Title

The TOTAL trial dilemma: a survey among professionals on equipoise regarding fetal therapy for severe congenital diaphragmatic hernia.

Short running title

A survey on equipoise and fetal therapy.

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Conflict of interest

Prof Deprest reports being principal investigator of the TOTAL trial (University Hospitals Leuven).

Prof Dierickx reports being member of the Data and Safety Monitoring Committee of the TOTAL trial (University Hospitals Leuven).

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What is already known about this topic?

- In fetal medicine, it has been quite difficult to successfully run randomized clinical trials (RCT)
- Equipoise is a prerequisite for executing any RCT
- The RCT investigating the role of fetoscopic endoluminal tracheal occlusion (FETO) in fetuses with severe Congenital Diaphragmatic Hernia (CDH) also has met significant resistance

What does this study add?

- We conducted a knowledge, attitude and practice-survey among fetal medicine specialists on the antenatal management of CDH
- Half of respondents thinks that outcome in CDH cannot be predicted reliably, though still consider fetal therapy
- Half of respondents support the concept of an RCT but 70% feel that not offering FETO on parental request is a psychological burden
- Ambivalence to a randomized trial and the perceived psychological burden determines clinical practice

Data-availability statement

The data that support the findings of this study may be requested with motivation to the corresponding author. The data are not publicly available due to regulatory restrictions.

Abstract

Objective:

Running randomized clinical trials(RCT) in fetal therapy is challenging. This is no different for fetoscopic endoluminal tracheal occlusion(FETO) for severe left-sided Congenital Diaphragmatic Hernia(CDH). We assessed the knowledge, attitude and practice(KAP) of maternal-fetal medicine specialists towards the antenatal management of CDH, and the randomized controlled clinical (RCT) “Tracheal Occlusion To Accelerate Lung growth-trial”.

Methods:

A cross-sectional KAP-survey was conducted among 311 registrants of the 18th World Congress in Fetal Medicine.

Results:

The overall knowledge of CDH and FETO was high. Remarkably only 45% considers prenatal prediction of neonatal outcome reliable. Despite, in their clinical practice they perform severity assessment (80%) and refer families for FETO either within the context of an RCT (43%) or on patient request (32%). Seventy percent perceives *not* offering FETO on patient demand seems as if no treatment is provided to a fetus with predicted poor outcome. Only 20% of respondents considers denying access to FETO on patient demand not as a psychological burden. Conclusion:

Often the views of individual respondents contradicted with their clinical practice. It seems that, for severe CDH, clinicians face personal and practical dilemmas that undermine equipoise. To us, this indicates the tension between the clinical and scientific obligations physicians experience.

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Introduction

In fetal medicine, it has been quite difficult to successfully run randomized clinical trials (RCT). For instance, the recent trial on prenatal treatment of urinary tract obstruction was discontinued because of poor recruitment¹. Among other factors, delay in high-quality evidence finding, may cause clinicians and their patients to develop their own bias, based on small, heterogenic, observational studies, and potentially leading to the loss of equipoise². This has also been the case for the antenatal management of congenital diaphragmatic hernia (CDH).

In CDH the partial or complete absence of the diaphragm leads to herniation of the abdominal organs into the thoracic cavity, which impairs prenatal lung development³. Prenatal diagnosis is made in two thirds of cases^{4,5}, and the severity of the condition can be prenatally assessed⁶. Fetuses diagnosed with severe left-sided CDH have less than 25% chance of postnatal survival^{7,8}. This makes it a candidate condition for fetal surgery. There is experimental and clinical evidence that fetoscopic endoluminal tracheal occlusion (FETO) improves lung size hence neonatal outcome^{9–11}. Because of lack of robust evidence for benefit of FETO^{12,13}, FETO is being investigated in an RCT, entitled “Tracheal Occlusion To Accelerate Lung growth (TOTAL)”¹⁴. Patients are randomized to either undergo FETO or to be expectantly managed antenatally, followed by standardized perinatal management and postnatal repair of the defect.

