Fetal Cardiac Function: Technical Considerations and Potential Research and Clinical Applications

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Fetal echocardiography was initially employed to detect structural anomalies [1], but its use in fetal cardiac function assessment has recently been proposed [1–5]. Fetal cardiac dysfunction may be due to an intrinsic myocardial disease or to a secondary adaptive mechanism. The latter is particularly important because the heart seems to be a central organ in the fetal adaptive response to a variety of insults [5–8]. Consequently, assessment of fetal cardiac function may be helpful in the diagnosis or monitoring of several fetal conditions [4–8]. In addition, given the substantial evidence indicating the occurrence of programming of adult cardiovascular disease in fetal life [9], cardiac function assessment might help to predict perinatal and long-term cardiovascular outcomes.

Evaluating fetal cardiac function is particularly challenging [1, 2]. There are obvious difficulties in trying to...
measure cardiac function in a small, moving, and changing patient, which are discussed in detail in the next section. An additional challenge is that fetal cardiac dysfunction is essentially subclinical [6–8]. Fetuses rarely go into cardiac failure, and when they do, the outcome is generally dire, with very few exceptions [4–8]. The results of cardiac examination in most fetuses in which cardiac function is of interest will be completely normal by child or adult cardiology standards. Thus classical indices used to determine the existence of cardiac failure in postnatal life are of little use in fetuses. Fortunately, adult cardiology has substantially developed in the last few years and a variety of new methods able to identify extremely subtle changes in cardiac function are now available [10]. Implementation of these technologies in the fetus is far from straightforward, but these advances have already shown highly promising results [11–14]. More detailed evaluation of cardiac function will allow new pathophysiological insights into a number of fetal conditions and possibly new clinical applications. We believe that a well-developed field of knowledge and specialization in fetal cardiac function in the course of the next 5–10 years can realistically be envisioned.

In this review we provide a very brief overview of currently available techniques to measure fetal cardiac function, the technical challenges and precautions required for its evaluation, and a noncomprehensive summary of the available data on fetal cardiac assessment in a variety of fetal conditions.

Pathophysiological Basis of Fetal Cardiac Dysfunction

The primary function of the heart is to eject blood in order to provide adequate perfusion of organs [15]. The heart achieves this function by contracting its muscular walls around a closed chamber to generate sufficient pressure to eject blood from the ventricle through the aortic/pulmonary valve and into the aorta/pulmonary artery (systole). Adequate filling of the ventricle from the atria (diastole) is also essential [15, 16]. To maintain normal cardiac function, both systolic and diastolic processes must be preserved and time events must occur in a synchronized manner.

Cardiac Cycle in Normal Conditions

The normal cardiac cycle involves five major phases [15]. The first phases, considered together as the diastolic or ventricular filling stage, involve movement of blood from the atria into the ventricles [15]. The next phases, or systolic period, involve the movement of blood from the ventricles to the aorta and the pulmonary artery. The phases are as follows:

1. **Isovolumetric relaxation phase**: diastole starts after aortic/pulmonary valve closure with an isovolumetric relaxation period. While the myocardium starts to relax no blood enters or ejects from the ventricles and the intraventricular pressure drops.
2. **Early diastole**: when ventricular pressure lowers the atrial pressure, the filling phase starts with the mitral/tricuspid valve opening and blood from the atria filling the ventricle in a passive manner.
3. **Atrial contraction period**: the atria contract and complete the filling of the ventricle (late diastole).
4. **Isovolumetric contraction phase**: systole is started by contraction of cardiomyocytes, which increases intraventricular pressure. This increase in pressure then opens the aortic/pulmonary valve (isovolumetric contraction time) while there is no change in volume.
5. **Ejection period**: finally, when the ventricular pressure has increased sufficiently to open the aortic/pulmonary valves, the myocardium starts to deform and the blood is ejected from the ventricle.

These main components of the cardiac cycle define the main features of cardiac blood flow movement and myocardial motion and deformation [15–18].

Definition of Heart Failure, Cardiac Dysfunction, and Remodeling

Heart failure is defined as the inability of the heart to supply sufficient blood flow to meet the body’s needs [19]. This is usually a late event that can be easily recognized by cardiomegaly, atrioventricular insufficiency, and fetal hydrops [4]. Heart failure can also be quantified by measuring a significant decrease in cardiac output or ejection fraction [4, 19].

However, in the initial stages of an insult, the heart usually manages to adapt and there is a long subclinical period of cardiac dysfunction before end-stage heart failure [4–6]. During this period of cardiac adaptation, changes in cardiac function, as well as in the heart’s shape and size, can be measured. These changes are the heart’s attempt to adapt to the insult, a process known as cardiac remodeling [20].

Determinants of Fetal Cardiac (Dys-)function

Changes in cardiac function and shape will depend mainly on the causal insult but are also determined by myocardial contractility, fiber orientation, tissue elastic-
ity, heart geometry, segment interaction, loading conditions, electrical activation, and myocardial perfusion [10]. In the fetal heart, myocardial maturation and fetal blood circulation are also critical factors [21]. The most important determinants of fetal cardiac function are discussed below.

Myocardial Contractility

Myocardial contractility is the intrinsic ability of cardiac muscle to develop force for a given muscle length [15, 16] and may be affected by genetic deposition to cardiac diseases or by hypoxia [10, 16]. Myocardial contractility essentially conditions myocardial motion and deformation during systole [10, 16]. If the velocities measured at all points within a moving object are the same, then the object will be described as having motion [10]. If, on the other hand, different points within a moving object are moving at different velocities, then the object will exhibit deformation [10] and alter its shape:

- Myocardial motion is defined as the distance covered by one point over a certain period of time and is determined by displacement (distance) and velocity (distance divided by time).

- Myocardial deformation is defined as the change in the length/thickness of a segment (two points) and is determined by strain (percentage of change) and strain rate (velocity of segment change).

When myocardial fibers contract, all segments deform and then the heart's base moves toward the apex to eject blood [10]. Global longitudinal myocardial motion is usually measured at the mitral/tricuspid annulus as this fibrose area (with no intrinsic capacity for deformation) reflects the motion of all myocardial segments. Conversely, myocardial deformation should be assessed in a specific myocardial segment reflecting regional function.

