Recent Topics in Obstetrical Ultrasound in Japan—Fetal Tachyarrhythmia and Bradyarrhythmia

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ABSTRACT

Fetal arrhythmia is frequently found in daily clinical practice. Extrasystole is the most common type of fetal arrhythmia, which is mostly benign and transient. Meanwhile, bradyarrhythmia and tachyarrhythmia are problematic as they cause fetal heart failure. Fetal tachyarrhythmias include supraventricular tachycardia (SVT), atrial flutter (AFL), and ventricular tachycardia (VT). Supraventricular tachycardia are the most commonly reported type of fetal tachyarrhythmia whose mechanisms are classified into AV re-entrant tachycardia (AVRT), AV nodal re-entrant tachycardia (AVNRT), and intra-atrial re-entrant tachycardia (IART). Fetal therapy is performed in cases where extending the gestation period is required. For the fetal therapy of SVT, the classification by VA intervals is used. In 2019, a Japanese prospective study has proposed a protocol of fetal therapy for supraventricular tachyarrhythmia. The efficacy of fetal therapy was 90% ($n = 44/49$) overall. In fetal bradyarrhythmias, a ventricular rate of <55 bpm is defined as a risk for hydrops fetalis. A prospective study of hydroxychloroquine is currently being conducted in Japan as its prophylactic efficacy was found. An accurate diagnosis is needed to provide appropriate treatment. The recent advancement of ultrasound equipment has enabled higher-resolution imaging than conventional equipment with high temporal and spatial resolutions. In our research, a template matching technique is employed to track tissue architecture in which the speckle pattern is moved to the most similar orientation. With this technique, we estimated the timings of the P and R waves. The reproducibility of such detection for fetuses is currently insufficient. There is still room to be improved.

Keywords: Extrasystole, Fetal arrhythmia, Fetal tachyarrhythmias.

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INTRODUCTION

A fetal arrhythmia occurs in 1–5% of all fetuses and is frequently found in daily clinical practice.^{1–4} This disease is classified into three broad categories based on heart rate: bradyarrhythmia, tachyarrhythmia, and extrasystoles. Extrasystole is the most common type of fetal arrhythmia; however, it disappears spontaneously in most cases during the fetal and neonatal periods. Thus, few cases require interventions.^{5,6} Meanwhile, bradyarrhythmia and tachyarrhythmia are problematic as they cause fetal heart failure. Fetal tachycardia is a condition for which fetal therapy is indicated, and its therapeutic options are divided according to the type of this disease. Given that drug selection is associated with the prognosis of fetal arrhythmia, an accurate diagnosis of this disease is vital.^{7–10} Currently, fetal tachycardia is diagnosed based on ultrasonography because fetal electrocardiography (fECG) and magnetocardiography (fMCG) are unavailable in many medical facilities. The diagnosis of this condition is not technically difficult; however, while performing ultrasonography, understanding the fetal position and angle of the fetal heart and blood vessels is required to diagnose fetal tachycardia accurately. Also, sweep speed should be appropriately adjusted to diagnose tachycardia. There still is a difficulty requiring experience and moderate level skills.

Tachyarrhythmia

Fetal tachyarrhythmias which are rather often encountered in practice include supraventricular tachycardia (SVT), atrial flutter (AFL), ventricular tachycardia (VT). These classifications are based on the difference in electrophysiological mechanisms of each condition.

Atrial Flutter

During AFL, the second most common fetal tachyarrhythmia, reentrant excitation occurs in the right atrium when excitation

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conduction moves around the right atrium instead of the normal electrical conduction. Such electrical impulses cause the atria to beat faster, approximately 300 beats per minute (bpm) or more. However, atrioventricular conduction is at a 2:1 or 3:1 ratio because the conduction ability of the atrioventricular node is limited by the refractory period (Fig. 1).

Ventricular Tachycardia

Ventricular tachycardia shows frequent ventricular contraction, independent of atrial contraction (i.e., atrioventricular dissociation) in the absence of reverse conduction to the atrium. As a result, blood flow from the atrium to the ventricles per stroke differs. Reflecting this dissociation pulsed-wave Doppler shows heterogeneous wave height of a ventricular waveform (Fig. 2). Furthermore, a superior vena cava waveform is also heterogeneous and masked by a ventricular waveform when atrial and ventricular contractions overlap. Pulsed-wave Doppler has a potential utility for prenatal diagnosis of fetal ventricular tachycardia secondary to long QT

