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Consensus diagnostic criteria and monitoring of twin anemia–polycythemia sequence: Delphi procedure

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KEYWORDS: diagnostic criteria; monitoring; multiple pregnancy; TAPS; twin; twin anemia–polycythemia sequence

CONTRIBUTION

What are the novel findings of this work?
Consensus-based antenatal and postnatal diagnostic criteria of twin anemia–polycythemia sequence (TAPS), as well as cut-off values for the parameters involved, monitoring interval and perinatal and long-term survival outcomes, were agreed upon by a panel of experts. There was no agreement on the indication for intervention or optimal management.

What are the clinical implications of this work?
These findings have the potential to change the way in which clinicians and researchers diagnose TAPS. The addition of middle cerebral artery (MCA) peak systolic velocity (PSV) discordance to the pre-existing MCA-PSV criterion for antenatal diagnosis of TAPS is likely to impact clinical practice significantly by identifying more TAPS cases.

ABSTRACT

Objectives *Twin anemia–polycythemia sequence (TAPS) is associated with increased perinatal morbidity and mortality. Inconsistencies in the diagnostic criteria for TAPS exist, which hinder the ability to establish robust evidence-based management or monitoring protocols. The main aim of this study was to determine, by expert consensus using a Delphi procedure, the key diagnostic features and optimal monitoring approach for TAPS.*

Methods *A Delphi process was conducted among an international panel of experts on TAPS. Panel members were provided with a list of literature-based parameters for diagnosing and monitoring TAPS. They were asked to rate the importance of the parameters on a five-point Likert scale. Consensus was sought to determine the cut-off values for accepted parameters, as well as parameters used in the monitoring of and assessment of outcome in twin pregnancy complicated by TAPS.*

Results *A total of 132 experts were approached. Fifty experts joined the first round, of whom 33 (66%) completed all three rounds. There was agreement that the monitoring interval for the development of TAPS should be every 2 weeks and that the severity should be assessed antenatally using a classification system based on middle cerebral artery (MCA) peak systolic velocity (PSV), but there was no agreement on the gestational age at which to start monitoring. Once the diagnosis of TAPS is made, monitoring should be scheduled weekly. For the antenatal diagnosis of TAPS, the combination of MCA-PSV ≥ 1.5 MoM in the anemic twin and ≤ 0.8 MoM in the polycythemic twin was agreed. Alternatively, MCA-PSV discordance ≥ 1 MoM can be used to diagnose TAPS. Postnatally, hemoglobin difference ≥ 8 g/dL and intertwin reticulocyte ratio ≥ 1.7 were agreed criteria for diagnosis of TAPS. There was no agreement on the cut-off of MCA-PSV or its discordance for prenatal intervention. The panel agreed on prioritizing perinatal and long-term survival outcomes in follow-up studies.*

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Conclusions *Consensus-based diagnostic features of TAPS, as well as cut-off values for the parameters involved, were agreed upon by a panel of experts. Future studies are needed to validate these diagnostic features before they can be used in clinical trials of interventions.*

INTRODUCTION

Twin anemia–polycythemia sequence (TAPS) is defined as the presence of anemia in the donor twin and polycythemia in the recipient twin in monochorionic twin pregnancy, and is associated with an increased risk of perinatal morbidity and mortality[1]. It was first described following laser surgery for twin-to-twin transfusion syndrome (TTTS) in 2006 by Robyr *et al.*[2], while its spontaneous onset was first described in 2007 by Lopriore *et al.*[3]. In fact, the copresence of an anemic and a polycythemic neonate in twin pregnancy was reported back in the 17th century[4]; however, it was not identified as TAPS until the 21st century[3].

The ISUOG twin pregnancy guidelines recommend monitoring for the development of TAPS in all monochorionic twin pregnancies from 20 weeks' gestation and, in particular, those that were complicated by TTTS and were treated by fetoscopic laser surgery, using ultrasound assessment of middle cerebral artery (MCA) peak systolic velocity (PSV) every 2 weeks[5]. However, there is large variation in clinical practice in ultrasound monitoring for TAPS, probably largely as a result of the lack of robust evidence on the accuracy of diagnostic criteria, natural history and management of twin pregnancies complicated by TAPS. One-third of the Maternal–Fetal Medicine specialists in the USA do not routinely assess MCA-PSV in twin pregnancies[6]. Furthermore, some national guidelines, such as those of the Society for Maternal-Fetal Medicine, have not recommended monitoring for TAPS in view of the lack of evidence that such monitoring with MCA-PSV Doppler improves perinatal outcome[7]. Moreover, recent studies have reported that delta MCA-PSV > 0.5 multiples of the median (MoM) could have greater diagnostic accuracy for predicting TAPS compared with the current MCA-PSV cut-off criteria, and that the fetal intertwin MCA-PSV MoM difference is a good predictor of neonatal intertwin hemoglobin concentration difference and potentially of TAPS[8,9].

