INTRODUCTION

Progress in the fields of fetal cardiology and fetal surgery have been seen not only in singleton pregnancies but also in multiple pregnancies. Proper interpretation of prenatal echocardiography is critical to clinical decision making, family counseling and perinatal management for obstetricians, maternal fetal medicine specialists, neonatologists and pediatric cardiologists. Fetal echocardiography (FE) is one of the most challenging and time-consuming prenatal examinations to perform, especially in multiple gestations. Performing just the basic fetal exam in twin gestations may take an hour or more. Thus, it is not practical to perform this exam in all cases of multiple gestations. Therefore our review and recommendations are related to fetal echocardiography in twin gestation.

Key words: fetal echocardiography, twin pregnancy, TTTS, TRAP, TAPS, SIUGR

How to Cite this Article:
FE recommendations in twin gestations based on existing publications and our own experience.

Recent data from the United States, England and Wales demonstrate decreasing rates of higher-order multiple births and represent, for the first time, a striking change in trend when compared with the previous steep 4-fold increase since the early 1980s. However, the incidence of twin pregnancies continues to increase. The reasons for these changes are probably new embryo transfer guidelines and wider availability of multi-fetal pregnancy reduction procedures. Because actual numbers of higher-order multiples are by far lower than the number of twins, and because twins are predictably associated with significant perinatal morbidity and mortality, the implications of the increasing twin birth rates are alarming.

Therefore our review and recommendations are related to fetal echocardiography in twin gestation.

**GENERAL CONSIDERATIONS:**

During the 1st trimester, the presence of multiple pregnancy should be documented on ultrasound images; gestational age according to the last menstrual period and fetal biometry should be provided separately for each fetus, chorionicity and amnionicity should be determined and shown on the images as recommended by ISUOG guidelines. During subsequent visits, this documentation with images should be presented to an obstetrician, and in selected cases to a fetal cardiologist, maternal fetal medicine specialist, neonatologist, or specialist in genetics.

In patients whose twin pregnancy is a result of IVF, gestational age can be determined from the date of embryonic transfer (optimally, the data on the type of IVF technique, number of embryos transferred, and center where it was performed should be mentioned in the report).

Genetic testing during the 1st trimester should follow the recommendations for singleton pregnancies, depending on the accuracy of pre-implantation genetic diagnosis or cell-free DNA for multiple pregnancies.

The early multiple pregnancy should be confirmed after 12th weeks of pregnancy and in case of “vanishing” twin the care in such pregnancy should be the same as in singleton pregnancy, although analysis or cell-free DNA testing may not be as accurate in these cases. In case of conjoined twins several options would exist including termination of pregnancy. However this review would not be related to the conjoined twin pregnancy despite that conjoined twins might be a specific prenatal fetal cardiac problem.

Fetal biometry in the 2nd and 3rd trimester should be assessed based on combination of at least 3 parameters: BPD, HC, AC and FL for each of the twins.

For symmetrical twins in dichorionic pregnancy further ultrasound exams should be performed at 3-to 4-week intervals starting from week 18th and nuchal translucency measurement may be of importance.

For symmetrical twins in monochorionic pregnancy further ultrasound exams should be performed at 2-week intervals starting from week 16th, increasing to every week if abnormalities in size, amniotic fluid, fetal bladder, or umbilical artery Doppler finding are noted.

In the case of symmetrical growth of monochorionic twins optimally fetal echocardiographic exams should be conducted as planned procedure at 18-22 weeks of gestation, or earlier in very high risk cases (e.g., diabetics with elevated hemoglobin A1C levels or enlarged nuchal translucency).
In the case of asymmetrical growth of monochorionic twins in the 1st trimester, fetal echocardiographic exams should be performed earlier, at 14-15 weeks, as the so-called urgency exam.

In monochorionic pregnancies the presence of specific syndromes, such as TTTS, TRAP, TAPS and SIUGR, should be ruled out at every ultrasound exam. In case of early suspicion of one of these syndromes fetal echocardiography is recommended as early as possible.