At the start of the TOTAL trial, the ethical character of randomization was extensively discussed, including questioning whether the clinical community was in equipoise¹⁵. Equipoise, the existence of genuine uncertainty within a community regarding the benefits of one treatment compared to another, is a prerequisite for executing any RCT¹⁶. Implying genuine uncertainty, RCTs aim to be consistent with the ethical duties of doctors, as patients should not be allocated to an inferior therapy.

At the start of the TOTAL trial, it was agreed that equipoise was present, as FETO as a therapy still remained an experimental procedure, and existing preferences for therapy among clinicians mainly depended on the availability of FETO¹⁵. That debate delayed the start of the trial with two years¹⁷.

Together with the generic challenges of patient recruitment in fetal treatment trials due to the relatively rareness and detection rates of the conditions, the TOTAL-trial is taking now 10 years to be concluded. Recently, some clinicians questioned again the ethical character of randomization for severe CDH cases, and some centers withdrew from the TOTAL trial, based on their loss of equipoise. To catch up with actuality, the organizers of the 18th World Congress in Fetal Medicine organized a debate on the prenatal management of CDH session¹⁸. This world congress is the largest annual conference in fetal medicine. The discussants debated whether FETO should be offered exclusively within an RCT or also offered outside the research setting^{19,20}. The conference provided a suitable setting to assess the knowledge, opinions and practice of fetal- maternal specialists on the antenatal management of CDH. We thought this would not only inform us on the views of specialist on the TOTAL-trial, but also on how this may impact design and execution of this and any future fetal treatment trials.

Methods

This is an international, cross-sectional and anonymous knowledge, attitude and practice (KAP) survey to which the 2186 registrants of the 18th World Congress in Fetal Medicine (Alicante, Spain, June 2019) were invited to participate. The survey was specifically designed around a debate regarding the provision of FETO for severe left-sided CDH, either exclusively within an RCT or on patient preference.

Design

We designed this survey to assess the knowledge, attitude and behavior of physicians involved in fetal medicine, regarding the option for patients to have FETO, either on request or within the running global TOTAL trial ^{21,22}, according to the World Health Organization KAP-guidelines ²³. The University Hospitals Leuven was the sponsor of this study.

A draft survey was designed based on a thorough literature search and discussion with selected experts in fetal surgery and ethics (appendix 1). First, the expected knowledge to comprehend the dilemma was determined (condition, diagnosis, treatment, prognosis and ethics) (*Knowledge*)^{7,9,11,12,15–17,24–28}, as well as the different clinical management pathways for mothers with fetuses diagnosed with isolated severe left sided CDH (*Practice*). Based on the literature regarding RCTs and equipoise, and the discussion preceding the TOTAL trial ^{15,16,29–38}, statements were formulated to create contrasting opinions (*Attitude*). The agreed draft was pilot-tested for readability and understandability among a group of fetal-maternal researchers (appendix 1), by means of the ‘think-aloud’ method: the fetal-maternal specialists were asked to read the question and repeat in their own words what the question was asking, followed by an explanation of how they would

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answer the question and why³⁹. Questions were amended accordingly. As a final step, the survey was scored for content validity by a group of clinicians and researchers from the University Hospitals Leuven familiar with management of fetuses or neonates with CDH (neonatologists, researchers, fetal-maternal specialists, fetal surgeons, pediatric surgeons, n=8) (appendix 1). Clinicians were asked to rank each question on relevance, ranging from 1-4 (1 = not relevant; 4 = highly relevant). The item-level content validity index (I-CVI) was calculated, and questions with an I-CVI < 0.75 were excluded (three in total; two for knowledge, one for attitude) (appendix 2).⁴⁰ Each knowledge question had one right answer, based on the available literature^{9,11,16,25,28}. Therefore, each respondent received a 'knowledge score' ranging from 0 to 8 correct questions. As mentioned earlier, the attitude statements were made to divide participants according to different attitudes. The expert group decided that respondents agreeing to statement A3 confirm equipoise. Similarly, agreeing to statement A7 and disagreeing to statement A8 indicated a preference for FETO exclusively within an RCT (proponent of RCT); conversely disagreeing to statement A7 and agreeing with statement A8, indicating a preference for offering FETO outside the research setting (opponent of RCT) (detailed in appendix 2). The practice questions queried whether respondents assess and counsel patients carrying a fetus with CDH. In an effort to assess their practice, we combined respondents that offer (n=160) and refer for FETO (n=86) into one group (total n=246) and divided them in three categories, based on how they manage their patients: (1) FETO only within an RCT, (2) FETO on request of the parents, (3) leave the decision to a tertiary center or to the parents (appendix 2).