The incidence, as well the natural history, of TAPS is likely to vary according to whether the diagnostic criteria rely only on the presence of MCA-PSV > 1.5 MoM in the donor twin and MCA-PSV < 1.0 MoM in the recipient or the delta MCA-PSV, regardless of whether MCA-PSV is normal in the donor or recipient twin. Furthermore, the incidence is also likely to vary according to the intertwin MCA-PSV discordance threshold used.

Inconsistencies amongst clinicians and researchers with regards to the diagnostic criteria used for the definition of TAPS are likely to yield further confusion and difficulty in comparing studies, combining data in a meta-analysis or establishing robust evidence-based management or monitoring pathways. In order to attempt to improve the outcomes of these pregnancies, it is imperative that researchers and clinicians first agree on a standard definition for TAPS. The main aim of this study was to reach expert consensus on the diagnostic criteria of TAPS, using a Delphi methodology. We also attempted to reach expert consensus on the parameters involved in the monitoring of these pregnancies, and those representing the key pregnancy outcomes.

METHODS

We applied the Delphi methodology as it is a well-established instrument with which to reach consensus from a panel of experts for research questions that cannot be answered with empirical evidence and complete certainty[10]. The Delphi methodology aims to refine the opinions of participating experts, while minimizing confounding factors present in other group response methods[11]. It is based on the scoring of a series of structured statements that are revised, fed back to the participants and repeated in multiple rounds, in increasing detail, until consensus has been reached[12].

We identified panel members based on their publication record as lead or senior authors in studies on TAPS, or by the suggestion of confirmed panel members. When inviting panel members, we specifically sought wide geographic representation in order to ensure generalizability of the consensus definitions. The votes of all panel members are weighed equally within the Delphi process. Experts who did not complete a particular round were not invited to subsequent rounds. The results were reported according to the guidelines for reporting reliability and agreement studies (GRRAS)[13].

Data collection

Data were collected in three consecutive rounds between November 2018 and April 2019 by online questionnaires that were presented to panelists through a unique token-secured link for each round. Responses were captured in Limesurvey version 2.50. Non-responders received reminder emails after 2 and 4 weeks, and were excluded from subsequent survey rounds if no response was obtained. Each round included the option of offering additional items or suggestions, as well as withdrawal of items from the procedure. Newly suggested items were categorized and considered carefully by the panel for their applicability in this procedure. Details were collected regarding the countries in which the experts practise, self-reported expertise, the invasive procedures they perform and the annual average number of dichorionic and monochorionic twins delivering at their hospitals/institutions.

First round

Based on a literature review, parameters that could potentially be included in the diagnosis, screening,

monitoring and assessment of pregnancy outcomes were presented to the panel for scoring. The panel was also given the opportunity to suggest additional parameters that they considered to be relevant. Some of the included parameters were not specific for the diagnosis of TAPS, but reflect the possible need to exclude other pathologies, such as TTTS. The panel was asked to rate the literature-based parameters for TAPS on a five-point Likert-scale (1 = very unimportant, 2 = unimportant, 3 = neutral, 4 = important, 5 = very important). The predefined cut-off for inclusion of parameters in the consensus-based diagnostic criteria for TAPS was a median score of 5 on the Likert scale.

Second round

In the second round, accepted and newly recommended items from the first round were presented to the panel with the answer options 'yes' or 'no'. Items in the first round that had scored the predefined cut-off of a median Likert score of 5 were considered as inclusions and presented to the panel for verification for inclusion, while items with a median score of 4 were presented to verify exclusion. Items with a median Likert score of 3 or lower were considered rejected and verification of rejection was requested. A predefined cut-off level of 70% agreement was used to define consensus for these questions. In the third round, parameters that fell within a 60–70% agreement range were presented to the panel for reconsideration.

Third round

In the third round, parameters with a median Likert score of 5 were presented to define whether they should be a solitary and/or a contributory parameter. A solitary parameter was defined as one sufficient to diagnose TAPS, even if all other parameters are normal. A contributory parameter was defined as one that would require other abnormal parameter(s) to be present to diagnose TAPS. Furthermore, the panel was asked to specify cut-off values for each parameter. The proposed cut-off values were literature based. Experts were asked to determine cut-offs for solitary and contributory parameters separately, as these thresholds could potentially differ.

