OBSTETRICS

Effectiveness of electronic fetal monitoring with additional ST analysis in vertex singleton pregnancies at >36 weeks of gestation: an individual participant data metaanalysis

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OBJECTIVE: The purpose of this study was to assess the effectiveness of electronic fetal monitoring (EFM) alone and with additional ST analysis (EFM + ST) in laboring women with a singleton term pregnancy that is in cephalic presentation in the prevention of metabolic acidosis by the application of individual patient data metaanalysis.

STUDY DESIGN: We conducted an individual patient data metaanalysis using data from 4 randomized trials, which enabled us to account for missing data and investigate relevant subgroups. The primary outcome was metabolic acidosis, which was defined as an umbilical cord-artery pH <7.05 and a base deficit that had been calculated in the extra cellular fluid compartment >12 mmol/L. We performed 8 explanatory subgroup analyses for 8 different endpoints.

RESULTS: We analyzed data from 12,987 women and their newborn infants. Metabolic acidosis was present in 57 women (0.9%) in the EFM + ST group and 73 women (1.1%) in the EFM alone group (relative risk [RR], 0.76; 95% CI, 0.53–1.10). Compared with EFM alone, the use of EFM + ST resulted in a reduction in the frequency of instrumental vaginal deliveries (RR, 0.90; 95% CI, 0.83–0.99) and fetal blood samples (RR, 0.49; 95% CI, 0.44–0.55). Cesarean delivery rates were comparable between both groups (RR, 0.99; 95% CI, 0.91–1.09). Subgroup analyses showed that EFM + ST resulted in fewer admissions to a neonatal intensive care unit for women with a duration of pregnancy of >41 weeks (RR, 0.61; 95% CI, 0.39–0.95).

CONCLUSION: EFM + ST does not reduce the risk of metabolic acidosis, but it does reduce the need for instrumental vaginal deliveries and fetal blood sampling.

Key words: cardiotocography, fetal blood sampling, fetal electrocardiogram, instrumental vaginal delivery, metabolic acidosis

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Perinatal asphyxia is associated with several short- and long-term complications that vary from mild hypoxic ischemic encephalopathy to cerebral palsy and death.[1-3] Fetal monitoring during delivery helps identify fetuses at risk of asphyxia. A relatively new method for continuous fetal monitoring is the STAN method (Neoventa Medical, Gothenburg, Sweden) in which the classification of the electronic fetal monitor (EFM) is combined with ST analysis of the fetal electrocardiogram. Similar to the postpartum electrocardiogram, information can be evaluated about the amplitude of the T-wave in relation to the QRS-complex (T/QRS ratio) and the conduction in the ST segment. Changes in the fetal electrocardiogram in combination EFM abnormalities could be an indication of fetal hypoxia, as shown in previous animal studies.[4,5] Westgate et al[6] were the first to conduct a random-

ized controlled trial (RCT) on the effect of intrapartum fetal electrocardiogram monitoring. Four subsequent RCTs focused on automatically detected T/QRS changes rather than absolute values of T/QRS.[7-10] All 5 RCTs were inconclusive; 4 of the studies showed no statistically significant effect.[6,8-10] In one study, ST analysis significantly reduced the incidence of metabolic acidosis. [7]

To study the effect of ST analysis + EFM compared with EFM alone, metaanalyses were performed with the use of aggregated data (ADMA).[11-13] These metaanalyses showed a nonsignificant reduction of metabolic acidosis when intrapartum ST analysis was used. These metaanalyses relied on published data. Because not all RCTs reported all endpoints of interest, some endpoints were excluded from the metaanalyses.[11-13] Another limitation of these metaanalyses was that they did not investigate subgroups. Obviously, more information on relevant endpoints and subgroups was collected in the individual studies than was reported. A metaanalysis that uses individual participant data (IPDMA) allows for a more thorough investigation of endpoints and relevant subgroups by taking all this information into account. Furthermore, in IPDMA, it is possible to account for missing data.

In view of the shortcomings of conventional metaanalyses with the use of ADMA, we performed an IPDMA using data from RCTs to investigate the additional effect of ST analysis in EFM.

Materials and Methods

This study was conducted based on a previously written, but unpublished, protocol. The reporting of the IPDMA was carried out according to the preferred reporting items for systematic reviews and metaanalyses (PRISMA) guidelines.[14]

Objective

The main objective of this study was to assess the effectiveness of the combination of ST analysis of the fetal electrocardiogram and EFM compared with EFM alone in laboring women with a term singleton pregnancy that was in cephalic presentation in the prevention of metabolic acidosis by means of an IPDMA.

Search strategy and selection criteria

Trials were identified by a search the following electronic databases for phase III trials of EFM + ST analysis compared with EFM alone, in laboring women with a term singleton pregnancy in cephalic presentation: Cochrane Central Register of Controlled Trials, PubMed, MEDLINE, Embase, ClinicalTrials.gov, and controlled-trials.com, following the search strategy of Becker et al.[11] Two review authors (E.S. and A.K.) independently assessed inclusion criteria, study quality, and risk of bias. Discrepancies were resolved by third author (R.H.H.G.). The risk of bias was assessed by 2 independent reviewers (E.S. and A.K.) who used a modified version of the risk of bias tool that was developed by the Cochrane collaboration that contains specific items that assess adequate sequence generation (ie, computer-generated random number, the use of a random number table, or other truly random process), allocation concealment (ie, web-based or telephone central randomization), incomplete outcome data, and other possible sources of bias.[15] Selective outcome reporting was not considered an issue because IPDMAs rely on IPD rather than reported outcomes. Studies were included if they had a low risk of bias, were focused on T/QRS changes of the fetal electrocardiogram, were completed before Dec. 1, 2011, and the principal investigators had provided the IPD relating EFM + ST analysis vs EFM alone. The relevant baseline characteristics and outcomes of interest, which are described later, were extracted by one of the authors (E.S.). Data quality (eg, discrepancies between published and shared data) was assessed independently by 2 review authors (E.S. and A.K.), and a third author (R.H.H.G.) resolved discrepancies.