Fiber Orientation

Myocardial contraction is a complex three-directional motion involving longitudinal contraction, radial contraction, and rotation (circumferential axis) [16]. These components are mainly determined by the complex geometry of myocardial fibers and muscle band orientation [22, 23].

- Longitudinal motion consists of the movement of fibers from the apex to the base of the heart and is mainly determined by endocardial longitudinal fibers, which are those farthest from the epicardial blood supply and consequently the most sensitive under milder degrees of hypoxia. Therefore, longitudinal motion usually becomes abnormal in the very early stages of cardiac dysfunction [10, 11, 16].

- Radial motion is perpendicular to the epicardium and is determined by radial fibers mainly located in the mid part of the ventricular wall. Radial motion usually becomes abnormal in the late stages of fetal deterioration [10, 16, 19].

- The circumferential axis is perpendicular to both the longitudinal and the radial axes. In the left ventricle myocardial wall, the geometry of the myofibers changes smoothly from a right-handed helix in the subendocardium to a left-handed helix in the subepicardium such that the angle of the helix varies continuously from positive at the endocardium to negative at the epicardium [22, 23]. Therefore, the base and apex of the left ventricle rotate in opposite directions, leading to the twisting motion being described as 'the wringing of a linen cloth to squeeze out the water'. Rotation and twisting have been shown to become abnormal in the very early stages of cardiac dysfunction [24]. However, very few studies have successfully assessed rotation in utero, and therefore its utility in fetal life remains to be elucidated [25].

Changes in Myocardial Maturation during in utero Development

During gestation, maturational changes occur within the myocardium leading to changes in elasticity and contractility throughout the pregnancy [26]. Once the structural details have been organized during the embryonic period, the fetal heart continues to grow by cell division until birth, and continued growth thereafter is due to cell enlargement [26]. The density and compaction of myofibrils increases particularly in early pregnancy, but contractility and elasticity continue to improve during the second half of pregnancy [27]. Changes in myocardial maturation should be taken into account when evaluating and interpreting fetal cardiac function.

Ventricular Loading

Volume and pressure loading conditions will determine cardiac function [10]:

- Preload is the muscle length prior to contractility and is dependent on ventricular filling or blood volume in end-diastole [15, 16]. The most important determining factor for preload is venous return. Volume overload [e.g. due to fetal anemia, twin-to-twin transfusion syndrome (TTTS), valve leakage, etc.] will mainly lead to heart dilatation to help the heart manage the increased blood volume more efficiently [20].
– Afterload is the tension (or the arterial pressure) against which the ventricle must contract and depends on the maximum tension of the myocardial muscle mass in end-systole [15, 16]. Afterload for the left ventricle is determined by aorta pressure, while afterload for the right ventricle is determined by pulmonary artery pressure. Pressure overload (e.g. due to valvular stenosis or TTTS) will mainly lead to myocardial hypertrophy in order to increase the contractile mass to overcome the elevated afterload [20].

Particularities of Fetal Circulation

In contrast to postnatal life, the fetal systemic circulation is fed from the left and right ventricles in parallel, but with a small proportion of the right output being spared for the lungs [21]. The well-oxygenated blood is directed from the umbilical vein through the ductus venosus (DV) across the inferior vena cava, through the foramen ovale, left atrium, and ventricle and up the ascending aorta to join the low oxygenated blood in the descending aorta. Deoxygenated blood from the superior and inferior vena cava is directed through the right atrium and ventricle, pulmonary trunk, and ductus arteriosus.

Additionally, the three shunts – DV, ductus arteriosus, and foramen ovale – are essential distributional arrangements, making fetal circulation a flexible and adaptive system for intrauterine life [21]. The hemodynamic properties and functional ranges of these shunts are important determinants of the development of the fetal heart and circulation during the second and third trimesters. Understanding the particularities of fetal circulation is essential for adequate comprehension of fetal cardiac function changes in normal and pathological conditions.

**Main Techniques and Indices Used to Assess Fetal Cardiac Function**

Traditionally, fetal cardiac function was assessed by measuring blood flow through conventional Doppler or cardiac morphometry in 2D or M-mode. More recently, direct assessment of myocardial motion and deformation has been proposed using tissue Doppler imaging (TDI) and 2D speckle tracking imaging [10, 28, 29]. Lately, 4D spatiotemporal image correlation (STIC) has also been proposed to more accurately evaluate cardiac dimensions and volumes [30]. A detailed list of the most common techniques used in the fetus is provided in table 1 and described below.

**Conventional Doppler**

As the primary function of the heart is to eject blood in order to provide adequate perfusion of organs, blood flow assessment is a common approach to evaluate fetal cardiac function [1, 31]. Conventional Doppler allows blood outflow (systole) and inflow (diastole) in the heart, as well as time events, to be evaluated:

– Doppler measurement of flow through the outflow tracts reflects systolic function. This measurement can be multiplied by the area of the outflow tracts to calculate the stroke volume, the amount of blood ejected per heart beat [15]. Combining this information with the fetal heart rate allows cardiac output (volume per minute) to be estimated, which should normally be expressed as the cardiac index (cardiac output adjusted by fetal weight) [15, 31]. Cardiac output is a classical parameter to assess cardiac function but only becomes abnormal in the very late stages of deterioration when the heart fails to adapt and insufficient blood is ejected to meet organ requirements [31].

– The main Doppler indices used to evaluate diastolic function are the early diastolic filling/atrial contraction) E/A ratios and precordial vein pulsatility indices [1, 18, 31]. Doppler allows evaluation of the blood flow filling the ventricle, which typically has a biphasic pattern reflecting E and A. Calculation of the E/A ratio essentially reflects ventricular relaxation [19] but this parameter is of little use in fetal life as it is strongly affected by respiratory and corporal movements, and a high fetal heart rate usually leads to temporarily fused E/A waves [2, 3]. Another important limitation of this ratio is that impaired relaxation can be reflected by an increased, decreased, or pseudo normal value, hampering interpretation [19]. Diastolic function can also be indirectly evaluated with Doppler assessment of the precordial veins, which reflect pressure changes in the right atrium and indirectly provide information on diastolic function of the right heart [2, 3]. The DV is the most commonly used vessel in fetal medicine as it is known to reflect impaired relaxation and has been used in clinical practice as an early marker of disease [32, 33].

