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EDITORIAL

What We Know and What We Don't Know About the Adaptation to Pregnancy and Left Ventricular Diastolic Dysfunction

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Pregnancy is associated with hemodynamic changes that can affect the maternal heart. Cardiac output increases by 20% at 8 weeks of gestation. Peripheral vasodilation reduces systemic vascular resistance by 20–30%, resulting in a 40% increase in cardiac output.[1] Although there have been various reports on ventricular contractility during pregnancy, the increase in cardiac output is mainly affected by increased heart rate.[2,3] At this time, it is known that the left ventricle dilates, and the wall thickness and left ventricular mass increase.[4,5] The ratio between the ventricular end-diastolic dimension and wall thickness, represented by the relative wall thickness, is thought to remain stable during normal pregnancy,[2–6] unlike in pregnant women with hypertension, as shown in **Figure**. These functional and geometric changes in normal pregnancy may be a reasonable adaptation to compensate for increased cardiac output while reducing myocardial oxygen demand.[1] So what is happening to cardiac diastolic function in the pregnant female? This question has not been fully elucidated. It is well known that the prevalence of left ventricular diastolic dysfunction in the general population is associated with

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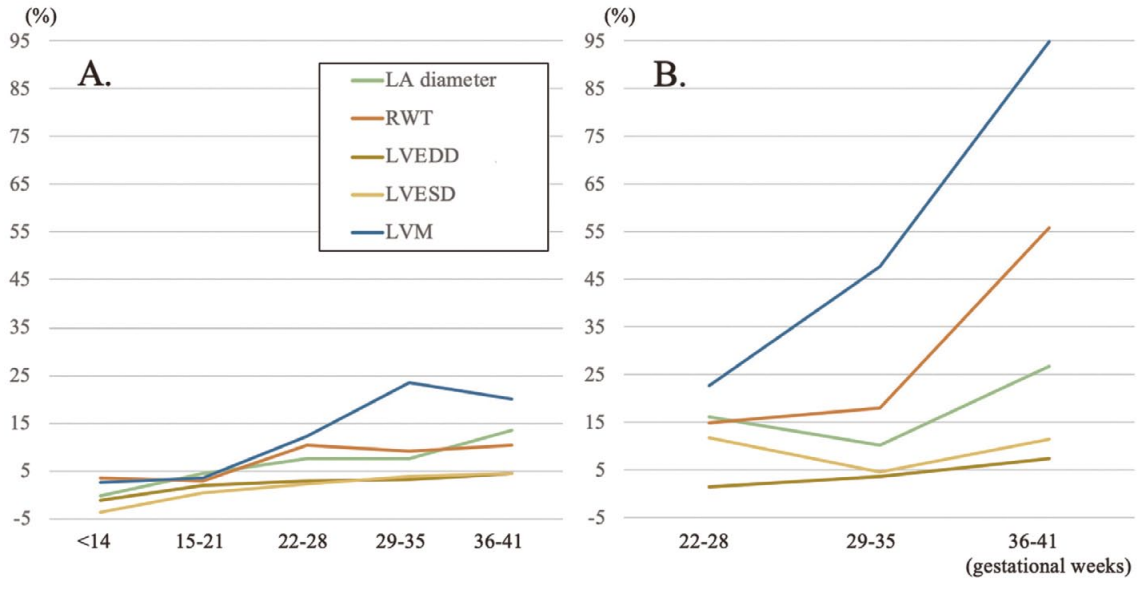

Figure. Changes in geometric indices during (**A**) normal pregnancy and (**B**) pregnancy complicated by hypertension. The vertical axis shows the relative change (%) compare with baseline. LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVM, left ventricular mass; RWT, relative wall mass. Modified with permission from De Haas et al[2] and Nii et al.[3]

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Table. Comparison of Reports on the Association Between Changes in Cardiac Diastolic Function and Pregnancy

	Subjects	Age (years)	Timing of echocardiography	Results
Kimura et al (2019)[13]	397 normal pregnant women	34	3rd trimester vs. within 4 days of delivery	Both E and A increased significantly, but the increase in E was slight, resulting in a decrease in E/A E' decreased and E/E' increased right after delivery significantly, but were within the normal range
Pintaudi et al (2013)[8]	55 pregnant women with abnormal glucose tolerance and 53 normal pregnant women	35 vs. 32	29 weeks of gestation	Only A and A' increased, and E, E' and E/A did not change significantly
Melchiorre et al (2012)[6]	50 women with PE and 50 low-risk pregnant women	32 vs. 32	37–42 weeks of gestation	20 PE women and 7 low-risk women met the 2009 ASE criteria for the diagnosis of DD
Soma-Pillay et al (2016)[11]	96 women with severe PE and 45 normal pregnant women	29 vs. 27	2–7 days after delivery and after 1 year follow up	Women who developed early-onset PE requiring delivery before 34 weeks were at significant risk of developing cardiac DD 1 year after delivery
Zandstra et al (2010)[7]	301 women with a recent history of a placental syndrome	32 vs. 33	6 months postpartum	DD occurred in 24% of the 62 women with metabolic syndrome compared with 6.3% of 239 without
Aggarwal et al (2017)[14]	1,172 Hispanic/Latina women in The Echocardiographic cohort Study of Latinos	56	Cohort study of non-pregnant women	Higher parity was associated with increased cardiac mass, volumes and the presence of DD, meeting the 2009 ASE criteria

