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RESEARCH ARTICLE

Diagnosis and management of selective fetal growth restriction in monochorionic twin pregnancies: A cross-sectional international survey

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Abstract

Objective: To identify current practices in the management of selective fetal growth restriction (sFGR) in monochorionic diamniotic (MCDA) twin pregnancies.

Design: Cross-sectional survey.

Setting: International.

Population: Clinicians involved in the management of MCDA twin pregnancies with sFGR.

Methods: A structured, self-administered survey.

Main Outcome Measures: Clinical practices and attitudes to diagnostic criteria and management strategies.

Results: Overall, 62.8% (113/180) of clinicians completed the survey; of which, 66.4% (75/113) of the respondents reported that they would use an estimated fetal weight (EFW) of <10th centile for the smaller twin and an inter-twin EFW discordance of >25% for the diagnosis of sFGR. For early-onset type I sFGR, 79.8% (75/94) of respondents expressed that expectant management would be their routine practice. On the

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For affiliations refer to page 8.

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other hand, for early-onset type II and type III sFGR, 19.3% (17/88) and 35.7% (30/84) of respondents would manage these pregnancies expectantly, whereas 71.6% (63/88) and 57.1% (48/84) would refer these pregnancies to a fetal intervention centre or would offer fetal intervention for type II and type III cases, respectively. Moreover, 39.0% (16/41) of the respondents would consider fetoscopic laser surgery (FLS) for early-onset type I sFGR, whereas 41.5% (17/41) would offer either FLS or selective feticide, and 12.2% (5/41) would exclusively offer selective feticide. For early-onset type II and type III sFGR cases, 25.9% (21/81) and 31.4% (22/70) would exclusively offer FLS, respectively, whereas 33.3% (27/81) and 32.9% (23/70) would exclusively offer selective feticide.

Conclusions: There is significant variation in clinician practices and attitudes towards the management of early-onset sFGR in MCDA twin pregnancies, especially for type II and type III cases, highlighting the need for high-level evidence to guide management.

KEY WORDS

clinical trial, cord occlusion, definition, diagnosis, fetal growth restriction, feticide, fetoscopic laser surgery, intervention, intrauterine demise, morbidity, mortality, multiple, neonatal, pregnancy, prognosis, small for gestational age, stillbirth, surgery, survey

1 | INTRODUCTION

Approximately 30% of twin pregnancies are monochorionic.¹ In complicated monochorionic twins, the placental angioarchitecture predisposes both twins to adverse outcomes, emphasising the need for a uniform diagnostic and management approach.² Selective fetal growth restriction (sFGR), when one fetus grows normally whilst the other is growth restricted, affects approximately 10%–15% of monochorionic diamniotic (MCDA) twin pregnancies. Recently, sFGR in MCDA twin pregnancies was defined by the Delphi consensus,³ which states that either one solitary parameter (estimated fetal weight, EFW, of one twin <3rd centile) or at least two of four contributory parameters (EFW of one twin <10th centile, abdominal circumference of one twin <10th centile, EFW discordance of $\geq 25\%$ and umbilical artery (UA) pulsatility index of the smaller twin of >95th centile) are required for a diagnosis of sFGR in MCDA twin pregnancies. Early-onset sFGR, occurring before 24 weeks of gestation, is less common but poses greater fetal risks and substantial management difficulties due to pre-viable gestation and implications for iatrogenic prematurity in the larger co-twin.^{4–8} sFGR in MC twin pregnancy is classified into three types, based on UA Doppler flow patterns: type I (positive end-diastolic flow, EDF) has the best outcome; type II (absent/reversed flow) has the worst prognosis; and type III (variable absent/reversed flow) has an unpredictable course.⁹ All of the three main management options carry specific disadvantages: (i) expectant management carries a risk of intrauterine demise (IUD) of the sFGR twin, with risks of death or disability to the larger co-twin; (ii) the selective termination of the sFGR twin may not be acceptable or available to some parents, and is associated with a small risk of demise of the larger co-twin; and (iii) fetoscopic laser surgery could be technically challenging, and in some cases may worsen the outcomes for the sFGR twin by increasing the risk of demise following placental dichorionisation, and may

create a fetofeto conflict later in pregnancy, with iatrogenic prematurity for the larger twin.¹⁰

