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Consensus protocols for management of early and late twin-twin transfusion syndrome: Delphi study

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Contribution

What are the novel findings of this work?

A consensus was obtained after four rounds of Delphi surveys. FLP can be offered as early as 15 weeks gestation for selected cases. TTTS management should be tailored according to Doppler severity between 16- and 18-weeks. FLP can be considered up to 28 weeks of gestation.

What are the clinical implications of this work?

Expansion of gestational age ranges for FLP is emphasized by this study. Providing a standardized, unified and agreed-upon treatment protocol should advance the quality of future studies, guide clinical practice, and most importantly, improve patient care.

ABSTRACT

Objectives: Fetoscopic laser photocoagulation (FLP) is a well-established treatment for twin-twin transfusion syndrome (TTTS) between 16 to 26 weeks' gestation. Strong scientific evidence and uniform guidelines regarding the best clinical management of early (prior to 16 weeks and between 16 to 18 weeks) and late (after 26 weeks) TTTS are currently lacking. The aim of this study was to construct a structured expert-based clinical consensus for the management of early and late TTTS.

Methods: A Delphi procedure was conducted to reach a consensus on the clinical management by an international panel of experts. Participants were chosen by their clinical expertise, affiliation, and relevant publications. A four-round Delphi survey was initiated. The questionnaires were sent using SurveyMonkey, an online survey platform, and responses were collected anonymously. In the first round, a core group of experts was asked to answer open-ended questions regarding the indications, timing and modes of treatment for early and late TTTS. In the following two rounds, participants were asked to grade each statement on a Likert scale (1-5) and to add any suggestions or modifications. At the end of each round, the median score for each statement was calculated. Statements with a median grade of five without suggestions for change were accepted as the consensus. Statements with a median grade of below four were considered non-consensus and excluded from the Delphi. Statements with a median grade of four were modified according to suggestions and reconsidered in the next round. In the last round, participants were asked to agree or disagree on the statements, and statements with more than 70% agreement without suggestions for change were considered the consensus.

Results: A total of 122 scholar clinicians met the inclusion criteria and were invited to participate. Fifty-three agreed to participate in the study. Of those, 75.4% completed all four rounds. Following four rounds, a consensus regarding optimal management of early as well as late TTTS was obtained. FLP can be offered as early as 15 weeks gestation for selected cases. Between 16-

and 18-weeks gestation, management should be tailored according to Doppler severity. FLP can be considered up to 28 weeks of gestation.

Conclusions: The Delphi method allowed the construction of a generally agreed upon treatment protocol for early and late TTTS. Nevertheless, this protocol can be modified at the discretion of the operators, and their experience and tailored to the specificity of each case. This should advance the quality of future studies, guide clinical practice, and improve patient care.

INTRODUCTION

Twin-twin transfusion syndrome (TTTS) is one of the most common complications seen in monochorionic pregnancies, with a reported frequency of up to 15%. [1]. While the pathophysiology of TTTS is not fully understood, it is mainly related to the unbalanced vascular anastomosis on the placenta and release or suppression of vasoactive mediators [2, 3], causing one fetus to be hypovolemic (donor) while the other is hypervolemic (recipient). This process results in oligohydramnios in the donor fetus and polyhydramnios in the recipient fetus representing the hallmark of TTTS diagnosis [4]. Left untreated severe TTTS prior to 24 weeks is associated with poor fetal survival rates [5].

Fetoscopic laser photocoagulation (FLP) of anastomotic vessels is the mainstay of TTTS treatment [6]. In this method, placental vascular anastomoses are ablated to abolish the unbalanced shared circulation [6]. FLP is associated with a significantly improved dual survival rate of more than 60% and reduces the rate of neurodevelopmental impairment to less than 14% [7-9]. In addition to FLP, other management modalities that can be considered include pregnancy termination, selective reduction [10], and amnioreduction of the excessive fluid in the recipient fetus sac [4]. Expectant management with judicious delivery timing is also an option in cases presenting late in pregnancy [11].

FLP is routinely offered for TTTS between 16 to 24 weeks of gestation, in accordance with published randomized controlled studies [3, 4]. Nevertheless, tertiary centers may encounter cases that present earlier or later and face true dilemmas regarding treatment options. In this study, we aim to reach an expert consensus on the general clinical guidelines for the management of early (prior to 16 weeks and between 16 to 18 weeks) and late (after 26 weeks) TTTS using the Delphi methodology.

