VIA MEDICA

RECCOMENDATIONS

Ginekologia Polska
2022, vol. 93, no. 3, 256–263

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2021.0244

The Polish Society of Gynecologists and Obstetricians guideline for the diagnostic assessment and management of multiple-gestation pregnancy complicated by fetal growth restriction

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"This Guideline presents current management strategies which, in justified cases and after detailed analysis of a given clinical situation, may be modified and altered, which in turn might aid its future modification and update".

AIM

The aim of the Guideline is to unify the diagnostic-therapeutic management of multiple-gestation pregnancies complicated by fetal growth restriction in at least one fetus.

INTRODUCTION

Fetal growth restriction (FGR) refers to a condition in which a fetus fails to attain its genetically predetermined growth potential. The rate of multiple pregnancies continues to rise both, in Poland and worldwide. According to Statistics Poland, neonates from multiple-gestation pregnancies accounted for 2.51% of all births in 2019 [1]. Multiple-gestation pregnancy carries an increased risk for complications, including a 5-fold higher risk for intrauterine fetal demise and a 7-fold higher risk for neonatal death [2]. Mean neonatal birth weight is dependent upon gestational multiplicity and *e.g.*, in the US has been estimated at 3296 g for a singleton, 2336 g for twin, 1660 g for triplet and 1291 g for quadruplet gestation [3]. Multiple-gestation pregnancies require special care and, in the event of complications, consultation and specialist management at a tertiary referral center.

DEFINITIONS AND ABBREVIATIONS

A-A — arterio-arterial anastomoses
AC — abdominal circumference

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Received: 7.12.2021 Accepted: 9.12.2021 Early publication date: 28.02.2022

AEDF — absent end-diastolic flow
AGA — appropriate for gestational age — fetus and neonate with estimated fetal weight or birth weight between 10–90 percentile for its gestational age
CRL — crown-rump-length
CTG — cardiotocography
DC — dichorionic
DV — ductus venosus
EDF — end-diastolic flow
EFW — estimated fetal weight
FGR — fetal growth restriction — a condition when a fetus fails to attain its genetically predetermined growth potential, after excluding other known causes (chromosomal aberrations, intrauterine infections, congenital defects)
Hypotrophy — refers to a condition when a neonate is born with features of restricted growth
IUGR — intrauterine growth restriction — synonym of FGR
LGA — large for gestational age — fetus and neonate with estimated fetal weight or birth weight of > 90 percentile for its gestational age
MC — monochorionic
MCA — middle cerebral artery
MoM — multiple of median
pc — percentile
REDF — reversed end-diastolic flow
Selective FGR (sFGR) — growth restriction of one fetus in a multiple-gestation pregnancy
SGA — small for gestational age — fetus with estimated fetal weight (EFW) on ultrasound between 3 and 10 percentile for its gestational age, without hemodynamic symptoms on Doppler ultrasound or a neonate with birth weight below 10 percentile
SLPCV — selective laser photocoagulation of communicating vessels
STV — short term variability
TAPS — twin anemia-polycythemia sequence
TORCH — Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex, others
TRAP — twin reversed arterial perfusion syndrome
TTTS — twin-to-twin transfusion syndrome
UA — umbilical artery
UV — umbilical vein

DIAGNOSTIC ASSESSMENT AND MANAGEMENT OF MONOCHORIONIC PREGNANCY

Determination of gestational age and chorionicity at first-trimester ultrasound

An ultrasound examination should be performed in every pregnant patient between 11 + 0 and 13 + 6 weeks of gestation to determine gestational age, chorionicity, the risk for trisomy and preeclampsia, and to exclude severe anatomical defects [e.g. anencephalia, twin reversed arterial profusion (TRAP) syndrome]. Early determination of chorionicity is crucial due to different clinical implications and in order to provide adequate perinatal care of the pregnant woman. The clinical implications include:

1. first-trimester miscarriage: dichorionic pregnancy (DC) — 2%, monochorionic pregnancy (MC) — 10%;
2. perinatal mortality: DC — 2%, MC — 4%;
3. fetal growth restriction of at least one fetus: DC — 10%, MC — 15%;
4. preterm (< 32 weeks of gestation) delivery: DC — 5%, MC — 10%;
5. severe fetal defects: DC — 1%, MC — 4%.

