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CLINICAL OPINION

Five years to the term breech trial: The rise and fall of a randomized controlled trial

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Objective: On the basis of the end points of neonatal morbidity and death, the authors of the term breech trial concluded unequivocally that cesarean delivery was safer for breech babies.
Study design: Analysis of the original and new data gives rise to serious concerns as far as study design, methods, and conclusions are concerned. In a substantial number of cases, there was a lack of adherence to the inclusion criteria. There was a large interinstitutional variation of standard of care; inadequate methods of antepartum and intrapartum fetal assessment were used, and a large proportion of women were recruited during active labor. In many instances of planned vaginal delivery, there was no attendance of a clinician with adequate expertise.
Results: Most cases of neonatal death and morbidity in the term breech trial cannot be attributed to the mode of delivery. Moreover, analysis of outcome after 2 years has shown no difference between vaginal and abdominal deliveries of breech babies.
Conclusion: The original term breech trial recommendations should be withdrawn.

The term breech trial (TBT) aimed to provide evidence-based guidance on the controversy as to the preferred mode of delivery of breech babies.[1] The trial was performed in 121 centers in 26 countries and included 2183 women at term with fetuses in the breech presentation who were assigned randomly for delivery by either planned cesarean delivery (PCS) or by planned vaginal delivery (PVD). The primary outcomes that were measured were maternal and neonatal death and morbidity. I am the chairman of one of the participating centers that contributed 27 patients to the study.

Almost immediately, the conclusions of the trial were accepted by the medical community. Rarely in medical history have the results of a single research project so profoundly and so ubiquitously changed medical practice as in the case of this publication (TBT). A recent survey, which was performed in >80 centers in 23 countries, concluded that 92.5% of the surveyed centers have completely abandoned planned vaginal breech delivery in favor of cesarean delivery.[2]

It was the aim of the present study to demonstrate that the TBT has been based on serious methodological and clinical flaws that do not permit the results to be generalized and that the conclusions of the TBT were prematurely adopted by the medical community.

Material and methods

The original TBT publication and the publication-specific website were assessed including an examination

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of proposed and actually implemented inclusion criteria, adherence to protocol, the clinical design, a discussion of results, and the applicability of conclusions. In addition, a Medline search was conducted to identify related studies. Various combinations of the following key words and terms were used for search: Names of authors of the TBT paper, *breech delivery*, *term*, *term breech trial*, *cesarean delivery*, *RCT* (randomized controlled trial), and *randomized trial*.

Results

Violation of inclusion criteria

The following items were among the inclusion criteria of the TBT trial: planned delivery, no evidence of hyperextension of the fetal head, live singleton fetus, estimated fetal weight $\leq$4000 g.

Planned delivery

The results of the TBT indicate a significant advantage of PCS, as opposed to PVD, but only if preterm cesarean delivery was performed before or during early labor (odds ratio, 0.13; 95% CI, 0.05-0.38; $P < .001$). For those women for whom cesarean delivery was performed during active labor, there was only a borderline difference in perinatal outcome in favor of PCS, when compared with PVD (odds ratio, 0.57; 95% CI, 0.32-1.02; $P = .06$).[3] Noteworthy, in the PCS group and in the PVD group, 50% and 83% of women, respectively, were recruited during the active phase of labor.

No evidence of hyperextension of the fetal head

Hyperextension of the fetal head is a widely accepted contraindication for vaginal delivery and cannot be assessed properly by clinical examination only. Imaging studies are performed for this purpose as a necessary prerequisite in the decision-making process. In >30% of women in both arms of the TBT, there were no imaging studies performed to ascertain whether hyperextension of the fetal head was present. Clearly, a fetus with a hyperextended head who was delivered vaginally would be at a disadvantage as compared with a fetus who was delivered by cesarean delivery, thereby skewing the results in favor of cesarean delivery.

Live singleton fetus

The study protocol required that only live singleton fetuses at term should be included in the study. Yet, among the 16 cases of perinatal death in the study, there were 2 sets of twins, 1 case of anencephalus, and 2 stillbirths, the latter having occurred apparently before the randomization process. These data raise serious questions concerning the overall adherence to the inclusion criteria. The authors explained in a subsequent paper that many of the participating centers had no routine access to ultrasound evaluation.[4] Results from such centers are hardly acceptable in modern obstetrics and are not applicable to centers where standards of modern obstetrics are followed.

