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The role of estimated fetal weight discordance in dichorionic twin pregnancies

Short title: EFWd in dichorionic twins

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ABSTRACT

Evaluation of relative fetal growth in the form of estimated fetal weight discordance (EFWd) is a necessary element of any ultrasound examination in twin pregnancies. It is one of the criteria for the diagnosis of selective fetal growth restriction (sFGR) according to the most established worldwide guidelines. Apart from the effectiveness of this parameter for the diagnosis of sFGR, it may also be used as an independent factor for risk stratification of neonatal and maternal complications. Furthermore, numerous studies have proven the greater prognostic value of EFWd in dichorionic pregnancies, which may result from differences in the pathogenesis of fetal growth abnormalities in mono- and dichorionic pregnancies. Because of the variability of this parameter throughout pregnancy, there is an ongoing discussion regarding replacing or individualizing it with percentile charts. An additional element, complementary to EFWd in assessing the risk of complications in twin pregnancies is the use of this measurement in combination with Doppler assessment, which increases its predictive value. The use of EFWd as one of the factors influencing care and decision-making in dichorionic twin pregnancies seems to be a simple and effective method, however, further research assessing the use and possible applications of this indicator is necessary.

Keywords: intertwin discordance; estimated fetal growth; dichorionic twins; twin pregnancies

INTRODUCTION

Twin pregnancies are associated with a higher risk of complications, including abnormal fetal growth. This issue is usually managed with stricter antenatal fetal surveillance which consists of serial ultrasound examinations assessing fetal growth and fetal wellbeing [1]. One of the monitored fetal parameters, unique for multiple pregnancies, is estimated fetal weight discordance (EFWd). Excessive discordance in estimated fetal weight is one of the criteria for diagnosis of selective fetal growth restriction (sFGR) and is an independent factor increasing the risk of stillbirth and morbidity of the smaller twin [2, 3]. The differences between cutoff values and criteria used for diagnosis of sFGR, concerns regarding relevant use and selection of centile charts as well as similarities during sFGR in singleton and dichorionic twin pregnancies are the subject of an ongoing debate between obstetricians throughout recent years. The need for a consensus regarding the diagnostic criteria as well as the management of patients whose pregnancies are complicated by sFGR has also been stressed recently [4, 5]. Apart from the assessment of fetal growth abnormalities, EFWd is an important predictive tool for both maternal and fetal complications. It is especially notable in dichorionic twin pregnancies and thus EFWd may become a promising tool for optimization of perinatal care in these pregnancies [2, 6]. This review will focus principally on EFWd assessment in dichorionic twin pregnancies as an independent predictive factor of neonatal and maternal complications, its use in the diagnosis and management of patients with pregnancies complicated by sFGR as well as the most promising alternatives which may soon complement or replace EFWd assessment. Other possible applications of EFWd in the assessment and prediction of complications in dichorionic twin pregnancies will also be discussed as the knowledge of these applications may allow more optimal management and decision making.

sFGR in dichorionic twin pregnancy — diagnosis and management

There are currently several similar established schemes for the diagnosis of sFGR in dichorionic twin pregnancy. Each one of them includes EFWd as one of the diagnostic criteria. According to ISUOG (International Society of Ultrasound in Obstetrics and Gynecology), the diagnosis of sFGR is made if EFW of one twin is < 10% and EFWd is 20% or above. The authors of this guideline also suggest stricter antenatal surveillance in patients

with EFWd of 25% and more due to a significantly higher risk of stillbirth and perinatal death [7]. The most recent European guideline, based on the Delphi procedure, suggests the diagnosis of sFGR when EFW of one fetus is $< 3\%$ or the combination of two out of three following criteria is present: EFW of one fetus $< 10\%$, EFWd $\geq 25\%$, or UA-PI (uterine artery pulsation index) of the smaller fetus $> 95\%$ [4]. ACOG (American College of Obstetrics and Gynecology) in its most recent 2021 guideline on twin and higher order pregnancies identifies patients with EFWd $\geq 20\%$ as requiring stricter antenatal surveillance while not defining the criteria for the diagnosis of sFGR based on this parameter [8]. Currently there is no consensus regarding the superiority of any of the guidelines, but the initial prospective studies show that the use of Delphi criteria when compared with ISUOG criteria is associated with fewer cases of sFGR and similar outcomes. These findings suggest that the use of Delphi criteria may lead to a lower false positive rate [9].