The volume of amniotic fluid in twins should be estimated on the basis of maximal volume pocket (MVP), rather than based on amniotic fluid index (AFI) as recommended in singleton pregnancies.\(^{13,14}\)

**DICHORIONIC PREGNANCY**

Examinations conducted according to the same schedule as for singleton pregnancies.\(^4,5,6\)

*To confirm normal heart anatomy in both twins. In case of abnormalities we would recommend:*

**Twin A with an isolated congenital heart defect (CHD) and twin B healthy:**

Although no clear recommendations regarding intrauterine pharmacotherapy or surgical treatment have been established thus far in either critical CHD or posing a risk of heart failure, these options should be discussed with a pregnant woman and her partner.

**Twin A with CHD and extracardiac malformation and twin B healthy:**

While the abnormal fetus can be a subject of selective termination, this, however, does not exclude the risk of complications (e.g. premature ruptured membranes, miscarriage, preterm birth) in the normally growing fetus.\(^5\)

In the situation of a cardiac problem in one of the twins, for instance CHD or even a tumor, both fetuses require fetal echocardiography and longitudinal monitoring to avoid premature delivery and ensure proper development of both fetuses.

Congestive heart failure in one of the twins requires the consideration of in
utero treatment before making a decision regarding emergency cesarean section. 16

MONOCHORIONIC PREGNANCY

Ultrasound examination between 11w0d and 13w6d performed according to the FMF standards; a difference in nuchal translucency (NT) between twins may be the first manifestation of abnormal cardiac function and twin-to-twin transfusion syndrome (TTTS) 16,17.

Whenever NT of one fetus exceeds 3.5 mm or 90th% for CRL, an early echocardiographic examination is recommended at about 14 weeks, since cardiologic abnormalities may often precede the other later sonographic markers of TTTS 16,17,18.

In case of symmetric twin growth and no abnormalities on ultrasound exam and echo exam at 14th week, further control exams should be scheduled at 2-week intervals.

In case of a difference in fetuses size (CRL> 1wk GA) or NT measurements, or abnormal flow in tricuspid valve (TV) in one of the twins, further ultrasound exams should be scheduled once a week.

In case of a sudden increase in abdominal size of the pregnant woman, raising suspicion of a progressive polyhydramnios, urgent ultrasonography and echocardiography should be performed irrespective of gestational age.

Concerns for TTTS or selective intrauterine growth restriction (SIUGR):

1. Twin gestations should be referred to tertiary center which specialize in fetal diagnosis and fetal therapy for further surveillance.

2. At the tertiary center baseline examination including complete fetal echocardiography to confirm the diagnosis, determine current hemodynamic status of both fetuses is performed.

Serial fetal echocardiography and Doppler recordings may show hemodynamic changes in the fetal circulation of discordant twins. Sometimes these changes may be temporal 18. In the majority of cases, however, the abnormalities can progress:

The recipient twin may have progressive volume and pressure overload, congestive heart failure, and hydrops. Recipient twin echocardiographic findings, which typically include valvar regurgitation/stenosis, ventricular hypertrophy, and diastolic/systolic dysfunction, tend to occur predominantly in the right heart, with relative sparing of the left heart. To prevent the progression to fetal heart failure and hydrops surgical treatment options are

<table>
<thead>
<tr>
<th>Fetal hydrops</th>
<th>Normal (2 points)</th>
<th>1 point Ascites, pleural effusion, or pericardial effusion</th>
<th>2 points Skin edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal venous Doppler Cardiomegaly (CT ratio = cardiac area/thoracic area)</td>
<td>Normal venous Doppler CT ratio ≤ 0.35</td>
<td>Venous duct atrial systolic reversal CT ratio &gt;0.35 &amp; &lt;0.50</td>
<td>Umbilical venous pulsations CT ratio &gt;0.50</td>
</tr>
<tr>
<td>Abnormal myocardial function</td>
<td>Ventricular SF &gt;0.28 &amp; no valve regurgitation</td>
<td>SF &lt;0.28 or TR or semilunar valve regurgitation</td>
<td>TR + dysfunction or any MR</td>
</tr>
<tr>
<td>Abnormal arterial Doppler</td>
<td>Normal umbilical artery diastolic flow</td>
<td>Absent end-diastolic flow in the umbilical artery</td>
<td>Reverse end-diastolic flow in the umbilical artery</td>
</tr>
</tbody>
</table>

*CT = cardiothoracic, MR = mitral regurgitation, SF = shortening fraction, TR = tricuspid regurgitation*

Table 4: Cardiovascular Profile Score by Shah (2008)
offered in the majority of fetal centers. Based on the precise diagnosis and twins condition a surgical treatment is discussed with parents to be (e.g. selective laser therapy)\textsuperscript{19}.