METHODS

Purpose and rationale

In the present study, we have aimed to evaluate the diagnosis and management of TTTS cases that occurred before 18 weeks and after 26 weeks. As most TTTS cases occur between 18-26 weeks, the high-quality evidence and studies, including controlled trials, only included patients within this gestational age range. Accordingly, high-quality evidence for TTTS cases diagnosed earlier and later is lacking. However, the diagnosis and management of early and late TTTS cases is a day-to-day challenge for fetal medicine experts, necessitating a universal guideline drawn outside the gold standard of high-quality published papers.

We used the Delphi methodology to attempt to achieve consensus amongst an international panel of TTTS experts. The Delphi technique is a well-established qualitative research method to systematically collect expert opinions and generate consensus for a research question that existing evidence could not answer [12]. The consensus is reached through an iterative process of questionnaires assessing experts' agreement on several phrases representing different management options [12]. Characteristics that give prominence to the Delphi technique compared to other qualitative expert group discussions are the technique's flexibility, the potential to include an unlimited number of experts, the participants' anonymity, revising each round based on the experts' comments, and the potential for experts to revise their answers in subsequent rounds [13]. Therefore, we used the Delphi technique to conduct the current study in accordance with the Guidance on Conducting and Reporting Delphi Studies (CREDES) recommendations [14].

Study design and expert panels

The online platform “SurveyMonkey.com” was used to set up the survey rounds, send the questionnaires, collect the responses and comments, and analyze the final answers. On this

platform, each participant could answer the questions and comment anonymously, and the final results are presented in aggregate format.

We identified two groups who participated in our study. A core group was composed of 24 international fetal medicine specialists affiliated with academic university centers experienced in fetal interventions. Our core group specifically represented a wide geographic affiliation in order to ensure generalizability of the consensus definitions. All had numerous publications in the field.

A second expert group was then selected based on the number of publications as first or senior author. PubMed was systematically searched for the records published in the last ten years by the following search strategy:

> (Twin twin transfusion syndrome[Title]) OR (Twin-twin transfusion syndrome[Title]) OR (TTTS[Title]) OR (feto-fetal transfusion syndrome[Title]) OR (Fetofetal Transfusion[Title]) OR (FFTS[Title]) OR (Placental anastomosis[Title]) OR (Fetoscopic laser coagulation[Title]) OR (Fetoscopic ablation[Title]) OR (Quintero Staging[Title])

All the authors with more than two publications as first or senior authors on the subjects listed above were considered experts and asked to join the study. Five consecutive invitations were sent to maximize the number of participants.

At the beginning of each round, it was noted that answering the questions is considered as the consent of participants to enter the study. The study protocol was approved by the IRB committee.

Delphi rounds

1st round Brainstorming session

The online brainstorming session was held with the participation of the 24 core panelists. They were asked to thoroughly describe in free text their management protocol for TTTS cases at three

different gestational ages: before 16 weeks, between 16-18 weeks, and after 26 weeks. Their responses were summarized in the form of fact phrases. Moreover, a scoping literature review was done to gather all the published evidence regarding the topic. All types of studies, including case reports, case series, and cohort studies, were reviewed to complete the fact phrases generated from the brainstorming session. The final version of the fact phrases was sent to all core panelists for their review and comments.

2nd and 3rd rounds

In the second round of the survey, all the parameters obtained from the preceding session were categorized into three gestational ages (<16, 16-18, and >26 weeks gestation). For the gestational ages before 16 weeks and between 16-18 weeks, statements were classified into the three domains of expectant management, pregnancy termination/selective reduction, and FLP. For the TTTS cases presented after 26 weeks, the statements were restated separately for Quintero stages 1 and 2-4 into the four domains of expectant management, selective reduction, the timing of delivery, amnioreduction, and FLP.