Fetal weight >4000 g

Most clinicians would be very reluctant to delivery large breech babies vaginally, and this is also the advice given in textbooks and by professional societies. Fetuses with a birth weight exceeding 4000 g were significantly overrepresented in the PVD group (5.8 % vs 3.1% for PVD and PCS, respectively; $P = .002$). Randomization was performed after gestational week 37, and PCS was scheduled for gestational week 38 while the women in the PVD group awaited labor. Therefore, for significantly more women in the PVD group than in the PCS group, the time interval between randomization and delivery exceeded 7 days (15% and 28.9% for PCS and PVD delivery, respectively; $P < .0001$). Consequently, significantly more fetuses had a "chance" for continuous intrauterine growth in the PVD group than in the PCS group; therefore, significantly more babies in the PVD group had a birth weight that exceeded 4000 g than in the PCS group, thereby skewing the results in favor of PCS.

Incompatible variation of standard of care between participating centers

Participating centers had substantially different levels of standard of care. A center was categorized as providing "a high standard of care" if cesarean delivery could be performed within 10 minutes, if there were the immediate availability of resuscitation by providing oxygen through bag/mask or endotracheal intubation and positive pressure ventilation, and if there were personnel and infrastructure available to provide ventilation for >24 hours. A center was categorized to provide the "usual standard of care" if these criteria could not be met. A high standard of care was provided by 35.2% of the centers and by a usual standard of care by 64.8 % of the centers.

Particularly worrisome is the time frame of up to 60 minutes allowed for emergency cesarean delivery in the latter category. It makes a great difference, if emergency cesarean delivery can be performed after 10 minutes or after 60 minutes. This is also true for emergency intubation at 30 minutes, which is a contradiction in terms. To compare PVD with PCS under these circumstances puts the PVD arm at a definite disadvantage, and the perinatal morbidity and mortality data that were accumulated in centers that can only provide usual standard of care (per definition of the TBT) are most certainly not applicable to most centers in the Western world.

No attendance of clinicians with adequate expertise

In the TBT, it was required that a clinician who was experienced and skilled at vaginal delivery by self-definition

confirmed by his or her head of department should be in attendance at vaginal birth. Actually, women in the PVD group who eventually also delivered by the vaginal route were attended in 18.5% of cases by obstetricians in training, in 2.9% by licensed midwifes, and in 1 case even by a midwife in training. If one looks at infants who were born with significant morbidity, it is revealed that 22 of 69 of such newborn infants (31.9%) or infants with perinatal death were attended by obstetricians in training, by obstetricians without experience, and in 1 case by a midwife without experience, which is a situation that would be regarded as unacceptable in most institutions in Western countries.

Most cases of perinatal mortality were not related to the mode of delivery

The TBT was designed to assess whether the mode of delivery of breech babies would affect perinatal outcome. A total of 16 cases of perinatal death were reported in the study, including 2 stillbirths that occurred before randomization. The relationship between neonatal morbidity and mode of delivery has been questioned in the past.[5]

A careful and critical analysis of the perinatal mortality cases reveals the following:

In 8 of the 13 cases of the PVD group, the neonatal death of vaginally delivered infants was not associated with the mode of delivery: Case 2 represented the intrauterine death of a twin, probably before enrolment, with a birth weight of 1150 g; case 3 represented intrauterine death during the second stage of labor (the authors do not mention a difficult delivery, so it must be assumed that death occurred during the early second stage); cases 6 and 9 represented babies who were discharged home well and who died of sudden infant death during sleep or died after severe vomiting and diarrhea; case 10 represented intrauterine death during labor and before delivery; cases 12 and 13 represented respiratory problems in the neonatal period; and case 15 represented cephalic presentation and intrauterine fetal death, probably before enrolment.

In the PVD group, 4 additional cases of neonatal death occurred after what was described as difficult vaginal delivery (cases 4,7,8, and 14). Noteworthy, case 4 was probably growth retarded (birth weight, 2400 g) and case 7 had malformations (small head, low set ears, and deep set eyes). One additional infant in the PVD group who had fetal heart rate anomalies was delivered by cesarean delivery after a difficult attempt of vaginal delivery (case 1).

In the PCS group, 1 additional neonatal death occurred in a newborn infant who had been assigned to the PCS group but was delivered vaginally in what was described as a difficult vaginal delivery (case 5). Noteworthy, this infant was probably growth retarded (birth weight, 2550 g). One additional patient had been assigned to the PCS group and was delivered by cesarean delivery. In this case, fetal heart rate anomalies were observed, and a ruptured myelomeningocele was diagnosed after delivery.

