ABSTRACT
Fetal or intrauterine growth restriction (FGR/IUGR) affects approximately 5–8% of all pregnancies and refers to a fetus not exploiting its genetically determined growth potential. Not only a major cause of perinatal morbidity and mortality, it also predisposes these fetuses to the development of chronic disorders in later life. Apart from the timely diagnosis and identification of the causes of FGR, the obstetric challenge primarily entails continued antenatal management with optimum timing of delivery. In order to minimise premature birth morbidity, intensive fetal monitoring aims to prolong the pregnancy and at the same time intervene, i.e. deliver, before the fetus is threatened or harmed. It is important to note that early-onset FGR (< 32 + 0 weeks of gestation [wks]) should be assessed differently than late-onset FGR (≥ 32 + 0 wks). In early-onset FGR progressive deterioration is reflected in abnormal venous Doppler parameters, while in late-onset FGR this manifests primarily in abnormal cerebral Doppler ultrasound. According to our current understanding, the “optimum” approach for monitoring and timing of delivery in early-onset FGR combines computerized CTG with the ductus venosus Doppler, while in late-onset FGR assessment of the cerebral Doppler parameters becomes more important.

ZUSAMMENFASSUNG
Die fetale oder intrauterine Wachstumsrestriktion (FGR/IUGR) tritt in ca. 5–8% aller Schwangerschaften auf und definiert einen Fetus, der sein genetisch vorgegebenes Wachstumspotenzial nicht ausschöpft. Sie stellt einen Hauptgrund der perinatalen Morbidität und Mortalität dar und ist zudem mit einer Prädisposition für die Entwicklung chronischer Erkrankungen im weiteren Leben assoziiert. Die geburthilfliche Herausforderung stellt neben der rechtzeitigen Diagnose und der Ursachenklärung einer FGR vor allem die weitere Schwangerschaftsbetreuung mit der Wahl des optimalen Entbindungszeitpunkts dar. Ziel einer intensiven fetalen Überwachung ist es, eine Schwangerschaftsprolongation zur Mini-
Introduction

Growth of the healthy fetus usually follows a linear pattern, i.e., with constant percentile growth, thus exploiting its genetically determined growth potential. A fetus diagnosed to be small at ultrasound requires a structured diagnostic work-up in order to achieve an optimal ante- and perinatal management.

Fetal or intrauterine growth restriction (FGR/IUGR) affects approximately 5–8% of all pregnancies and refers to a fetus not exploiting its genetically determined growth potential. Presently, FGR is classified into early (early-onset < 32 + 0 weeks of gestation [wks]) and late FGR (late-onset ≥ 32 + 0 wks) [1]. FGR is one of the main causes of perinatal morbidity and mortality, and this is especially true when fetal growth problems are not recognised as such before delivery [2]. Moreover, fetal growth restriction apparently predisposes to the development of chronic disorders in later life [3–6].

The percentage of fetuses with FGR due to (relative) uteroplacental dysfunction and/or concomitant relative maternal heart failure increases particularly in late and prolonged pregnancy, and this is associated with a corresponding perinatal risk [7].

Apart from the timely diagnosis and identification of the causes of FGR, the obstetric challenge primarily entails continued antenatal management with optimum timing of delivery. Intensive fetal monitoring aims to prolong the pregnancy in order to minimise preterm morbidity, and at the same time to intervene, i.e. deliver, before the fetus is threatened or harmed. This review summarises the current recommendations of the German AWMF guideline 015/080 “Intrauterine Growth Restriction” [1].

Definitions

The definitions of constitutionally small fetuses and those with fetal growth restriction in international guidelines and literature vary greatly [8]. In particular, the terms “small for gestational age” (SGA) and FGR must be differentiated with regard to content and thus clinical management. In line with the guidelines, this review uses the terms SGA and FGR (IUGR) solely in terms of fetal growth and does not consider any other fetal conditions.

SGA fetuses consistently demonstrate growth rates below the 10th percentile [1]. In many cases this is more a reflection of constitutional factors such as gender, parental height and ethnicity and is usually not linked to a medical condition. SGA fetuses continue to grow linearly and do not exhibit other parameters of fetal distress (e.g., oligohydramnios or Doppler abnormalities); however, it should be noted that the lower the percentile, the higher the morbidity and mortality risk: SGA fetuses with growth below the 3rd percentile have a significantly higher morbidity and mortality risk despite constant percentile growth [9].