Gestational age, based on the date of the last menstruation, should be verified on ultrasound using the crown-rump-length (CRL) of both fetuses. In case of discrepancies in the estimated delivery dates calculated using the CRL of both fetuses over seven days, it is advised to use the CRL-based date calculated for the larger fetus [4]. During the ultrasound test, chorionicity needs to be described and a print of the scan should be included in the chart. If the test is performed before 10 weeks of gestation, the number of gestational sacs, amniotic sacs, and embryos needs to be determined. If the test is performed later, chorionicity may be determined using the following parameters on ultrasound:

- presence of the twin peak [λ (lambda) sign — dichorionic pregnancy] or the T sign (tau, also know as the „T" sign — monochorionic pregnancy) (Fig. 1);
- the thickness of the intertwin membrane (< 1.8 mm in monochorionic pregnancy [5]) and the number of layers of the membrane (2 — monochorionic, 4 — dichorionic);
- the number of placental masses (the placenta in approximately 3% of monochorionic pregnancies comprises of two lobes [5, 6]). It is also important to bear in mind that placental fusion may occur (a seemingly single placental disc may in fact consist of two developmentally independent separate discs), especially when the ultrasound is performed at the end of the second trimester or in the third trimester.

Based on the presence of the λ or the T sign, it is possible to determine chorionicity with > 95% sensitivity, which reaches its peak before 14 weeks of gestation [7, 8].

In case of a monochorionic pregnancy, it is also necessary to determine amnionicity. If the pregnancy is monoamniotic, it is essential to exclude the presence of conjoined twins.

Early determination of chorionicity is necessary to plan the management of the pregnancy in the event of the risk for pregnancy-specific complications such as TTTS, TAPS, or TRAP. If it is not possible to univocally determine chorionicity, it is advised to deem the pregnancy monochorionic, which affects further monitoring and management.

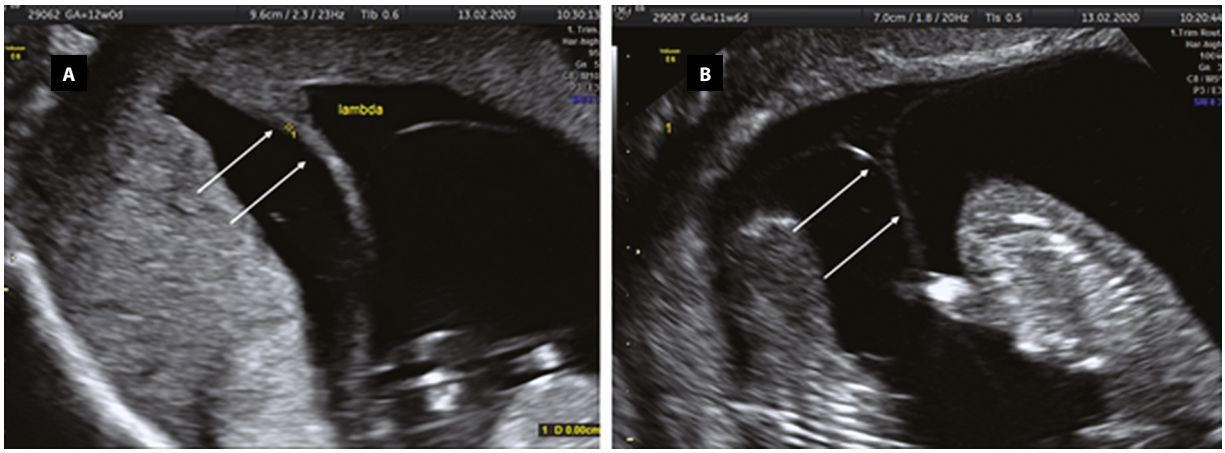

Figure 1. Ultrasound symptoms signs of monochorionic and dichorionic pregnancy; **A.** λ sign**; B.** T sign

