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Research paper

Myocardial function of hydropic fetuses at the time of diagnosis

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Abstract

Introduction: Fetuses with heart failure are at risk of developing hydrops fetalis due to ventricular dysfunction. Therefore, we aim to assess myocardial function in hydropic fetuses at the time of diagnosis. **Material and methods:** Fetal echocardiography was performed using a Toshiba Aplio XG ultrasound system. The mitral annular plane systolic excursion (MAPSE) and the tricuspid annular plane systolic excursion (TAPSE) as well as isovolumetric contraction time (ICT´), ejection time (ET´), and isovolumetric relaxation time (IRT´) for the left and right ventricle were measured using pulsed wave tissue Doppler imaging (pw TDI). The myocardial performance index (MPI´) was calculated. E´- and A´-wave peak velocities were assessed for both ventricles and the E´/A´ ratio was calculated. Results were compared to gestational age-matched healthy controls without Doppler alterations or anatomic malformations by using the unpaired Student's *t*-test. **Results:** 30 hydropic fetuses were included. Mean gestational age (GA) was 25 (18–33) weeks. Left ventricular MPI´ was 0.66 (0.32–1.46, SD = 0.28) and significantly higher in hydropic fetuses ($p < 0.05$) than in healthy controls (MPI´ controls 0.58 [0.42–0.79, SD = 0.11]). Fetuses with altered Doppler parameters (UA, DV) showed no significant changes in their myocardial function compared to hydropic fetuses with physiological Doppler flow patterns. **Conclusion:** In fetuses with hydrops and normal Doppler parameters, analysis of myocardial function by pw TDI may help to detect pre-clinical alterations days before manifest changes in fetal circulation. This may lead to adjusted fetal surveillance and optimised pre- and perinatal management.

Key words: fetal echocardiography, hydrops fetalis, ventricular dysfunction, pulsed Doppler echocardiography.

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Introduction

Hydrops fetalis is defined as an abnormal fluid collection in at least two fetal soft tissues and serous cavities (e. g. skin oedema and/or abdominal ascites, pleural and/or pericardial effusion). In general, hydrops can be differentiated into two subgroups: immune hydrops fetalis, which is caused by red cell alloimmunisation (e.g. Rh(D), Kell); and nonimmune hydrops fetalis (NIHF). NIHF accounts for approximately 90% of all hydrops cases [1]. There are a vast spectrum of possible aetiologies of NIHF, and therefore a detailed anomaly scan including fetal echocardiography and assessment of the cardiovascular function of the fetus is mandatory for management and proper counselling of the parents. Responsible for the development of NIHF is an imbalance of fluid homeostasis between the vascular and interstitial compartment caused by various fetal disorders. In fetuses with heart failure ventricular dysfunction leads to an elevation of ventricular end-diastolic pressure, atrial pressure, and finally central venous pressure. Together with a more permeable capillary membrane, a low oncotic intravascular pressure, and consecutively lower lymphatic drainage of tissue, these fetuses are at risk of development of hydrops fetalis [2, 3]. Thoracic anomalies like echogenic lung lesions or hydrothorax may lead to mediastinal shift followed by distortion of the inferior vena cava and ductus venosus as they enter the right atrium. This leads to altered filling patterns of the heart, elevated venous pressure, and low cardiac output.

Fetal surveillance is usually performed by Doppler assessment of the fetal circulation. In particular, alterations of venous flow patterns indicating increasing atrial pressure (e.g. increased ductus venosus pulsatility and umbilical venous pulsations) correlate with adverse outcomes of affected fetuses [4]. Unfortunately, these alterations represent end-stage heart failure. Improving pre- and perinatal management assessment of myocardial function may be helpful. The aim of the study was to analyse myocardial function in hydropic fetuses at the time of diagnosis.

Material and methods

Thirty hydropic fetuses in which a complete examination according to the study protocol was feasible between 2012 and 2015 were included. Myocardial function was assessed by measuring the mitral annular plane systolic excursion (MAPSE) and the tricuspid annular plane systolic excursion (TAPSE), both reflecting longitudinal ventricular function. Isovolumetric contraction time (ICT´), ejection time (ET´), and isovolumetric relaxation time (IRT´) for the left and right ventricle in were measured by using pulsed wave tissue Doppler imaging (pw TDI). The myocardial performance index (MPI´) was calculated (MPI´ = (ICT´+ IRT´)/ET´). E´- and A´-wave peak velocities were assessed for both ventricles, and the E´/A´ ratio was calculated as a measure of diastolic myocardial function. Results were compared to gestational age-matched healthy controls without Doppler alterations or anatomic malformations by using the unpaired Student's *t*-test.