– Doppler is usually used to assess blood flow but can also be used to calculate time periods [31]. Of great interest are isovolumetric contraction and relaxation times, defined as the time elapsed from the start of contraction/relaxation and the closure/opening of the outflow valve, respectively. These periods, particularly the isovolumetric relaxation time (IRT), become abnormal in the very early stages of dysfunction, reflect-
An increase in the time required to properly relax the myocardium. Time events can be displayed individually or as a composite parameter, such as the myocardial performance index (MPI), which takes several systolic and diastolic time events into account [34, 35]. The MPI is considered a marker of global cardiac function and it has been shown to be a highly sensitive parameter of dysfunction [36, 37].

**M-Mode**

M-mode techniques are traditionally used in a transverse cardiac view to measure the difference in end-systolic and end-diastolic ventricular diameter and to calculate ejection fraction by applying the Teicholz formula [30, 38]. Ejection fraction is defined as the percentage of blood ejected in each heart cycle [38]. Although ejection fraction is the essential parameter characterizing heart failure in adulthood [19], it is usually altered only in the late stages of deterioration as it mainly reflects radial function [30, 39].

M-mode can be also applied in the long axis of the heart to evaluate tricuspid and mitral annular displacement, which have been proposed as sensitive markers of cardiac dysfunction as they reflect global longitudinal function [11, 40].

### Table 1. Most commonly used systolic and diastolic parameters to assess fetal cardiac function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Techniques</th>
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<td><strong>Systolic function</strong></td>
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<tr>
<td>Blood volume estimation</td>
<td></td>
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<tr>
<td>Ejection fraction</td>
<td>Fraction of blood ejected from the ventricle with each heart beat</td>
<td>2D, M-mode, 2D speckle tracking</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>Volume of blood being pumped by the ventricle per minute</td>
<td>2D, conventional Doppler, STIC</td>
</tr>
<tr>
<td><strong>Myocardial motion</strong></td>
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<tr>
<td>Annular displacement</td>
<td>Distance of the movement of the atrioventricular valve annulus</td>
<td>M-mode or 2D speckle tracking</td>
</tr>
<tr>
<td>Systolic annular peak velocity</td>
<td>Speed of movement of the atrioventricular valve annulus in systole (S’)</td>
<td>Spectral or color TDI</td>
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<tr>
<td><strong>Myocardial deformation</strong></td>
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<td></td>
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<tr>
<td>Strain</td>
<td>Amount of deformation (change in length of a myocardial segment from its original length)</td>
<td>Color TDI or 2D speckle tracking imaging</td>
</tr>
<tr>
<td>Strain rate</td>
<td>Speed of deformation (change of strain over time)</td>
<td>Color TDI or 2D speckle tracking imaging</td>
</tr>
<tr>
<td><strong>Diastolic function</strong></td>
<td></td>
<td></td>
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<tr>
<td>Precordial vein blood flow patterns (DV and others)</td>
<td>Pattern of blood in precordial veins during atrial contraction that indirectly reflects cardiac compliance</td>
<td>Conventional Doppler</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>Ratio between early (E) and late (A) ventricular filling velocity</td>
<td>Conventional Doppler</td>
</tr>
<tr>
<td>Diastolic annular peak velocities</td>
<td>Speed of movement of the atrioventricular valve annulus in early (E’) and late (A’) diastole</td>
<td>Spectral or color TDI</td>
</tr>
<tr>
<td>E/E’ ratio</td>
<td>Transmitral-to-mitral annular diastolic velocity ratio</td>
<td>Conventional Doppler and spectral TDI</td>
</tr>
<tr>
<td>IRT</td>
<td>Time between closure of the aortic valve and opening of the mitral valve</td>
<td>Conventional Doppler or spectral/color TDI</td>
</tr>
<tr>
<td><strong>Global cardiac function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPI</td>
<td>Ratio between isovolumetric times (contraction plus relaxation) and ejection time</td>
<td>Conventional Doppler or spectral/color TDI</td>
</tr>
</tbody>
</table>

STIC = Spatiotemporal image correlation; TDI = tissue Doppler imaging; IRT = isovolumetric relaxation time; MPI = myocardial performance index.
Tissue Doppler Imaging

While conventional echocardiographic techniques are based on blood flow, TDI uses frequency shifts in ultrasound waves to calculate myocardial velocity, which is characterized by a lower velocity and a higher amplitude [17, 41]. TDI can be applied online to evaluate annular or myocardial velocities. Offline TDI analysis also allows deformation parameters (strain and strain rate) to be assessed:

- Peak velocities evaluated at the mitral or tricuspid annulus reflect global systolic (S’) or diastolic (E’ and A’) myocardial motion and have been demonstrated to be an early and sensitive marker of cardiac dysfunction [42, 43].
- Peak systolic strain and strain rate assessed at each myocardial segment provide information on myocardial deformation and interaction with neighboring segments [17]. These parameters are also early markers of cardiac dysfunction [42].

Although TDI may provide valuable information on global and regional myocardial motion and deformation, this technique should be used with caution in the fetal heart as it has several major limitations, as described below [28].

2D Speckle Tracking

Recent reports have described the use of non-Doppler technology. 2D speckle tracking techniques allow myocardial deformation to be quantified by using frame-by-frame tracking of bright myocardial areas (speckles) [10]. 2D speckle tracking requires post-processing and off-line analysis of 2D images and allows myocardial strain and strain rate to be measured. Despite its potential advantages, this is a recent technique that still requires validation for use in the fetal heart [29, 44].