SGA fetus must be differentiated from FGR, since in the latter cases the fetus does not realise its genetically determined growth potential. This results in the typical flattened growth curve, i.e., a “crossing of centiles”. Often FGR fetuses also demonstrate growth below the 10th percentile, i.e., they are “small for gestational age”, but a flattened growth curve (and thus FGR) may also appear in fetuses with an estimated weight above the 10th percentile, especially in third trimester late-onset FGR.

FGR is one of the most common causes of obstetric complications with unfavourable perinatal and neonatal outcome, particularly in the context of prematurity. The fetuses in question exhibit a higher prevalence of poor long-term neurological development as well as cardiovascular and endocrinological disorders [3–6]. Almost 30–50% of all intrauterine deaths are related to FGR [10].

According to current expert opinion, fetal abdominal circumference or estimated fetal weight < 3rd percentile and abnormal indices of the umbilical artery are decisive parameters for the definition of early-onset or late-onset FGR [11]. According to the current German guideline, the following definitions apply to SGA and FGR (see box) [1]:

| DEFINITION |
|-----------------|-----------------|
| SGA/FGR definition according to AWMF Guideline 015/080 |
| SGA           |
| • Estimated fetal weight or birth weight < 10th percentile |
| FGR           |
| • Estimated fetal weight < 10th percentile and/or |
| • “crossing of centiles” growth and |
| • Abnormal umbilical artery Doppler ultrasound or |
| • Abnormal uterine artery Doppler ultrasound or |
| • Oligohydramnios |

mierung der Frühgeburtssmorbidität zu erreichen, aber rechtzeitig vor einer fetalen Bedrohung oder Schädigung zu intervenieren, d.h. zu entbinden. Zu beachten ist, dass eine frühe FGR (< 32 + 0 SSW) und eine späte FGR (≥ 32 + 0 SSW) unterschiedlich beurteilt werden sollen. Eine zunehmende Verschlechterung spiegelt sich bei einer frühen FGR in Auffälligkeiten venöser Doppler-Parameter wider, bei einer späten FGR vor allem in der zerebralen Doppler-Sonografie. Die „optimale“ Methode zur Überwachung und Entscheidung zur Entbindung stellt bei einer frühen FGR nach derzeitigem Kenntnisstand die Kombination von computerisiertem CTG und Ductus venosus dar, bei einer späten FGR tritt die Beurteilung der zerebralen Doppler-Parameter in den Vordergrund.
Aetiology and Epidemiology

The pathogenesis of fetal hypotrophy includes maternal, fetal and placental factors (Table 1) [1]. In many cases, the different underlying pathophysiological mechanisms ultimately culminate in placental failure, which occurs as a result of unsuitable transformation of the maternal spiral arteries due to inadequate invasion of extravillous trophoblasts and thus deficient uterine perfusion. This leads to placental hypoxia with secondary injury to the villous architecture [12].

Diagnostic Work-up

Prenatal management according to the maternity guidelines includes regular monitoring of the fundal height. Since the available clinical examinations can only provide limited information, the diagnostic work-up should be extended (initially by ultrasound) in case of abnormalities, i.e., “abdominal circumference too small/fundal height too low”. Fig. 1 summarises the examination algorithm in suspected SGA/FGR.

Checking the gestational age

The diagnosis of FGR includes the most accurate assessment of the gestational age possible. Ideally, this is based on the crown-rump length (CRL) in the first trimester. This parameter provides the most reliable information [13]; in case of discrepancies in an otherwise unremarkable embryo, the (anamnestic) gestational age should be corrected by ultrasound, if it differs by at least 7 days from the age determined by ultrasonography – unless the date of conception is definitely known (e.g. IVF/ICSI) [1].

If CRL measurements are not available (e.g., if pregnancy is diagnosed late), the gestational age may also be estimated from the biparietal or transcerebellar diameter.

A discrepancy between the gestational age calculated based on the last period and according to ultrasound may be the first sign of an early developmental disorder. Such cases call for further assessment and intensive monitoring.

Fetometry

Apart from estimated weight, fetal abdominal circumference is the most important indicator of impaired fetal growth. Fetal weight can be determined with the Hadlock formula, which is recommended in increased risk of FGR [1]. It should be noted that parental characteristics need to be taken into account when estimating weight.

