Selective fetal growth restriction in a monochorionic twin pregnancy: a Dilemma for clinicians and a challenge for researchers

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Introduction

Despite advances in antenatal care, fetal growth restriction (FGR) continues to contribute to excess perinatal mortality and morbidity. The literature has recently been enriched with several landmark studies on FGR, which will facilitate standardization of the diagnostic criteria, identification of the at-risk fetus, prenatal screening, candidate preventors and optimal management. However, these studies have focused on singleton pregnancies and largely excluded twin gestations. Recently, an international consensus definition of FGR, as well as a consenus on the essential variables for reporting research studies on FGR, in singleton pregnancies has been published[1,2].

Twin pregnancy is disproportionately represented in stillbirths, neonatal deaths and cerebral palsy.[3-5] Focused efforts to address this excess risk are urgently needed. Intrauterine demise of one monochorionic twin is associated with a 25% risk of death of its co-twin or neurological damage due to their shared circulation.[6] Two major contributors to the increased risk are twin to twin transfusion syndrome (TTTS) and fetal growth restriction (FGR). Randomised controlled trials and Cochrane reviews have addressed the former, but none the latter. Selective FGR (sFGR) is increasingly recognized as a major complication of twins because of significant links with stillbirth and poor neurological outcomes.[7-10] However, high quality evidence on how best to manage this important condition is lacking, based only on limited observational studies, and current practice varies among centres and clinicians.

Variation in current practice

An online survey of 29 UK fetal medicine specialists demonstrated wide variation in the diagnostic criteria, management and, more importantly, the gestational age threshold for delivery of these twin pregnancies. More than half (57%) define sFGR as estimated fetal weight (EFW) of one twin less than the 10th centile with EFW discordance of 25% or more, while 36% use a threshold of 20% (rather than 25%). A minority (11%) use EFW less than the 10th centile regardless of the inter-twin discordance. When asked about management options for early-onset (less than 24 weeks) sFGR, most (93%) pursued expectant management. Other options included Laser photocoagulation of the placental communicating blood vessels (57%), selective reduction of the smaller twin (71%) and termination of the entire pregnancy (50%). When asked about management according to the

pattern of the umbilical artery Doppler,[11] the responses varied, most likely taking into account the expected prognosis. The presence or absence of umbilical artery (UA) end-diastolic flow (EDF) in the affected twin at the time of diagnosis forms the basis of the classification system devised by Gratacos et al.[11] Positive EDF is classified as Type I and absent or reversed EDF (AREDF) as Type II. The 'intermittent AREDF' unique to monochorionic pregnancies is classified as Type III (Figure 1). In this group, the presence of large diameter arterio-arterial (AA) anastomoses permits a cyclical compensatory flow from the normal twin that can be observed in cyclical normalisation in the EDF in the small twin, promoting longer survival of the small twin but also facilitating acute transfusion events that can lead to unexpected fetal death or neurological damage. Although the overall perinatal survival in pregnancies affected by Type 1 sFGR (with positive EDF in the UA Doppler) is as high as 97%, survival in sFGR with AREDF (types 2 and 3) is significantly lower, with a high risk of intrauterine demise that may be particularly unpredictable in Type 3 sFGR.[7]

The majority (82%) of UK fetal medicine specialists do not consider active fetal intervention in type 1 sFGR; however, 43% would be willing to participate in a trial of expectant management versus active fetal intervention. Around half (57%) deliver these pregnancies at 34-36 weeks' gestation, while 32% deliver at 32-33 weeks. More than one third (36%) routinely offer active fetal intervention for type 2 sFGR, while a further 43% would offer it only to selected cases. The majority (71%) would be willing to participate in a trial of expectant management versus active fetal intervention, reflecting clinicians' need for more evidence to guide management. Half deliver these pregnancies at 32-33 weeks' gestation, 29% at 30-31 weeks and 18% at 28-29 weeks. Comparable figures were reported in type 3 sFGR, with more than a third (36%) routinely offering active fetal intervention. The majority (75%) would be willing to participate in a trial of expectant management versus active fetal intervention. More than half (57%) deliver these pregnancies at 32-33 weeks, 32% at 30-31 weeks, and 14% before 29 weeks.