Management options, as well as the diagnostic criteria, monitoring protocols and gestational age at delivery, vary among fetal medicine units.¹¹ The NIHR-funded FERN project (Intervention or Expectant Management for Early Onset Selective Fetal Growth Restriction in Monochorionic Twin Pregnancy) is a feasibility prospective mixed-methods cohort study of three distinct work packages (WPs): (i) WP1, a prospective UK multicentre study; (ii) WP2, a qualitative study exploring the views of parents and clinicians; and (iii) WP3, a consensus development to determine the feasibility of a trial.¹² This clinician questionnaire survey was undertaken as a part of WP3 to identify current practices in the management of sFGR in MCDA twin pregnancies.

2 | METHODS

2.1 | Design and setting

This was a cross-sectional questionnaire survey conducted between June 2022 and December 2022 as a part of the FERN WP3 project. The survey was launched on the FERN website and disseminated via social media, conferences and society meetings, and by personal contact with experts. Participation in the survey was voluntary and respondents did not receive any compensation. To increase visibility, we reposted the survey monthly. The target participants for this survey were clinicians around the globe involved in the management of sFGR in MCDA twin pregnancies, encompassing fetal medicine specialists, obstetricians and neonatologists. The weblink to the survey led to a participant information sheet stating the objective of the survey, names of the FERN researchers, information about data confidentiality and

informed consent to participate in the survey (FERN WP3 Clinician Survey).

2.2 | Survey (Appendix S1)

This structured, self-administered survey was drawn from a review of existing literature, developed by the FERN core group, and then ratified and approved by a group of co-applicants, patient representatives and key stakeholders, for relevance, clarity, technicality and comprehensiveness. The survey comprised a series of closed-ended questions (with free-text options) designed to elicit information on various aspects of the diagnosis and management of sFGR in MCDA twin pregnancies and could be completed in approximately 15 min.

The survey was designed to collect information regarding:

1. Demographic characteristics of the participants, their region of practice and level of expertise, gauged by the average number of MCDA twin pregnancies catered for by their centre and the type of services offered.
2. Diagnostic criteria and frequency of surveillance in these pregnancies.
3. Management options and timing of delivery in both early- and late-onset sFGR cases, based on their practice and experiences, rather than local protocols.

Free-text spaces were provided, where applicable, and survey responses were stored in the FERN Research Electronic Data Capture (REDCap) database. Data were extracted in an Excel (Microsoft, Redmond, WA, USA) spreadsheet. Descriptive statistics (frequencies) were calculated as a function of the total number of respondents who completed all the questions within a specific subsection. Data were analysed using SPSS 20.0 (IBM, Armonk, NY, USA).

3 | RESULTS

A total of 180 respondents visited the survey link, 62.8% (113/180) of which took part in the survey. Of those who took part, 62.8% (71/113) reported being fetal medicine specialists and 47.8% (54/113) also offered fetal therapy. The demographic characteristics of the participants are presented in Table 1. Of the respondents who took part, 57.5% (65/113) practiced in Europe, whereas 42.5% (48/113) reported being based in other continents, such as Africa, Asia, Australia and the Americas. Of the respondents who participated, 39.8% (45/113) stated that their centre provided care to 20–50 MCDA twin pregnancies annually, whereas 33.6% (38/113) reported seeing more than 50 MCDA twin pregnancies annually.

Regarding the diagnostic criteria, although 66.4% (75/113) of the participants reported that they would use an estimated fetal weight (EFW) of <10th centile for the smaller twin and an inter-twin EFW discordance of $\geq 25\%$ for the

TABLE 1 Demographic characteristics of the participants who responded to the survey.