According to the definition of FGR, assessment should include not only the current estimated weight, but also the growth curve in order to detect flattening of the latter, especially since FGR is not limited to weights below the 10th percentile.

Amniotic fluid

Amniotic fluid volume is often reduced in FGR, as this disorder can be accompanied by fetal oliguria. But usually the amniotic fluid volume is unremarkable [1, 14]. Evaluation of the amniotic fluid volume may be based on the “single deepest pocket” (SDP) technique or measurement of the amniotic fluid index (AFI) [15], with the SDP appearing to be more useful in predicting adverse outcome [16].

If the suspected diagnosis of SGA/FGR is confirmed, this should be followed by further evaluation of the causes and assessment of the fetal condition. This includes Doppler ultrasound assessment of the uteroplacental unit (uterine and umbilical arteries) and possibly other fetal vessels (middle cerebral artery, ductus venosus), as well as detailed diagnostic ultrasonography. In addition, differential diagnosis may profit from genetic assessment of any chromosomal pathology and/or fetal infection when planning the subsequent management [1].

Detailed diagnostic ultrasonography

Differential diagnostic assessment of possible FGR calls for further differentiated diagnostic organ work-up (along the lines of the German DEGUM II criteria) (Fig. 1) [1]. It should be noted that structural abnormalities of the fetus are indicative of genetic-syndromal diseases, especially in early-onset and multiple pathologies [17]. At least the genetic analysis should be offered.

Doppler ultrasound

Doppler ultrasound is mandatory in suspected SGA/FGR, not only for the differential diagnosis of SGA/FGR, but also for determining the cause of the FGR. Higher indices in the uterine and umbilical arteries indicate placental disorder along the lines of placental

Table 1: Causes and risk factors of fetal growth restriction (according to [1]).

<table>
<thead>
<tr>
<th>Origin</th>
<th>Causes and risk factors</th>
</tr>
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</table>
| Maternal | - Preexisting diseases (e.g., diabetes, hypertension, cardiac disorder, renal disorder, autoimmune disorder (antiphospholipid syndrome, systemic lupus erythematosus), chronic respiratory disorder, severe anemia)  
- Hypertensive disorders of pregnancy, pre-eclampsia  
- Prior FGR (either previous pregnancy or maternal FGR)  
- Substance abuse (nicotine, alcohol, drugs)  
- Low socio-economic status  
- Infertility treatment  
- Weight (increased or very low body mass index)  
- Age (< 16 years; ≥ 35 years)  
- Embryo-/fetotoxic drugs and teratogens |
| Fetal | - Chromosomal disorder and syndromal disease  
- Intrauterine infection  
- Malformation  
- Multiple pregnancy |
| Placental | - Abnormal placentation  
- Placental infarctions  
- Chronic placental abruption  
- Umbilical cord pathology (velamentous insertion, single umbilical artery)  
- Placental mosaic  
- Placental tumours |
failure. When diagnosing FGR, other fetal vessels (middle cerebral artery, ductus venosus) should be examined as well to evaluate the fetal condition [1].

Screening, Prediction and Prevention

At present, there is no screening approach available combining good sensitivity and specificity with negative or positive predictive value [18]. Similar to the first-trimester risk evaluation in pre-eclampsia, screening for fetal growth restriction can be performed by combining the maternal medical history, Doppler ultrasound of the uterine arteries, mean arterial blood pressure, and the biochemical marker PAPP-A [19]. Even if the detection rate does not match that of pre-eclampsia screening, it can be used to detect some pregnancies with a high risk of FGR which will then be closely monitored.

In the second trimester Doppler ultrasound of the uterine arteries in low-risk cohorts is only of limited use, while in a cohort at risk it offers a moderate predictive benefit for early detection of FGR [20]. Therefore, Doppler ultrasound of the uterine arteries when screening for FGR is regarded as somewhat under discussion [21]. However, abnormal findings should prompt regular ultrasound studies of growth and Doppler checks (uterine and umbilical arteries).

The combination of Doppler ultrasound and angiogenic factors (e.g., sFlt-1/PlGF ratio) appears to improve the FGR prediction, as does the combination of fetal biometry and the angiogenic marker [22–24]. However, further studies are still needed before widespread clinical use.