Limitations of the published evidence

High quality studies outlining the natural history of a well characterized cohort of MC twins complicated by sFGR managed conservatively are scarce. There are several important questions which lack robust answers based on existing literature, such as the incidence of superimposed TTTS in MC twins complicated by sFGR and whether this differs according to

the gestational age at the onset of sFGR. Furthermore, studies from tertiary fetal medicine centres might overestimate the incidence of sFGR due to their high risk populations with referral cases which are often complicated. Moreover, studies which exclude the twin pregnancies complicated by intrauterine demise could also be biased as they could underestimate the incidence of sFGR. Therefore, in order to ascertain the incidence of sFGR, a large cohort of unselected MC twin pregnancies should be followed up using regular ultrasound assessment every 2-3 weeks with robust documentation of the fetal biometry, amniotic fluid volume and fetal Doppler. The incidence of sFGR should be made based on the antenatal ultrasound data, which should be confirmed at birth. It is important to acknowledge though that the recently published consensus on the diagnostic criteria of sFGR used antenatal ultrasound data, but no postnatal diagnostic criteria was selected to confirm the diagnosis at birth.[12]

Active fetal intervention, such as Laser photocoagulation, carries a number of risks, not least demise of the smaller twin, which may also put the larger baby at risk. On the other hand, expectant management may be associated with very preterm birth of both twins and the inherent morbidity associated with prematurity. Discussions with parents around the best way to manage these pregnancies are hampered by the unpredictable nature of the condition and the lack of available evidence. In summary, there is very little published evidence on the best way to manage these pregnancies. The findings of this survey highlight the pressing need for a randomized controlled trial to provide clear evidence to guide clinicians and parents experiencing this distressing condition and facing these difficult decisions.

National and international guidelines

The most recently published guidelines have also highlighted this lack of evidence. The ISUOG guidance on twin pregnancy states that "*There is limited evidence to guide the management of monochorionic twins affected by sFGR*", while the most recent Royal College of Obstetricians and Gynecologists (RCOG) guidance on twin pregnancy states that "*Due to a lack of available high quality evidence, there is no clear guidance on how to manage sFGR in twin pregnancies*".[9] Based on expert opinion, these pregnancies should have follow-up ultrasound scan at least weekly[8]. In cases where the ductus venosus Doppler

shows absent or reversed a-wave, indicating a substantial risk of fetal demise of the smaller twin, before 26 weeks of gestation, the option of selective termination should be considered in order to protect the normally grown fetus from serious harm should the smaller twin die in utero[6]. Delivery will be indicated if the gestation is above 26 weeks[8]. In cases where the ductus venosus Doppler is normal, early delivery at or beyond 32 weeks, after a course of steroids, is indicated in type 2 and type 3 sFGR (Figure 2)[8]. Table 1 and Figure 2 outline the rate of progression, perinatal mortality and morbidity in sFGR according to the pattern of the umbilical artery Doppler, as reported in the most recent meta-analysis[7]. However, it is important to highlight the limitations and the high risk of bias of the included studies in this meta-analysis[7].

Consensus agreement on the diagnostic criteria for sFGR

In an attempt to standardize the management of these pregnancies, we recently published a consensus agreement on the diagnostic criteria for sFGR in monochorionic twin pregnancies (Table 2).[12] We have recently highlighted the large variation in outcome reporting in studies of TTTS, which makes it very challenging to compare the results of different studies or combine their data in a meta-analysis.[13] Meta-analyses are hampered by variable outcome reporting and definitions, precluding rapid resolution of important clinical questions. We have found similar heterogeneity in outcome reporting in studies investigating sFGR[14]. Therefore, the development of a core outcome set for studies of interventions for sFGR, as is the case in TTTS, is likely to be very useful. The development of both core outcome sets is already in progress.

What are the next steps?

The next step is to reach a consensus on the design of a study to establish the best management option(s). As these complicated pregnancies which might require prenatal intervention are uncommon, multicentre observational studies and large international trials hold the key. We envisage that such a trial should be preceded by a feasibility study to address a range of questions, including whether randomization should be individual or cluster, number of arms, inclusion criteria, prevalence, number of eligible pregnancies,

feasibility of evaluating cost-effectiveness, timing of randomization, the best intervention and comparator in the control group, management protocol, primary endpoint, recruiting sites, and the proportion of eligible women that will agree to participate. Participation of pregnant women in this study, while essential, raises an ethical dilemma when the outcome could be the loss of one or both twins. However, in sFGR in a monochorionic twin pregnancy this risk is inherent in both expectant management and active fetal intervention, hence the need for this trial. Therefore, any such study should target pregnancies with the most guarded prognosis. Prognostic variables, including earlier gestational age at diagnosis, type II sFGR and abnormal ductus venosus Doppler; are significantly associated with increased risk of adverse perinatal outcome for the smaller twin. Interestingly, the presence of TTTS was not associated with adverse perinatal outcome in these pregnancies[10,15].