Fig. 1: Dual M-mode ultrasound of atrial flutter case. Dual M-mode records the motion of the ventricular and atrial walls from the different ROI at the same time. In this atrial flutter case, the atrial rate is 412 bpm with a fixed 2:1 atrioventricular block

syndrome which is characterized by prolongation of the QT interval and is associated with an increased risk of sudden cardiac death by intermittent or persistent VT (Torsade de Pointes, TdP).¹¹ Separate visualization facilitates the diagnosis of dyssynchrony between atrial and ventricular contraction during VT or TdP. We reported a case of fetal VT secondary to long QT syndrome which prenatal diagnosis was made by pulsed-wave Doppler.¹¹ In the report, its prenatal diagnosis using echocardiography was compared with that using MCG resulting that serial Doppler recordings are comparable to fetal magnetocardiography in prenatal diagnosis of arrhythmias. In addition, the Doppler approach provides functional assessment, which can help guide management.¹¹

Supraventricular Tachycardia

Supraventricular tachycardia are the most commonly reported type of fetal tachyarrhythmia defined by a 1:1 AV conduction relation with a heart rate of >180 bpm.¹² Reentry is the most common mechanism of SVT, which are classified into AV re-entrant tachycardia (AVRT), AV nodal re-entrant tachycardia (AVNRT), and intra-atrial re-entrant tachycardia (IART) (Fig. 3). Fetal SVT easily causes heart failure as well as other fetal tachyarrhythmias.^{13,14} Fetal therapy is performed in cases where extending the gestation period is required to prevent premature birth or heart failure. An accurate diagnosis is needed to provide an appropriate treatment according to the protocol. For the fetal therapy of SVT, the classification by VA intervals is used. It depends on the published literature reporting the difference of response to the antiarrhythmic drugs between long VA and short VA group.¹⁵ The VA time is the interval between ventricular contraction and the next atrial contraction and is used to define the following two types: short and long VA times. The VA time is shorter than the atrioventricular (AV) time, which is the interval between atrial contraction and the next ventricular contraction, is short VA times, and the VA time is longer than the AV time in long VA times. In the presence of a short VA interval, a reentry mechanism with slow anterograde and fast retrograde conduction is the most likely diagnosis while long VA interval represents the inverse manner. The classification by VA intervals is depending on the published literature reporting the difference of response to the antiarrhythmic drugs between long VA and short VA group.^{7,15,16} In 2019, a Japanese prospective study has proposed a protocol of fetal therapy for

Fig. 2: In the case of ventricular tachycardia, pulsed-wave Doppler of the superior vena cava and aortic artery flow shows heterogeneous wave height of a ventricular waveform with atrioventricular dissociation

Fig. 3: Pulsed-wave Doppler of superior vena cava (SVC) and aortic artery flow in a case of AVNRT. The superior vena cava waveform of atrial kick is heterogeneous and masked by a ventricular waveform when atrial and ventricular contractions overlap

supraventricular tachyarrhythmia. A protocol of therapy proposed for fetal tachyarrhythmia (supraventricular tachyarrhythmia) from Japanese group is shown in Figure 4.¹⁰ In the study, the treatment protocol was determined by considering the absence or presence of hydrops fetalis when fetal tachyarrhythmias were classified into SVT with short VA, SVT with long VA or AFL. The efficacy of fetal therapy was 90% ($n = 44/49$) overall and 75% ($n = 3/4$) in fetuses with tachyarrhythmia who concomitantly had hydrops fetalis. The onset of a new arrhythmia, fetal death, and reproducibility of arrhythmia after birth were confirmed in mothers and fetuses.

Dissociation between Electrophysiological Phenomena and Actual Heart Movement

M-mode ultrasonography can simultaneously record atrial and ventricular movements. Based on such a feature, atrial and ventricular contractions are regarded as end diastole and systole, respectively. During diastole, the enlargement of the ventricles causes the flow of blood from the atrium to the ventricles, and atrial contraction at the end of the ventricular diastole forces more blood to flow into the ventricles (atrial kick). This hinders the atrioventricular valves from closing and forces them to open again during atrial contraction. The myocardial potential generated by atrial contraction and myocardial potential produced by ventricular contraction corresponds to P and QRS waves, respectively, on ECG. Taken together, M-mode ultrasonography estimates electrophysiological phenomena based on atrial and ventricular movements. Pulsed-wave Doppler shows a reverse wave toward the superior vena cava during atrial contraction, which is regarded as A wave. Furthermore, a ventricular waveform is regarded as a V wave. M-mode ultrasonography estimates electrophysiological phenomena in the heart based on the timing of the actual myocardial movement. Pulsed-wave Doppler estimates electrophysiological phenomena in the heart, based on the changes in blood flow associated with cardiac contraction. However, both methods do not directly evaluate electrophysiological phenomena in the heart. Thus, some dissociations exist between the findings

Fig. 4: A protocol of therapy proposed for fetal tachyarrhythmia (supraventricular tachyarrhythmia) from Japanese group. The intrauterine treatment protocol is determined by VA intervals. (Miyoshi et al. Japan Fetal Arrhythmia Group. Antenatal Therapy for Fetal Supraventricular Tachyarrhythmias: Multicenter Trial. *J Am Coll Cardiol* 2019;74:874–885.)