Another debated subject is the use of proper percentile charts in fetal growth monitoring. Currently, some authors advocate the use of individualized charts for twin pregnancies, according to some, independent for mono- and dichorionic pregnancies [10]. Others suggest that the use of singleton percentile charts may cause a higher detection rate and thus stricter monitoring in pregnancies with an elevated risk of stillbirth [7]. According to recent studies, both prospective and retrospective, percentile charts individualized for twin pregnancies allow better selection of the population that is associated with a higher risk of perinatal morbidity and mortality [11–13]. Furthermore, the use of such charts allows the reduction of the population under strict antenatal surveillance as well as the avoidance of unnecessary interventions [14, 15]. Unfortunately, the consensus in this area has not yet been achieved, principally due to concerns about exclusion from monitoring of some twin pregnancies with an elevated risk of perinatal morbidity and stillbirth (which is elevated independently in twin pregnancies, regardless of other comorbidities) [5].

EFWd assessment and possible alternatives

Estimated fetal weight discordance in twin pregnancies is always present to some degree. To this day several cut-off values have been proposed to define this finding as pathological [16]. Assessment based on a single cut-off value, despite facilitating decisions on the diagnosis and management of sFGR, does not take the physiological variations of EFWd throughout the pregnancy into account. This may lead to overdiagnosis of abnormal EFWd in late pregnancy and underdiagnosis in its earlier stages [1]. According to Amyx et al., the median of EFWd in uncomplicated dichorionic twin pregnancy shifts from about 5.9% at 15

weeks to about 8.4% at 38 weeks [17]. Stirrup et al. assessed the value of the 95th of EFWd in dichorionic pregnancies which changed from 18.1% at 20 weeks to 21.9% at 30 weeks [1]. The authors suggest that the implementation of percentile charts based on gestational age for EFWd assessment may be beneficial for the identification of the high-risk population as well as management optimization. Nevertheless, because of the limited data available, further research in this area is required [1].

There are also alternative parameters postulated for the assessment of relative fetal growth in twin pregnancies. One of them is AC (abdominal circumference) discordance. AC values in dichorionic pregnancies are like those observed in singletons up to 32 weeks of gestation and lower afterward [10]. A study by Stirrup et al. found that the value of AC discordance measured between 20 and 30 weeks is relatively constant at the level of about 10–11% [1]. Gelman et al. found that AC discordance acquired in a single measurement in the third trimester has a similar predictive value to EFWd in predicting low birth weight in dichorionic twin pregnancies. The highest diagnostic value was found for the level of 7.1% (AUC-0.72) [18]. Furthermore, the values of AC discordance > 30% are an independent predictive factor of neonatal morbidity and NICU (neonatal intensive care unit) admission [19]. These features of AC discordance as well as the simplicity of assessment based on a single measurement make this parameter a promising tool for relative fetal growth assessment in twin pregnancies [1]. However, to date, the value of this parameter in the prediction of neonatal morbidity and mortality has not been sufficiently studied.

Although there are multiple options available for individualization of EFWd assessment concerning chorionicity and gestational age as well as promising alternatives for relative fetal growth monitoring in twin pregnancies, EFWd at the level of 20% or 25% is still the most widely accepted cut-off value [4, 7, 8]. This is mostly due to the simplicity of measurement, without the need for additional diagnostic tools, as well as its well-documented correlation with infants' prognosis.

EFWd as a risk factor for neonatal morbidity and mortality in dichorionic twin pregnancies

EFWd is a valuable parameter in dichorionic twin pregnancies also because the birth weight discordance in twins is an independent risk factor for neonatal mortality and morbidity. EFWd as of the most recent ultrasound examination is also the most intuitive and effective method of birth weight discordance evaluation [2, 3, 20–22].

Neonatal and perinatal mortality, the risk of stillbirth, NICU admission as well as numerous neonatal morbidities are directly related and proportional to birth weight discordance in twin pregnancies [2, 3, 22]. Di Mascio et al., in their systematic review and meta-analysis of 20 studies, found that birthweight discordance of only 15% or more increases the risk of neonatal respiratory and neurological morbidity as well as perinatal mortality and stillbirth in dichorionic twins. This finding further highlights the importance of EFWd assessment in these pregnancies. Birthweight discordance $\geq 20\%$ was found to be independently associated with the risk of all assessed morbidities and the risk rose proportionally to the discordance [2]. This study, however, did not find significant differences between neonatal morbidity and mortality rates in larger and smaller twins. The risk of morbidities in monochorionic twins included in this study was not significantly associated with EFWd. This finding suggests its greater role in dichorionic twins as well as probable differences in the pathogenesis of neonatal morbidities [2]. Another meta-analysis by D'Antonio et al. assessed the risk of twin mortality and found that in dichorionic pregnancies the smaller twin has an elevated risk of stillbirth [odds ratio (OR) 2.75 (1.31–5.76)] and perinatal death [OR 2.27 (1.15–4.48)] in cases of EFWd $\geq 20\%$. In cases with EFWd $\geq 25\%$, the risk of neonatal death is also elevated [OR 4.66 (1.8–12.4)] [3]. This study has also found an association between neonatal death and EFWd $\geq 25\%$ in monochorionic pregnancies with no significant difference in risk between smaller and larger twins [3].