3. In the case of a surgical procedure, control fetal echocardiography examinations are recommended: in our Polish centers (in Gdansk and in Lodz) we would perform echo a day before exam and post-procedure, within the next 24 hours, on the 3\textsuperscript{rd} and 7\textsuperscript{th} day (in a hospital setting), and then at 14-day intervals (in an outpatient setting). According to J. Pruetz it usually performed FE a pre-op and 14-28 days post op. Subsequent FE are performed if fetal CHD persists or CHD is suspected.

Laser ablation of placental anastomoses might influence myocardial function in the postoperative period and only detailed fetal echocardiography may reveal early changes in fetal myocardial contractility \textsuperscript{20}. Shortened IRT intervals or improved shortening fraction of the ventricles may reflect an improvement of diastolic or systolic (respectively) function in recipients \textsuperscript{21}.

Optimally each examination should include parameters listed in Table 1, however Willruth and group of Gembruch would also recommend speckle tracking if available\textsuperscript{22,23}.

**SINGLE FETAL DEMISE**

Twin pregnancies are at higher risk for fetal mortality when compared with singleton pregnancies. Single fetal demise occurs in 3.7 – 6.8 % of all twin pregnancies and considerably increases the complication rate in the co-twin including fetal loss, premature delivery, and end-organ damage\textsuperscript{24}, especially of the fetal brain.

In the case of intrauterine demise of one of the twins so far attention was focus on central nervous system on the survivor twin or umbilical blood flow\textsuperscript{25,26,27}, however nowadays it is not enough and fetal echocardiography is strongly recommended in such a case\textsuperscript{28}.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Donor</th>
<th>Recipient</th>
<th>Recipient cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Oligohydramnios</td>
<td>Polyhydramnios</td>
<td>None</td>
</tr>
<tr>
<td>II</td>
<td>Bladder absent</td>
<td>Bladder seen</td>
<td>None</td>
</tr>
<tr>
<td>III</td>
<td>Abnormal Doppler</td>
<td>Abnormal Doppler</td>
<td>None</td>
</tr>
<tr>
<td>III A</td>
<td>+/- Abnormal Doppler</td>
<td>+/- Abnormal Doppler</td>
<td>Mild</td>
</tr>
<tr>
<td>III B</td>
<td>+/- Abnormal Doppler</td>
<td>+/- Abnormal Doppler</td>
<td>Moderate</td>
</tr>
<tr>
<td>III C</td>
<td>+/- Abnormal Doppler</td>
<td>+/- Abnormal Doppler</td>
<td>Severe</td>
</tr>
<tr>
<td>IV</td>
<td>Hydrops</td>
<td>Hydrops</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Death</td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Cincinnati Scale by Habli (2008)
fetus. In many cases, the reversed flow between fetuses resolves spontaneously, which is the most favorable outcome. However, an intervention is required in the remaining cases, as growth of the acardiac fetus results in progressively increasing myocardial strain in the pump fetus. One option of treatment is fetoscopic laser occlusion of the vessel supplying non-oxygenated blood to the acardiac twin.

An important question is when this invasive intervention should be taken ... as early as possible or as late as possible ... 

Fetal echo has been used to risk stratify fetuses with TRAP using abnormalities of cardiac size, combined cardiac output, AV valve regurgitation and valve sizes (aortic and mitral) in order to predict outcomes or indicate need for fetal intervention. Alternative treatments are symptomatic treatment (i.e. pharmacological support of myocardial function in the pump fetus, the earlier the symptoms develop and the worse is prognosis. Aside from fetal biometry and amniotic fluid volume, another key parameter which should be monitored in the case of SIUGR is Doppler evaluation of peripheral blood flow. In particular, Doppler flow patterns in the umbilical vessels can deteriorate with gestational age. Initially, there is increased resistance observed in...
the umbilical artery, followed by absence of end-diastolic flow (AEDF) and eventually reversal of end-diastolic flow (REDF), which may be followed within days to a few weeks by fetal demise of the growth-restricted fetus with potential harmful consequences to the other twin.