All ultrasound examinations were performed by expert sonographers at our department who have been trained in the assessment of myocardial function (J. D., R. A.-F.). As previously described, analysis of intraobserver and interobserver variability was performed with Cronbach's alpha and intraclass correlation coefficient (ICC), and it indicated good or strong agreement [5].

Transabdominal echocardiograms were performed in a standardised manner with transverse and longitudinal planes using a Toshiba Aplio XG system (Toshiba Medical Systems Corporation, Otawara, Tochigi, Japan) with a 5-Mhz transducer and equipped with tissue Doppler software. All measurements were digitally recorded and stored as clips or still frames on our archiving system (PIA fetal database). All Doppler recordings were obtained at an insonation angle < 10°, and angle correction was not used.

For assessment of TAPSE and MAPSE, M-mode echocardiography was used (Figure 1). For TAPSE the maximal excursion between the tricuspid annulus and the right ventricular wall from end-diastole to end-systole was measured in an apical or basal four-chamber view. MAPSE was measured in the same way at the mitral annulus. Both TAPSE and MAPSE reflect longitudinal cardiac function with standard values of 5.2 ±0.9 mm (TAPSE) and 4.5 ±1.1 mm (MAPSE) [6].

To acquire ICT´, ET´, and IRT´ in pw TDI, the sample volume was placed in an apical four-chamber view at the lateral wall of the left and right ventricle next to the AV valve (Figure 1). This Doppler-derived technique measures the peak velocity of the myocardium itself and allows approximation of the longitudinal contractility of the heart. The Nyquist limit was reduced to directly assess myocardial motion of low velocities, the wall filter was set to exclude high-frequency signals, and the gain was reduced to depict a clear tissue signal with low background noise. ICT´ was measured from the end of the mitral valve closing click to the beginning of the aortic valve opening click. ET´ was measured from the beginning of the aortic opening click until the end of the aortic valve closing click, and the IRT´ from the end of the aortic closing click to the beginning of the mitral valve opening. E´- and A´-wave peak velocities were measured in the same loop. For descriptive statistical analysis SPSS for Mac OS 23.0 was used.

Results

In 30 hydropic fetuses myocardial function was measured according to the protocol at the day of referral to our centre. Mean gestational age at presentation in our centre was 25 (18–33) weeks of gestation. Two fetuses had immune hydrops because of rhesus incompatibility, and 28 had NIHF. In eight fetuses subsequently a syndrome was diagnosed (Table 1). One fetus presented with high cardiac output status because of sacrococcygeal teratoma (SCT). Three fetuses had echogenic lung lesions with cardiac compression and/or mediastinal shifting. One patient had AV-block because of lupus SSA antibodies. In 15 fetuses hydrops was considered "idiopathic" in the absence of structural malformations and other pathogenetic factors (e.g. infection, aneuploidy, feto-maternal incompatibility).

In 23 fetuses hydrothorax was part of hydrops fetalis. In 20 cases it was bilateral at the time of diagnosis (87%).