Antenatal diagnosis of FGR is essential, since this has a positive effect not only on the course of pregnancy but also on neonatal outcome [2, 25]. Despite closely monitored management internationally and also in Germany, the number of unidentified antenatal FGR cases is still large [1, 25].

According to maternity guidelines, fetometry is performed between 18 + 0 and 21 + 6 wks and 28 + 0 and 31 + 6 wks. This approach detects early-onset FGR quite well, but does not identify the majority of late-onset growth restrictions (approx. 70–80%
of FGR), particularly if no Doppler ultrasound evaluation or subsequent biometry is performed.

In order to improve this situation, the definition of FGR requires that the assessment should include not only the current estimated weight, but also the growth curve in order to detect flattening of the latter, especially since FGR is not limited to weights below the 10th percentile. In case of irregularities, further studies, i.e., repeat biometry, Doppler ultrasound and possibly measurement of the angiogenic markers could be performed [26]. This is particularly important, since early/correct diagnosis of FGR can reduce the perinatal risk [27].

An (additional) late biometry at ≥ 36 wks improves the FGR detection rate by a factor of 3 [28, 29]. Combined with the assessment of fetal growth over time it is possible to detect a subgroup with high perinatal risk [28, 30]. Pathologies on Doppler ultrasound (maternal, fetoplacental or fetal) correlate with less favourable perinatal outcome [27, 31, 32]. 15–20% of cases with late-onset FGR exhibit abnormal cerebral perfusion – with unremarkable blood flow in the umbilical cord; by determining the cerebroplacental ratio (CPR) fetuses with and without growth problems at increased risk of unfavourable perinatal outcome can be detected more easily [33–35]. The combination of biometry, uterine Doppler ultrasound and CPR in the third trimester can detect the majority of fetuses with a high risk of intrauterine fetal death (IUFT) [31], but appears to be of little help in detecting SGA/FGR in non-selected populations [36]. The combination of fetal biometry and measurement of angiogenic factors (especially the sFlt-1/PIGF ratio) also seems to be useful in FGR detection [23, 37, 38].

Unlike in pre-eclampsia, the administration of low-dose aspirin appears to be only moderately successful in the prevention of FGR (although the trial did not have enough statistical power for the prevention of FGR) [39]; this also requires further studies. The results of the German multicentre trial on the benefit of NO-donor PETN in women with pathological Doppler ultrasound of the uterine arteries in the second trimester are expected soon [40].

SGA/FGR Management

FGR management is a challenge for all involved: Fetal hypoxemia should be diagnosed early to avoid irreversible damage and intrauterine death. On the other hand, in order to minimise the sequence of prematurity pregnancy should not be terminated too early.

Parents must be involved in all decisions and the consequences of the different options must be explained to them. In particular, the increased risk of intrauterine fetal death under “watchful waiting” must be contrasted with the increased mortality and morbidity risk of prematurity at delivery. Thus, close antenatal and perinatal cooperation with the neonatologists is necessary to provide the parents with adequate information.

It is important to note that early-onset FGR should be assessed differently than late-onset FGR. In early-onset FGR progressive deterioration is reflected in abnormal venous Doppler parameters, while in late-onset FGR this manifests primarily in cerebral Doppler sonography (▶Table 2) [1, 41].

No individual monitoring approach can predict the outcome of FGR in valid fashion; a combination of different approaches is recommended. In order to improve the perinatal outcome, FGR monitoring requires in particular ultrasonography and above all Doppler ultrasound.

Management of pregnancies with SGA or FGR fetuses relies on a combination of different examination techniques, which are summarised in ▶Fig. 2 [1]. Monitoring of fetal growth, amniotic fluid volume, and arterial and venous fetal vessels is mandatory; CTG/computerised CTG monitoring also provides important information on the fetal condition [1, 42].

Biometric monitoring

Serial ultrasonic monitoring of fetal growth is essential in the management of fetuses with SGA/FGR. However, it should be noted that – also due to the limitations of weight estimation by ultrasonography – the intervals between examinations should not be too short: the interval between such examinations should be at least 2, preferably 3 weeks [1, 43].