The final version of the survey (appendix 3) consisted of 25 multiple-choice questions (first question on informed consent):

- Demographic information of the participant (6 questions).
- Information about the participant's **knowledge** on CDH and FETO (8 questions).
- The participant's **attitude** to CDH and FETO (8 questions).
- The participant's **practice** in patients with a fetus with severe CDH (the population of interest to the TOTAL trial) (3 questions).

Participants and data-collection

The World Congress in Fetal Medicine is a large international conference typically attended by clinicians, who have a specific interest in maternal-fetal medicine. They are considered as representative of health care professionals who first see patients with the prenatal diagnosis of CDH, hence relevant to our research. Attendees were invited to this survey during the conference by distributing flyers and showing a link to the survey before and after the debate.

In addition, an invitation was sent by email to all attendees of the conference 10 days later. The survey remained open until 6 weeks after the conference. The online survey (LimeSurvey version 2.00+ Build 130708, The LimeSurvey Project Team, Hamburg, Germany) was accessible from June 26th 2019 until August 10th 2019. Participating in the survey was anonymous.

Data-analysis

Descriptive statistical analysis was conducted with IBM SPSS version 26.0 (IBM Corporation, New York, NJ, USA). The Mann-Whitney U test was used to compare knowledge scores between groups. A value of $P < .05$ was considered significant. All data are reported as number, percentage, median and interquartile range (IQR).

Poll

Prior to the debate, we conducted an on-site poll on the prenatal management of CDH by real time tele-voting to measure the impact of the debate on whether there is still equipoise on fetal therapy^{19,20}. This debate was part of the program of the World Congress in Fetal Medicine.

Participants answered four questions (Appendix 4) about their view on the possibility to offer FETO outside the context of a trial, and immediately after.

Ethics

This study was approved by the Ethics Committee of the University Hospitals Leuven (S62866). At the start of the survey, all participants were shown instructions to the survey and asked to provide confirmation of informed consent by ticking a box. The anonymous data were kept in an electronic database located on the protected server allocated to the PI. This is a password protected domain and access was limited to the personnel involved in the study (PI, sub-investigators, administrators). The data will be stored for 5 years after the end of the study.

Results

Four-hundred and sixty-seven attendees started the questionnaire (initial response rate 22%). Of those, 156 (33%) did not finish the questionnaire, either while filling out the demographic questions (n=68/156, 44%) or later on (n=88/156, 56%). Eventually, this left us 311 completed questionnaires of which 44 were completed on the day of the debate. The demographics of participants are displayed in **Table 1**. Over 80% were maternal fetal medicine (MFM) specialists, fetal surgeons or obstetricians, 75% had 6 years of clinical experience or more and 64% were involved in research.

1. Knowledge

Table 2 displays the answers to the eight questions measuring knowledge. On average, respondents correctly answered 6 out of the 8 questions (median 6.0, IQR 5.0-7.0; n=311). Only 45% (n=139/311) agreed that neonatal survival in isolated left sided CDH can be reliably predicted in the prenatal period. There was a lack of knowledge 'on the availability of emergency in utero balloon removal in tertiary care hospitals' and 'evidence from RCTs on FETO' in 44% and 42% respectively. Of all professional categories, fetal surgeons scored the highest on knowledge questions (7 out of 8 questions; 5.75-8.0, n=25) (**Figure 1**). Those involved in MFM-research had a knowledge score of 6 (5.0-7.0, n=197). Respondents who attended the debate scored higher than those who did not (6.0 [5.0-7.0, n=234] vs 5.0 [4.0-6.0, n=77]; P=0.021).