Variables	n (%)
Level of experience (n = 113)	
Fetal therapy specialist	54 (47.8)
Fetal medicine specialist	71 (62.8)
Consultant obstetrician	10 (8.9)
Obstetrician in training	7 (6.2)
Neonatologist	3 (2.7)
Sonographer	3 (2.7)
Region of practice (n = 113)	
Europe	65 (57.5)
United Kingdom	28 (24.8)
International	48 (42.5)
Africa	1 (0.9)
Asia	19 (16.8)
Australia	2 (1.8)
North America	12 (10.6)
South America	14 (12.4)
Type of centre (n = 113)	
Fetal medicine centre with <20 MCDA twin pregnancies per year	24 (21.2)
Fetal medicine centre with 20–50 MCDA twin pregnancies per year	45 (39.8)
Fetal medicine centre with >50 MCDA twin pregnancies per year	38 (33.6)
Other	6 (5.3)
Practice level (n = 113)	
Prenatal screening (including twin pregnancies), but not diagnosis	9 (8.0)
Prenatal diagnosis (including twin pregnancies), but not fetal therapy	46 (40.7)
Fetal therapy in twin pregnancies	54 (47.8)
Other	4 (3.5)

diagnosis of sFGR, less than one-third (31.9%, 36/113) would employ these criteria exclusively (Figure S1; Table 2). Other criteria that were commonly used by the respondents for the diagnosis of sFGR in MCDA twin pregnancies included: an EFW of <10th centile for the smaller twin and an inter-twin EFW discordance of $\geq 20\%$; an abdominal circumference of <10th centile for the smaller twin and an inter-twin EFW discordance of $\geq 25\%$; and the solitary criterion of an EFW of <3rd centile for the smaller twin in 20.3% (23/113), 20.3% (23/113) and 19.5% (22/113) of cases, respectively.

Figure 1 and Table S1 describe the practice of respondents regarding the frequency of surveillance in cases of sFGR in MCDA cases according to Gratacós' classification and gestational age at diagnosis.⁹ Among the participants, 66% (62/94) and 59.6% (56/94) reported that they would follow a policy of weekly surveillance for cases of type I sFGR, diagnosed before and after 24 weeks of gestation, respectively. On the other hand, for type II and type III sFGR, respondents

were notably divided in their preference for either weekly or twice-weekly surveillance of these pregnancies.

Figure S2 and Table S2 present the practice of the respondents according to the ultrasound parameters that they routinely recorded in cases of sFGR in MCDA twin pregnancies. For early-onset type I sFGR, 95.7% (90/94) and 91.5%

TABLE 2 Criteria used by respondents for diagnosis of selective fetal growth restriction (sFGR) in monochorionic diamniotic (MCDA) twin pregnancies.

Criteria for diagnosis	n (%) ^a
EFW of <10th centile for the smaller twin plus an inter-twin EFW discordance of $\geq 25\%$	75 ^b (66.4)
EFW of <10th centile for the smaller twin plus an inter-twin EFW discordance of $\geq 20\%$	23 (20.3)
EFW of <10th centile for the smaller twin	11 (9.7)
EFW of <3rd centile for the smaller twin plus an inter-twin EFW discordance of $\geq 25\%$	16 (14.2)
EFW of <3rd centile for the smaller twin plus an inter-twin EFW discordance of $\geq 20\%$	10 (8.8)
EFW of <3rd centile for the smaller twin	22 (19.5)
EFW of <5th centile for the smaller twin plus an intertwin EFW discordance of $\geq 25\%$	12 (10.6)
EFW of <5th centile for the smaller twin plus an intertwin EFW discordance of $\geq 20\%$	5 (4.4)
EFW of <5th centile for the smaller twin	2 (1.8)
AC of <10th centile for the smaller twin plus an inter-twin EFW discordance of $\geq 25\%$	23 (20.3)
AC of <10th centile for the smaller twin plus an inter-twin EFW discordance of $\geq 20\%$	7 (6.2)
Other	7 (6.2)

Abbreviations: AC, abdominal circumference; EFW, estimated fetal weight.

^aTotal number of responses is not equal to 113 as respondents could choose more than one option.