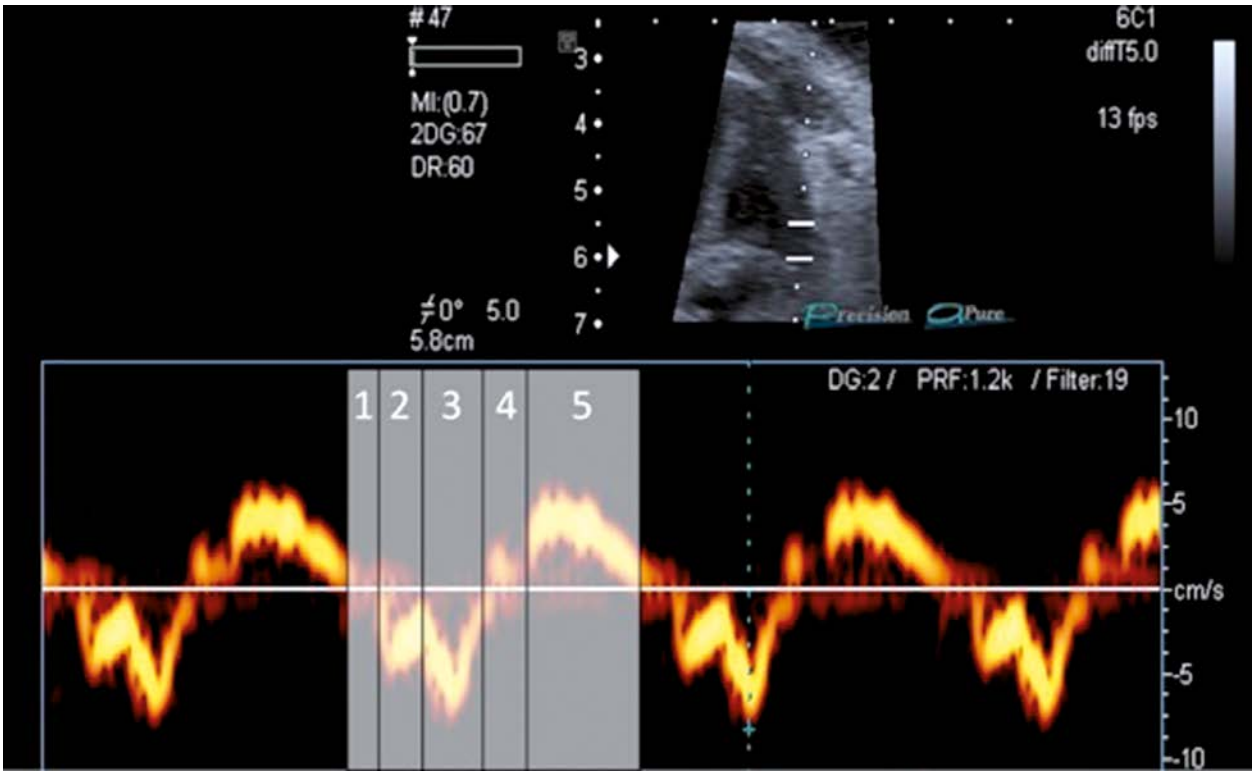

Figure 1. Cardiac cycle in pulsed wave tissue Doppler imaging. The sample volume is placed in the lateral wall of the ventricle. 1 – isovolumetric relaxation time, 2 – E-wave, 3 – A-wave, 4 – isovolumetric contraction time, 5 – ejection time

Cardiac compression was observed in three cases. The fetus with heart block had cardiomegaly (CTR > 0.6). Seven fetuses had AV-valve regurgitation.

Doppler assessment of the fetal circulation showed increased umbilico-placental resistance with absent end-diastolic flow (AEDF) in four fetuses and increased pulsatility in the ductus venosus reflecting increased pressure within the right atrium in eight fetuses. No fetus presented with reduced MCA pulsatility index (brain sparing).

Pulsed wave tissue Doppler imaging-derived time intervals for the left ventricle were ICT′ 0.051 s (range 0.029–0.129 s, standard deviation – SD = 0.02), ET′ 0.170 s (0.091–0.237 s, SD = 0.03), and IRT′ 0.056 s (0.037–0.128 s, SD = 0.02). Mean MPI′ was 0.66 (0.32–1.46, SD = 0.28). Mean E′/A′ ratio for the left ventricle was 0.70 (0.44–1.73, SD = 0.24).

Right ventricular time intervals were ICT′ 0.046 s (range 0.024–0.069 s, SD = 0.01), ET′ 0.172 s (0.101–0.256 s, SD = 0.03), and IRT′ 0.049 s (0.036-0.077 s, SD 0.01). Mean MPI′ was 0.58 (0.3–1.19, SD = 0.17). Mean E′/A′ ratio for the right ventricle was 0.65 (0.33–0.89, SD = 0.15).

MAPSE was 4.8 mm (1.2–7.2 mm) and TAPSE 6 mm (3.2–8.1 mm).