Long-term complications of twins with increased EFWd

Birthweight discordance in twin pregnancies is an important factor not only in the risk stratification for perinatal morbidity but also plays a significant role in further neurological development of these children. Halling et al. comparing pairs of twins with birthweight discordance $\geq 20\%$ at the age of 2–3.5 have found that the smaller of the twins achieved lower scores in cognitive, linguistic, and motor development. The differences in cognitive development were significant even after adjustment for prematurity, although these were more pronounced in pregnancies delivered before 33 weeks [23]. Goyen et al. in a study comparing neurodevelopment in 20 pairs of twins born prematurely, with birthweight discordance $> 15\%$ and very low birthweight found lower Griffith scale scores and lower somatic growth in the smaller of the twins [24]. In a recent retrospective study comparing the differences in early and late morbidities between mono- and dichorionic twins with increased EFWd, Kim et al. found a more frequent developmental delay in dichorionic twins between 1 and 2 years of age ($p < 0.001$). Dependence of abnormal long-term development on increased EFWd further

emphasizes the significant role of this parameter as a predictor of not only the early but also late morbidity in children from dichorionic twin pregnancies [25].

Maternal morbidity in pregnancies complicated by increased EFWD

Apart from the increased morbidity in children born from twin pregnancies complicated by increased birthweight discordance, the risk of maternal complications is also found in these pregnancies. Fetal growth abnormalities often share the pathophysiological mechanism with preeclampsia spectrum disorders. This relation is found also in twin pregnancies and thus the higher incidence of preeclampsia in pregnancies complicated by sFGR is not surprising [26]. Among the monitored parameters, EFWD is an important predictive factor of preeclampsia-related complications in dichorionic twin pregnancies. Qiao et al. have found a significant increase in the risk of preeclampsia for every 10% of EFWD which suggests a proportional relation between EFWD and preeclampsia risk. This relation was found regardless of the presence of SGA in any of the twins. This stresses the independent role of EFWD in the prediction of preeclampsia-related maternal complications. Furthermore, this study did not show such a correlation in monochorionic pregnancies, although the authors suggest that it may have been caused by the earlier time of delivery in patients with monochorionic twin pregnancies (before the development of preeclampsia) [27].

The relation between hypertensive disorders of pregnancy and relative fetal growth in dichorionic pregnancies is also confirmed by a study by Sparks et al. which found a higher incidence of EFWD $\geq 20\%$ both with [aOR 2.94 (1.57–5.48)] and without SGA [aOR 2.68 (1.48–4.87)] in patients with hypertension in pregnancy. In patients with chronic hypertension, the risk was increased approximately twofold. Higher discordance between twins within pairs was also found in this group. The study has found no significant correlation between hypertension in pregnancy and the incidence of SGA below the 5th and 10th percentile in one or both twins (while using singleton percentile charts) [28].

Zhu et al. in a recent study, apart from the elevated risk of hypertensive disorders of pregnancy in cases with increased EFWD, have also found a correlation between these complications and the discordance in crown-rump length (CRL) $\geq 10\%$ measured in the late first trimester. The patients in this group had an increased risk of early-onset preeclampsia [risk ratio (RR) 2.27 (1.28–4.03)]. (29) EFWD $> 20\%$ at 24 weeks is also associated with a higher incidence of preeclampsia [OR 5.47 (1.68–17.81)] in dichorionic twin pregnancies [6]. The results suggest a relation between abnormal development of the placentas and relative fetal growth in dichorionic twin pregnancies which becomes apparent from the early stages of

the pregnancy. When confirmed in further studies, EFWd may serve as an additional predictive factor of hypertensive disorders, allowing better monitoring throughout the pregnancy and warranting preventive interventions.