4D Spatiotemporal Image Correlation

4D STIC permits 3D reconstruction of the fetal heart over time. This technique is based on a sweep (volume data set) of the fetal heart containing a complete reconstructed cardiac cycle. From this saved volume, any target region of interest can be obtained at any stage of the cardiac cycle [3, 30]. 4D STIC has been proposed to measure ventricular volumes that allow more accurate estimation of the cardiac output and ejection fraction. The off-line analysis also allows mitral/tricuspid annulus displacement to be assessed. 4D STIC is a promising technique that requires further studies to improve its applicability in fetal cardiac function assessment [3, 30].

The most suitable parameters for assessing fetal cardiac function will mainly be determined by the cause of the dysfunction. Abnormal values of ejection fraction or cardiac output are usually found in the late stages of deterioration, and therefore more sensitive parameters have been proposed for earlier diagnosis and monitoring of fetal cardiac dysfunction. In most cases of cardiac dysfunction, diastolic parameters (such as DV or IRT) are the first to be altered, reflecting impaired relaxation and compliance due to a stiffer or less effective heart. Similarly, parameters reflecting longitudinal function (such as annular displacement or velocities) are typically affected in the early stages as compared to radial function (such as ejection fraction).

Technical Considerations when Measuring Cardiac Function in the Fetus

Fetal heart evaluation is challenging due to the smallness of the fetal heart, the high heart rate, and limited access to the fetus far from the transducer. Fetal echocardiography requires specific training and expertise to ac-
quire images and interpret the results. Several limitations should be taken into account when assessing fetal cardiac function (table 3). These limitations are particularly important in techniques requiring offline analysis (4D STIC, color TDI, and 2D speckle tracking).

**Fetal Position, Movement, and Size**

Several intrinsic particularities of the fetus such as its position, movements, and small size require expertise to acquire adequate images and may sometimes hamper complete evaluation. The fetus lies far down in the maternal abdomen and thus maternal adiposity, oligoamnios, or an anterior placenta may interfere with image quality. Fetal position changes constantly, requiring different angles to view the fetal heart. Optimal viewing can be impossible if the fetal spine is persistently in an anterior position, while evaluation of longitudinal or radial motion requires an apical/basal or transverse view, respectively. Both conventional and tissue Doppler are critically affected by the angle of acquisition, which should be as close to 0 as possible [17, 38]. Other techniques such as 4D STIC or M-mode are less angle dependent but a good angle is still required to obtain reliable results. Fetal corporal and respiratory movements may also interfere with the quality of acquisition. Additionally, the fetal heart is much smaller than the adult heart and varies with gestational age. Therefore, normality ranges throughout pregnancy are always required to calculate z-scores and standardize measurements. Some fetal conditions may affect heart size (e.g. leading to cardiomegaly) and therefore reference values adjusted by heart size or specific fetal biometries may be necessary to correctly adjust parameters that strongly depend on myocardial size (such as annular displacement or myocardial velocities) [45]. The smallness of the fetal heart also reduces the accuracy of estimates of cardiac or vessel dimensions. This consideration is particularly important in parameters estimated on the basis of formulas that include several measurements (e.g. cardiac output), which show a relatively wide variability as the error induced by one inaccurate dimen-

<table>
<thead>
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<th>Fetal condition</th>
<th>Mechanism</th>
<th>Clinical applicability</th>
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<tr>
<td>Congenital heart disease</td>
<td>Intrinsic myocardial disease together with volume and pressure overload</td>
<td>First-trimester DV to predict structural heart disease</td>
<td>First-trimester tricuspid regurgitation to predict structural heart disease</td>
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<td></td>
<td></td>
<td>Cardiovascular criteria (mitral inflow and qualitative ventricular contractility)</td>
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<td></td>
<td></td>
<td>[56] for valvuloplasty in aortic stenosis</td>
<td>[52] Annular peak velocities to predict long-term cardiovascular outcome in aortic stenosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systolic and diastolic function for the differential diagnosis of cardiomyopathies [58, 59]</td>
<td>[57] Strain to predict outcome [29, 55]</td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td>Hypertrophic cardiomyopathy due to hyperglycemia</td>
<td></td>
<td>Cardiac morphometry and function to predict long-term cardiovascular outcomes</td>
</tr>
<tr>
<td>Placental insufficiency</td>
<td>Chronic hypoxia together with volume and pressure overload</td>
<td>DV to monitor and predict short-term outcomes in early FGR</td>
<td>MPI to predict perinatal mortality in early FGR</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>MPI and annular peak velocities measured by TDI to diagnose and monitor late FGR</td>
</tr>
<tr>
<td>TTTS</td>
<td>Hypertrophic cardiomyopathy in the recipient due to volume and pressure overload</td>
<td>DV atrial flow in the recipient for staging TTTS (Quintero staging)</td>
<td>CHOP score to characterize cardiovascular dysfunction in the recipient</td>
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<tr>
<td>Congenital diaphragmatic hernia</td>
<td>Left heart underdevelopment secondary to cardiac compression</td>
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<td>MPI to predict short- and long-term outcomes</td>
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<td>Trisomy 21</td>
<td>Intrinsic myocardial abnormality</td>
<td>First-trimester DV to predict structural heart disease</td>
<td>First-trimester DV, tricuspid regurgitation, MPI, and shortening fraction to predict structural heart disease</td>
</tr>
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</table>

DV = Ductus venosus; STIC = spatiotemporal image correlation; MPI = myocardial performance index; FGR = fetal growth restriction; TTTS = twin-to-twin transfusion syndrome; TDI = tissue Doppler imaging.
sion is multiplied in the final calculation [31]. Furthermore, heart size strongly limits any attempt to differentially evaluate the endocardial and epicardial layers within the myocardium, which is too thin to be assessed separately. All of these limitations warrant specific training and a critical mentality to properly acquire and interpret functional fetal echocardiography [1].