2. Attitude

The first attitude statement (A1) polled the absolute increase in survival (%) respondents felt FETO should induce, to be considered as more effective than postnatal management. Options were 5-10%

(8%), 10-30% (43%), 30-50% (32%) or >50% (18%), with the answers between brackets. In other words, respondents were quite divided: 50% expected FETO to increase survival by 5- 30% whereas the others expected it to be more than 30%. The answers to the other attitude statements are displayed in **Table 3**. Nearly 60% (n=186) of respondents agreed with the statement that the exact risks and benefits of FETO are unclear, hence were considered to be in equipoise. The vast majority (n=219/311; 70%) acknowledges that not offering FETO to patients demanding it, is a psychological burden. Half of respondents were considered as proponents of an RCT (A7) (n=161/311; 52%).

Relation to knowledge

To assess the correlation between knowledge and attitude, we analyzed individual knowledge scores of participants to certain attitude statements. Respondents who earlier stated they considered an increase of survival of less than 30% beneficial(A1), had a comparable knowledge score to that of those hoping for a more than 30% increase in survival (6.0 [5.0-7.0, n=157] vs 6.0 [5.0-7.0, n=154]; P=0.221).

Statement A3 indicated that the exact benefits and risks of FETO are unclear and was purposely designed to assess participants whether they were in equipoise. Those who agreed with this statement, had a higher knowledge score (6.0 [5.0-7.0, n=186] vs 5.0 [4.5-5.5, n=125]; P<0.001).

Statement A7 and A8 were included to prompt a clear statement of respondents in which context FETO should be offered. Those who agreed with statement A7, hence were considered as proponents of offering FETO within an RCT, had a higher knowledge score (6.0 [5.0-7.0, n=161] vs 5.5 [5.0-6.0, n=150]; P=0.031). Similarly, those who disagreed with statement A8, and thus were also

considered as supportive of FETO being offered within an RCT, scored higher than those who agreed with this statement (6.0 [5.0-7.0, n=131] vs 5.0 [4.5-5.5, n=180]; $P<0.001$). Of note is that 67% of proponents and 77% of opponents were consistent in their answers to both questions (NS).

Figure 2 displays the number of respondents, categorized as being a proponent or opponent of an RCT, providing right answers to the eight knowledge questions. The difference between proponents and opponents was most noticeable beyond the third knowledge question.

3. Practice

Table 4 displays how participants manage their patients in a clinical setting. A minority of respondents do not see pregnant women carrying a fetus with CDH (n=19; 6%) or do not assess severity nor counsel themselves (n=38; 12%). Four out of five (n=246/311; 79%) respondents assess and counsel patients on severity assessment. Of these, only half (n=118/246; 48%) would refer or offer patients FETO within an RCT and a quarter (n=69/246; 28%) on patient request. The remainder (n=59/246; 24%) would leave the decision in the hands of a tertiary center or the parents.

The last question queried the practice of respondents when parents insisted on having FETO. In that situation, 41% of respondents (n=128/311) would offer or refer patients for this procedure. Only 25% (n=79/311) stated they felt FETO should only be offered within an RCT. There were only seven respondents (2%) who would advise their patients against FETO, either in or outside an RCT. Of note is that one third of all respondents (31%; n=97/311) had never been in this situation or did not have an opinion.

Relation to knowledge

Participants who were involved in the assessment of pregnant women carrying a fetus with CDH, had a higher knowledge score than those who did not (6.0 [5.0-7.0, n=246] vs 5.0 [4.0-6.0, n=65]; $P<0.001$). However, only half of the former (n=122/246; 50%), agreed that one can reliably predict neonatal survival. Those only offering or referring patients to FETO within an RCT had a comparable knowledge score to those who do not 6.0 [5.0-7.0, n=118] vs 6.0 [5.0-7.0, n=128]; $P=0.105$).

Relation to attitude

How respondents manage patients clinically, is displayed in **Figure 3**. It displays their practice regarding referral for FETO, either as “within an RCT”, “per patient preference”, or “indifferent”, i.e. meaning the ultimate decision is only taken after consultation at the tertiary prenatal management center.