ASE, the American Society of Echocardiography; DD, diastolic dysfunction; PE, preeclampsia.

aging, coronary artery disease, hypertension, diabetes mellitus, and left ventricular systolic dysfunction.[7] It has been reported that diastolic dysfunction is likely to occur during pregnancy in cases of glucose tolerance, hypertension, or nephropathy (**Table**). Pintaudi et al reported lateral mitral annulus late diastolic velocity and A wave velocity increased in pregnant females with impaired glucose tolerance compared with normal pregnant cases.[8] Scantlebury et al reported that women with hypertensive pregnancies also had larger left atrial size and lower mitral E/A ratio after adjusting for demographic variables.[9]

Preeclampsia is a form of gestational hypertension syndrome, defined as the first onset of hypertension after 20 weeks of pregnancy and with proteinuria.[10] It normalizes by 12 weeks after parturition, but it has been reported that women who develop early-onset preeclampsia requiring delivery before 34 weeks are at significant risk of developing cardiac diastolic dysfunction 1 year after delivery.[11] Another study has shown a 10-fold increase in myocardial contraction band necrosis in rats, suggesting increased collagen deposition.[12] In other words, cardiomyocyte injury and fibrosis occur in preeclampsia, resulting in diastolic dysfunction.

So, what changes in diastolic function occur in normal pregnancy cases?

In this issue of the Journal, Kimura et al[13] report their use of echocardiography to evaluate 397 normal pregnant women during the 3rd trimester and within 4 days after delivery. Although it needs to be noted that in this study diastolic dysfunction was defined only by velocity (e') <7 cm/s and peak early filling velocity (E)/e' ratio >15, they reported the following results. First, diastolic function slightly decreased after delivery and was associated with the prevalence of hypertensive disorders, with correlations with age and left ventricular mass index. Second, cardiac diastolic dysfunction occurred in 0.3% of women with a normal pregnancy. Melchiorre et al report that mild diastolic dysfunction and impaired myocardial relaxation were observed in 17.9% and 28.4%, respectively, of normal pregnant women at term.[4]

Although in only a few subjects, Nii et al evaluated left ventricular remodeling in normal pregnancy by cardiac MRI.[3] As reported previously, increased left ventricular mass was observed, but there was no significant difference in the left ventricular global longitudinal strain by feature tracking and native T1 mapping between pregnant and non-pregnant women. At 1 month after parturition, the pregnancy-related left ventricular hypertrophy disappeared, which means the remodeling can be attributed to an increase in cardiomyocyte volume and/or intravascular compartment, not myocardial edema or fibrosis. The remodeling can be an adaptive response to increased cardiac workload. Therefore, slightly decreased diastolic function in normal pregnancy might be caused by the geometric changes related to the observed ventricular dilatation and not indicate a deterioration in myocardial function.

However, some reports suggested that pregnancy itself can be a risk of diastolic dysfunction. A report from a cohort of women over 45 years of age showed that the proportion of women with diastolic dysfunction among those with a history of births was significantly higher than among women with no history of births.[14] In particular, 81% of women with more than 5 births had left ventricular diastolic dysfunction. In the multivariate models, higher parity was significantly associated with the greater left ventricular end-systolic volumes, end-diastolic volumes, left atrial volume indices, and diastolic dysfunction, but was not associated with left ventricular ejection fraction. The mechanisms underlying cardiovascular adaptation during pregnancy that persists after pregnancy are also not well understood. Various plasma concentrations of estrogen and progesterone are both known to induce hypertrophy and may be a part of the physiological hypertrophy of pregnancy.[15] However, little is known about the long-term effects of these repeated adaptations in women with a multiple pregnancy history.

In some cases, pregnancy itself may cause diastolic dysfunction, which may lead to heart failure with preserved ejection fraction, although the risk of developing diastolic dysfunction is still unknown among normal pregnant

women without apparently complications.

There are still many unclear issues regarding the changes in cardiac diastolic function associated with pregnancy. The relevance of maternal cardiovascular dysfunction to pregnancy complications deserves further investigation.

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