The fact phrases were sent to the expert group. First, they were asked for their demographic features, including their region of practice, academic degree, years of experience in diagnosing and treating TTTS, the annual number of referred monochorionic pregnancies, and the annual number of FLP performed for TTTS in their institute. The experts were then asked to rate each fact phrase based on the Likert scale from 1 (completely disagree) to 5 (completely agree). In addition, they had the option to comment on each phrase and suggest their modified version. Upon completing the task, authors received a copy of their responses and had access to revise that by the deadline. A reminder email was sent to non-respondents two times within the two weeks interval, and the non-respondents were excluded from the subsequent rounds.

At the end of the second round, the results were collected and presented to the core group. Phrases with a median score of five without suggestions for modification were considered the consensus and further processing was not required. Phrases with a median score of three or less were considered non-consensus and were eliminated from the next round without further ado. Fact phrases with a median score of four were modified by the core group based on the comments received by the participants in the prior round. The revised statements were re-submitted to be evaluated by all participants int the third round. During the entire process, phrases were modified and presented for reconsideration and led in a manner to achieve a consensus on clinical treatment plans and guidelines. Nevertheless, only phrases that were reviewed and received a score of 5 by the entire cohort were accepted. The third round was managed in the same methodology where experts that participated in the second round were invited to provide answers once again. A reminder email was sent twice within a two-week period and non-responders were excluded from the study.

4th round

All the phrases from the third round with a median score of four with suggestions for modification were revised according to the comments and entered for reconsideration in the final round. In this round, experts were asked only to agree or disagree with each statement. Agreements of more than 70% of experts were considered as consensus. The final list of consensus and non-consensus phrases were sent to the core group of experts for their final approval.

RESULTS

The summary of Delphi rounds is shown in Figure 1. In the first brainstorming round, 24 experts were invited to answer the questionnaire. The first round allowed the construction of 90 phrases to be rated on the Likert scale in the proceeding second round. Overall, 122 experts were invited to participate in the survey, and fifty-three (43.4%) completed the survey. Their demographic feature and level of expertise is shown in Table 1. At the conclusion of this round, 8 phrases received a median score of five and were considered consensus and 56 phrases received a median score of three or less and were removed from further analysis. The summary of the second round is reported in Supplementary file 1. Twenty-six phrases with a median score of four were merged and modified based on experts' comments and re-presented in the third round for reconsideration.

In the third round, the 53 experts that participated in the second round were invited again. Of those, 42 (79.2%) completed the survey. Twenty phrases were presented in this round which is shown in Supplementary file 2. Seven management options reached a median score of five and were considered a consensus. The rest of the statements had a median score of four and were modified according to the comments received from the participants.

In the fourth round, 42 experts were invited and 40 (95.2%) completed the survey. They were asked to agree or disagree on eleven phrases from the previous round, and all of the statements reached the agreement level of higher than 70% (Supplementary file 3). The consensus list of the Delphi study is shown in Tables 2.

DISCUSSION

In this study, we were able to address the unresolved subject of early and late TTTS. By methodologically using the Delphi technique, we obtained the consensus of experts regarding diagnostic parameters and treatment options in very early (<16 weeks), early (16-18weeks), and late (>26 weeks) TTTS. Our main findings were: 1) prior to 16 weeks: the classical classification system can be of limited value and focus should be given to Doppler measurements. While selective reduction should be discussed, FLP can be offered for selected cases as early as 15 weeks. 2) At 16 to 18 weeks, immediate FLP should be offered when abnormal ductus venosus (DV) Doppler flows are seen. 3) FLP can be offered after 26 and up to 28 weeks for selected cases.

The US Food and Drug Administration approved an investigational device exemption for fetoscopes, limiting their use to treat TTTS from 16 to 26 weeks of gestation. The 16 weeks threshold most probably originates from the following reasons: simple interventions such as amniocentesis are usually postponed after 16 weeks, most TTTS cases will occur after 16 weeks, and lastly, earlier presentation is rare, which is reported in 0-11.76% of the studies [15]. Moreover, international societies recommend to start monitoring for signs of TTTS no earlier than 16 weeks [16, 17]. For those reasons, early-onset TTTS might be underdiagnosed or under-reported in the available literature. Our results show that specific attention should be given to this group of patients. While classical Quintero staging criteria might not apply, amniotic fluid levels, Doppler studies and fetal echocardiogram data may be utilized to define the severity and deterioration of the disease. It has been shown in many publications that in severe cases of TTTS (stage 2-4), FLP should be offered after 16 weeks [6]. However, we achieved a consensus of expert' opinion implying that FLP can be offered as early as 15 weeks, and the threshold for intervention might be higher with treatment indicated only for stages 3 and 4. In our expert panel view, stage 2, at this early gestational age, can be monitored expectantly with repeated ultrasound scans.