In age-matched healthy controls PW TDI-derived time intervals for the left ventricle were ICT′ 0.043 s (range 0.027–0.069 s, SD = 0.01), ET′ 0.165 s (0.128–0.203 s, SD = 0.02), and IRT′ 0.053 s (0.035–0.075 s, SD = 0.01). Mean MPI′ was 0.58 (0.42–0.79, SD = 0.11). Mean E′/A′ ratio for the left ventricle was 0.64 (0.32–1.07, SD = 0.17). Right ventricular time intervals were ICT′ 0.049 s (range 0.027–0.075 s, SD = 0.01), ET′ 0.166 s (0.136–0.227 s, SD = 0.02), and IRT′ 0.052 s (0.029–0.085 s, SD = 0.01). Mean MPI′ was 0.62 (0.33–0.93, SD = 0.15). Mean E′/A′ ratio for the right ventricle was 0.62 (0.33–0.86, SD = 0.15). MAPSE was 5.4 mm (3.4–9.5 mm) and TAPSE 6.7 mm (4.5–9.0 mm). Table 2 summarises functional parameters.

Table 1. Genetic disorders of hydropic fetuses

Syndrome	*n*
Down syndrome	3
Turner syndrome	3
Cornelia de Lange syndrome	1
Array auffällig	1

Hydropic and healthy fetuses were compared via unpaired Student's *t*-test. Left ventricular MPI′ values were significantly higher in hydropic fetuses ($p < 0.05$). Other study parameters did not differ significantly between groups.

Fetuses with altered Doppler parameters (UA, DV) showed no significant changes in their myocardial function compared to hydropic fetuses with physiological Doppler flow patterns.

Discussion

Our report demonstrates myocardial function in hydropic fetuses at the time of diagnosis in our tertiary centre. Bellini et al. classified NIHF into the following groups of disorders: cardiovascular disorders (21.7%), chromosome imbalances (13.4%), haematological abnormalities (10.4%), infections

Table 2. Pulsed wave tissue Doppler imaging-derived parameters of myocardial function of hydropic fetuses and age-matched controls

Parameters	Mean (s)	Standard deviation – SD
Hydropic fetuses		
Left ventricle		
ICT´	0.051	0.02
ET´	0.170	0.03
IRT´	0.056	0.02
MPI´	0.66	0.28
E´/A´ ratio	0.70	0.24
Right ventricle		
ICT´	0.046	0.01
ET´	0.172	0.03
IRT´	0.049	0.01
MPI´	0.58	0.17
E´/A´ ratio	0.65	0.15
Age-matched controls		
Left ventricle		
ICT´	0.043	0.01
ET´	0.165	0.02
IRT´	0.053	0.01
MPI´	0.58	0.11
E´/A´ratio	0.64	0.17
Right ventricle		
ICT´	0.049	0.01
ET´	0.166	0.02
IRT´	0.052	0.01
MPI´	0.62	0.15
E´/A´ratio	0.62	0.15

ICT´ – isovolumetric contraction time, ET´ – ejection time, IRT´ – isovolumetric relaxation time, MPI´ – myocardial performance index

(6.7%), intra-thoracic masses (6.0%), lymph vessel dysplasias (5.7%), twin-to-twin transfusion syndrome and placental causes (5.6%), syndromes (4.4%), urinary tract malformations (2.3%), inborn errors of metabolism (1.1%), extra-thoracic tumours (0.7%), gastrointestinal disorders (0.5%), miscellaneous causes (3.7%), and idiopathic (17.8%) [7].

Optimisation of intrauterine surveillance is essential for parental counselling and prognosis of hydropic fetuses. The antepartum management depends on the underlying cause of hydrops.

For fetuses with pleural effusions leading to mediastinal shifting, cardiac compression, and, finally, lung hypoplasia, intrauterine therapy should be offered. Thoraco-amniotic shunting is an effective approach by ensuring a continuous drainage which leads to thoracic decompression. Hydrops fetalis has been identified to predict adverse pregnancy and neonatal outcome with a survival rate of approximately 47% compared to 94% in non-hydropic fetuses with hydrothorax [8].

Treatment of thoracic masses like echogenic lung lesions associated with NIHF involves drainage of pleural effusions or glucocorticoid administration as well as destructive techniques like laser or radiofrequency ablation [9–11].

Fetal tumours like sacrococcygeal teratoma can lead to cardiac failure, resulting in NIHF. These fetuses may be selected for minimally invasive intrauterine therapy (e.g. radiofrequency ablation, laser ablation) to reduce blood supplementation towards the tumour and, in consequence, reduce the cardiac load [12].