Respondents managing patients based on severity (n=246) (**Table 4**), and who are in equipoise (A3, n=149), of those 54% (80/149) refer or offer FETO uniquely within an RCT and 23% (34/149) upon patient request. In 23% of cases, they would leave the decision in the hands of a tertiary center or parents. Conversely, those who disagreed with the equipoise statement (A3; n=83), refer or offer FETO within an RCT in 36% (n=30/83) and 39% on patient request (n=32).

Respondents who consider ‘not offering FETO to parents who ask for it, as a psychological burden’ (A5) (n=176/246), followed patient preference for FETO in 32% (n=57/176). Seventy-five respondents (43%) still referred patients for trial participation. Of those who disagree with the statement that not offering FETO is a psychological burden (A5; n=49), 71% (n=35/49) refer or offer FETO within an RCT and 14% (n=7/49) on patient request.

Of the proponents of the RCT who assess patients (n=124), 68% offer FETO within an RCT (n=84/124) while 13% on patient request only (n=26/124). In contrast, opponents (n=104) refer or offer on patient request in 47% (n=49/104) while 26% (n=27/104) as participant of a trial. When using statement A8 to define the practice of opponents and proponents, practice was similar.

In summary, two-thirds of proponents offer FETO within an RCT and half of opponents offer FETO on patient request.

Poll

Table 5 displays the answers to the on-site poll prior and after the debate. Before, 15% of the respondents at the debate were of the opinion that FETO should be exclusively offered within the context of an RCT (n=45/307). That percentage that went up to 39% after the debate.

Discussion

We assessed the knowledge, attitude and practice of professionals to better understand the factors determining clinical equipoise with regards to the TOTAL trial. The majority of respondents was clinically involved in fetal medicine. They had a high level of knowledge on CDH and available treatment options; with fetal surgeons having more knowledge on the more procedural specific questions. Remarkably, 45% indicated they were *not* convinced that the outcome of fetuses with CDH can be reliably predicted prenatally. However, at the same time they express opinions on fetal therapy, with two thirds being in equipoise. The vast majority of respondents refers to the psychological burden on parents of not offering FETO on parental request, when prenatal assessment predicts poor outcome. The views and practice of respondents often differed, indicating that clinicians face personal and practical dilemmas undermining equipoise. Around 25% offers FETO on patient request.

According to the International Fetal Medicine and Surgery Society, accurate prenatal prediction of outcome is mandatory to consider fetal intervention. Though the vast majority of our respondents are professionals in clinical practice, half of them doubt prenatal prediction is possible for a fetus with CDH. This may suggest the fetal medicine community questions the accuracy of current assessment methods and prediction models. At the same time the vast majority of respondents seem to perceive CDH as a severe congenital malformation with overall poor outcome. When parents request fetal therapy, only 2% of respondents advise against it, which may indicate that the vast majority feels there is need for, and perhaps also that there is a potential benefit of interventions that improve the outcome. The latter suggests that the concept of fetal therapy is well known or at least to some extent accepted among respondents.

Though most participants were in equipoise, the translation into daily clinical practice is inconsistent. When facing mothers carrying a fetus with severe CDH, only half of respondents in equipoise, would refer or offer FETO *within the context of an RCT*. Our survey did not probe for the reasons for this apparent ambivalence, and we can only speculate about their reasons. One may be that respondents feel an RCT is not the optimal way to solve this question⁴¹, given 35% of these respondents *do not support* the RCT. Clinicians may experience discomfort with randomly allocating pregnant patients or they might feel that prenatal therapy is superior to postnatal management.

Earlier studies show that clinicians experience ‘hunches’ or ‘gut feeling’, steering them to prefer one treatment option^{42,43}. This personal bias is more pronounced when there is a delay in scientific evidence finding, which is the case with this trial¹⁷. In the case of an unborn child with an a priori low chance of postnatal survival, this individual bias may be even stronger^{42,44–46}. This has earlier complicated the start of the TOTAL trial¹⁵, as well as other trials in prenatal therapy^{2,47}.