Even if one assumes that all 5 infants of the PVD group and the 2 infants from the PCS group died as a result of complications related to vaginal delivery and based on an "intention to treat" (ITT) approach, a 2-tailed Fisher's exact test (5/1038 vs 2/1038) reveals no statistical significant difference in mortality rates between the groups ($P = .45$). The conclusion that most cases of perinatal death were not related to the mode of delivery is also no longer being disputed by the authors of the TBT.[6]

Conclusions that are based on various categories of neonatal morbidity

The TBT conclusions are based on various categories of neonatal morbidity, but long-term assessment (2 years) of composite morbidity/mortality rates revealed no difference in outcome between breech infants delivered by PCS or PVD. In the TBT, the authors reported serious neonatal morbidity in 3.8% of neonates who were delivered vaginally versus 1.4% of the infants who were delivered by cesarean delivery ($P = .003$). The important point is that the TBT assessed short-term outcome, but the authors continue to promote a general recommendation as related to the preferred mode of delivery for term breech babies.

Four years after the publication of the TBT, the authors report that most of the cases of perinatal morbidity were not related to the mode of delivery.[6] After the exclusion of lethal anomalies, the authors present composite data on 69 infants who either died or had serious morbidity. Of these 69 cases, 43 deaths were not related to the mode of delivery. Su et al[6] present and categorize adverse perinatal outcome in 4 tables, namely labor-associated (Table I), delivery-associated (Table II) and two additional tables, which list 18 additional infants with severe morbidity or death that was, according to the authors, unrelated to labor and delivery or unexplained.

None of these cases should have been enrolled in the study, or they should have been removed from analysis once they were found to be ineligible after enrollment.

Therefore, of the 69 cases of composite perinatal morbidity and death on which all the conclusions of the TBT are based, there remain only 16 cases that could be related to the mode of delivery. A 2-tailed Fisher's exact test that compared 11 of 1039 versus 5 of 1039 deliveries for PVD and PCS, respectively, does not reveal a statistical significance ($P = .2$)

Table I Twenty-five infants with substantial morbidity that, according to the authors, was due to labor; the inclusion of 7 of these infants is not justified

Case	Morbidity
2 and 9	Stillbirth, fetal heart tones disappeared before cesarean delivery
3 and 4	Intrauterine growth restriction
15	Macrosomia, cephalic presentation (birth weight, 4720 g), attended by midwife without experience
14 and 19	Apgar score 3 at 5 minutes but normal cord pH

Data adapted from Su et al.[6]

Table II Twenty-six infants with substantial morbidity that, according to the authors, was due to delivery; the inclusion of 10 of these infants is not justified

Case	Morbidity
4, 6, 8, and 12	Stillbirth, not clear if related to delivery
4, 6, 9, 13, and 19	Probably intrauterine growth restriction (birth weight, 2115-2550 g)
7	Congenital malformations
17	Brachial plexus injury and hypotonia at <1 day (these are usually transient events without long-term sequel)
23	Footling fetus who was not eligible for inclusion

Two cases of very severe neonatal morbidity (spinal cord injury and basal scull fracture) occurred in infants who were delivered by PCS (ie, precisely by the delivery method that, according to the authors, should provide protection for this type of injury). Data adapted from Su et al.[6]

Comment

Grant[7] stated that the TBT "…is an example of a randomized trial that was impeccable as regards its methodological design but questionable as regards its clinical design." One must add that the methods design of the TBT also deserve criticism. The design of the TBT had major inherent flaws, some of which related to the study design and some that were inherent to RCTs in general.

Concerning study design, the recruitment of women in active labor in most cases is problematic and raises concern whether a laboring woman is actually in a state to provide informed consent for random assignment in any clinical trial. Moreover, a large interinstitutional variance of standard of care, inappropriate assessment of head attitude in the fetus in a large number of cases, significantly more macrosomic babies in the PVD arm, and an apparent lack of clinical expertise in substantially more clinicians attending to patients in the PVD arm than in the PCS arm have apparently skewed the outcome in favor of PCS.