RESULTS

We invited 132 publishing experts on TAPS to join this Delphi procedure. In the first round, an expert panel of 50 (38%) participants joined, of whom 33 (66%) completed the entire Delphi procedure. Response rates were 74% (37/50) in the second round and 89% (33/37) in the third round. Details regarding the self-reported expertise, specialization and demographic characteristics of all 50 participants are shown in Table 1, and details of the 33 participants who completed all three rounds are shown in Table S1. A list of the experts who completed the Delphi procedure is included in Table S2.

Table 1 Demographic characteristics of 50 experts on twin anemia–polycythemia sequence (TAPS) who responded to first round of Delphi survey

Characteristic	n *(%)*
Region of practice	
Europe	17 (34)
North America	22 (44)
South America	1 (2)
Asia/Australia	10 (20)
Africa	0 (0)
Level of care	
General/routine obstetric center	0 (0)
Fetal medicine center offering prenatal diagnosis but no fetal therapy	4 (8)
Fetal medicine center offering prenatal diagnosis and fetal therapy	46 (92)
Number of monochorionic twin deliveries at expert's hospital*	
< 20	3 (6)
20–29	12 (24)
30–39	6 (12)
40–49	8 (16)
≥ 50	21 (42)
Unknown	0 (0)
Number of dichorionic twin deliveries at expert's hospital*	
< 50	5 (10)
50–99	16 (32)
100–149	9 (18)
150–199	13 (26)
≥ 200	7 (14)
Unknown	0 (0)
Invasive procedures performed at expert's hospital	
Amniocentesis	50 (100)
Embryo and fetal reduction in multiple pregnancy	45 (90)
Chorionic villus sampling	49 (98)
Fetoscopic laser photocoagulation	38 (76)
Bipolar cord occlusion	36 (72)
Interstitial radiofrequency/laser ablation	40 (80)
Other†	16 (32)

*On annual basis. †Cardiac balloon procedures, myelomeningocele repair, intrauterine transfusion, shunting, fetal cardiac interventions, open fetal myelomeningocele repair, drainage of fetal fluid collections, fetal cystoscopy, fetoscopic endoluminal tracheal occlusion, fetal endoscopic tracheal intubation, cordocentesis, shunt for pleural effusion, embolization of chorioangioma, balloon valvuloplasty, microwave ablation, open fetal surgery.

In the first round, we presented 97 parameters to the panel (Table S3). Figures 1 and S1–S3 demonstrate the Likert scores of each parameter included in the diagnostic criteria, screening, monitoring and postnatal assessment of twin pregnancies complicated by TAPS. All the parameters suggested by members of the expert panel were presented in the following round for voting.

Table 2 lists the agreed parameters for the definition, screening, monitoring and postnatal assessment of twin pregnancy complicated by TAPS. The parameters identified as important for monitoring once the diagnosis has been made were fetal Dopplers and signs of fetal hydrops. The parameters identified as important to consider during the monitoring for development of TAPS were MCA-PSV in each twin and its discordance,