In fetuses with immune hydrops fetalis because of rhesus (D) alloimmunisation presenting with severe anaemia, intrauterine transfusion of red blood cells is recommended. Intravascular transfusion might be challenging in early gestational ages. In these cases, intraperitoneal transfusion is feasible [13].

To monitor fetuses at risk of cardiac decompensation, Huhta et al. introduced the cardiovascular profile score. Risk stratification is based on a multivariate approach of indirect and direct parameters of cardiovascular function, assessed by B-mode, M-mode, colour, and spectral Doppler [14]. The evaluated parameters are the presence of hydrops fetalis, spectral Doppler examination of the fetal venous system (umbilical vein and ductus venosus; increased pulsatility – absent a-wave wave reversal), and arterial Doppler (umbilical artery; increased pulsatility – absent end-diastolic forward flow-reversal of end-diastolic flow; and middle cerebral artery; redistribution of blood flow, brain sparing), assessment of heart size (C/T area ratio, cardiac area/chest area [normal 0.2–0.35]; C/T circumference ratio, cardiac circumference/chest circumference [normal < 0.5]), and evaluation of heart function (fractional shortening by M-mode [DD-SD/DD, normal > 0.28], colour and spectral Doppler of the atrioventricular valves; tricuspid or mitral valve regurgitation, biphasic- monophasic filling pattern and semilunar valves; valve regurgitation). The main disadvantage of this scoring system is that all of the used underlying parameters represent late- or end-stage situations of the fetal cardiovascular compensatory mechanisms. From these conventional parameters the examination of venous blood flow patterns seems to be most sensitive for imminent cardiac failure as an increased pulsatility in the precardiac veins reflects rising intra-atrial pressure.

Conventional Doppler-derived MPI has been proposed to improve fetal surveillance. Falkensammer et al. found Hydrops fetalis to be associated with biventricular dysfunction and congestive heart failure. They concluded that the "Tei-index may be useful in the serial assessment of myocardial dysfunction in the fetus with hydrops" [15]. In our study at the time of diagnosis of hydrops fetalis only left ventricular MPI´ was elevated. This finding might be explained by the relatively small number of patients in our study. In addition, cardiac dysfunction might aggravate within gestation.

One disadvantage of Doppler-derived MPI is the lack of valid and reproducible information about right ventricular function.

We implemented measurement of myocardial function by tissue Doppler techniques in our centre and hypothesised that is a more sensitive method to detect early signs of cardiac compromise. We recently published data on myocardial function in monochorionic twins with twin-to-twin transfusion syndrome undergoing laser ablation of placental anastomoses and observed longer ICT intervals in recipient fetuses irrespective of Doppler alterations [5]. The prolongation results in an elevated MPI in these fetuses. This finding is consistent with other reports of pathologic fetal conditions.

Mean MPI′ values for the left and right ventricle were 0.66 and 0.58, respectively, which is within the normal compared to published data of normal fetuses [16]. Compared to age-matched healthy controls left ventricular MPI′ values were significantly higher, indicating impaired global ventricular performance in these fetuses. MAPSE and TAPSE measurements reflecting longitudinal function were not altered.