Monitoring of fetal growth in monochorionic pregnancy

Fetal growth curves in multiple-gestation pregnancies differ from those of singleton pregnancies. In multiple-gestation pregnancies, the growth rate begins to slow down at a certain point in pregnancy. In a twin pregnancy, as compared to a singleton pregnancy, the first symptoms of growth restriction begin to appear at 30–32 weeks of gestation and are manifested more vividly in monochorionic as compared to dichorionic twins [9–11]. Based on the up-to-date reports, it is not possible to unequivocally recommend using the centile charts designed specifically for twin or singleton pregnancies to evaluate the growth of the fetuses from a twin pregnancy. However, to achieve better prediction for neonatal complications, it seems prudent to determine the estimated weight of the twins using the centile charts designed specifically for monochorionic and dichorionic twin gestations [11–13].

In monochorionic pregnancy, biweekly ultrasound testing is recommended, starting at 16 weeks of gestation and continued for the reminder of the pregnancy. Such close monitoring allows for an early diagnosis of transfusion syndromes (TTTS, TAPS) as well as detection of fetal growth abnormalities. The evaluation of fetal anatomy between 18 and 22 weeks of gestation is an important element of ultrasound diagnostics due to higher risk for anatomical abnormalities, especially in monochorionic pregnancies.

In twin gestations, it is very important to label the fetuses during the ultrasound, e.g., 'Twin 1' and 'Twin 2' or 'Twin A' and 'Twin B'. Consistent labeling, regardless of fetal presentation during the subsequent tests, is vital as it ensures adequate assessment of their growth. The same approach is recommended for all multiple gestations.

At 16 weeks of gestation, the umbilical cord insertion should be assessed, if possible. Abnormal cord insertion, i.e., marginal or velamentous, may be indicative of uneven placental sharing, thus being a predictive factor for growth restriction. In subsequent ultrasound tests, the following parameters should be evaluated: fetal bladder diameter, amniotic fluid volume in both amniotic sacs, estimated fetal weight (preferably using Hadlock 2 formula [14]), pulsatility index in the umbilical artery (UA) and the middle cerebral artery (MCA), as well as peak velocity of systolic blood flow in MCA. In justified cases, possible hemodynamic abnormalities need to be analyzed by evaluating ductus venosus (DV) and umbilical vein (UV) blood flow. If significant discordance in the estimated fetal weight (EFW) is suspected, the difference should be calculated using the following formula:

[(EFW of the larger fetus – EFW of the smaller fetus) / EFW of the larger fetus] × 100%

Selective fetal growth restriction in monochorionic pregnancy

Selective fetal growth restriction (sFGR) complicates approximately 15% of all monochorionic gestations. Already a difference of > 20% in estimated fetal weight is associated with a higher risk for complications and is an indication for close monitoring of fetal wellbeing [15–17]. Selective FGR is diagnosed if:

- EFW of < 3 pc for its gestational age is found in one of the fetuses
- or if 3 out of the 4 criteria below have been met:
- EFW of < 10 pc for its gestational age in one of the fetuses;
- abdominal circumference (AC) of < 10 pc for its gestational age in one of the fetuses;
- a difference of ≥ 25% EFW between the two fetuses;
- UA pulsatility index of > 95 pc for its gestational age in the smaller fetus [18].