Prompt termination of the pregnancy at a tertiary neonatology center with an intensive care unit should be considered as early as AEDF was observed. In early pregnancy, in which the abnormalities of the umbilical flow manifested relatively early and patient is eligible for surgical treatment, a fetoscopic procedure can be offered; this includes either selective cord occlusion in the fetus with SIUGR or laser coagulation of the placenta with closing all possible anastomoses between fetuses and resultant creation of dichorionic pregnancy.

**TWIN ANEMIA POLYCYTHEMIA SEQUENCE (TAPS)**

Twin anemia-polycythemia sequence (TAPS) is a rare condition in monochorionic twin pregnancies. Small intertwin placental vascular communications allow transfusion, which results in a hemoglobin difference in the twins in the absence of oligohydramnios or polyhydramnios. It may be useful to pay attention on the different echogenicity of the placenta (part of it maybe hyperechogenic and part hypoechogenic).

Fetoscopic laser surgery is the only curative treatment, but is challenging in TAPS because of the absence of polyhydramnios and the presence of minuscule anastomoses.

The other option could be intra-uterine transfusion. TAPS may be some time very difficult to distinguish from TTTS, as findings might be overlapping.

The principal ultrasonographic parameter determined in fetuses with TAPS is flow velocity in the middle cerebral artery; this parameter is used to calculate the risk for fetal anemia from the following formula:

$$\text{http://www.perinatology.com/calculators/MCA.htm}^{38}$$

**PHARMACOLOGICAL TRANSPLACENTAL AND/OR INDIRECT THERAPY IN FETAL HEART FAILURE**

Whenever one or both fetuses present with the signs of heart failure, transplacental or indirect therapy should be considered and discussed with parents to be. An example
of indirect treatment is administration of adenosine to the umbilical vein; this option is limited solely to the cases of persistent, severe tachyarrhythmias that are resistant to transplacental treatment.

However, although middle cerebral artery measurement of the peak systolic velocity has been well studied and documented to relate to anemia in the donor twin, its sensitivity and specificity for determining polycythemia in the recipient twin has not been as thoroughly studied.

Another example of indirect treatment are intrauterine blood transfusions; indications for this treatment include TAPS, evidence of anemia in one fetus during the course of laser therapy-ineligible SIUGR, TTTS or TRAP, or the signs of anemia found on necropsy of one of the fetuses with any of the syndromes mentioned above.

Transplacental pharmacotherapy should be considered whenever a persistent, severe tachyarrhythmia is diagnosed in one or both fetuses. The typical anti-arrhythmic agents used are digoxin, amiodarone, sotalol, flecainide, and propranolol with the same principles of administration that apply to singleton pregnancy.\[39,40,41\]. The status of both the fetus(es) and their mother should be monitored throughout the treatment.

Another example of transplacental treatment is management of heart failure in recipient fetus with TTTS. The treatment of choice are digitalis, initially administered intravenously, and then orally after achieving an appropriate concentration of the drug in the blood of pregnant woman. If fetal hydrops is noted in the recipient twin, intravenous treatment via cordocentesis may be more efficient, since trans-placental delivery of drugs may be impaired.

Frequently, the treatment is initiated already prior to the scheduled selective photocoagulation of communicating vessels to improve myocardial status and cardiovascular performance of the recipient fetus.

Due to similar reasons, transplacental digoxin is also sometimes implemented in pump fetuses with TRAP sequence ineligible for early fetoscopic procedure.

In some centers since the treatment is laser surgery in TTTS – Digoxin is not used any longer.

Sometimes maternal Nifedipine is introduced to improve outcomes in TTTS\[42\].