**Fetal Heart Rate and Frame Rate Requirements**

Proper acquisition, processing, and interpretation are even more critical in techniques requiring offline analysis, such as TDI or 2D speckle tracking [28, 29]. Software tools for offline analysis of deformation were initially designed for the adult heart with a low heart rate, fixed position, and electrocardiographic (ECG) co-registration [28, 29, 46]. Therefore, the intrinsic characteristics of the fetal heart may hamper correct performance of the algorithms and therefore limit their reliability. Because of the restricted access to the fetal heart far down in the maternal abdomen, fetal ECG co-registration is impossible. ECG co-registration is critical to identify time events and, for example, to be able to assess post-systolic events [46]. ECG co-registration is also mandatory for the correct functioning of offline cardiac software tools. Recent reports have proposed the use of dummy ECG by manual indication of time events based on the underlying M-mode [13] or 2D images [14] in order to improve offline analysis of both TDI and 2D speckle tracking. Additionally, while the required frame rate for proper offline analysis is reasonably well defined in the adult heart [17], a higher frame rate would probably be necessary for the fetal heart (as the heart rate is about 2–3 times faster in fetuses than in adults) but optimal values remain to be defined. Poor quality acquisitions with a low frame rate or lack of ECG co-registration may lead to incorrect results. A clear example of inconsistent data is the disagreement in reports on longitudinal strain changes throughout gestation, which were described as increasing in the first studies performed with low frame rate acquisitions but were shown to decrease by recent studies using more appropriate methodology [12, 13, 47]. Although recent reports using acquisitions at a high frame rate and dummy ECG have improved the feasibility of these techniques [12–14], several limitations such as the variable view of the fetal heart and the smallness of the heart (with potentially insufficient myocardium to allow analysis in early gestational ages) remain to be overcome.

**Differences between Fetal and Postnatal Life**

Most echocardiographic techniques are derived from parameters previously developed and validated in the adult heart. However, unlike in the adult heart, changes in fetal cardiomyocyte maturation (myocardium stiffness and intrinsic contractility) and loading occur during gestation and within the myocardium [26, 27]. Additionally, the fetal circulation pattern differs from that in the adult, with a predominant right heart and both circulations being connected [21]. This pattern may also change during pregnancy, which may hamper the understanding of cardiac adaptation due to different insults (volume or pressure overload, hypoxia, cardiac compression, etc.) in utero. Therefore, all of these changes should be taken into account when interpreting the results of fetal echocardiography.

**Lack of Validation of Techniques in the Fetal Heart**

Because invasive study of the fetal circulation is not feasible, most of the techniques used in fetal functional echocardiography have not been validated, limiting their interpretation. Additionally, there are discrepancies in the literature on many cardiac function parameters regarding methodology, normal values, and interpretation. For example, measurement of MPI using either blood flow or valve clicks as landmarks leads to different normality values [48]. Another example is the Teichholz formula for ejection fraction, which assumes a normal adult heart geometry, which the fetal heart cannot meet [38]. Moreover, the E/E’ ratio has been demonstrated to correlate with intracavitary pressure at end-diastole [49], but its significance in fetal life is unknown. Therefore, the results of fetal echocardiography should be critically evaluated, taking into account gestational age and the methodology used. Finally, TDI and 2D speckle tracking techniques have been validated for deformation analysis in the adult heart by experimental settings including sono-micrometry [17]. However, no validation studies using invasive procedures can be performed to ascertain the real strain and strain rate values in the fetal heart during the maturation process. Despite these limitations, recent reports have demonstrated that deformation can be assessed in a reproducible manner when the appropriate methodology is employed [12–14]. However, many studies do not properly describe the methodology used or acknowledge potential limitations. Critical reading of all studies on fetal cardiac function, particularly of those using new technologies, is mandatory before accepting their results and conclusions.

As described above, fetal cardiac function assessment may have major limitations and therefore any technique or parameter proposed for its assessment should follow several steps for validation before being incorporated into...
clinical practice. The first phase is to demonstrate feasibility and reproducibility in well-designed and conducted studies. Use of the proposed parameter following strict methodological criteria is also critical to ensure proper applicability. Then, the behavior of the parameter in normal fetal conditions (physiology), as well as in each clinical disease (pathophysiology), must be described before the technique or parameter can applied in clinical conditions.

Research and Clinical Applications of Fetal Cardiac Function Assessment

Congenital Heart Disease

First-Trimester Screening of Congenital Heart Disease

Cardiac function assessment in the first trimester may help in the early detection of congenital heart disease. DV flow [2, 50] and tricuspid regurgitation [51] are associated with an increased prevalence of cardiac defects. Fetal nuchal translucency above the 95th percentile, DV atrial reversed flow, or tricuspid regurgitation are present in 35, 28, and 33% of fetuses with cardiac defects, respectively, and in 5, 2, and 1% of those without cardiac defects [51]. A combination of these three markers may permit detection of about 50% of cardiac defects, with a false-positive rate of 8% [51].

Fetal Cardiac Function in Congenital Heart Disease

Evaluation of cardiac function in fetuses with congenital heart disease has been proposed to better understand the pathophysiology of these diseases, predict the perinatal outcome, and guide and monitor any in utero therapy. Huhta [4] proposed a cardiovascular score, including the presence of hydrops, cardiomegaly, abnormal myocardial function (measured as a monophasic inflow pattern, tricuspid/mitral regurgitation, or reduced shortening fraction), abnormal ductus venosus or umbilical artery or vein Doppler. This score showed a high sensitivity and specificity in identifying fetuses with cardiac defects at high risk of perinatal mortality [52]. These data paved the way for future studies incorporating newer techniques for the evaluation of cardiac function. However, various types of congenital heart disease show specific differences in volume and/or pressure load, as well as distinct degrees of cardiac remodeling and adaptation. Preliminary studies have evaluated the potential contribution of TDI and 2D speckle tracking techniques in congenital heart disease of various types [53–55]. Peak annular velocities, ventricular strain, and the left/right ventricular strain ratio have been proposed as prognostic markers in these entities [53–55]. Fetuses with left heart obstruction (hypoplastic left heart syndrome and critical stenosis of the aorta) show reduced left ventricular strain and left/right ventricular strain ratio values, while right ventricular values are maintained within the normal range [53–55]. In contrast, right heart defects such as Ebstein’s anomaly lead to reduced longitudinal right ventricular strain with increased left/right ventricular strain ratio values [55]. Additionally, deformation parameters within normal ranges with a similar left/right ventricular strain ratio have been reported in other anomalies such as tetralogy of Fallot, double outlet right ventricle and atrial/ventricular septal defects [54, 55]. The above mentioned findings suggest that specific cardiovascular profile scores adjusted for the type of cardiac defect might provide clinically useful information. Confirmation of this hypothesis requires further research with large samples.