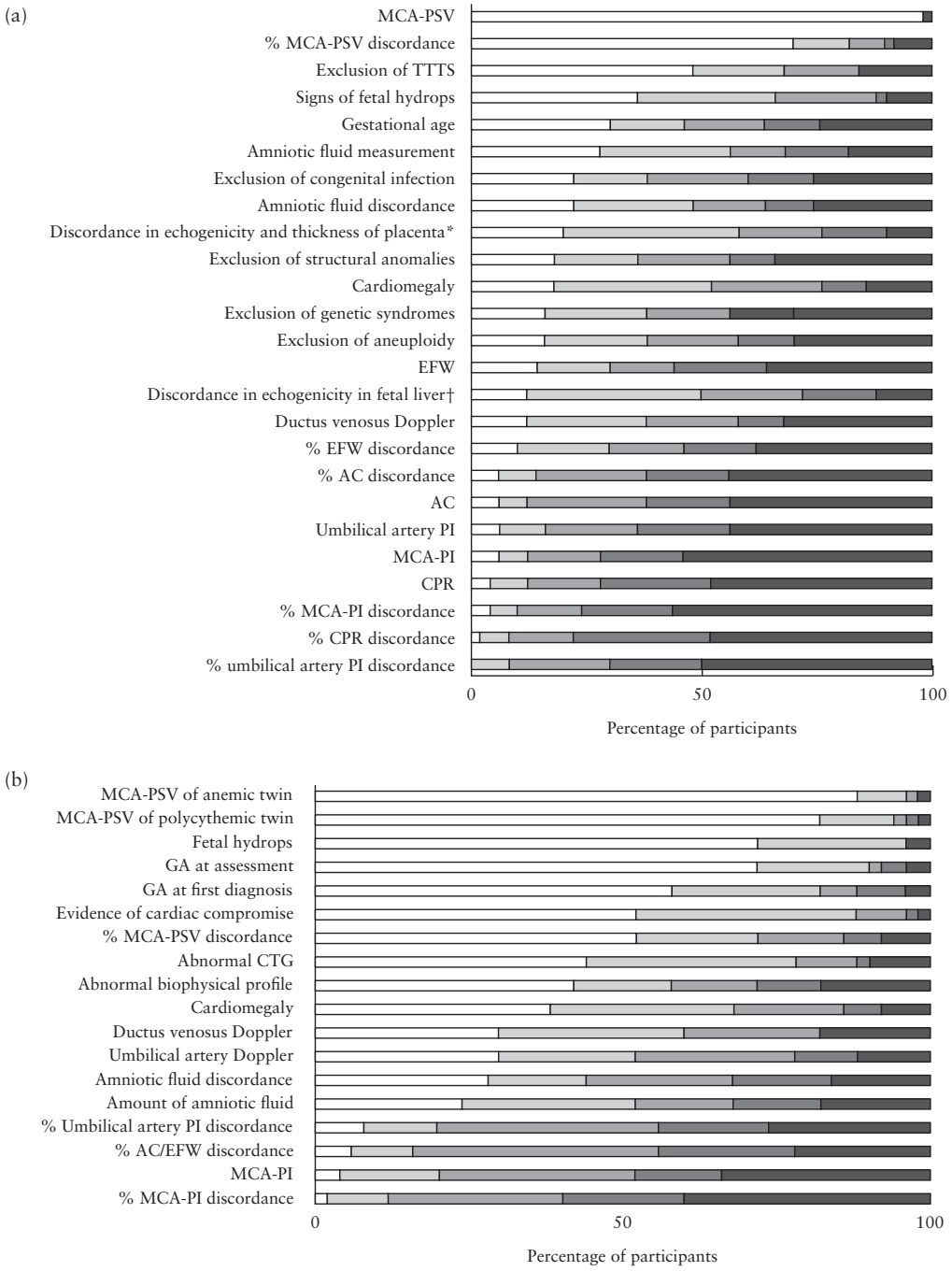

Figure 1 Importance of parameters describing diagnostic criteria (a) and those included in monitoring for development (b) of twin anemia–polycythemia sequence, as assessed by 50 experts in first round of Delphi procedure, rated using Likert scale: 1 = very unimportant (■); 2 = unimportant (■); 3 = neutral (■); 4 = important (□); 5 = very important (□). *Dark-thin *vs* echogenic-thick; †Starry sky *vs* echogenic. AC, abdominal circumference; CPR, cerebroplacental ratio; CTG, cardiotocograph; EFW, estimated fetal weight; GA, gestational age; MCA, middle cerebral artery; PI, pulsatility index; PSV, peak systolic velocity; TTTS, twin-to-twin transfusion syndrome.

evidence of cardiac compromise, signs of fetal hydrops and gestational age at first diagnosis and at assessment (Table 2). The parameters to include in the postnatal assessment and follow-up included gestational age at birth, hemoglobin level, reticulocyte count, need for transfusion/exchange transfusion, brain abnormalities detected on ultrasound or MRI, limb thrombosis and long-term assessment of the twins. Seventy-eight parameters were rejected (Table S4).

In the third round, the panel agreed the cut-off values for the diagnostic parameters. For the antenatal diagnosis of TAPS, the combination of MCA-PSV ≥ 1.5 MoM in the anemic twin and ≤ 0.8 MoM in the polycythemic twin was agreed. Alternatively, intertwin MCA-PSV discordance can also be used to diagnose TAPS. The optimal threshold for MCA-PSV discordance was agreed to be ≥ 0.5 MoM by 49% (16/33) of the experts and ≥ 1.0 MoM by 33% (11/33). Therefore, there was

Table 2 Parameters for definition, screening, monitoring and postnatal assessment of twin pregnancies complicated by twin anemia–polycythemia sequence (TAPS) that were agreed on by expert consensus in Delphi procedure