Another reason may be that in RCTs, in particular those involving potentially life-saving treatments, randomization may be considered as denying access to the potential benefits of the novel intervention and taking away the parents’ last hope⁴⁸. The high percentage of respondents indicating that not offering FETO on parental request is a psychological burden to prospective parents, supports this. As FETO is not ‘new’, parents may have found information through various channels, and developed their own bias and are desperate for a potential life-saving intervention for their unborn child.

These reasons may challenge the equipoise throughout a long-lasting fetal treatment trial, but should not discourage researchers to design and execute fetal treatment trials in the future. Offering a therapy upon parental request, with a low but tangible risk for maternal complications⁴⁹, and known

fetal risks^{24,50,51}, may not be in the patient's best interest³². An RCT should protect patients from potential harm and concurs with the principle of non-maleficence^{52,53}, as well as providing future patients with high quality evidence on the preferred treatment. In situations in which parents have to make decisions with potentially far-reaching consequences for their unborn child, this is essential.

Remarkably, one third of respondents considered to be *not in equipoise*, still refers or offers FETO within an RCT. Also, a quarter of the opponents to an RCT, still refers or offers for trial participation. Again, we can only speculate about those respondents' motivations. Maybe they feel peer pressure, fear being accused of functioning as a back door, or they simply want to contribute to the quest for best evidence even if individual equipoise is lost⁵⁴. Also, there may be no local access to FETO outside the context of an RCT. Our observation that many specialists attending a debate on equipoise on this matter, change their mind after hearing the arguments for an RCT, probably underscores their ambivalence to this matter.

Strengths and limitations

We acknowledge several weaknesses to our study. First, the response rate was less than desirable. Second, one out of three respondents starting the questionnaire did not complete it. There might be several reasons for that. One explanation may be that the questionnaire was too complex and answering too time consuming. However, this seems unlikely, as almost half (44%) did not proceed beyond the demographic questions. We could also have insisted more by sending more reminders, or have provided respondents an incentive. Third, respondents may not be representative of the "larger community". We first advertised the survey at the end of the debate. Three out of four respondents indeed attended the debate, so that we assume that this successfully sparked attendees' interest, but

in this group, centers participating to the TOTAL may be overrepresented. Due to the anonymous character of the study, we cannot determine from which center the participants originated. Fourth, logistic restrictions (e.g. patient's inability to travel) or regional availability of FETO has not been queried and may affect practice. Fifth, participants were invited after the debate, which may have altered their opinions. Sixth, to assess knowledge, we arbitrarily created an unprecedented scale to score knowledge from 0-8, and we weighed all knowledge questions equally.

Despite, this study also has its strengths. First, to our knowledge, this is the first study to assess the knowledge, opinions and practice of professionals in maternal-fetal medicine regarding fetal therapy for CDH and an ongoing RCT. Second, we collected 311 completed surveys, over 80% of these by professionals involved in fetal medicine. Three out of four had more than 6 years of experience and two out of three were involved in research in fetal medicine. We consider them as relevant and representative for the clinicians patients see. This study therefore provides accurate insight regarding the knowledge, attitudes and practice of these specialists on a topic under debate.

Conclusion

Surveyed specialists were divided on whether FETO for severe left sided CDH should be offered exclusively within a randomized control trial or upon request of parents. The findings of this study indicate a tension between the clinical and scientific obligations of fetal medicine specialists when dealing with patients eligible for an RCT. While equipoise should be their guidance, apparently for many clinicians this situation evokes personal and practical dilemmas. This may also affect the successful execution of future fetal therapy trials.

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TABLES

Table 1: Demographic variables of study participants.

Data are displayed as n(percentage)

Table 2: Distribution of answers to the eight knowledge questions.

*Data are displayed as n (percentage); * was defined as the correct answer; n=311 complete surveys.*

Table 3: Distribution of answers to the attitude statements.

*Data are displayed as n(percentage); * was defined as the correct answer; n=311 complete surveys.*

Table 4: Practice of respondents when seeing a pregnant woman with a fetus with severe left sided isolated CDH.