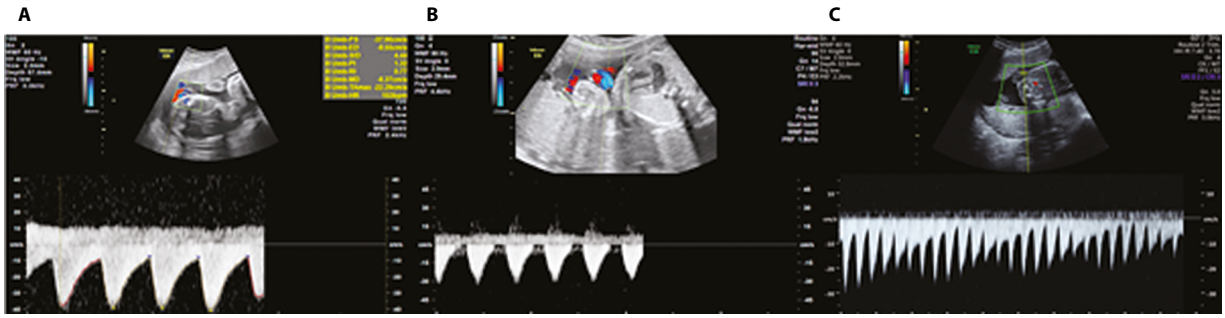

Figure 2. Blood flow range in the umbilical artery in 3 types of sFGR in monochorionic pregnancy; **A.** Type 1; **B.** Type 2; **C.** Type 3

Depending on time of diagnosis, sFGR may be classified into early-onset (diagnosis before 24 weeks of gestation) and late-onset (diagnosis after 24 weeks of gestation) growth restriction [15]. Each patient with a pregnancy complicated by sFGR should be referred to a tertiary referral center.

In case of early-onset sFGR, amniocentesis or cordocentesis to test for genetic abnormalities should be considered.

Selective FGR is usually the consequence of unequal placental sharing by the fetuses and/or a cord abnormality in the smaller twin (e.g. velamentous cord). Furthermore, anastomoses which connect the venous and/or arterial vessels of the circulatory systems of both twins can be found in most monochorionic placentas. Vascular anastomoses in the placenta affect pregnancies with sFGR in two ways. On one hand, blood exchange through arterio-arterial (A-A) anastomoses to the FGR twin often allows to prolong the time from sFGR diagnosis to delivery in a monochorionic pregnancy, as compared to the FGR diagnosis in a singleton pregnancy [19]. On the other hand, in case of intrauterine demise of the FGR fetus, the presence of vascular anastomoses carries the risk of mortality or central nervous system damage to the appropriately grown twin (AGA) [20].

If sFGR is diagnosed, it is recommended to repeat ultrasound-based evaluation of fetal biometry every two weeks. Doppler ultrasound should be performed every week to measure:

- pulsatility index in UA and MCA;
- peak systolic velocity in MCA;
- waveform flow through DV and UA.

Amniotic fluid volume should also be assessed. Doppler evaluation is used to identify the type of sFGR, to monitor the condition, and to exclude concomitant TTTS or TAPS. Abnormal blood flow in the ductus venosus (absent or negative A-wave) or CTG abnormalities [automatic measurement of short term variability (STV) is the preferred computation to assess CTG of fetuses with FGR: 26-28+6 weeks STV < 2.6 ms; 29–31 + 6 weeks STV < 3 ms; 32–33 + 6 weeks STV < 3.5 ms; > 34 weeks STV < 4.5 ms; or repetitive decelerations] are the decisive indicators for elective delivery [21].

The prognosis varies, depending on the blood flow range in the umbilical artery. The following 3 types of sFGR can be distinguished [22] (Fig. 2).

1. Type 1 — positive end-diastolic flow (EDF) in the UA — accounts for 80% of all early-onset sFGR pregnancies [14]. The mortality rates for the smaller twin and for both twins have been estimated at 2% and 2%, respectively [22]. Weekly surveillance of the blood flow is recommended because deterioration of fetal wellbeing and disease progression is observed in 25% of the cases [22, 23]. Elective delivery is recommended at 34–36 weeks of gestation [24];
2. Type 2 — absent or reverse end-diastolic flow (AEDF, REDF) in the UA — accounts for 15% of all early-onset sFGR pregnancies [15]. Type 2 is characterized by an uneven sharing of the placental territory (a smaller fragment of the placenta sustains the sFGR twin) and a smaller number and diameter of vascular anastomoses, which hinders their compensatory capacity [24]. In case of expectant management, fetal demise of the smaller twin or both twins occurs in 8% and 10% of the cases, respectively and 6% of the neonates die within their first month of life [22]. Deterioration of the blood flow parameters is observed in 70–90% of the cases [25]. According to Ishii et al. [26], survival free from neurological complications is reported in only 37% of the sFGR and 55% of the larger twins. In order to monitor fetal wellbeing, assessment of DV blood flow, CTG, weekly biophysical profile — if need be — and elective delivery — depending on the test results, are recommended. Deterioration is typically observed before 30 weeks of gestation [23].