References

1. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, Silver RM, Wynia K, Ganzevoort W. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet* Gynecol 2016; **48**: 333-9.

2. Khalil A, Gordijn SJ, Beune IM, Klaske W, Ganzevoort W, Figueras F, Kingdom J, Marlow N, Papageorghiou AT, Sebire N, Zeitlin J, Baschat AA. Essential variables for reporting research studies on fetal growth restriction – a Delphi consenus. *Ultrasound Obstet Gynecol* 2018 (in Press)

3. Office for National Statistics. Birth characteristics in England and Wales: 2016. 2017;(October):1–20.

4. Blondel B, Macfarlane A, Gissler M, Breart G, Zeitlin J, PERISTAT Study Group. General obstetrics: Preterm birth and multiple pregnancy in European countries participating in the PERISTAT project. *BJOG* 2006; **113**:528–535.

5. Mead J. Stillbirth claims. Clin Risk. SAGE PublicationsSage UK: London, England; 2010; **16**:77–80.

6. Hillman SC, Morris RK, Kilby MD. Co-twin prognosis after single fetal death: a systematic review and meta-analysis. *Obstet Gynecol* 2011; **118**: 928-940.

7. Buca D, Pagani G, Rizzo G, Familiari A, Flacco ME, Manzoli L, Liberati M, Fanfani F, Scambia G, D'Antonio F. Outcome in monochorionic twin pregnancies with selective intrauterine growth restriction according to the umbilical artery Doppler pattern of the smaller twin: a systematic review and meta-analysis. Ultrasound in obstet and gynecol 2017; **50**:559-568.

8. Khalil A, Rodgers M, Baschat A, Bhide A, Gratacos E, Hecher K, Kilby MD, Lewi L, Nicolaides K, Oepkes D, Reed K, Raine-Fenning N, Salomon LJ, Sotiradis A, Thilaganathan B, Ville Y; ISUOG Clinical Standards Committee. ISUOG Practice Guidelines: The Role of Ultrasound in Twin Pregnancy. Ultrasound Obstet Gynecol 2016; **48**:669-670.

9. Royal College of Obstetricians and Gynaecologists. Green-top Guideline No. 51. Mangement of monochorionic twin pregnancy. November 2016.

10. Monaghan C, Kalafat E, Binder J, Thilaganathan B, Khalil A. Prediction of adverse pregnancy outcome in monochorionic- diamniotic twin pregnancies complicated by selective fetal growth restriction. *Ultrasound Obstet Gynecol*. 2018 Apr 28. doi: 10.1002/uog.19078. [Epub ahead of print]

11. Gratacós E, Lewi L, Muñoz B, Acosta-Rojas R, Hernandez-Andrade E, Martinez JM, Carreras E, Deprest J. A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin. *Ultrasound Obstet Gynecol* 2007; **30**:28–34.

12. Khalil A, Beune I, Hecher K, Wynia K, Ganzevoort W, Reed K, Lewi L, Oepkes D, Gratacos E, Thilaganathan B, Gordijn SJ. Consensus definition and essential reporting parameters of selective fetal growth restriction in twin pregnancy: a Delphi procedure. Ultrasound Obstet Gynecol. 2018 Jan 24. doi: 10.1002/uog.19013. [Epub ahead of print]

13. Perry H, Duffy JMN, Umadia O, Khalil A. Outcome reporting across randomised trials and observational studies evaluating treatments for Twin-Twin Transfusion Syndrome: a systematic review. Ultrasound Obstet Gynecol. Wiley-Blackwell; 2018 Apr 1. doi: 10.1002/uog.19068. [Epub ahead of print]

14. Sileo FG, Duffy JMN, Townsend R, Asma Khalil. Outcome Reporting in Studies Evaluating Interventions for Selective Fetal Growth Restriction in Monochorionic Diamniotic Pregnancy: A Systematic Review. *Ultrasound Obstet Gynecol* 2018 (in Press)