Apart from the risk of hypertensive disorders that is rooted in the pathogenesis of sFGR, increased birthweight discordance ($\geq 20\%$) is also associated with a higher incidence of PPH (postpartum hemorrhage). In a study by Cao et al., a correlation was found between increased birthweight discordance and the incidence of PPH $\geq 1000\text{mL}$ [OR 1.62 (1.05–2.51)] and PPH requiring invasive treatment [OR 1.62 (1.00–2.63)]. This association was especially apparent in patients with twin pregnancies complicated by FGR and sFGR, although these complications were not predictive of PPH. The authors have also found a stronger correlation between birthweight discordance and PPH in dichorionic twin pregnancies [30]. Another disorder associated with increased EFWd in early pregnancy is placenta previa. Kim et al. have found a higher incidence of placenta previa in patients with EFWd $> 20\%$ measured between 20 and 24 weeks [OR 7.4 (1.56–35.06)]. The study however has not shown a significant correlation between this condition and increased EFWd measured in the third trimester (28–32 weeks). Despite the higher incidence of placenta previa which is often associated with an elevated blood loss in the peripartum period, the researchers have not found an association between EFWd and PPH [6]. Because of the inconsistent results and relatively small study populations, further research is required to evaluate the use of EFWd in the prediction of complications other than the preeclampsia spectrum. However, if these associations are confirmed, EFWd may become a useful parameter in selecting a high-risk population that requires especially careful peripartum monitoring.

The use of Doppler in risk stratification of twin pregnancies with increased EFWd

Doppler assessment of fetal vessels is an important element of the diagnosis and management of singleton pregnancies complicated by FGR [31]. The role of Doppler in twin pregnancies is also notable but, due to a smaller number of studies evaluating its utility as well as potential differences in the pathogenesis of FGR in twin pregnancies, its predictive may be lower and thus may require modifications to the cut-off values to optimize its use for risk stratification [32, 33].

Additionally, scientific societies agree that Doppler assessment is an important part of antenatal surveillance in twin pregnancies complicated by sFGR or increased EFWd [4, 7, 8]. In dichorionic pregnancies, most guidelines suggest a protocol similar to the one that is used in singleton pregnancies complicated by FGR, including assessment of the blood flow in UA

and MCA [7]. This assessment has a proven predictive value in twin pregnancies with sFGR with the established PI cutoff values of $< 5\%$ for MCA and $> 95\%$ for UA. This allows the identification of a patient group with a higher risk of neonatal morbidity and NICU admission [19]. In a large retrospective study assessing the value of fetal Doppler in stillbirth risk stratification in sFGR twin pregnancies, Khalil et al. found a predictive value of UA-PI and CPR (cranial-placental ratio) MoM, EFWd, and CPR discordance (CPRd). The highest predictive value was found for the combination of EFWd and CPRd (AUC 0.96), which seems to be a promising parameter that may facilitate the management of patients with sFGR [34]. However, due to the retrospective character of the study, the value of these prognostic factors requires further research.

ISUOG guidelines suggest the use of a singleton-based protocol for the management of dichorionic twin pregnancy complicated by sFGR. This protocol consists of serial Doppler evaluations of UA and MCA flow at least every two weeks. Doppler-based severity grading nor the adequate cut-off values for determining earlier delivery have not been established for dichorionic twin pregnancies. The authors suggest that such pregnancies should be managed by facilities experienced in twin pregnancies complicated by sFGR and the decision about the delivery should be individualized [5, 7].

Further research aiming at the systematization of Doppler use in dichorionic pregnancies is undoubtedly one of the chief priorities. Such studies may provide a powerful tool for the optimization of care and facilitate the decision-making in dichorionic pregnancies complicated by sFGR.

CONCLUSIONS

Despite the most common use of EFWd in twin pregnancies complicated by sFGR, the assessment of relative fetal growth is an important part of the ultrasound examination that does not require additional measurements but also enables the provider to identify patients with increased risk of both maternal and neonatal morbidity [2]. Regardless of its utility, further optimization of this parameter is needed, based on individualization of the cut-off values concerning the week of gestation as well as the implementation of different, more versatile measurements in the assessment of relative fetal growth [1, 17]. The lack of relevant tools for risk stratification in dichorionic twins based on the current guidelines warrants further research on the use of EFWd and Doppler [19, 34]. An important area for future research is also the difference in the pathogenesis of fetal growth abnormalities between mono- and dichorionic pregnancies. That may allow the relevant assessment of the role EFWd

plays in dichorionic pregnancies and the proper use of this parameter in improving the quality of patient care [2, 27].

Article information and declarations

Author contributions

Mateusz Kryczka — the majority of the review not mentioned below.

Mateusz Stępień — parts of the article regarding the role of Doppler in pregnancies complicated by increased EFWd.

Prof. Włodzimierz Sawicki — supervision, final editorial process.

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Conflict of interest

The authors declare no conflict of interest.

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