Fig. 5: Fetal magnetic cardiography provides single-averaged fMCG. PR time is accurately measured with this technique

obtained using these procedures and those obtained using fMCG. In our institution, the electrical PR interval (ePR) was measured using fMCG (Fig. 5), and the superior vena cava and ascending aorta (SVC-AAo method) and the hepatic vein and descending aorta (HV-DAo method) were simultaneously measured using pulsed-wave Doppler to determine the mechanical PR interval (mPR). The results showed that mPR was longer than ePR (Fig. 6) (unpublished data). That is, a time lag exists between ePR, which represents changes in myocardial potential, and mPR, which represents myocardial tissue movements. Arrhythmia is a disease entity characterized by abnormal electrical conduction. ECG records the myocardial potential. That is, it does not directly record electrical conduction. The electrical impulse is propagated throughout the myocardium, stimulating the atria to contract. Myocardial potential during atrial contraction is observed on ECG. M-mode ultrasonography directly shows the movement of contraction. Pulsed-wave Doppler indicates the blood flow associated with contraction (Fig. 7).

Fig. 6: The electrical PR interval (ePR) was measured using fMCG, and the mechanical PR is measured by pulsed Doppler. ROI was placed on the superior vena cava and ascending aorta (SVC-AAo method) and the hepatic vein and descending aorta (HV-DAo method). Mechanical PR interval is longer than the electrical PR interval showing the dissociation between the electrical activity and mechanical activity of heart (unpublished data). ePR: electrical PR interval, mPR(SVC-AAo): mechanical PR interval measured by dual gate pulsed Doppler. ROI was placed in SVC and ascending aorta. mPR(HV-DAo): mechanical PR interval measured by dual gate pulsed Doppler. ROI is placed in SVC and ascending aorta

Development of a New Diagnostic Technology

B-mode scan ultrasonography is a basic procedure and requires no special skills. Four-chamber view (4CV), the most basic plane to observe the heart, facilitates the visualization of the heart and the acquisition of imaging data. The recent advancement of ultrasound equipment has enabled higher-resolution imaging than conventional equipment with high temporal and spatial resolutions. Furthermore, video clip quality remains high upon increasing the

Fig. 7: The impulse from electrical conduction system propagates throughout the myocardial tissue making contraction of myometrium. ECG or MCG records the myocardial potential during myometrial contraction. Meanwhile, M-mode ultrasonography records the movement of contracting cardiac muscle wall and pulsed-wave Doppler indicates the blood flow associated with contraction. Each method records different parts of cardiac activity leading to some chronological dissociations

frame rate. The combined use of such a high-quality video and tracking technology allows the tracing of the movement of each pixel in each frame. A template matching technique is employed to track tissue architecture in which the speckle pattern is moved to the most similar orientation. The template matching technique is a machine vision technique that identifies the parts on an image that match a predefined template (Fig. 8). This technique can detect myocardial movements, allowing for the identification of the speed and timing of myocardial movements.¹⁷ In a previous study, with this technique, we estimated the timings of the P and R waves using sonograms simultaneously recorded neonatal ECG. Subsequently, an algorithm which was devised based on the pattern that was synchronized with neonatal ECG was created with deep learning of artificial intelligence (AI). After the evaluation of reliability of the algorithm with the non-learning newborn's data, this algorithm was applied to fetal data. The results revealed that neonatal echocardiography detects timings corresponding to the P and QRS waves on ECG in nearly 100% of non-learning neonates. The reproducibility of such detection for fetuses is currently insufficient. To increase accuracy, more cases would be required (Fig. 9).

Bradyarrhythmia

Bradyarrhythmia is defined as a ventricular rate of <100 bpm. Physicians should focus on atrial and ventricular contraction rates while diagnosing bradyarrhythmia. If there is a 1:1 ratio, sinus bradycardia is diagnosed; whereas in other cases, an atrioventricular block is diagnosed. Immune-mediated blocks occur as a result of atrioventricular node deterioration associated with autoantibody-mediated inflammation. RO antigens recognized by anti-SS-A antibodies are a ribonucleoprotein complex that comprises two subunits (52 and 60 kDa). Particularly, anti-RO52 antibodies that recognize the 52-kDa subunit are involved in the onset of atrioventricular blocks.¹ Tissue disorders associated with autoantibodies exert an adverse influence on atrioventricular nodes and the entire heart, resulting in the onset of endocardial fibroelastosis, rupture of the chordae tendineae, dilated cardiomyopathy, and pericardial effusion.