In utero Cardiac Intervention

Fetal aortic balloon valvuloplasty improves the perinatal and postnatal outcome of critical aortic stenosis [56]. Monophasic mitral inflow and qualitative left ventricular dysfunction are included in the selection criteria to predict progression to hypoplastic left heart syndrome and eligibility for prenatal intervention [56]. Additionally, left ventricle diastolic dysfunction including TDI peak velocity assessment has been suggested as a prognostic marker of poor long-term outcome in these cases [57].

Differential Diagnosis of Cardiomyopathies

Assessment of fetal cardiac function has been proposed as a diagnostic and prognostic tool in fetal cardiomyopathies [58, 59]. Hypertrophic cardiomyopathy is characterized by increased ventricular wall thickness that leads to impaired relaxation together with systolic dysfunction (demonstrated by a decreased shortening fraction), present in almost half of all cases. In addition, most fetuses with dilated cardiomyopathy will have systolic dysfunction with or without chamber enlargement but without increased wall thickness. The presence of diastolic dysfunction is similar in both types of disease (about 60% of cases) including abnormal venous flows (umbilical vein pulsations and biphasic inferior vena cava flow), a decreased E/A ratio, and an increased IRT. Although the presence of systolic dysfunction and significant atrioventricular valve regurgitation are risk factors for mortality, diastolic dysfunction (particularly abnor-
Fetal growth restriction (FGR), caused by placental insufficiency, affects up to 10% of all pregnancies and is a major cause of perinatal mortality and severe morbidity [42]. Early- and late-onset FGR are increasingly being recognized as distinct forms of the disease in view of their differences in incidence, pathophysiology, and natural history [43]. The heart is a central organ in fetal adaptive mechanisms to placental insufficiency, and cardiac dysfunction is recognized as being among the central pathophysiologic features of both early- and late-onset FGR [44–47].

Late-Onset FGR
Small fetuses near term have long been considered to be constitutionally small with a good prognosis [85]. However, recent evidence suggests that a proportion of these fetuses represent true forms of late FGR with a mild degree of placental insufficiency (not reflected by umbilical artery Doppler) and poorer perinatal [86] and long-term results, including suboptimal neurodevelopment [87, 88] and a higher postnatal cardiovascular risk [9, 89, 90], compared with normal weight newborns. Al-
though few studies have evaluated cardiac function in late FGR fetuses, recent data suggest that these fetuses might also show features of cardiac dysfunction [91–93]. Increased cord blood levels of troponins have been demonstrated in a small proportion of later small-for-gestational-age newborns [91]. Additionally, more than 30% of late-onset small-for-gestational-age fetuses even with normal umbilical artery Doppler show increased values of MPI [92, 93] and decreased annular peak velocities [92]. Therefore, sensitive cardiovascular parameters may be useful to identify the subgroup of small fetuses at higher perinatal and long-term risk.

FGR and Postnatal Cardiovascular Risk

Postnatal persistence of cardiovascular remodeling has recently been demonstrated in a cohort of 5-year-old children who suffered early or late FGR [89]. FGR children show changes in cardiac shape (more globular morphology), subclinical cardiac dysfunction (increased heart rate and reduced stroke volume and myocardial peak velocities), and vascular remodeling (increased blood pressure and carotid intima media thickness). Both cardiac and vascular changes are present in early and late FGR, with a tendency toward worse results in early-onset cases. These data are in line with previous historic cohort studies [9] and animal models [90] demonstrating a strong association between small size at birth and increased adult cardiovascular mortality. These findings suggest that FGR induces primary cardiac changes, which could explain the increased predisposition to cardiovascular disease in adult life. An interesting hypothesis is that fetal cardiac function assessment might help to identify FGR cases at high cardiovascular risk later in life, therefore allowing timely preventive interventions.

Twin-to-Twin Transfusion Syndrome

TTTS complicates 10–15% of monochorionic twin pregnancies and is characterized by unbalanced chronic blood transfer from one twin, defined as the donor twin, to the other, defined as the recipient, through placental anastomoses [94]. Significant hemodynamic changes are commonly observed in both fetuses in TTTS including hypervolemia in the recipient and hypovolemia in the donor, resulting in chronic activation of the renin-angiotensin system and release of vasoactive factors, which leads to pressure overload in both fetuses [95].

Prenatal Cardiac Function in TTTS

Significant changes in fetal cardiac function despite a normal heart structure have also been reported. Most changes are described in the recipient, in which volume and pressure overload lead to cardiomegaly and hypertrophy, usually with impaired relaxation but preserved systolic function [96]. Volume overload is reflected by increased umbilical blood flow [97, 98] and ductus venous pulsatility [37, 95, 96], tricuspid and mitral insufficiency, cardiomegaly [95, 96, 99, 100], and increased levels of ANP and BNP [37, 101]. Pressure overload leads to cardiac hypertrophy in more than half of recipients [95, 96, 100, 102], usually with an increase in ejection fraction [96, 99]. This cardiac hypertrophy explains the impaired relaxation and increased ventricular filling pressures that lead to reduced E/A ratios or a monophasic Doppler inflow profile [37, 96, 103] together with increased E/E’ ratios [102] and MPI (mainly due to an increased IRT) [37, 96, 103, 104]. Ten to twenty percent of recipients also show some degree of right tract obstruction (pulmonary stenosis, dysplasia, insufficiency, or atresia) [37, 96]. Most studies report preserved systolic function until the end stages when ejection fraction can decrease in recipients. However, a recent study reported a reduced right ventricular systolic strain and strain rate in recipients [37], which supports the concept of subclinical systolic dysfunction from the early stages of TTTS. In contrast, most studies report no significant changes in the donor’s cardiac function [96, 102] apart from arterial and venous (umbilical artery and vein and DV) Doppler changes, reflecting hypovolemic status [37].