15. Peeva G, Bower S, Orosz L, Chaveeva P, Akolekar R, Nicolaides KH. Endoscopic Placental Laser coagulation in Monochorionic Diamniotic Twins with Type II Selective Fetal Growth Restriction. *Fetal Diagn Ther* 2015; **38**:86-93

Table 1. The rate of progression, recommended monitoring and gestational age at delivery in stable cases of selective fetal growth restriction (sFGR) in monochorionic twin pregnancies, according to the pattern of the umbilical artery Doppler (Bucca et al 2017; ISUOG guideline 2016)

	Type 1 sFGR	**Type 2 sFGR**	**Type 3 sFGR**
Progression	16%	69%	10%
Monitoring	weekly	weekly	weekly
Gestational age at delivery	34-36 weeks	30-32 weeks	30-32 weeks

Table 2. Consensus diagnostic criteria for selective fetal growth restriction in monochorionic (MC) twin pregnancies. (Khalil 2018)

Any MC twin pregnancy with the solitary parameter	**MC twin pregnancy with at least two contributory parameters**
EFW in one twin below the 3rd centile	EFW of one twin <10th centile
	AC of one twin <10th centile
	EFW discordance >25%
	Umbilical artery PI of the smaller twin >95th centile

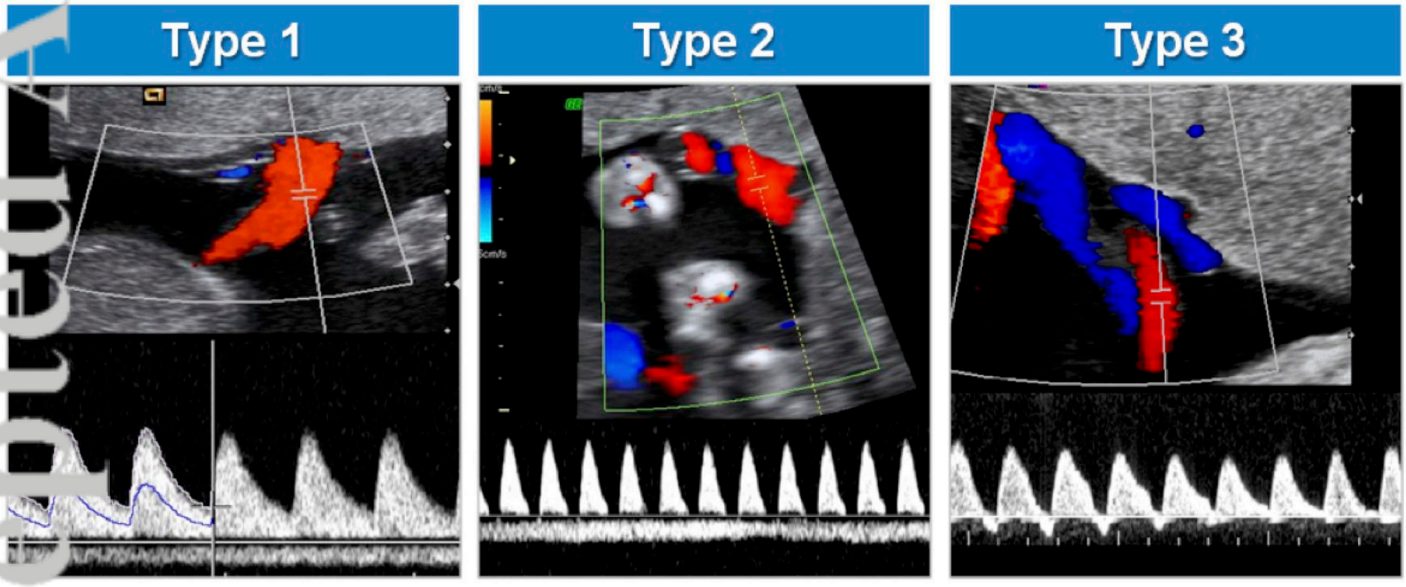
EFW: estimated fetal weight; AC: abdominal circumference; PI: pulsatility index

Figure legends

Figure 1. Classification of selective fetal growth restriction in monochorionic twin pregnancy. In Type I, the umbilical artery Doppler waveform has positive end-diastolic flow, while in Type II there is absent or reversed end-diastolic flow (AREDF). In Type III there is a cyclical/intermittent pattern of AREDF.