Parameter	*Votes (% in favor)*
Diagnostic criteria	
MCA-PSV	100
MCA-PSV discordance	97
Screening	
MCA-PSV	100
MCA-PSV discordance	97
Monitoring once diagnosis is made	
Fetal Doppler	100
Fetal hydrops	97
Monitoring for development of TAPS	
MCA-PSV discordance	95
Evidence of cardiac compromise	97
Fetal hydrops	100
Gestational age at assessment	100
Gestational age at first diagnosis	86
MCA-PSV in anemic twin	100
MCA-PSV in polycythemic twin	100
Pregnancy outcome and postnatal follow-up	
Brain abnormalities on ultrasound or MRI	100
Gestational age at birth	100
Hemoglobin level	100
Limb thrombosis	95
Long-term assessment of the twins	100
Need for transfusion/exchange transfusion	100
Reticulocyte count	95

MCA, middle cerebral artery; MRI, magnetic resonance imaging; PSV, peak systolic velocity.

> 80% agreement for intertwin MCA-PSV discordance ≥ 1.0 MoM. Postnatally, hemoglobin difference ≥ 8 g/dL and intertwin reticulocyte ratio ≥ 1.7 were agreed for the diagnosis of TAPS. There was no agreement on the cut-off of MCA-PSV or its discordance for prenatal intervention. There was agreement that the monitoring interval for the development of TAPS should be 2 weeks and that the severity should be assessed antenatally using a classification system according to MCA-PSV, but there was no agreement on the gestational age at which to start monitoring. Once the diagnosis is made, monitoring should be scheduled weekly.

DISCUSSION

Summary of study findings

In this study, consensus based diagnostic criteria for TAPS were established through a Delphi procedure. The combination of MCA-PSV ≥ 1.5 MoM in the anemic twin and ≤ 0.8 MoM in the polycythemic twin was agreed. Alternatively, MCA-PSV discordance ≥ 1 MoM can be used to diagnose TAPS. The postnatal diagnostic criteria included intertwin hemoglobin difference ≥ 8 g/dL and reticulocyte ratio ≥ 1.7.

There was agreement that monitoring for TAPS should be scheduled every 2 weeks and that the severity should be assessed using an antenatal classification system according to MCA-PSV. The panel reached consensus on a number of parameters that are important during the monitoring and postnatal follow-up of these pregnancies (Table 2).

Interpretation of study findings

The incidence of TAPS varies in the literature, but it is reported to affect 2–5% of otherwise uncomplicated monochorionic twin pregnancies and 3–16% of pregnancies complicated by TTTS treated by laser surgery[1,4,14–17]. These estimates are based on the original diagnostic criteria of MCA-PSV > 1.5 MoM in the donor twin and MCA-PSV < 0.8 MoM in the recipient twin. It is very likely that the incidence would increase if the recent diagnostic criterion of MCA-PSV discordance, regardless of whether MCA-PSV is within the normal range in either twin, was employed[8,9].

We noted similar parameters for the diagnosis and screening of TAPS, but with lower cut-offs for screening than for diagnosis. In fact, screening in this context actually refers to monitoring using MCA-PSV for the development of the disorder, so the parameters to consider are the same as the diagnostic criteria. The World Health Organization defines screening as 'the presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations or other procedures that can be applied rapidly and easily to the target population'[18]. There are no established screening markers that could identify those pregnancies prior to its clinical onset.

Clinical and research implications

It is important to realize that the performance of the antenatal diagnostic criteria for the postnatal diagnosis of TAPS is not 100%[8]. According to the most recent studies, the sensitivity and specificity of the MCA-PSV cut-off values (donor > 1.5 MoM, recipient < 1.0 MoM) to predict TAPS are 46% and 100%, respectively, while the positive (PPV) and negative (NPV) predictive values are 100% and 70%, respectively. Fishel-Bartal *et al.* have demonstrated that monochorionic twins diagnosed with polycythemia at birth often had MCA-PSV values > 1.0 MoM prior to delivery, and they therefore questioned the accuracy of this cut-off[14]. Furthermore, they reported a strong correlation between delta MCA-PSV and intertwin hematocrit difference[14]. Interestingly, delta MCA-PSV > 0.5 MoM has sensitivity and specificity of 83% and 100%, respectively, while the PPV and NPV were 100% and 88%, respectively[8]. Therefore, using fetal delta MCA-PSV is likely to identify more twin pregnancies complicated by TAPS antenatally. It remains to be determined whether these proposed diagnostic criteria would lead to better identification of twin pregnancies destined to develop adverse perinatal outcome. Therefore, the diagnostic criteria outlined in this Delphi consensus should be validated in prospective observational studies before they can be used in clinical