The Children’s Hospital of Philadelphia (CHOP) score has been proposed to assess severity in TTTS [5]. This score incorporates the donor’s umbilical artery evaluation and assessment of cardiac hypertrophy, dilation, impaired systolic or diastolic function, ativoventricular valve regurgitation, pulmonary valve structural or Doppler abnormalities, and venous Doppler abnormalities in the recipient. A composite score of 0–20 is generated, with 0 representing the best possible score and 20 indicating severe TTTS. However, this score has not been shown to be of clinical use as a diagnostic or prognostic marker in TTTS [96].

Several studies have evaluated the correlation between cardiac function and TTTS severity, demonstrating that cardiomegaly, systolic dysfunction, and right outflow tract obstruction are more prevalent in advanced Quintero stages [98, 102]. However, cardiac changes may be present even in early Quintero stages as 20–60% of recipients in stages I–II may have cardiac hypertrophy, tricuspid regurgitation, or increased MPI or BNP or troponin T blood levels [44, 96, 102, 104]. Some authors have proposed cardiovascular scores to stratify the severity of
TTTS [5], but cardiovascular function (parameter or score) has not been shown to be of clinical use as a diagnostic or prognostic marker in TTTS [96].

Treatment based on coagulation of placental anastomosis by fetoscopy improves cardiac function in recipients as measured by a decrease in DV-PI [37, 97], MPI, and the presence of tricuspid regurgitation and EA fusion [37, 96]. In contrast, donors may show transient signs of relative hypervolemia reflected by an increase in umbilical vein flow, DV-PI [37, 97], tricuspid regurgitation [37], and even hydrops [97] that usually regresses within 4 weeks [37].

Postnatal Cardiac Function in TTTS

Most studies report normal postnatal cardiac evaluation in TTTS pregnancies treated by fetoscopy [105], with the exception of some recipients with pulmonary stenosis requiring postnatal valvuloplasty [95, 106, 107]. However, a recent study evaluating TTTS survivors at school age has demonstrated reduced diastolic function in recipients and abnormal cardiac dimensions in some donors [108]. Persistent pulmonary hypertension after birth has also been described in some recipient twins [109]. Moreover, recipient twins show increased blood pressure levels already in the neonatal period [110, 111], while donors have lowered arterial distensibility [112, 113], which might be a response to the chronic activation of the renin-angiotensin system. Therefore, further studies to assess the cardiovascular outcome of twin survivors are warranted.

Congenital Diaphragmatic Hernia

Left heart underdevelopment [8, 114, 115] is commonly observed in fetuses with congenital diaphragmatic hernia. This finding has been attributed to compression of the left atrium by herniated abdominal organs (mainly the liver), redistribution of fetal cardiac output, and/or low pulmonary venous return. Although left ventricular volumes are about one third smaller than in normal fetuses, cardiac shifting or dimensions do not predict postnatal outcome in fetuses with isolated left-sided congenital diaphragmatic hernia [116]. This finding is supported by the observation that cardiac dimensions are not related to significant changes in cardiac function (as measured by ejection fraction or MPI) [8] and by the fact that the growth of the heart generally catches up after surgical correction in the neonatal period and that cardiac size is normal in long-term survivors of isolated congenital diaphragmatic hernia [117].

However, recent data in children has shown that MPI, systolic/diastolic time, and plasma levels of BNP are able to predict neonatal mortality and the need for extracorporeal membrane oxygenation [118–120]. Additionally, tracheal occlusion improves MPI by shortening the isovolumic contraction time interval [8]. Therefore, future studies are warranted to evaluate the potential value of cardiac function parameters to monitor and predict outcome in these fetuses.

Miscellanea

Several other fetal anomalies have been reported to be associated with cardiac dysfunction and are commonly due to heart compression, volume overload, or a direct insult to the myocardium.

Large intrathoracic masses such as a congenital cystic adenomatoid malformation with mediastinal deviation have been described as compressing the heart and affecting cardiac volume loading, sometimes leading to heart failure and hydrops [121, 122]. Signs of diastolic dysfunction (increased E/A ratio and right MPI) and poor filling secondary to cardiac compression and a tamponade effect (cardiomegaly, reduced cardiac output, preserved ejection fraction, and increased reversal atrial contraction in the inferior vena cava) usually appear before hydrops is observed [121, 122].

Similarly, sacrococcygeal teratoma or arteriovenous malformations, characterized by high blood flow through the tumor (volume overload), can also lead to heart failure [123, 124]. The inferior vena cava and the cardiac ventricles dilate due to increased venous return from the tumor, even though these fetuses typically maintain a normal shortening fraction as intrinsic contractility is not affected until the final stages. Similarly, a dilated superior vena cava and cardiomegaly develop in deteriorating fetuses with large cerebral arteriovenous malformations such as an aneurism of the vein of Galen. In both conditions, neonatal outcomes are poorer in fetuses that develop hydrops prior to delivery, and recognition of more subtle signs of cardiac failure may prompt antenatal intervention or delivery [123, 124].

Absence of the DV with extrahepatic shunt that directly connects umbilical vein flow with the heart causes volume overload that may lead to cardiomegaly, tricuspid regurgitation, heart failure, and hydrops in half of these cases [125, 126].

Lower urinary tract obstruction with massive bladder distension may cause vascular compression, leading to an increased cardiothoracic ratio, small pericardial effusion, ventricular hypertrophy, and diastolic dysfunction (altered E/A ratio and increased DV-PI) [127].

Fetal anemia leads to hyperdynamia, relative volume overload, and hypoxia, which may cause cardiomegaly,
heart failure, and hydrops. Surviving children who received intrauterine transfusions show a reduction in left ventricular mass and atrial area with preserved ventricular function in childhood [128].

Acute parvovirus B19 infection in pregnancy may lead to severe anemia caused by the destruction of red blood cell precursors but may also be a result of hypoalbuminemia, hepatitis, myocarditis, and placentitis, which can culminate in cardiac failure and subsequent hydrops fetalis or fetal death [129]. Cardiac failure may be a result of severe anemia but may also be associated with myocarditis, which can cause arrhythmias or even cardiac arrest without evidence of anemia, cardiac failure, or hydrops [129, 130].