^bOnly 36/113 (31.9%) respondents reported that they would strictly use the first criteria listed for the diagnosis of monochorionic diamniotic (MCDA) twin pregnancies with selective fetal growth restriction (sFGR).

(86/94) of the respondents would routinely record fetal biometry and UA Doppler, respectively, whereas 85.1% (80/94) and 81.9% (77/94) would also evaluate middle cerebral artery (MCA) and ductus venosus (DV) Doppler. In early-onset type II sFGR, 95.4% (84/88) and 93.2% (82/88) of the respondents would routinely record fetal biometry and UA Doppler, whereas 87.5% (77/88) and 90.9% (80/88) also evaluated MCA and DV Dopplers. For early-onset type III sFGR, 94.0% (79/84) of the respondents reported routinely recording fetal biometry and UA Doppler, whereas 89.3% (75/84) additionally evaluated the cerebral and venous Doppler traces.

Regarding late-onset type I sFGR, 95.7% (90/94) and 91.5% (86/94) of respondents would routinely record fetal biometry and UA Doppler, respectively, whereas 86.2% (81/94) and 81.9% (77/94) would also assess the MCA and DV Doppler traces. In late-onset type II sFGR, 96.6% (85/88) and 95.4% (84/88) of respondents routinely recorded fetal biometry and UA Doppler, whereas 88.6% (78/88) and 92.0% (81/88) also evaluated MCA and DV Doppler traces. For late-onset type III sFGR, 94.0% (79/84) and 94.0% (79/84) of respondents reported routinely recording fetal biometry and UA Doppler, whereas 90.5% (76/84) and 89.3% (75/84) additionally evaluated the cerebral and venous Doppler traces.

Figure 2 and Table 3 describe the distribution of respondents according to initial management options they would employ in the management of cases of sFGR. This includes both an overall respondent cohort and a specialised subgroup of respondents who provided fetal therapy.

For early-onset type I sFGR, 79.8% (75/94) of the respondents would opt for expectant management, whereas 19.1% (18/94) would refer the mother to a fetal intervention centre or offer fetal intervention. However, among the respondents who provided fetal therapy, 95.7% (45/47) would choose expectant management, with only 2.1% (1/47) considering an intervention. In early-onset type II sFGR, 19.3% (17/88) of respondents preferred expectant

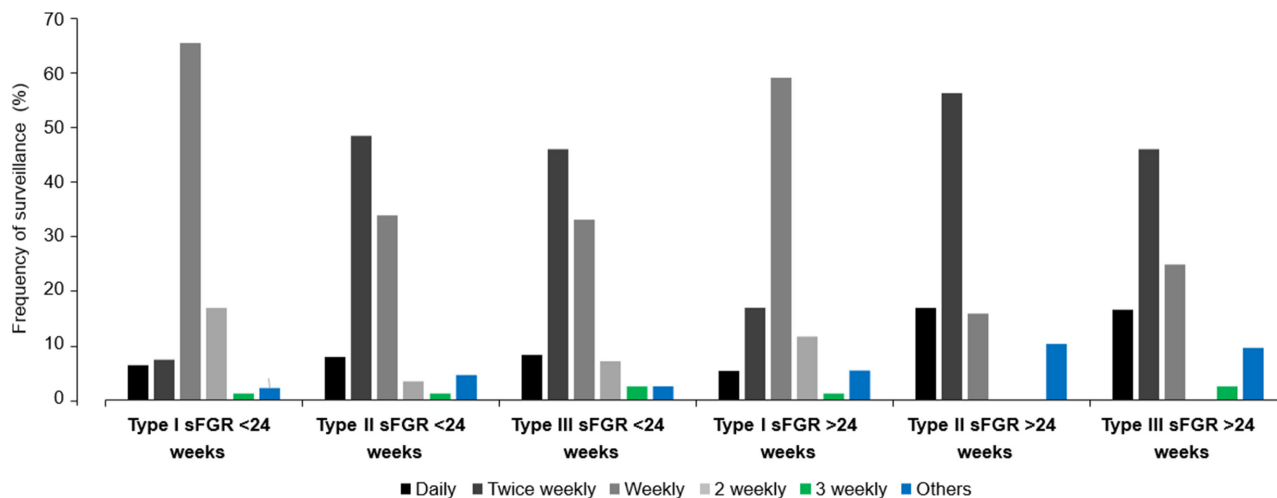


FIGURE 1 Distribution of respondents according to the frequency of surveillance of monochorionic diamniotic (MCDA) twin pregnancies with selective fetal growth restriction (sFGR).