Figure 2. The perinatal mortality and morbidity of monochorionic twin pregnancy complicated by selective fetal growth restriction (Buca et al 2017).

IUD: intrauterine demise; NND: neonatal death; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome



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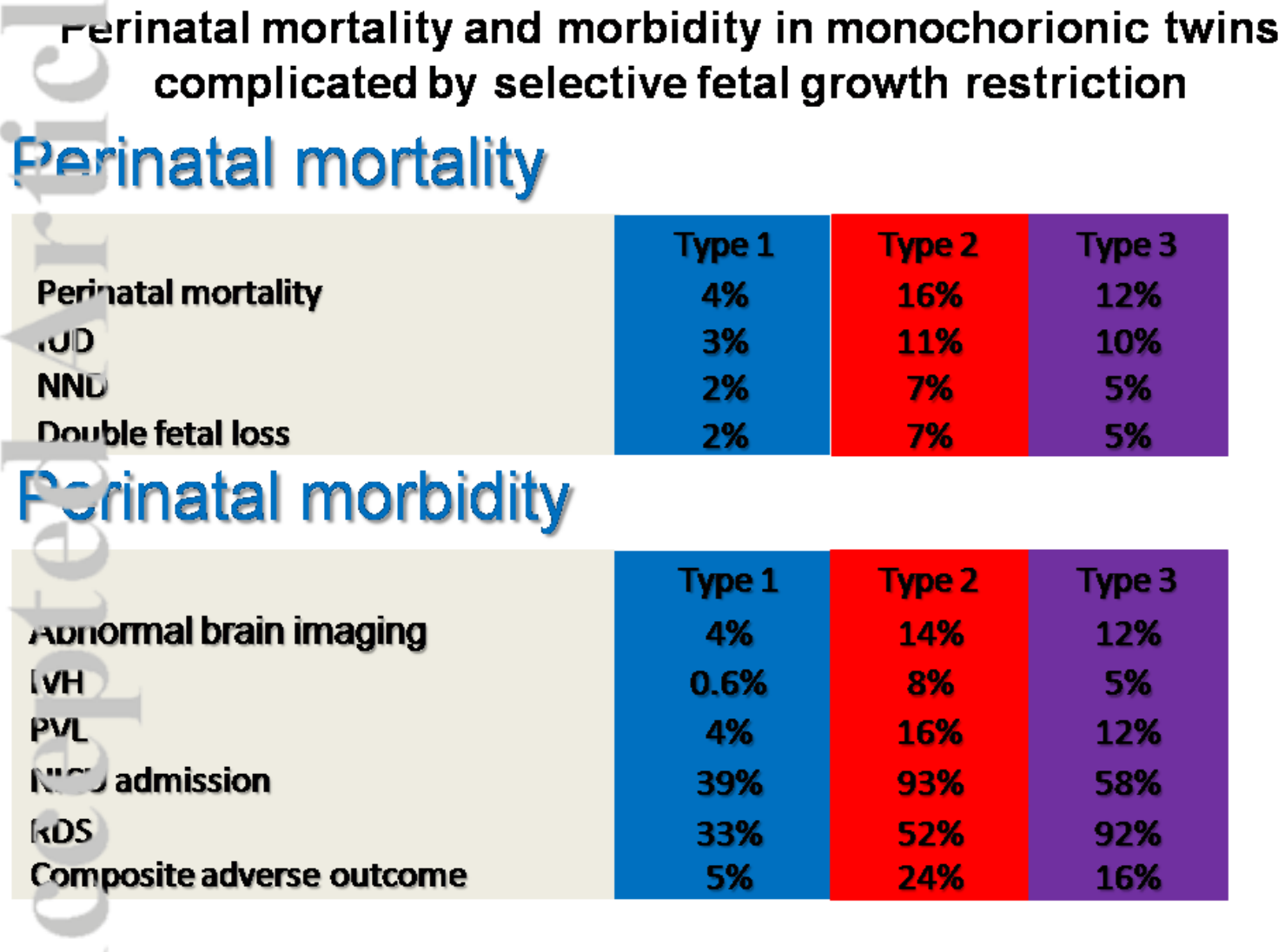

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