡張早期波)の減高とA波(心房収縮期波)の増高を認め，拡張能の指標であるE/Aの低下が観察されている．ほかにも弁輪拡大と機能的な僧帽弁，三尖弁，肺動脈弁逆流や，少量の心嚢液貯留は通常の妊娠においてもしばしば観察される．また，下大静脈は妊娠子宮の増大に伴って圧迫され，妊娠後期には右房流入部位において血管径が縮小していることが多い．腹部静脈の圧迫は循環血液量にも関係する．妊婦では体位による循環血液量の変動が大きく，左側臥位では仰臥位の約10～20%多いことが知られている．約1割の後期妊婦では仰臥位低血圧をきたすことがあるため，長時間の仰臥位での検査には注意が必要である．

循環器疾患合併妊娠においては，妊娠前あるいは妊娠による循環変化がまだ軽微である妊娠初期に最初の心エコー検査を行い，妊娠リスクのアセスメントをすることが望ましい．低～中等度リスク患者の場合，心負荷が最大に近づく妊娠20週後半に再検し，改めて血行動態の評価を行う．あとはリスクや自他覚症状に応じて検査を追加することが薦められている．

ハイリスク患者や，自他覚症状の出現を認めた場合などにおいては，必要に応じてさらに頻回のアセスメントが必要である．大動脈径が40 mm以上のMarfan症候群の患者では，1～2週間ごとに超音波検査による大動脈径の測定が望ましいとされ，肺高血圧症合併患者では入院管理とともに頻回の超音波検査による肺高血圧の評価が必要である．

産褥期には心機能が低下する場合もあり，再度の血行動態評価が必要となる．産科の1カ月健診は全員受診するため，検査を施行するよい機会である．妊娠・分娩による心血管系への生理的な影響は3～6カ月ほど続くため，重症度に応じて半年間は定期的な経過観察が必要である．さらに，妊娠・分娩の影響だけでなく，母乳授乳を含めた育児行為が心負荷となりうるため，ハイリスク例では分娩後半年以降も血行動態評価を含めた経過観察が必要であろう．

2. 胸部X線検査，心臓カテーテル検査，心臓CT検査

肺うっ血や右心拡大の評価など，胸部X線検査が有用な場合も多く，また，肺塞栓症や大動脈解離，心筋梗塞などを疑う際はCTやカテーテル検査が必要となる．これらの検査は，胎児放射線被曝の問題から診療上有益と判断した場合にのみ施行すべきである．実際は，胎児線量が50 mGy未満では，被曝による胎児の発達遅滞，中枢神経障害，奇形のリスクの増大は現在のところ認められておらず，胸部X線写真による胎児線量は<0.01 mGy，胸部CTで<1 mGyと，比較的安全に行える検査である(表2)．

3. MRI検査

放射線被曝がないという点で，妊娠中の心臓MRI検査は安全度が高いと考えられる．右心系の評価や，複雑心奇形・術後症例などでは心臓超音

表 3　おもな循環作動薬の妊娠中内服

抗心不全薬	・急性心不全に対する，フロセミド，hANP(ヒト心房ナトリウムペプチド製剤)，カテコールアミンの使用は可能 ・慢性心不全に対する利尿薬の使用は，過度の利尿による子宮循環の低下，羊水過小や胎児利尿による脱水や電解質バランスの異常に注意 ・ACE(アンジオテンシン変換酵素)阻害薬あるいは ARB(アンジオテンシン受容体拮抗薬)は胎児の腎障害や羊水過小をきたすため，妊娠中の使用は禁忌 ・アルドステロン拮抗薬は通常の投与量では安全とされる
抗不整脈薬	・β遮断薬は子宮内胎児発育不全，新生児の徐脈や低血糖に注意が必要であるが，母体有益投与 ・アミオダロンは児の甲状腺機能異常をきたすことが知られているが，多くは一過性である．半減期が長いため，この薬剤の影響を胎児に与えたくなければ，受胎の数カ月前には投与を中止する必要がある ・頻脈発作時のアデノシン三リン酸(ATP)の静脈内投与や電気的除細動は妊婦でも安全に行える
抗凝固・抗血小板薬	・ワルファリンは骨形成異常などの催奇形性を有し，かつ，胎盤を通過するため，児にも出血性合併症を起こす(妊娠初期と後期の使用は禁忌) ・ヘパリンは催奇形性なく，胎盤を通過しないため，胎児に影響しない ・アスピリンなどの抗血小板薬に催奇形性や胎児毒性は認められていないが，分娩時出血をきたすため，分娩 1 週前までに中止が必要
降圧薬	・従来，メチルドーパ，ヒドララジンが妊娠中の降圧薬として頻用 ・Ca 拮抗薬はヒトでの催奇形性報告はなく，妊娠中も使用可能 ・ACE 阻害薬・ARB は，妊娠中の使用禁忌
肺高血圧治療薬	・プロスタサイクリン誘導体製剤は胎児の体内でも産生される物質であり，妊娠中使用による大きな有害事象の報告もないことから，母体肺高血圧症に対する使用の有益性は，胎児のリスクを上まわると考えられる ・エンドセリン受容体拮抗薬は動物実験において催奇形性を認め，妊娠中の使用は禁忌