Based on Doppler findings, type 2 sFGR monochorionic twins may be classified as:

- type 2a — peak systolic velocity in the middle cerebral artery (MCA PSV) < 1.5 MoM (multiple of median) and positive A-wave in DV;
- type 2b — MCA PSV ≥ 1.5 MoM and/or absent or negative A-wave in DV [27].

3. Type 3 — cyclical change from positive to absent and reversed end-systolic flow. The variability is the consequence of large (> 2 mm diameter) intertwin arterio-arterial anastomoses, which are characterized by bidirectional blood flow [27, 28]. Large A-A anastomoses account for over 90% of all vascular connections in type 3 sFGR [29]. In order to visualize it, a Doppler gate should be positioned in such a way so as to include the umbilical artery of the sFGR twin as close to the placental cord insertion as possible. Often, both placental cord insertions are located not far from each other and it is also possible to visualize the A-A anastomosis, connecting the umbilical arteries of both umbilical cords. Turbulent blood flow and — after positioning of a Doppler gate — a distinct bidirectional flow allow for visualization of such an anastomosis. Type 3 accounts for approximately 4% of all early-onset sFGR and is associated with the highest disproportion in the sharing of the placental territory between both fetuses. The vascular tree from the sFGR fetal cord may cover up to a 10-fold smaller area of the placenta as compared to the AGA twin [28]. Type 3 sFGR is associated with a risk of fetal demise: 7% for one fetus and 6% for both twins [22]. In the event of sFGR twin demise with no symptoms and no deteriorating parameters on Doppler ultrasound, neurological damage to the other twin occurs in 15–20% of the cases [15, 22]. Weekly assessment of DV blood flow, CTG, and biophysical profile — if need be — is recommended to monitor fetal wellbeing [24]. Due to the risk for fetal demise to both fetuses and neurological morbidities, elective delivery ought to be considered after 32 weeks of gestation and after a course of antenatal corticosteroids was administered [19].

Surveillance of fetal wellbeing is the management of choice in sFGR type 2 or 3. Selective laser photocoagulation of the communicating vessels (SLPCV) in the placenta may be considered to separate placental parts of both twins and to protect the eutrophic fetus from the complications associated with the demise of the other twin. However, it is important to bear in mind that the etiology of sFGR is frequently associated with uneven placental sharing between the fetuses and not only with the presence of anastomoses, which may have a beneficial effect on the development of the sFGR twin. Also, the procedure presents a significant technical challenge due to the absence of differences in the amniotic fluid volume (as compared to the procedure conducted in TTTS), is associated with the risk for preterm labor, premature rupture of the membranes and infection, and in 20% of the cases the dividing membrane between the fetuses in monochorionic diamniotic pregnancy ruptures, which results in a worse perinatal outcome [30]. After a successful laser procedure, intrauterine demise of the smaller twin is observed in 55% of the cases [22]. If laser ablation of the placental anastomoses is performed in type 3 sFGR, intrauterine demise of the sFGR twin is observed in 33% of the cases [31]. During a 28-day follow-up, no neurological morbidity was found in any of the neonates after laser therapy for type 3 sFGR. The SLPCV outcome in case of type 2 sFGR depends on the initial Doppler findings. In type 2a, 93% of AGA and 50% of sFGR fetuses survive, whereas in type 2b, 92% of AGA and 0% of sFGR fetuses survive [27].