In response to a series of letters,[8-11] the authors discuss the relationship between the state of labor and outcome and state that "…we repeated the test for interaction after subdividing labor by whether it was early or active at the time of randomization, and the results did not change…."[12] Yet, in a subsequent paper, the authors report that cesarean delivery during active labor and vaginal birth have a different outcome and conclude that there "… was .., a dose-response relationship between the progression of labor and the risk of adverse perinatal outcome…".[3] This is a clear contradiction for which the authors have yet to provide an explanation. Others have also voiced concerns about study design and applicability of results: during the past 4 years, there has been a growing number of publications in which serious concerns about the applicability of the conclusions of the TBT were raised.[13-15] Keirse[16-18] has pointed to the lack of internal consistencies of data that were provided by the group in different publications, namely percentages of deliveries that were attended by experienced clinicians and discrepancies between presented data sets. These concerns were addressed unconvincingly by the authors. In 2004, Kotaska[19] pointed out that the high rate of breech deliveries in the TBT (57%) may have presented an artificial increase over the usual comfort level for breech deliveries (United States, 24%; Sweden, 36%; Israel and Switzerland, 38%; France, 39%; Norway, $>50\%$). Indeed, retrospective studies from these countries do not confirm the morbidity and mortality data from the TBT, provided that stringent criteria for breech delivery are applied for vaginal breech delivery.[20]

An additional problem of the TBT relates to 2 of the known potential drawbacks of an RCT, namely improper randomization and the failure to randomly assign all eligible patients. Both drawbacks are manifested in the TBT. The fact that centers recruited between 1 and 215 patients obviously means that not all eligible patients were recruited. Improper randomization may also have been the reason that an unacceptable number of stillbirths, twins, and babies with intrauterine growth retardation and congenital malformations were included in the study. For the sake of the ITT design, most of ineligible cases remained in the study for analysis. This is overstretching of a statistical method. The basic purpose for an ITT analysis is to properly handle noncompliant patients in a RCT. In essence, an ITT analysis assesses treatment policy rather than the potential benefit in patients who received treatment exactly as planned.[21] Yet, the research question posed by the TBT did not only relate to policy

but also to the question whether a PCS would be of potential benefit to a woman with a baby in breech presentation. An ITT design does not mean that randomly assigned patients who are found later to be ineligible and the inclusion of which would clearly favor 1 study arm should remain in the study at any cost. To leave ineligible patients in the ITT analysis supports the policy question but introduces bias that is related to the clinical benefit question.

Another potential major drawback of an RCT, which was also manifested in the TBT, is the need for surrogate end points that can be assessed after a relative short time period. This may lead to premature conclusions, such as in the TBT where short-term neonatal morbidity was chosen as an end point. On the basis of their interpretation of the accumulated data, the authors concluded unequivocally that cesarean delivery was safer for term breech delivery than vaginal delivery. A repeated analysis of the data after 2 years, however, revealed that the initial conclusion could no longer be maintained and that actually there was no difference in outcome between the 2 groups. This was true for both neonates[22] and mothers.[23] Yet, until now the authors continue, in all subsequent publications, to reiterate their original conclusions.

Major opinion-making institutions, such as the American College of Obstetricians and Gynecologists[24] and the Cochrane collaboration,[25] who endorsed the recommendations soon after the publication of the TBT have since remained silent on this issue.

This should not have come as a surprise. The recommendations of the TBT were not only awaited anxiously by obstetricians of mainly Western countries but also almost gratefully accepted. It is much easier to plan an abdominal delivery than a vaginal delivery, and it requires less expertise to do so. Moreover, in the current medicolegal environment, in which litigation for a performed cesarean section is a rare event but vaginal delivery carries increased risks for litigation, obstetricians easily can be convinced not to take this risk. Consequently, the conclusions of the TBT are perceived today by many obstetricians as a badly needed set of arguments for PCS, which they would have preferred anyway. Therefore, I have serious doubts whether the option of vaginal breech delivery can be salvaged at all, be it by the existing critical publications related to the TBT, the discussion presented here, or even a comprehensive and unequivocal withdrawal of the TBT conclusions by the authors themselves, which is overdue. Most probably, the point of no return has been reached as far as planned vaginal breech delivery is concerned, despite the fact that evidence is still lacking. The consequences of this situation are many superfluous cesarean deliveries with consequential morbidity to women and the vanishing of obstetric expertise with increased risks to those breech babies who must be delivered vaginally. The group who has designed, initiated and conducted the TBT is one of the most important research institutions in modern obstetrics and has contributed tremendously to current knowledge in our profession. They should now accept responsibility and withdraw the conclusion of their TBT.

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