波検査による評価が困難な場合があるが，心臓 MRI 検査はこのような場合であっても心室容積や血行動態の評価に有用と考えられる．従来，胎児異常の精査のために MRI 検査が汎用されてきたが，MRI 検査の胎児への危険性(熱・騒音・磁場などの影響)の詳細についてはわかっていないため，妊娠 13 週以降，診療上必要な場合にのみ施行することが望ましい．

4. 心電図検査

正常妊娠では心電図上に明らかな変化は認められない．ただし，心臓の位置変化に伴い，心臓の電気軸が左方に変位する．妊娠中，心拍数や循環血症量の増加に伴い，期外収縮や頻脈性不整脈の頻度は増加する．適時心電図検査が有用となる．

サイドメモ　妊娠中の薬剤使用

妊娠中に使用する薬剤の胎児への影響は，①催奇形性(妊娠 4〜10 週ごろ)と，②胎児毒性(妊娠 10 週〜)，の大きく 2 つに分けられる．胎児への影響と母体の治療効果を考慮し，内服の是非を決定する．胎児に及ぼす影響について母親の不安は大きいため，どのような薬剤も十分な説明と同意のうえに使用する．おもな循環器作用薬の妊娠中内服について表 3 に示す．また，わが国でもっとも汎用されている切迫早産治療薬はβ受容体刺激薬(塩酸リトドリン)であるが，その薬理効果により母体心拍数を上げ，不整脈や心不全の誘因となりうるため，多くの循環器疾患妊婦には勧められない．

おわりに

以上のような検査を必要に応じて施行し，循環動態の変化に耐容できているか評価する．また，妊娠週数に応じて妊娠中使用可能な薬剤(「サイドメモ」参照，表 3)を使用しながら母児予後を考慮した診療を行う．

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Editorial Comment

久馬論文に対するEditorial Comment

神谷千津子

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周産期心筋症と妊娠高血圧症候群

周産期心筋症(PPCM)は,「原因不明の妊産褥婦の心収縮力低下,心不全」と定義される除外診断名であり,heterogeneousな疾患群である.危険因子として,高齢,妊娠高血圧症候群,多胎妊娠や子宮収縮抑制剤(β刺激薬)の使用などが知られている.中でも,妊娠高血圧症候群を背景としたPPCMは,心機能が回復しやすく,heterogeneousな疾患群の中でも,ユニークな小集団と捉えられる[1].久馬論文でも,PPCMの8割が妊娠高血圧症候群を合併しており,1年以内に心機能が正常化している.

近年,妊娠高血圧症候群の発症機序は,胎盤形成期の子宮らせん動脈形成不全が,恒常的胎盤虚血を引き起こし,この虚血胎盤からsFlt1をはじめとする血管新生障害因子が増産され,母体の全身血管障害をきたすため,と考えられている.Pattenらは,心筋での血管内皮細胞増殖因子分泌低下をきたすモデルマウスが,微小循環障害を背景に,妊娠高血圧症候群と心筋症を発症する,と報告した[2].いまだ原因不明のPPCMにおいて,妊娠高血圧症候群との共通病態解明の試みは,とても重要である.