With this small study we focused on myocardial function of hydropic fetuses at the time of the first referral to our centre. Assessment of myocardial function can be challenging, especially in patients with co-existing polyhydramnios. The main advantages of pw TDI for the examination of fetal myocardial function are direct access to the right ventricle and good reproducibility. Although pw TDI-derived parameters are also affected by changes of ventricular loading conditions (e.g. increased pre- and afterload), assessment of fetal myocardial function is an important part of the echocardiographic examination of hydropic fetuses. It may be helpful in clinical decision making because it is attributed to the detection of small changes in myocardial performance earlier than conventional Doppler parameters, which are already altered in many cases at the time of diagnosis (e.g. AEDF, increased venous pulsatility). The latter represents end-stage situations with already manifest cardiac compromise, probably associated with adverse outcome due to a more or less rapid failure of adaptive mechanisms leading to myocardial insufficiency. However, in fetuses with hydrops and still normal Doppler parameters analysis of myocardial function by pw TDI may help to optimise fetal surveillance and, if conditions of myocardial performance are stable, to delay delivery, leading to an improved perinatal outcome. By adjusting follow-up intervals in fetuses with increasing IRT′ or changes in global myocardial function (expressed by increased MPI′ values), pre-clinical alterations may be detectable days before manifest changes in fetal circulation. This should be investigated in a longitudinal study with special regard to changes of myocardial performance within gestation and fetal outcome.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Sohan K, Carroll SG, De La Fuente S, Soothill P, Kyle P. Analysis of outcome in hydrops fetalis in relation to gestational age at diagnosis, cause and treatment. Acta Obstet Gynecol Scand 2001; 80: 726-730.
2. Bellini C, Hennekam RC. Non-immune hydrops fetalis: a short review of etiology and pathophysiology. Am J Med Genet A 2012; 158A: 597-605.
3. Huhta JC. Fetal congestive heart failure. Semin Fetal Neonatal Med 2005; 10: 542-552.
4. Tulzer G, Gudmundsson S, Wood D, Cohen AW, Weiner S, Huhta JC. Doppler in non-immune hydrops fetalis. Ultrasound Obstet Gynecol 1994; 4: 279-283.
5. Degenhardt J, Reinold M, Enzensberger C, Wolter A, Kawecki A, Kohl T, et al. Short-time impact of laser ablation of placental anastomoses on myocardial function in monochorionic twins with twin-twin transfusion syndrome (TTTS). Ultraschall Med 2017; 38: 403-410.
6. Carvalho JS, O'Sullivan C, Shinebourne EA, Henein MY. Right and left ventricular long-axis function in the fetus using angular M-mode. Ultrasound Obstet Gynecol 2001; 18: 619-622.
7. Bellini C, Hennekam RCM, Fulcheri E, Rutigliani M, Morcaldi G, Boccardo F, et al. Etiology of nonimmune hydrops fetalis: a systematic review. Am J Med Genet A 2009; 149A: 844-851.
8. Pellegrinelli JM, Kohler A, Kohler M, Weingertner AS, Favre R. Prenatal management and thoracoamniotic shunting in primary fetal pleural effusions: a single centre experience. Prenat Diagn 2012; 32: 467-471.
9. Curran PF, Jelin EB, Rand L, Hirose S, Feldstein VA, Goldstein RB, et al. Prenatal steroids for microcystic congenital cystic adenomatoid malformations. J Pediatr Surg 2010; 45: 145-150.
10. Wilson RD, Hedrick HL, Liechty KW, Flake AW, Johnson MP, Bebbington M, et al. Cystic adenomatoid malformation of the lung: review of genetics, prenatal diagnosis, and in utero treatment. Am J Med Genet 2006; 140: 151-155.
11. Ruano R, da Silva MM, Salustiano EM, Kilby MD, Tannuri U, Zugaib M. Percutaneous laser ablation under ultrasound guidance for fetal hyperechogenic microcystic lung lesions with hydrops: a single center cohort and a literature review. Prenat Diagn 2012; 32: 1127-1132.
12. Van Mieghem T, Al-Ibrahim A, Deprest J, Lewi L, Langer JC, Baud D, et al. Minimally invasive therapy for fetal sacrococcygeal teratoma: case series and systematic review of the literature. Ultrasound Obstet Gynecol 2014; 43: 611-619.
13. Fox C, Martin W, Somerset DA, Thompson PJ, Kilby MD. Early intraperitoneal transfusion and adjuvant maternal immunoglobulin therapy in the treatment of severe red cell alloimmunization prior to fetal intravascular transfusion. Fetal Diagn Ther 2008; 23: 159-163.
14. Hofstaetter C, Hansmann M, Eik-Nes SH, Huhta JC, Luther SL. A cardiovascular profile score in the surveillance of fetal hydrops. J Matern Fetal Neonatal Med 2006; 19: 407-413.
15. Falkensammer CB, Paul J, Huhta JC. Fetal congestive heart failure: correlation of Tei-index and cardiovascular-score. J Perinat Med 2001; 29: 390-398.
16. Comas M, Crispi F, Gómez O, Puerto B, Figueras F, Gratacós E. Gestational age- and estimated fetal weight-adjusted reference ranges for myocardial tissue Doppler indices at 24-41 weeks' gestation. Ultrasound Obstet Gynecol 2011; 37: 57-64.

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