Fetal echocardiography may also be applicable in the diagnostic process of complications of monochorionic diamniotic twin gestations [32]. Fetuses from sFGR-complicated gestation present with characteristic hemodynamic abnormalities. The cardiovascular system of the eutrophic fetus is at risk for increased cardiac pre- and afterload because it supplies a part of the circulatory system of the sFGR twin through the A-A anastomoses. As a consequence, hypertrophied heart muscle may be observed in the AGA twin [33], in extreme cases leading to the development of right ventricular outflow tract obstruction [34]. The sFGR twin presents with variable blood flow in the aortic isthmus, depending on vascular resistance in the placental vessels, as is the case in singleton pregnancies complicated by sFGR. In some twins with sFGR, together with abnormal umbilical artery flow (AEDF, REDF, and AREDF), abnormal reversed aortic isthmus flow, which is associated with a higher rate of neurological complications in the neonate and increased perinatal mortality rates, may be visualized (Fig. 3) [35].

Determination of the delivery date in monochorionic pregnancy remains a challenge and is based on several parameters, including gestational age and the range of hemodynamic abnormalities in the sFGR fetus. Data in the literature are limited. Therefore, the management should be tailored to the individual needs of the patient, who should be monitored at a tertiary referral center.

Twin-to-twin transfusion syndrome

Growth discordance between the estimated fetal weights or donor weight of < 10 pc for its gestational age may be one of the symptoms of TTTS. However, it is not the discordance in fetal weight but the polyhydramnios-oligohydramnios sequence, and others, that belong to the criteria for diagnosing TTTS. The matter has been discussed elsewhere, in the guideline for prenatal therapy.

Single intrauterine death in monochorionic pregnancy

A single intrauterine death occurs in 5% of twins and 17% of triplets [36]. Due to the presence of vascular anastomoses in the placenta, in the second or third trimester there is a 10% risk for fetal demise and 26% risk for neurological damage to the other fetus as a result of a sudden transfusion-related event, hypotension and hypoxia of the other

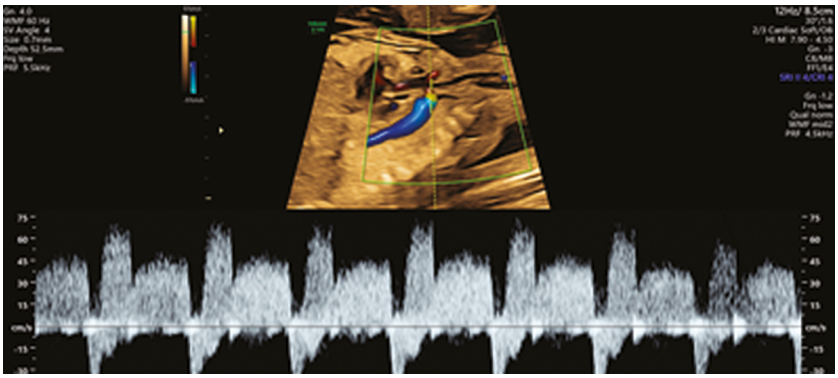

Figure 3. Reversed aortic isthmus flow in the sFGR twin

twin [37, 38]. If a single intrauterine death occurs before 34 weeks of gestation, immediate delivery is not beneficial for the other fetus because it does not lower the risk for central nervous system damage (which is the consequence of hemodynamic changes after cessation of the cardiac function of the first twin) and, additionally, it is associated with prematurity [38]. Surveillance of the other twin using ultrasound tests, performed at regular intervals, to assess peak systolic velocity in the MCA (to detect fetal anemia) and, in more advanced gestational age, to monitor CTG results (preferably automatic STV measurement) is recommended. MCA PSV is typically assessed daily, in the first days after the intrauterine demise of one twin. Intrauterine transfusions for fetal anemia lower fetal mortality rates but do not reduce the risk for neurological damage [39]. After 4–6 weeks, detailed inspection of the fetal brain using ultrasound needs to be performed to search for the consequences of hypoxia and anemia. Fetal MRI may also be considered as it has higher sensitivity for detecting symptoms of hypoxia in the central nervous system. The test is usually performed at least four weeks after the intrauterine demise of the first fetus [40]. In case of intrauterine demise of one of the fetuses in the third trimester, close monitoring of maternal condition is vital, among others due to the risk for coagulopathy.