*Data are displayed as n(percentage); *= three participants would offer termination of pregnancy or refer the patient, one would offer neonatal care, t<o state they only perform assessment and counseling.*

Table 5: Answers to poll on offering FETO outside the research setting or exclusively in an RCT.

A refers to presentation held by opponent of FETO exclusively in an RCT; B refers to presentation held by proponent of FETO exclusively in an RCT.

FIGURES

Figure 1: Knowledge score (range: 0-8) for professional categories.

Figure 2: Radar chart of percentage of participants with a correct answer per knowledge question.

Figure 3: Practice per attitude statement

Figure 1: Knowledge score (range: 0-8) for professional categories.

Figure 2: Radar chart of percentage of participants with a correct answer per knowledge question

In my opinion, in severe CDH, offering FETO as part of an RCT, is the only option as there is no evidence on its efficacy

In my opinion, in severe CDH, offering FETO only within an RCT is undesirable, as you are withholding a therapeutic option that may improve outcome

Legend:

- Opponents of RCT (n=150)
- Proponents of RCT (n=161)

Parameter	Number of participants (n=311)
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Table 1: Demographic variables of study participants. *Data are displayed as n(percentage)*

Gender	
Female	161 (52%)
Male	149 (48%)
NA	1 (<1%)
Main profession	
Maternal-fetal medicine specialist	217 (70%)
Trainee	26 (8%)
Fetal surgeon	25 (8%)
Obstetrician	12 (4%)
Sonographer	12 (4%)
Physician not involved in fetal medicine	10 (3%)
Radiologist	3 (1%)
Pediatrician	2 (1%)
Researcher fetal medicine	2 (1%)
Pediatric Surgeon	1 (<1%)
Geneticist	1 (<1%)
Country currently working in	
Europe	193 (62%)
Asia	36 (12%)
North America	29 (9%)
South America	21 (7%)
Africa	7 (2%)
Oceania/Australasia	7 (2%)
Other	18 (6%)
Years of experience in fetal medicine	
0-5	76 (24%)
6-10	61 (20%)
>10	170 (55%)
Currently involved in research in fetal medicine	197 (64%)
Attended the debate	234 (75%)

Table 2: Distribution of answers to the eight knowledge questions. Data are displayed as *n(percentage)*; * was defined as the correct answer; *n=311* complete surveys.

Statement		True	False	I don't know
K1	Clinical equipoise is a genuine uncertainty in the clinical community about which treatment is best for patients in a defined population	253 (81%)*	22 (7%)	36 (12%)
K2	The expected survival rate of severe lung hypoplasia, without prenatal treatment, is <30%	281 (90%)*	22 (7%)	8 (3%)
K3	Non-randomized studies suggest that FETO improves survival in neonates with severe isolated left-sided CDH	272 (87%)*	14 (5%)	25 (8%)
K4	There is sufficient evidence from randomized controlled trial(s) that FETO improves survival in neonates with severe isolated left-sided CDH	94 (30%)	181 (58%)*	36 (12%)
K5	Delivery before 34 weeks occurs in around 30% of the patients undergoing FETO	208 (67%)*	45 (14%)	58 (19%)
K6	For patients who underwent FETO, not staying close to a center offering emergency in utero balloon removal, increases the risks of neonatal death	272 (88%)*	22 (7%)	17 (5%)
K7	For patients who underwent FETO, the majority of tertiary care hospitals offer emergency in utero balloon removal	94 (30%)	175 (56%)*	46 (14%)

K8	In mid-trimester fetuses, one can reliably predict neonatal survival with isolated leftsided CDH	139 (45%)*	142 (45%)	30 (10%)
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Table 3: Distribution of answers to the attitude statements. *Data are displayed as n(percentage); * was defined as the correct answer; n=311 complete surveys.*