Doppler ultrasound

- Umbilical artery:
  Doppler ultrasound of the umbilical arteries permits haemodynamic changes to be detected in the course of the disease. In FGR normal resistance ratios also indicate a low risk of unfavourable perinatal outcome and low perinatal mortality [9]. The progosis worsens depending on the degree of increase in resistance [41]. In so-called ARED flow (absent/reversed end-diastolic flow) about 70% of the placental vessels are occluded [44], which in “reversed end-diastolic flow” increases the risk of perinatal mortality by a factor of 5. ▶Fig. 2 lists the recommended study intervals based on studies of progressive Doppler deterioration [45]. If the resistance in the umbilical arteries is unremarkable, two-week intervals appear to be adequate [46].

- Ductus venosus:
  In the care of early-onset FGR the ductus venosus is a key vessel [41], and management of early-onset FGR should base its assessment on the evaluation of this vessel [1]. Changes in the venous circulation including reversed blood flow usually appear later than changes in the arterial system [41]. Pathophys-

▶ Table 2 Early-/late-onset FGR (according to [42]).

<table>
<thead>
<tr>
<th>Early-onset FGR (&lt; 32 + 0 wks – 1–2%)</th>
<th>Late-onset FGR (≥ 32 + 0 wks – 3–5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem: Management</td>
<td>Problem: Diagnosis</td>
</tr>
<tr>
<td>Placental failure: major (abnormal fetoplacental perfusion, high correlation with pre-eclampsia)</td>
<td>Placental failure: minor (often normal fetoplacental perfusion, low correlation with pre-eclampsia)</td>
</tr>
<tr>
<td>Hypoxia ++: systemic cardiovascular adaptation</td>
<td>Hypoxia ±: central cardiovascular adaptation (“brain sparing”)</td>
</tr>
<tr>
<td>Fetal immaturity – higher hypoxia tolerance – longer course possible</td>
<td>Fetal maturity – low hypoxia tolerance – no (or very short) course</td>
</tr>
<tr>
<td>High morbidity and mortality, low prevalence</td>
<td>Low mortality (but main cause of IUFT), poor long-term outcome, higher prevalence</td>
</tr>
</tbody>
</table>
iologically, increasing cardiac dysfunction results in decreased diastolic blood flow or increased pulsatility in the ductus venosus including loss of the positive a-wave; absent a-wave or reverse blood flow is an indication of cardiovascular instability and may be a sign of imminent or already present acidemia [47–49], with the risk of intrauterine death doubling daily [45, 47].

### Middle cerebral artery:
Examination of the middle cerebral artery (MCA) can detect progressive hypoxaemia, since the increasing fetal compromise leads to a redistribution of blood (“brain-sparing effect”) [41]. MCA resistance decreases and is considered abnormal for a pulsatility index (PI) < 5th percentile [1].

While in early-onset FGR the predictive power of the MCA is limited with regard to predicting unfavourable perinatal outcome [50–52], the examination of the MCA, preferably when combined with examination of the umbilical artery as the so-called cerebroplacental ratio (CPR), gains importance in the management of late-onset FGR. On the one hand, CPR allows a more precise diagnosis of late-onset FGR [42], while various studies have demonstrated a benefit in predicting unfavourable perinatal outcomes in pathological CPR, i.e., ratios between umbilical artery and middle cerebral artery (< 5th percentile or < 1) [53–56].

### (Computerised) Cardiotocography (cCTG)
According to maternity guidelines cardiotocography (CTG) should always be performed as part of prenatal care if placental insufficiency is suspected [1]. However, it detects acute rather than chronic courses [41] and therefore should never be the sole monitoring technique when managing FGR [1].

To minimize the limitations of a CTG examination (subjective assessment), a computer-based analysis of the CTG can be employed. Major benefits of this technique include the higher degree of objectivity of the assessment as well as the option of analysing the short-term variation (STV) [57]. As in uncomplicated pregnancies, the STV increases with gestational age in FGR, but the STV values are generally lower [58]. An STV of 4.5 ms rules out fetal acidemia (NPV 100%) [59], while decreasing STV values are associated with earlier delivery, lower birth weight, lower pH of the umbilical artery, poorer acid-base status and worse neonatal outcome [60].

Measuring the STV and observing its course over time may detect subtle changes, which can be helpful for better timing of the delivery [61], thus underlining the use of this measure in FGR management; nevertheless, it must be taken into account that CTG changes in FGR only manifest themselves rather late [41, 61], and that the short-term variation is also affected by medication (e.g., with antenatal corticosteroids), which must therefore be considered when interpreting the results [1, 62, 63].