Preterm rupture of membranes, particularly in cases with intra-amniotic infection, is associated with changes in fetal cardiac function consistent with increased left ventricular compliance and systolic dysfunction measured as an increased E/A ratio [131, 132], shorter ejection time [133], and ventricular strain [132].

Cardiac function assessment in the first trimester may help in the early detection of trisomy 21, as the presence of tricuspid regurgitation, atrial reversed flow in the DV, increased right E/A ratio and MPI, and shortening fraction and stroke volume are associated with Down syndrome even in the absence of structural heart defects [134]. Signs of cardiac dysfunction persist in the second and third trimester in cases of trisomy 21 [135].

**Fetal Programming of Cardiovascular Diseases**

It is well-known that cardiovascular diseases in adulthood undergo a long subclinical phase over decades, which may already start in childhood [136]. Aside from well-described lifestyle factors and a genetic predisposition, it is widely accepted that in a proportion of cases cardiovascular disease has its origins in prenatal life [9]. Any insult during in utero cardiac development may lead not only to cardiac dysfunction during fetal life but also to epigenetic changes that may persist postnatally leading to permanent cardiac remodeling [9]. Fetal programming of adult cardiovascular diseases occurs when a stimulus or an insult in the in utero environment during a sensitive period of cardiovascular development permanently alters cardiovascular structure and function. This concept was first described a quarter of a century ago by Barker et al. [9] who crystallized the concept of fetal programming and early origin of adult disease by suggesting that stress in utero, as manifested by a low birth weight and increases in the risk of cardiovascular disease and stroke in specific areas of England and Wales. A number of studies support that it might be explained in part by fetal metabolic programming leading to diseases associated with cardiovascular disease, such as obesity, diabetes mellitus, and hypertension [137]. However, several studies have also demonstrated that FGR conditions cardiac dysfunction in utero [6, 81] that persists postnatally [89], supporting the hypothesis of a primary cardiovascular programming. Apart from FGR, other fetal conditions such as maternal diabetes [69, 70], TTTS [113], or in vitro fecundation [138] have also been proposed as prenatal conditionings for fetal cardiovascular programming.

The importance of early identification and intervention in pediatric risk factors for cardiovascular disease is now well recognized [139]; however, FGR or other fetal conditions are not usually listed among the conditions presumed to increase cardiovascular risk in current consensus guidelines [139]. Physicians should routinely incorporate pregnancy information into the individual medical history. Prenatal identification of high-risk population permits proper monitoring and early intervention that could improve the cardiovascular health of thousands of children yearly.

**Conclusions**

Fetal cardiac function may be affected by a number of congenital or environmental anomalies [4–8]. Although research efforts have recently recognized the potential value of monitoring cardiac function for clinical management, most parameters are still in the research phase. The exception is DV, which is already being used in clinical practice for staging TTTS [94] or monitoring early FGR [32]. Another example is the integration of some cardiac function parameters (mitral inflow and myocardial contractility) into the inclusion criteria for fetal valvuloplasty in critical aortic stenosis [56, 57]. Additionally, some cardiac parameters have already shown a strong correlation with outcome and may soon be incorporated into clinical practice. For example, cardiac function assessment has proven utility in the differential diagnosis of cardiomyopathies [58, 59] or prediction of perinatal mortality in congenital heart disease [52]. Similarly, first-trimester DV and tricuspid regurgitation assessment has an additional predictive value for Down syndrome and congenital heart disease [51]. In addition, some cardiac parameters with high sensitivity such as MPI or annular peak velocities have shown promising results in monitoring and predicting outcomes in FGR [79, 84] or congenital diaphragmatic hernia [8]. Other promising parame-
ters that have recently been proposed remain to be validated in fetal heart assessment. Conversely, cardiac function assessment does not have demonstrated utility in the staging or prognosis of TTTS [96].

Complete assessment and integration of the distinct components of systolic and diastolic function are crucial as no single simple test can fully evaluate fetal cardiac function. Several groups have suggested scoring systems [4, 5], which combine methods of assessment to provide a more global overview of cardiac function and which could be used as a prognostic marker or to define heart failure. Huhta [4] described a cardiovascular profile score that has been demonstrated to be useful in predicting the outcome of fetuses with hydrops [4] and congenital heart diseases [51]. Conversely, the CHOP score has not been shown to be clinically useful as a diagnostic or prognostic marker in TTTS [5, 96].

These scoring systems aim to standardize the current practice of multimodal assessment, which is partly based on subjective parameters such as grading ventricular dysfunction. Although scoring may be superior to single measurements in defining compromised cardiocirculatory function, there are still many limitations for the incorporation of the proposed scores in clinical practice. Scores need to be validated not only to predict perinatal mortality but also to predict morbidity and long-term outcomes. Many definitions of abnormal cardiac function need to be standardized. Cardiac function can be affected by various fetal abnormalities through volume or pressure overload, hypoxia, hyperglycemia, heart compression, direct myocardial damage, etc. Although disease-specific cardiovascular profile scores would most probably improve the predictive value for adverse outcome, constructing such a profile would be highly complex. Finally, the already proposed scores include traditional cardiac parameters, while new parameters such as MPI [36], annular peak velocities [43], or ventricular strain [44] have been demonstrated to be more sensitive in certain specific conditions. Therefore, studies to further evaluate the potential utility of recently proposed techniques and to define the best combination of parameters are warranted. New cardiovascular parameters should be incorporated with caution, taking into account all of the potential limitations of fetal echocardiography.

Despite these limitations, cardiac function can be adequately evaluated in most fetuses when appropriate expertise, equipment, and time are available. Many cardiac function parameters are sufficiently sensitive for selecting high-risk populations and predicting outcomes. Fetal cardiac function assessment is a promising tool that may soon be incorporated into clinical practice to diagnose, monitor, or predict outcomes in some fetal conditions. Thus, more research is warranted to further define specific protocols for each fetal condition that may affect cardiac function.

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References


55 Germanakis I, Matsi H, Gardiner HM: Myocardial strain abnormalities in fetal congenital heart disease assessed by speckle tracking echocardiography. Fetal Diagn Ther, in press.
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