trials of interventions. It is important, though, to realize that the postnatal diagnostic criteria of TAPS do not necessitate the finding of an anemic twin and a polycythemic twin at birth, but a large intertwin hemoglobin discordance was considered diagnostic. Similarly, as highlighted in this study, the antenatal diagnostic criteria should ideally include discordance in MCA-PSV and not only be based on high MCA-PSV in the donor and low MCA-PSV in the recipient. Almost 50% of experts agreed on a MCA-PSV discordance threshold of 0.5 MoM, whereas 33% opted for a threshold of 1.0 MoM. Although the majority of participants would therefore agree that a discordance of at least 1.0 MoM would fit with a diagnosis of TAPS, more research is needed to determine the optimal threshold for MCA-PSV discordance. The Delphi procedure showed agreement on the use of antenatal staging according to MCA-PSV. Tollenaar *et al.* proposed a new antenatal staging system using delta MCA-PSV instead of actual MCA-PSV values (Table S5)[8].

It is very likely that TAPS contributes to the excess fetal loss, and perinatal mortality and morbidity in monochorionic twin pregnancies. This is even more likely when TAPS is not detected prenatally until an advanced stage when one or both twins have developed hydrops or intrauterine demise. However, robust evidence of improved perinatal outcome when TAPS is diagnosed antenatally does not yet exist. Nevertheless, this dearth of evidence should not translate into a recommendation by national guidelines not to monitor twin pregnancies for the development of TAPS, particularly in monochorionic twin pregnancies complicated by TTTS and treated by fetoscopic laser, for which the development of TAPS and its associated adverse outcomes is well described[19].

Strengths and limitations

In order to minimize the potential for peer pressure from authoritative individuals, feedback was provided only at a group level. Rules around acceptance or rejection of parameters were pre-defined, with double-checking of possible interpretation of the answers in subsequent rounds. This enabled the participants to change their minds in light of feedback/group response from previous rounds. The recently published studies proposing new diagnostic criteria including the use of intertwin MCA-PSV discordance were not available at the beginning of the first survey[8,9], but could have influenced the expert choice in the cut-off threshold, which was determined in the last round.

A limitation is the relatively small number of available experts, as TAPS was first described only 10 years ago. It is a specialist area and there is limited knowledge and awareness of its diagnosis and management. Furthermore, only two-thirds of panel members completed all three rounds. Another limitation is the potential for selection bias associated with the inclusion of a group of experts who share similar opinions, which is an inherent weakness of the Delphi methodology. Nevertheless, the experts who agreed to participate were those most familiar with the concepts and clinical implications of TAPS. Finally, this study did not address the optimal management of TAPS once diagnosed; this would require evidence, ideally in the form of a randomized controlled trial.

Conclusions

Consensus-based diagnostic criteria for TAPS, as well as the cut-off values for those parameters, were agreed by consensus. Prospective observational studies are needed to validate these diagnostic criteria before they can be used in clinical trials of interventions.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Importance of parameters to be included in screening for twin anemia–polycythemia sequence, as assessed by 50 experts in first round of Delphi procedure, rated using Likert scale. *Dark-thin *vs* echogenic-thick. **Starry sky *vs* echogenic.

Figure S2 Importance of parameters to be included in monitoring once diagnosis of twin anemia–polycythemia sequence is made, as assessed by 50 experts in first round of Delphi procedure, rated using Likert scale.

Figure S3 Importance of parameters to be reported in postnatal outcome and follow-up of twin anemia–polycythemia sequence is made, as assessed by 50 experts in first round of Delphi procedure, rated using Likert scale.

Table S1 Demographic characteristics of 33 experts on twin anemia–polycythemia sequence who completed all three rounds of Delphi survey

Table S2 List of experts who completed all three rounds of Delphi consensus

Table S3 Parameters for definition, screening, monitoring and postnatal assessment of twin pregnancies complicated by twin anemia–polycythemia sequence included in first round of Delphi procedure

Table S4 Parameters for definition, screening, monitoring and postnatal assessment of twin pregnancies complicated by twin anemia–polycythemia sequence that were rejected in Delphi procedure

Table S5 Previous and proposed antenatal classification system for twin anemia–polycythemia sequence (TAPS)[8]