### Other Measures

#### Inpatient/outpatient management
In general, surveillance of pregnancies with FGR may be performed in an outpatient setting, as there is no evidence-based data on which to base indications for inpatient monitoring. With increasing severity and fetal impairment, however, inpatient monitoring can be helpful if close intervals between examinations become necessary. The link between early-onset FGR and pre-ec-
lampsia should also be noted. The decision for outpatient or inpatient care should be made on a case by case basis [1].

**Antenatal corticosteroid administration**

One challenge in obstetrics (and thus also in the management of FGR) is in estimating the time of expected delivery in the preterm setting. If delivery is expected within the next 7 days, corticosteroids should be administered [1,64]. The benefits of antenatal corticosteroids are also seen in growth-restricted fetuses. It should be noted, however, that corticosteroid administration may temporarily reduce heart rate variation as well as fetal body and respiratory movements; these changes normalise within 72 hours [1].

In addition to the “timing” of steroid administration noted above, it generally is true that non-critical administration of steroids should not be undertaken in all FGRs, since corticosteroids – in addition to their undisputed positive benefits – also have various negative effects (including reduced growth, delayed neurological development, stress, hypertension). In addition, fetuses with FGR, especially with increasing hypoxaemia, already possess high cortisol levels, and after 30 wks fetuses with FGR develop RDS much less often than eutrophic fetuses. There is insufficient data on the effect of steroids on long-term outcome in fetuses > 30 wks with FGR.

Therefore, the goal should be to avoid as much as possible antenatal steroid application, especially repeated courses in women who in the end do not give premature birth [65].

**Magnesium for fetal neuroprotection**

The antenatal intravenous administration of magnesium appears to have a neuroprotective effect and thus may help to reduce the risk of neurological damage. Since FGR correlates with an increased risk of fetal prematurity, (inter)national medical societies recommend the administration of magnesium sulphate before 32 + 0 wks for neuroprotection when birth is imminent [1,64].

**Birth/Delivery in SGA/FGR**

**Place of delivery**

In order to ensure immediate and continuous care in the FGR setting, delivery should proceed in a perinatal centre with neonatal intensive care unit and an experienced paediatric team [1].

**Time of delivery**

When planning the timing of delivery, the risks of preterm delivery must be weighed against those of continuing the pregnancy and/or the maternal risks. Maternal delivery criteria apply regardless of the gestational age and extent of the FGR.

In terms of the fetus, the timing of delivery is governed not only by the gestational age but also the Doppler ultrasound findings (Fig. 2). As noted above, early-onset FGR is accompanied by a serious deterioration, particularly in venous abnormalities (ductus venosus), while late-onset FGR is associated with cerebral vascular disorders (ACM, CPR). This is reflected in the recommendations of (inter)national guidelines and experts [1,42,66,67].

Note: Just like decelerations, the cut-off values (cCTG and duc-
utus venosus) given below are late signs of fetal deterioration. Some of these cases may already suffer from myocardial dysfunction and possibly hypotension, and the fetal adaptation mechanisms no longer fulfil their protective function. This implies that the significance of these parameters diminishes with increasing gestational age.

- **cCTG:**
  - In case of new-onset CTG pathologies (recurrent, unprovoked, and refractory decelerations at any time) delivery should be considered [1,61].
  - Delivery should be considered if STV is < 2.6 ms at 26 ± 0 to 28 ± 6 wks and < 3.0 ms at 29 ± 0 to 32 ± 0 wks (Fig. 2) [1,61].
- **Ductus venosus (early-onset FGR):**
  - According to current knowledge, pathological findings of the ductus venosus may be an indication for delivery if the fetus is viable and antenatal corticosteroids have been administered [1]. Depending on the gestational age and possible additional findings, delivery should be discussed with the expectant mother in case of increased resistance (> 95th percentile – accompanied by a decreased a-wave); in case of absent or reverse a-waves delivery is indicated [1,41,42,61,66].

According to our current understanding, the combination of computerised CTG and ductus venosus is the “optimum” approach for monitoring early-onset FGR [68]. If Doppler ultrasound of the ductus venosus is unremarkable and in the absence of cCTG pathology, it may nevertheless be appropriate to terminate the pregnancy earlier.