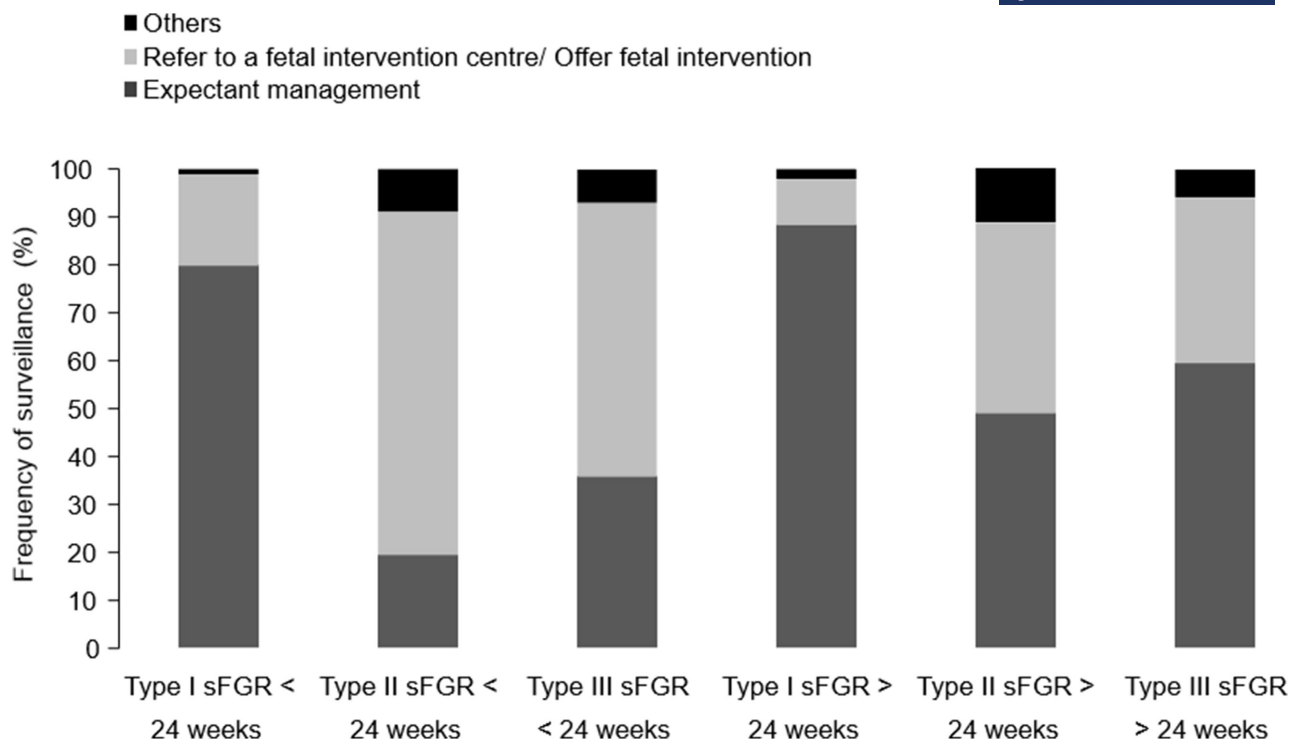


FIGURE 2 Distribution of respondents according to initial management options in monochorionic diamniotic (MCDA) twin pregnancies with selective fetal growth restriction (sFGR).

management, whereas 71.6% (63/88) would refer the mother to a fetal intervention centre or offer fetal intervention. Among respondents who provided fetal therapy, 26.1% (12/46) would opt for expectant management, and 60.9% (28/46) would offer intervention for early-onset type II sFGR. For early-onset type III sFGR, 35.7% (30/84) of the respondents would opt for expectant management, whereas 57.1% (48/84) would refer the mother to a fetal intervention centre or offer fetal intervention; however, 43.2% (19/44) of the fetal therapy specialists would recommend expectant management and 45.4% (20/44) would offer intervention in these cases.