The second scenario we inquired about was TTTS cases presented at 16 to 18 weeks. The motivation to investigate this age group was the higher rates of complications known when FLP is performed in early gestation. It is known that while usually the amniotic and chorionic membranes fuse at 12 to 15 weeks of gestation, this fusion improves as pregnancy progresses [18]. Early interventions as simple as amniocentesis have demonstrated higher rates of complications done at very early stages of pregnancy [19]. Moreover, studies have demonstrated higher rates of chorioamniotic separation when FLP was performed earlier [20]. Our results showed that the expert panel strongly recommends immediate FLP in those gestational ages only for symptomatic patients and stage 3 TTTS with abnormal DV Doppler. This allows a significant proportion of our patients to be managed expectantly with close ultrasound monitoring. Perhaps if no deterioration is seen, FLP can be performed at a more advanced gestational age reducing the potential for complications related to the intervention itself.

The third scenario of interest was TTTS cases presenting after 26 weeks. As the US Food and Drug Administration approved the fetoscopes for laser treatment up to 26 weeks, most of these cases are undergoing amnioreduction and planned delivery within the United States. However, some publications have shown similar outcomes of FLP performed after 26 weeks to those performed earlier [21-23]. Other limitations of FLP after 26 weeks are related to the size of the vessels which might be too large to coagulate, and poor visualization of the vascular equator due to greater distances, fetal vernix and larger fetuses obstructing the fetoscopic view. According to our study, the expert panel offered FLP up to 28 weeks if presumed to be technically feasible. Another important aspect that reached a consensus is the need to administer corticosteroids in this group of patients, as the fetuses are considered viable and can be delivered if complications occur.

As most TTTS cases occur between 16-26 weeks gestation, high-quality evidence including randomized controlled trials, only included patients within this gestational age range [24,

[25]. Accordingly, high-quality evidence for TTTS cases diagnosed earlier and later is lacking. Nevertheless, diagnosis and management of early and late TTTS cases is a day-to-day challenge for fetal medicine experts, necessitating a universal guideline drawn outside the gold standard of high-quality studies. The Delphi technique is a qualitative research method that entirely depends on the expert panel and systematically collects and summarizes the expert opinions on a research question [12]. It was chosen to address our research question due to the rarity of early and late TTTS and the diversity of management protocols between centers worldwide.

The limitation of our survey lies within the study's design, specific to the Delphi process with inherent risk of biasing participant's opinions. To overcome peer pressure or influence on the participants' answers we constructed the closed statements only after performing a brainstorming session with the coauthors. Further, to allow participants to express their opinions free of peer influences, we allowed free text additions to all closed statements. We concluded the study with a final round in which participants were asked to confirm and agree upon statements that were constructed earlier in the survey. A relatively low acceptance rate for participation among experts invited, although repeated requests were sent to encourage participation. We believe not all the experts targeted according to publications are clinically involved in the field. However, the demographic features of those who did participate showed that nearly 90% had experience of more than 10 years in TTTS management, and nearly half of them perform more than 50 FLP procedures in their centers annually. While the Delphi method itself is not considered evidence-based, it was utilized here as a valuable tool for incorporating expert knowledge and perspectives into evidence-based approaches to inform decision-making.

The main strength of this study is that we systematically summarized the experts' opinions on the management of early and late TTTS, for which the existing evidence is lacking in the literature. Accordingly, the consensus from the present study could significantly help fetal interventionists deal with this rare condition. However, it should be noted that this guideline cannot

be a gold standard, and the final decision should be made based on the competency and experience of the management team.

In conclusion, our study approached dilemmas in the diagnosis and management of TTTS that were left unanswered while clinicians faced them on a regular basis. We were able to construct a clean methodological evaluation of early and late TTTS and expand treatment opportunities. Clinical studies would be of added value to further validate statements that have reached a consensus on this platform.