- **Umbilical artery:**
  - With absent or reversed end-diastolic flow (AREDFlow) in the umbilical artery the prognosis can be poor [1,41,69], but the morbidity and mortality associated with preterm birth before 32 ± 0 wks is also rather high [70], while continued pregnancy offers clear benefits in outcome [71]. Taking this into account, for ARED-flow the current guideline recommends: In REDF, delivery may be considered from 30 ± 0 wks and should be performed at 32 ± 0 wks. In absent end-diastolic flow (AEDF) the mortality risk is lower, but delivery should be performed at 34 ± 0 wks [1]. In an otherwise unremarkable course, waiting until these weeks of pregnancy is possible and after two years does not result in any significant differences in morbidity and mortality [72].
  - Increased resistance in the umbilical artery (PI > 95th percentile) is also linked to increased risk in perinatal morbidity and mortality, but with low predictive power. With increased PI > 95th percentile, delivery is therefore recommended from 37 ± 0 wks [1].
- **Middle cerebral artery/cerebroplacental ratio:**
  - In the preterm setting (< 37 ± 0 wks), the prognostic power of the MCA is of limited use in predicting acidemia and poor perinatal outcome, and should not be used to determine delivery timing at this stage [1]. Delivery should be considered starting at 37 ± 0 wks if resistance in the MCA is low (PI < 5th percentile) [1].
At present, the cerebroplacental ratio (CPR) is still under contention, since precise limits in particular have not been clearly evaluated yet. Since some studies have shown that an abnormally low CPR is a predictor of poor perinatal outcome, delivery can be considered from 37 + 0 wks [1].

Since fetuses with isolated SGA, i.e. fetal growth < 10th percentile, unremarkable Doppler findings and no additional risks, have an increased risk of intrauterine death, despite a generally favourable outcome, earlier delivery from 38 + 0 wks may be considered in SGA fetuses as well. In fetuses with isolated SGA prolonged pregnancy should be avoided [1], because ultimately SGA and GFR cannot be reliably differentiated with current techniques of fetal monitoring (biometry, utero-umbilico-fetal Doppler, BPS, NST) in all cases, and relative uteroplacental failure is increasingly seen close to the expected date of delivery.

When Doppler ultrasound and cCTG are unremarkable, isolated growth arrest is not an independent factor for immediate termination of pregnancy. These constellations should always consider the gestational age and the measurement interval should be checked in order to minimise the systematic error when estimating the weight by ultrasonography [1].

Type of delivery

In addition to gestational age, parity and cervical maturation, various other factors such as the presence of abnormal findings (Doppler, cCTG) and other fetal or maternal specifics or complications must be taken into account when deciding on the type of delivery, and this decision must be made for each patient individually [1]:

In FGR with unremarkable Doppler findings or increased pulsatility in the umbilical artery (> 95th percentile) – not with ARED flow – labour can be induced and vaginal delivery attempted. However, the higher risk of complications must be taken into account mandating continuous intrapartum monitoring [1].

In abnormal Doppler findings such as increased resistance in the umbilical artery (not ARED flow) and in late-onset FGR with abnormal ACM/CPR values, induction of labour and vaginal delivery are possible, with continuous intrapartum monitoring mandatory [1].

In early-onset FGR with pathological cCTG, abnormal ductus venosus and/or especially in ARED-flow, caesarean section is usually recommended and performed, if only because of the increasingly impaired fetal condition that this situation signifies. Also in very early weeks of pregnancy caesarean section must be performed if the termination of pregnancy is indicated and when there is no meaningful option to induce delivery [1].

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Conflict of Interest

The authors declare that they have no conflict of interest.

References


Visan V, Sciprcaiu IS, Socolov D et al. Better prediction for FGR (fetal growth restriction) with the sFlt-1/PlGF ratio: A case-control study. Medicine (Baltimore) 2019; 98: e16069


Villalain C, Herranz I, Quezada MS et al. Fetal Biometry and Doppler Study for the Assessment of Perinatal Outcome in Stage I Late-Onset Fetal Growth Restriction. Fetal Diagn Ther 2018; 44: 264–270


Resnik R, Mari G. Fetal growth restriction: evaluation and management. 04.05.2020. Online (last access: 04.05.2020): www.uptodate.com


Vasconcelos RP, Brazil Frota Aragao JR, Costa Carvalho FH et al. Differences in neonatal outcome in fetuses with absent versus reverse end-diastolic flow in umbilical artery Doppler. Fetal Diagn Ther 2010; 28: 160–166