HFpEF症例とPPCMの病態

久馬らは,周産期に肺水腫をきたした症例を,心収縮能保持群(pEF群)と低下群(PPCM群)に分けて検討し,非常に興味深い結果である.産科出血は短時間に大量出血が起こるため,輸血量が多い上,輸血速度も速い.pEF群の中でも輸血症例は,血管内volume overと血管透過性亢進を反映した臨床データである.一方,無輸血のpEF患者とPPCM群は,妊娠高血圧症候群や多胎の合併など,臨床背景が類似している.妊娠高血圧症候群の病勢極期には,血管透過性亢進によるthird spaceへの体液移動が起こり,血管内虚脱となる.久馬らの心エコーデータ,BNPの比較的低値などは,この病態を反映していると考察される.その後,病勢安定とともに,third spaceから血管内へ体液がシフトし,血管内volumeが増加する.このような病態変化を反映して,pEF群の延長上にPPCM群があるのか,もともと,pEF群とPPCM群は,異なる病態をもつのか,という問いが生じる.もし,両群が同じ病態の延長線上にあるならば,third spaceへの体液貯留が著明であった妊娠高血圧症候群患者で,病勢安定期に心スクリーニングを行うことは,PPCMの早期診断につながるかもしれない.

ハイリスク妊娠におけるPPCM発症率

日本におけるPPCM発症率は1～2万分娩に1例と希少である.しかしながら,周産期集中管理が完備され,地域のハイリスク妊娠診療を行う久馬らの施設において,PPCM発症率は1500分の1であった.このように,地域の総合周産期センターや大学病院などのハイリスク妊娠診療施設では,PPCMは決して「稀な疾患」ではない.縦割り診療ではなく,産科―循環器間の協力体制の構築が,患者予後向上に大いに役立つだろう.

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特集 | 希少な心血管疾患を見直す

周産期(産褥)心筋症*

神谷千津子**

Key Words：peripartum cardiomyopathy, heart failure, pregnancy

はじめに

周産期(産褥)心筋症は，心疾患既往のない女性が，妊娠・産褥期に心不全を発症し，重症例では死に至る重篤な疾患である．息切れ，体重増加，浮腫などの心不全症状は，健常妊産褥婦も訴える症状であり，診断遅延の要因となっている．妊娠高血圧症候群，高齢，多胎，子宮収縮抑制剤の使用などが危険因子として知られている．これらの危険因子を持つ妊産褥婦では，心不全症状の訴えがないか注意し，過度の症状を認めれば，心不全を念頭において検査をすすめることが大切である．

診　断

1．急性心不全の診断

従来，産褥心筋症と呼ばれていたが，妊娠中に心不全診断される症例もあり，英語のperipartum cardiomyopathyを直訳し，周産期心筋症と呼ぶようになってきている．平成21年に行った全国アンケート調査では，妊娠中に心不全と診断された患者が3割，分娩から産後に診断された患者が7割であった．なかでも，分娩から産後1週間以内が最も多く，3分の1を占めた(図1)．

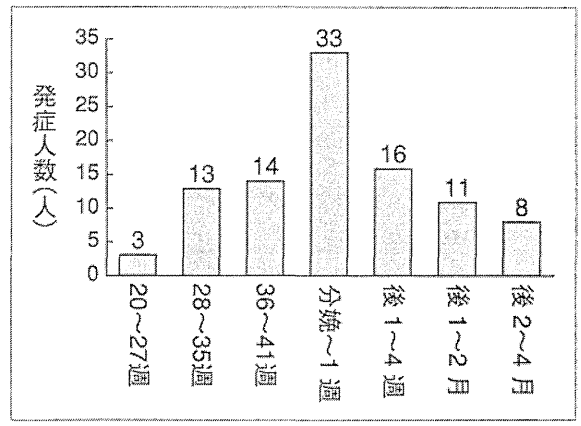

図1　わが国における周産期心筋症患者の心不全診断時期
(文献1)より)

診断時の症状は，息切れ80%，咳37%，浮腫37%，倦怠24%，動悸20%，体重増加16%，意識障害7%，ショック5%，胸痛5%の順であった(重複回答あり)[1]．息切れ，浮腫，動悸や体重増加は，健常妊産褥婦でも訴える症状であるため，診断遅延に陥りやすい．後述の危険因子とあわせ，息切れ，浮腫，倦怠感などの症状を訴える危険因子を持つ妊産褥婦においては，積極的な心不全スクリーニングが有用と考えられる．

画像検査として，うっ血性心不全の診断に胸部X線が有用である．胎児の放射線被ばくの問題から，妊婦のX線検査は躊躇されやすい．しかしながら，問題となる胎児被ばく量は最低でも50 mGy以上であるのに対し，母体胸部X線撮

* Peripartum cardiomyopathy.

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