Regarding late-onset type I sFGR, 88.3% (83/94) of respondents would prefer to adopt expectant management, whereas 9.6% (9/94) would refer the mother to a fetal intervention centre or offer fetal intervention. On the other hand, for late-onset type I sFGR, the fetal therapy providers were even more inclined towards expectant management, at 95.7% (45/47), with none recommending intervention. In late-onset type II sFGR, 48.9% (43/88) of respondents would opt for expectant management, whereas 39.8% (35/88) of respondents would either refer the mother to a fetal intervention centre or offer fetal intervention. Among the subgroup of fetal therapy specialists, 60.9% (28/46) preferred expectant management and 23.9% (11/46) would offer intervention. For late-onset type III sFGR, 59.5% (50/84) of respondents would opt for expectant management, whereas 34.5% (29/84) of respondents reported that they would refer the mother to a fetal intervention centre or offer fetal intervention. Among the subgroup of fetal therapy providers, 65.9% (29/44) chose expectant

management for the initial management of late-onset type III sFGR, whereas 25.0% (11/44) would consider intervention.

Table S3 presents the distribution of respondents according to the type of fetal interventions they would consider in MCDA twin pregnancies with sFGR. For early-onset type I sFGR, 39.0% (16/41) of respondents would consider fetoscopic laser surgery (FLS), whereas 41.5% (17/41) would offer either FLS or selective feticide and 12.2% (5/41) would exclusively offer selective feticide. For early-onset type II and type III sFGR cases, 25.9% (21/81) and 31.4% (22/70) would exclusively offer FLS, respectively, whereas 33.3% (27/81) and 32.9% (23/70) would exclusively offer selective feticide. Among respondents, 73.4% (69/94) would not consider fetal intervention for type I sFGR diagnosed after 24 weeks of gestation, compared with 36.4% (32/88) for type II sFGR and 45.2% (38/84) for type III sFGR cases, respectively.

Regarding the timing of delivery, 60.6% (57/94) of respondents believed that pregnancies with type I sFGR should be offered delivery at 34–36 weeks of gestation, whereas 21.3% (20/94) of the respondents would deliver these pregnancies at 32–33 weeks of gestation (Table S4). For type II and type III sFGR, there were diverse responses, with a tendency to deliver at earlier gestations. For type II sFGR, 44.3% (39/88) of the respondents stated that they would plan delivery at 32–33 weeks of gestation, whereas 28.4% (25/88) would prefer to time delivery earlier, at 31–32 weeks of gestation, in cases of type II sFGR. Similarly, for type III sFGR, 35.7% (30/84) of the respondents stated that they would recommend delivery at 32–33 weeks of gestation, whereas 33.3% (28/84) of

TABLE 3 Distribution of respondents according to initial management options in monochorionic diamniotic (MCDA) twin pregnancies with selective fetal growth restriction (sFGR).