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FIGURE LEGENDS

Figure 1. The flowchart of the Delphi study

EP: expectant management, TOP: termination of pregnancy, SR: selective reduction, FLP: fetoscopic laser photocoagulation

Tables

Characteristics	N (%)
Gender	
Female	18 (33.96)
Male	35 (66.04)
Race	
White/Caucasian	37 (69.81)
Black or African American	1 (1.89)
Hispanic or Latino	4 (7.55)
Asian or Asian American	10 (18.87)
Other	1 (1.89)
Region of practice	
North America	27 (50.94)
Europe	15 (28.30)
Asia	8 (15.09)
South America	2 (3.77)
Oceania	1 (1.89)
Years of experience in diagnosing and treating twin-to-twin transfusion syndrome (TTTS)?	
<2 years	3 (5.66)
2-5 years	0 (0.0)
5-10 years	4 (7.55)
>10 years	46 (86.79)

What is the estimated number of monochorionic pregnancies evaluated per year in your institute?	
<10	0 (0.0)
10-50	12 (22.64)
50-100	16 (30.19)
>100	25 (47.17)
What is the estimated number of fetoscopic laser photocoagulation for placental anastomosis performed annually at your institute?	
<10	3 (5.66)
10-30	14 (26.42)
30-50	15 (28.30)
50-70	12 (22.64)
>70	9 (16.98)
Academic degree	
Medical doctor	33 (62.26)
PhD	18 (33.96)
DO	2 (3.77)
Assistant professor	3 (5.66)
Associate professor	12 (22.64)
Professor	23 (43.40)

Table 1. Demographic data of 53 experts participating in the first round of Delphi

TTTS management prior to 16+0 weeks of gestation

- Prior to 16 weeks, TTTS presentation might not be in accordance with Quintero staging and require a less strict approach for diagnosis.
- Prior to 16+0 weeks, maximal vertical pocket, Doppler parameters (UA A\REDF and DV A\R a waves), and fetal echocardiography should be utilized to evaluate the severity and monitor signs of deterioration.
- Prior to 16+0 weeks, expectant management should be offered to TTTS cases with Quintero stage 2 and below, without maternal symptoms (shortness of breath, contractions, cervical length below 20mm) .
- Prior to 16+0 weeks, for patients managed expectantly, sonographic evaluation should be repeated once or twice weekly according to the severity of the disease, as well as monitoring maternal symptoms and cervical length.
- Selective reduction should be discussed with the patient as a treatment option for evolving TTTS prior to 16+0 weeks.*
- At 15+0 to 16+0 weeks, for monochorionic pregnancies complicated by TTTS stage 3 or 4, FLPC can be offered when the procedure is technically possible.

TTTS management between 16+0 to 18+0 weeks of gestation

- Patients diagnosed with TTTS and managed expectantly should have a full clinical and sonographic evaluation at least twice weekly.
- Fetal echocardiography parameters (including abnormal valves function, cardiac output, and contractility) can be utilized to support the diagnosis and treatment options.
- Immediate FLPC should be offered in TTTS cases with maternal symptoms (shortness of breath, contractions, cervical length below 20mm).
- Immediate FLPC should be offered in TTTS cases demonstrating A\R a-wave in the DV in either of donor or recipient fetus.

● FLPC can be considered for monochorionic pregnancies complicated by TTTS with concomitant. sFGR demonstrating intermittent or constant absent or reversed end-diastolic flow in the UA between 16+0 to 18+0 weeks.
TTTS management after 26+0 weeks of gestation
● TTTS cases that are managed expectantly should undergo full clinical and sonographic evaluation at least once a week, and potentially more frequently according to the severity of the disease. ● Antenatal corticosteroids treatment should be offered to TTTS cases that are considered viable after 24+0 weeks of gestation. ● Cases presented with TTTS stage 3 and 4 after 26 weeks and up to 28+0 weeks can be offered treatment with FLPC if the surgery is presumed to be technically feasible. ● Following 28+0 weeks of gestation, delivery should be considered for progressing TTTS cases stage 2 and above, who did not undergo and are not considered for FLPC. ● Cases that are not considered for FLPC and present with symptomatic TTTS after 26+0 weeks can be managed with amnioreduction. ● Monochorionic pregnancies complicated by asymptomatic TTTS stage 1 can be managed expectantly at least until 32+0 weeks.