Statement: In my opinion, in severe CDH, ...		I agree	I disagree	I don't know
A2*	FETO is the only option for increasing neonatal survival rate	166 (54%)	82 (26%)	63 (20%)
A3	The effect of FETO is unclear: the exact benefits and risks for the fetus are still unknown	186 (60%)	102 (33%)	23 (7%)
A4	Doing no FETO is withholding a proven treatment option	108 (35%)	157 (50%)	46 (15%)
A5	Not offering FETO to parents who ask for it is a psychological burden for the prospective parents, as it seems as if no treatment is provided in a fetus with predicted poor outcome	219 (70%)	63 (20%)	29 (9%)
A6	Not offering FETO is giving the current standard of care	109 (36%)	169 (54%)	33 (11%)
A7	Offering FETO as part of an RCT, is the only option as there is no evidence on its efficacy.	161 (52%)	124 (40%)	26 (8%)
A8	Offering FETO only within an RCT is undesirable, as you are withholding a therapeutic option that may improve outcome.	137 (44%)	131 (42%)	43 (14%)

Table 4: Practice of respondents when seeing a pregnant woman with a fetus with severe left sided isolated CDH. Data are displayed as n(percentage); *= three participants would offer termination of pregnancy or refer the patient, one would offer neonatal care, t<o state they only perform assessment and counseling

Statement: If I see a patient with a fetus with CDH...		Number of participants (n=311)
I assess severity and counsel, and if severe, I refer...		160 (52%)
	...to a center which will offer FETO within an RCT	81 (51%)
	...to a center which will offer FETO on the request of the parents	53 (33%)
	...to a tertiary center, regardless of what way the patient will be managed antenatally	26 (16%)
I assess severity and counsel, and if severe, I offer...		86 (28%)
	...FETO within an RCT	33 (38%)
	...FETO outside an RCT	16 (19%)
	...both options to parents	37 (43%)
I do not assess severity nor counsel, I refer...		38 (12%)
	...to a center which will offer FETO	6 (16%)
	...to a center which offers FETO within an RCT	7 (18%)
	...to a center which will offer FETO on the request of the parents	5 (13%)
	...to a tertiary center, regardless of how the patient will be managed antenatally	20 (53%)
I do not see patients with CDH		19 (6%)
Other		6 (2%)*

Table 5 Answers to poll on offering FETO outside the research setting or exclusively in an RCT *A* refers to presentation held by opponent of FETO exclusively in an RCT; *B* refers to presentation held by proponent of FETO exclusively in an RCT.

Q1 Can one reliably predict outcome in mid-trimester fetuses with isolated left-sided CDH?				
	A		B	
	<i>n</i>	%	<i>n</i>	%
<i>Yes,</i>	138	43	85	45
<i>No,</i>	125	39	82	43
<i>Impartial,</i>	26	8	17	9
<i>I don't have the right knowledge to answer</i>	35	11	6	3
	324		190	
Q2 Is there convincing evidence today that prenatal FETO improves survival in fetuses with isolated severe left-sided CDH?				
	A		B	
	<i>n</i>	%	<i>n</i>	%
<i>Yes,</i>	185	58	47	26
<i>No,</i>	91	29	103	56
<i>Impartial,</i>	27	9	27	15
<i>I don't have the right knowledge to answer</i>	14	4	6	3
	317		183	
Q3 Under the assumption one can reliably predict outcome in isolated severe left-sided CDH, one should today:				
	A		B	
	<i>n</i>	%	<i>n</i>	%
<i>Offer FETO exclusively in an RCT,</i>	45	15	72	39
<i>Offer FETO exclusively as therapeutic option,</i>	83	27	24	13
<i>Offer FETO either in an RCT or as a therapeutic option,</i>	145	47	78	43
<i>Not offer FETO at all,</i>	13	4	7	4
<i>I don't have the right knowledge to answer</i>	21	7	2	1
	307		183	
Q4 If parents insist on having FETO in their fetus with isolated severe CDH, one should offer the intervention:				
	A		B	
	<i>n</i>	%	<i>n</i>	%
<i>Yes,</i>	238	79	117	65
<i>No,</i>	30	10	49	27
<i>Impartial,</i>	15	5	10	6
<i>I don't have the right knowledge to answer</i>	18	6	5	3
	301		181	