	Overall cohort (n = 113)			Respondents who provided fetal therapy (n = 54)		
	Expectant management, n (%)	Refer to a fetal intervention centre/offer fetal intervention, n (%)	Others, n (%)	Expectant management, n (%)	Refer to a fetal intervention centre/offer fetal intervention, n (%)	Others, n (%)
Type I sFGR diagnosed before 24 weeks of gestation (n = 94)	75 (79.8)	18 (19.1)	1 (1.1)	45 (95.7)	1 (2.1)	1 (2.1)
Type II sFGR diagnosed before 24 weeks of gestation (n = 88)	17 (19.3)	63 (71.6)	8 (9.1)	12 (26.1)	28 (60.9)	6 (13.0)
Type III sFGR diagnosed before 24 weeks of gestation (n = 84)	30 (35.7)	48 (57.1)	6 (7.1)	19 (43.2)	20 (45.4)	5 (11.4)
Type I sFGR diagnosed after 24 weeks of gestation (n = 94)	83 (88.3)	9 (9.6)	2 (2.1)	45 (95.7)	0 (0)	2 (4.2)
Type II sFGR diagnosed after 24 weeks of gestation (n = 88)	43 (48.9)	35 (39.8)	10 (11.4)	28 (60.9)	11 (23.9)	7 (15.2)
Type III sFGR diagnosed after 24 weeks of gestation (n = 84)	50 (59.5)	29 (34.5)	5 (5.9)	29 (65.9)	11 (25.0)	4 (9.1)

Note: n = number of respondents who answered this question, with the percentage given in brackets. 'Others' included answers provided in the free-text boxes concerning delivery, amnio drainage and steroids.

the respondents felt that delivery should be recommended at 30–31 weeks of gestation.

4 | DISCUSSION

4.1 | Main findings

This is a comprehensive survey of clinicians in geographically diverse healthcare settings to identify current practices in the diagnosis and management of sFGR in MCDA twin pregnancies. Significant variation was observed among clinicians regarding the diagnosis, monitoring and management options, as well as the gestational age threshold for delivery. For early-onset sFGR in MCDA twin pregnancies, more than three-quarters of all respondents stated that type I sFGR should be managed expectantly with weekly surveillance. There was, however, a wide variation in the monitoring protocol and management for type II and type III sFGR cases, which are more likely to be associated with adverse outcomes. The fetal therapy specialists were more inclined towards expectant management in both early- and late-onset type I sFGR. Nonetheless, even among the fetal therapy providers, there was significant variation in clinical practice for early-onset type II and type III sFGR.

4.2 | Interpretation of study findings and comparison with published literature

There is limited knowledge about the natural history of sFGR in MCDA twin pregnancies; therefore, it is not surprising that there are unclear and varied recommendations from different societies, which is reflected in the wide variation of clinical practice noted in our survey findings. For example, there is heterogeneity in the diagnostic criteria proposed and adopted. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) and the recently developed Delphi consensus have adopted an inter-twin discordance of 25% to define sFGR, in addition to other criteria,^{2,3} whereas the Royal College of Obstetricians and Gynaecologists (RCOG), the National Institute for Health and Care Excellence (NICE), and the American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal–Fetal Medicine (SMFM) have proposed the more pragmatic criterion of an inter-twin EFW discordance of 20%.^{1,13,14} There is also notable heterogeneity in the guidance on the assessment of different Doppler parameters. Routine MCA peak systolic velocity surveillance has been advocated by the ISUOG,² whereas the ACOG guidelines recommend the assessment of the deepest vertical pocket, fetal bladder and growth surveillance only.¹⁴ Similarly, regarding the optimum management strategy for these pregnancies, the evidence, obtained from systematic reviews,¹⁵ meta-analysis,¹⁶ and retrospective observational studies,^{10,17–19} is limited by

the small numbers, heterogeneity in case definitions and study populations spread over a long time, with evolving clinical practices. The findings of our survey are also in line with the findings of a social media-based patient survey conducted in California, USA, which reported wide regional and provider differences in the management of MCDA twin pregnancies.²⁰

Twin-to-twin transfusion syndrome (TTTS) and sFGR are the two most common monochorionicity-related complications. For TTTS, level I evidence and observational studies have led to robust diagnostic and stage-based management guidelines that have contributed to significantly improved outcomes over the past decades.^{21–26} A similar strategy is warranted to improve the outcomes for sFGR in MCDA twin pregnancies.