Table 2. The consensus of management plans for early and late TTTS

*Local laws and regulations should be considered in this discussion

TTTS – twin twin transfusion syndrome; FLPC – fetoscopic laser photocoagulation; UA – umbilical artery; DV – ductus venosus; A\R - absent or reversed; EDF –end diastolic flow; sFGR – selective fetal growth restriction

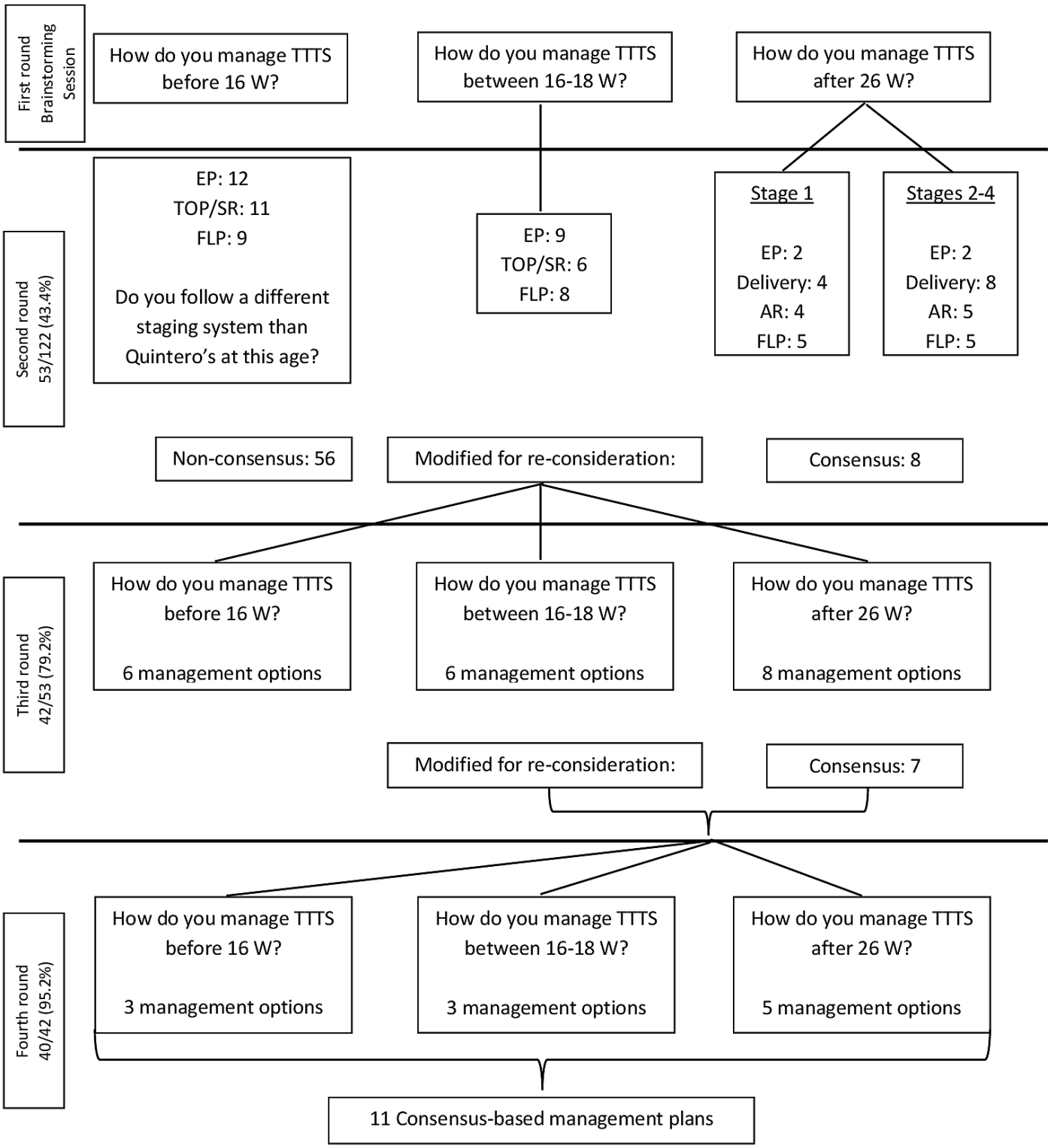

Figure 1.png