Fetal Therapy for Bradyarrhythmia

A ventricular rate of <55 bpm is defined as a risk for hydrops fetalis. Beta-stimulators are recommended in fetuses with bradyarrhythmia who have a ventricular rate of <55 bpm, or those who have a ventricular rate of 55 bpm or more if they concomitantly have congenital heart disease, abnormal cardiac function, or hydrops fetalis.^{1,18} Steroid treatment has limited efficacy or is ineffective in treating immune-mediated atrioventricular blocks; however,

Fig. 8: Template matching technique is a machine vision technique. Template matching technique identifies a part of reference image in the inspected frame which matches a template image in the predefined template

such treatment may be considered in patients with second- or first-degree atrioventricular blocks if they have inflammatory findings.^{1,19–21} Complete atrioventricular blocks are irreversible; however, a study has reported that a concomitant treatment using steroids and immunoglobulins initiated soon after the onset of a complete atrioventricular block is effective. Early detection of fetal arrhythmia may be associated with a favorable prognosis. However, regular pulse reportedly progresses to complete atrioventricular block within 24 hours in pregnant women who test positive for anti-SS-A antibodies.²¹ Steroid use is considered in treating myocarditis during immune-mediated blocks.

Prevention of Atrioventricular Block in Fetuses of Mothers whose Previous Children have Experienced Atrioventricular Blocks

The prevalence of SS-A antibodies in women is 1–2%. An atrioventricular block occurs in 2–4% of fetuses of SS-A antibody-positive mothers; however, this rate increases to 17–21% if their previous children have experienced atrioventricular blocks.²² Although providing prophylaxis is not recommended in all mothers who test positive for SS-A antibodies, prophylaxis with steroids is considered if their previous children have experienced atrioventricular blocks. A recent study revealed that maternal administration of hydroxychloroquine, a common drug used for treating systemic lupus erythematosus, from the tenth week of gestation has the potential in preventing atrioventricular block in pregnant women with high risk for recurrent atrioventricular block.²³ A prospective study of hydroxychloroquine is currently being conducted in Japan as its prophylactic efficacy was found.

Prediction of Clinical Outcome for Fetal Tachyarrhythmia or Bradyarrhythmia

Our recent study demonstrated that plasma natriuretic peptide levels in umbilical cord blood were correlated with the severity of heart failure in fetuses with congenital heart defects (CHDs) or arrhythmias.²⁴ Because of the requirement of an invasive procedure, applying an umbilical cord sample is not practical. Following this study, we conducted a single-center, exploratory, cross-sectional study to investigate the possibility of whether maternal serum biomarkers can diagnose fetal heart failure in fetuses with CHDs or

Figs 9A and B: The algorithm which detects the timings of the P and R waves based on the sonograms simultaneously recorded using neonatal ECG was developed. Neonatal echocardiography detects timings corresponding to the P and QRS waves on ECG nearly 100% in non-learning data (A). The reproducibility of P and QRS waves detection for fetuses is currently insufficient (B). (A) Non-learning neonatal data. 1st low, green line: newborn ECG, red line: pseudo-ECG described by AI. (B) Fetal data, 1st low, red line: pseudo-ECG described by AI

arrhythmias.²⁵ In this study, 10 fetuses with tachyarrhythmia and 3 with bradyarrhythmia were included. When fetal tachyarrhythmia was sustained for $\geq 50\%$ of the time on monitoring, fetal therapy using digoxin, sotalol, and flecainide was carried out, and when fetal bradyarrhythmia was complicated with a fetal ventricular rate < 55 bpm and myocarditis, beta-sympathomimetics and dexamethasone were used. Maternal serum samples were collected in the third trimester and 1 week after delivery. This study showed

that maternal serum concentrations of tumor necrosis factor- α , vascular endothelial growth factor-D, and heparin-binding epidermal growth factor-like growth factor were associated with fetal heart failure in fetal arrhythmia as well as a fetus with CHDs.

SUMMARY

It is possible to accurately diagnose fetal arrhythmia including tachy- and bradyarrhythmia by fetal echocardiography followed

by appropriate prenatal management. However, there is still room to be improved especially in severe cases. In this article, recent studies conducted in Japan were reviewed. In addition, the utility of the application of AI for this issue was introduced. Together with genetic surveillance and advanced technology including AI is becoming of importance.

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