DIAGNOSIS AND MANAGEMENT IN DICHORIONIC PREGNANCY

Monitoring of fetal growth in monochorionic pregnancy

Repeat ultrasound testing every four weeks to monitor fetal growth is recommended, starting at 20 weeks of gestation, and should be continued for the reminder of the pregnancy.

Fetal growth restriction in dichorionic twin pregnancy

Intrauterine growth restriction of one twin is diagnosed if:

- estimated fetal weight of one twin is < 3 pc for its gestational age

or if 2 out of the 3 criteria presented below have been met:

- estimated fetal weight of one twin of < 10 pc for its gestational age;
- EFW growth discordance of ≥ 25% between the fetuses;
- pulsatility index in the umbilical artery of the smaller twin of > 95 pc for its gestational age [18].

If FGR is diagnosed in one of the twins, it is recommended to monitor the volume of the amniotic fluid, blood flow in UA, MCA, and DV (especially if any abnormalities in the UA and/or MCA flow parameters are found) in the smaller twin, and CTG results (preferably automatic STV measurement), as is done in a singleton pregnancy [41]. Testing for congenital defects, signs of the TORCH syndrome, and genetic abnormalities is advised in early-onset FGR. If signs of early-onset FGR, fetal anatomical abnormalities or ultrasound markers for aneuploidy are present, it is justifiable to obtain the material of the FGR-fetus for genetic testing using amniocentesis or cordocentesis. Obtaining the samples from both fetuses might also be considered. The management is the same as in a singleton pregnancy with FGR [41]. Typically, elective delivery is recommended at 32–34 weeks of gestation.

INTRAUTERINE GROWTH RESTRICTION OF BOTH FETUSES IN TWIN PREGNANCY

Intrauterine growth restriction of both fetuses in a twin pregnancy is 3-fold less common than of one twin in a monochorionic pregnancy and 12-fold less common than of one twin in a dichorionic pregnancy. It is diagnosed in the following cases:

- estimated fetal weight of each fetus of < 3 pc for its gestational age

or

- estimated fetal weight of each fetus of < 10 pc for its gestational age and UA pulsatility index of > 95 pc for its gestational age.

Gestational age needs to be verified based on the first-trimester ultrasound. If intrauterine growth restriction is found in both twins, testing for genetic abnormalities, TORCH syndrome, and pathologies associated with abnormal trophoblast implantation (preeclampsia) should be considered. Fetal demise of at least one twin and neonatal mortality are reported in approximately 30% and 20% of the cases, respectively [42]. Close monitoring of fetal wellbeing (weekly assessment of amniotic fluid volume, blood flow in UA, MCA and DV, and CTG beyond 26 weeks of gestation), and maternal risk for preeclampsia is necessary.

PREMATURE LABOR IN TWIN PREGNANCY COMPLICATED BY SFGR

A single course of corticosteroids (betamethasone 2 × 12 mg i.m. or dexamethasone 4 × 6 mg i.m.) is recommended if the delivery is expected within 7 days, between 26 and 34 weeks of gestation, during 48 hours. If a course of corticosteroids was administered over 14 days earlier and there is a direct risk for preterm labor before 34 weeks of gestation, administration of a single additional course might be considered. Multiple courses of corticosteroids are not recommended.

In cases when the estimated delivery occurs before 32 weeks of gestation, magnesium sulphate infusion for neuroprotection of the fetuses is recommended (4 g $MgSO_4$ i.v. as a bolus over 20 min, followed by 1 g/h by infusion pomp until delivery over 24 h).

Elective cesarean section is recommended if sFGR is diagnosed in a twin pregnancy.

Placenta

Inspection of the placenta is advised: macroscopic appearance and histopathology findings need to be included in the medical records.

Conflict of interest

All authors declare no conflict of interest.

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