This sentiment is also reflected by parent groups, who have reported that their decision-making process was fraught with challenges and dilemmas because of the variations in practice and reported outcomes, coupled with an overall lack of consensus in the management of these complicated multiple pregnancies.²⁷

4.3 | Strengths and limitations

The survey was developed following a rigorous literature search and comprised questions pertinent to relevant clinical scenarios. Our survey has a global representation and reflects the attitudes and practices of fetal medicine specialists around the world. More than three-quarters of the survey respondents are fetal medicine specialists involved in making decisions about managing these high-risk pregnancies. Therefore, the survey findings should be considered reflective of current global practice, with a low risk of respondent bias. The provision of free-text spaces ensured the capture of relevant information that might not have been included or could have been inadvertently skipped in the provided options. The option of anonymity would also have enabled clinicians to provide candid answers about their clinical practices and preferences, even if these was not in line with the majority opinion on occasion. We intentionally refrained from assessing clinical outcomes, which are crucial for evaluating the clinical effectiveness of various management strategies, and from including a qualitative component. These aspects are currently being addressed separately and concurrently by other components of the FERN project.

Our limitations include the lack of consideration for gestational limits and legal restrictions, and cultural determinants related to termination of pregnancy (TOP) and viability, which may vary across different countries. Furthermore, our study did not differentiate findings based on the participant's country of practice. Despite our best efforts, we acknowledge that it is not possible to eliminate all potential biases, including those related to sampling, as not all referral centres for fetal therapy may have been included in the survey. Additionally, the non-availability of

non-response data may have an impact on the generalisability of our results.

4.4 | Implications for future research and clinical practice

This clinician survey, conducted as part of FERN WP1, will inform the FERN steering group in developing a list of scenarios and items crucial for planning a potential trial. These elements, combined with longitudinal data from the continuing multicentre prospective study (WP1) and qualitative research findings from patients and clinicians (WP2), will undergo a rigorous Delphi process or consensus meeting. This step is to evaluate the feasibility of conducting a randomised controlled trial comparing intervention versus expectant management for early-onset sFGR in MCDA twin pregnancies.

The results of our survey have provided valuable insights into current practices among experts in this field. Multiple ancillary factors influence clinician decision-making, including, but not limited to, the perceived gestation of viability, the availability of neonatal expertise and cultural attitudes towards TOP. These factors will be analysed in detail in WP2.

Most of the respondents in our survey appeared to adhere to professional society recommendations, although there is heterogeneity among the guidelines. However, it was also felt that the development and dissemination of existent clinical guidelines and regular educational activities are necessary to provide clinicians with the latest evidence to support clinical decision-making.

5 | CONCLUSION

Our survey provides insight into the diverse landscape of clinical practice and highlights significant variation in the attitudes (and practices) of clinicians, especially for early-onset type II and type III sFGR in MCDA twin pregnancies, such that we are poorly equipped to counsel women on management strategies. There is an unmet need to produce robust high-level evidence to address these questions and to optimise the outcome of these pregnancies, where the potential for adverse outcomes is high.

AUTHOR CONTRIBUTIONS

AK conceptualized the project and is the chief investigator of the FERN project, obtained the grant for the study, analysed the data, drafted the first version, revised it for intellectual content, approved the final version and is the corresponding author. SP collected the data, analysed it and drafted the first version of the paper, revised it and is a member of the study management team. TR is the FERN project study coordinator and revised the paper for intellectual content. AH, BT, BV, CC, JK, JS, KW, LH, MT, RA, RJ, ST, ZA and AS are the co-applicants for the study grant and revised the paper for intellectual content. JK is also the study statistician. OY

revised the paper for intellectual content. JM (Mendoza), JM (Marsden), MW, IO, DH, NF, SL are the PPIE co-applicants for the study grant and reviewed the protocol. DH, RP, EJ, LI, MP, TKM, AAB, JD, LL, KH, EL, DP, ATP, CB, DA, GA, MD, SN, TM, FDC, YY are the collaborators for the study grant and revised the paper for intellectual content. All co-authors accept responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available owing to privacy or ethical restrictions.

ETHICS APPROVAL

This study has received ethical approval from the Health Research Authority (HRA) South West – Cornwall and the Plymouth Ethics Committee (REC ref. 20/SW/0156; Integrated Research Application System, IRAS, ID 286337).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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