**DELIVERY IN COMPLICATED TWIN OR MULTIPLE PREGNANCY WITH A CARDIOLOGIC PROBLEM IN ONE OF THE FETUSES**

Two issues should be considered prior to delivery. The first of them are general rules and timing for delivery in multiple pregnancies; this issue has been discussed in detail in many obstetrical publications.\[12,13,41,43,44,45\].

Another problem is the presence of a cardiac defect or heart failure in one or both fetuses. All decisions regarding the timing and method for delivery should be made within a multidisciplinary team including an obstetrician, maternal fetal medicine specialist, neonatologist, fetal cardiologist, pediatric cardiologist and cardiac thoracic surgeon.

In the case of a fetus with congenital heart disease, historically, the method for delivery was typically established based on obstetrical indications. However, a contemporary definition of CHD is one that recognize there are various levels of severity some of which requires urgent intervention/treatment in the first 24 h of life to prevent death.\[45,46\]. Critical CHD cases may require delivery at specialized centers that can provide perinatal, obstetric, cardiology and cardiothoracic surgery care.\[47\]. Fetuses diagnosed in mid-gestation require detailed fetal diagnostics and serial monitoring during the prenatal period, in order to assess for ongoing changes and identify progression to a more severe cardiac status. In the case of CHD in twin gestations, the location and mode of delivery should be based on a group consensus regarding the optimal perinatal management for the affected twin.

In the situation when fetal heart failure and generalized hydrops has developed. This may preclude safe natural labor, and thus, elective cesarean section might be considered.

Optimally, the labor should take place at a specialist obstetrical center with a neonatal intensive care unit and cardiology/cardiac surgery department, or at a tertiary center.

In the previous decade, with the late detection of TTTS, lack of the possibility of laser treatment, lack of possibility of precise echocardiography monitoring, the main issue of delivery in twins was prematurity, the high mortality of newborns, and also the high rate of conjoined twins.\[45\]

Despite of huge progress in perinatal care in twins this decade, we should remember the Blickstein’s “citation": the vast majority of long-term morbidity related to monochorionicity at large does not come from complications of TTTS or TRAP sequence, but from ‘banal’ ones related to prematurity and growth restriction. Prematurity and growth restriction, however, are not specific to anomalous splitting of the zygote, but plague all multiple gestations simply because the human uterus is unable to carry multiples to the same extent that it carries singletons. Until a (real) advance is made to reduce the risks affecting all twins, irrespective of chorionicity, we shall continue to rely on the formidable remedies devised for individual cases of complicated monochorionic twin gestation.

**OTHER PRENATAL ISSUES**

Uterine artery Doppler evaluation in twin pregnancies beginning in the 1st trimester\[61\] could be the next important parameter monitor, however this protocol was focused mainly on the fetal echocardiography in twins.
POSTNATAL ISSUES

The delivery does not preclude further postnatal care of twins who prenatally had evaluation by fetal cardiologists. After delivery and transition each previous “twin”, especially twins who prenatally had evaluation by fetal cardiologists. The delivery does not preclude further postnatal care of twins who prenatally had evaluation by fetal cardiologists. Newborns should be referred to pediatric cardiologists, as among this population there is an increased prevalence of congenital heart defects both in former recipients and donors and they may also present elevated blood pressure in the first or second year of postnatal age. Whether the elevated blood pressure is related to their prenatal cardiovascular problems or to prematurity warrants future studies.

FINAL CONCLUSIONS

Fetal echocardiography in dichorionic pregnancy should be offered based on similar protocols as in singleton pregnancy. Fetal echocardiography in monochorionic pregnancy should be offered as early as possible (perhaps the 14th week of gestation) and used for monitoring fetal hearts in out-patient settings and in selected cases for monitoring invasive and/or pharmacological treatment in hospital settings. The main goal of fetal cardiac evaluation is to provide thorough and safe perinatal care for the fetuses, mothers, and obstetricians as well, and to ensure timely delivery. As fetal echocardiography in twins is difficult and time consuming is should be provided by fetal cardiologists or maternal-fetal medicine specialists, but preferably both in concert in tertiary centers, cooperating with obstetricians and pediatric cardiologists.

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Division of work: Katarzyna Leszczyńska: first draft, literature search Co-authors: work with manuscript Maria Respondok-Liberska: concept of the manuscript, figures, final version

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