Outcomes

The primary outcome was metabolic acidosis$_{BDecf}$, defined as an umbilical cord-artery pH below 7.05 and a base deficit calculated in the extra cellular fluid compartment (BD_{ecf}) above 12 mmol/L, calculated with the Sigaard-Andersen algorithm.[16] Secondary outcomes included metabolic acidosis$_{BDblood}$ that is defined as an umbilical cord-artery pH <7.05 and a base deficit calculated in blood (BD_{blood}) >12 mmol/L. Additional secondary outcomes were cord-artery pH <7.15, cord-artery pH <7.05, cord-artery pH <7.00, BD_{ecf} >12 mmol/L, BD_{blood} >12 mmol/L, 5-minute Apgar score <7, admission to a neonatal intensive care unit (NICU), hypoxic-ischemic encephalopathy, intubation, seizures, perinatal death, frequency of fetal blood samples, cesarean delivery, vaginal instrumental delivery, and the total frequency of operative deliveries. To increase comparability with a currently ongoing RCT that is being conducted by the National Institute of Child Health Development (NICHD) in the United States, we also used their primary outcome as one of our secondary outcomes. This outcome is a composite of intrapartum fetal death, neonatal death, Apgar score of ≤ 3 at 5 minutes, seizure(s), cord artery pH ≤ 7.05 and $BD_{ecf} \geq 12$ mmol/L, intubation for ventilation at delivery, or presence of neonatal encephalopathy.[17]

Subgroups

Secondary objectives were to assess the additional effect of ST analysis in different subgroups differentiated by the following: (1) gestational age defined as <37 weeks, 37-40 weeks, 40-41 weeks, or >41 weeks; (2) parity defined as nulli- or multiparous; (3) previous cesarean delivery (yes/no); (4) maternal diabetes mellitus (yes/no); (5) induced onset of labor (yes/no); (6) meconium-stained amniotic fluid (yes/no); (7) epidural anesthesia (yes/no); and (8) birthweight below the tenth percentile (yes/no). The subgroup effects were investigated for the primary outcome, metabolic acidosis$_{BDecf}$, and the following secondary outcomes: composite neonatal outcome, cesarean delivery, need for intubation, NICU admission, hypoxic-ischemic encephalopathy, instrumental vaginal delivery, and fetal blood sampling.

Analysis

All analyses were performed on all randomly assigned women in labor with a

TABLE 1
Characteristics of randomized controlled studies on ST analysis + EFM compared with EFM alone

Characteristic	Amer-Wahlin et al (Sweden) 2001[7]	Ojala et al (Finland) 2006[8]	Vayssiere et al (France) 2007[9]	Westerhuis et al (The Netherlands) 2010[10]
Type of study	Multicenter	Single center	Multicenter	Multicenter
n	5049	1472	799	5667
Inclusion criteria	Laboring women at >36 weeks of gestation; singleton fetus; cephalic position; continuous internal EFM needed	Laboring women at >36 weeks of gestation; singleton fetus; cephalic position; amniotomy decided	Laboring women at >36 weeks of gestation; singleton fetus; cephalic position; abnormal EFM or thick meconium-stained amniotic fluid (7%) during labor	Laboring women at >36 weeks of gestation; singleton fetus; cephalic position; age >18 years; indication for internal EFM
Exclusion criteria	None mentioned in article	Contraindication scalp electrode; admittance during second stage of labor	Contraindication scalp electrode; cardiac malformation	None mentioned in article
Index test	ST waveform + EFM (S21[a])[35]	ST waveform + EFM (S21)[35]	ST waveform + EFM (S21)[35]	ST waveform + EFM (S21 or S31[b])[35]
Controls	EFM	EFM	EFM	EFM
Allocation concealment	Yes; adequate	Yes; adequate	Yes; adequate	Yes; adequate
Sequence generation	Yes; adequate	Yes; adequate	Yes; adequate	Yes; adequate
Blinding of participants and medical professionals	No; not possible	No; not possible	No; not possible	No; not possible
Blinding of outcome assessors	Yes; adequate	Yes; adequate	Yes; adequate	Yes; adequate
Participant with incomplete primary outcome data, n (%)	731 (14.5)	36 (2.4)	34 (4.3)	549 (9.7)

STAN S21 and STAN S31; Neoventa Medical, Gothenburg, Sweden.
EFM, electronic fetal monitoring.

[a] STAN S21 fetal heart monitor that provides EFM + automatic ST analysis of the fetal electrocardiogram; [b] STAN S31 fetal heart monitor (modern version of STAN S21) that provides EFM + automatic ST analysis of the fetal electrocardiogram.

Schuit. Individual participant data metaanalysis of fetal ST analysis. Am J Obstet Gynecol 2013.

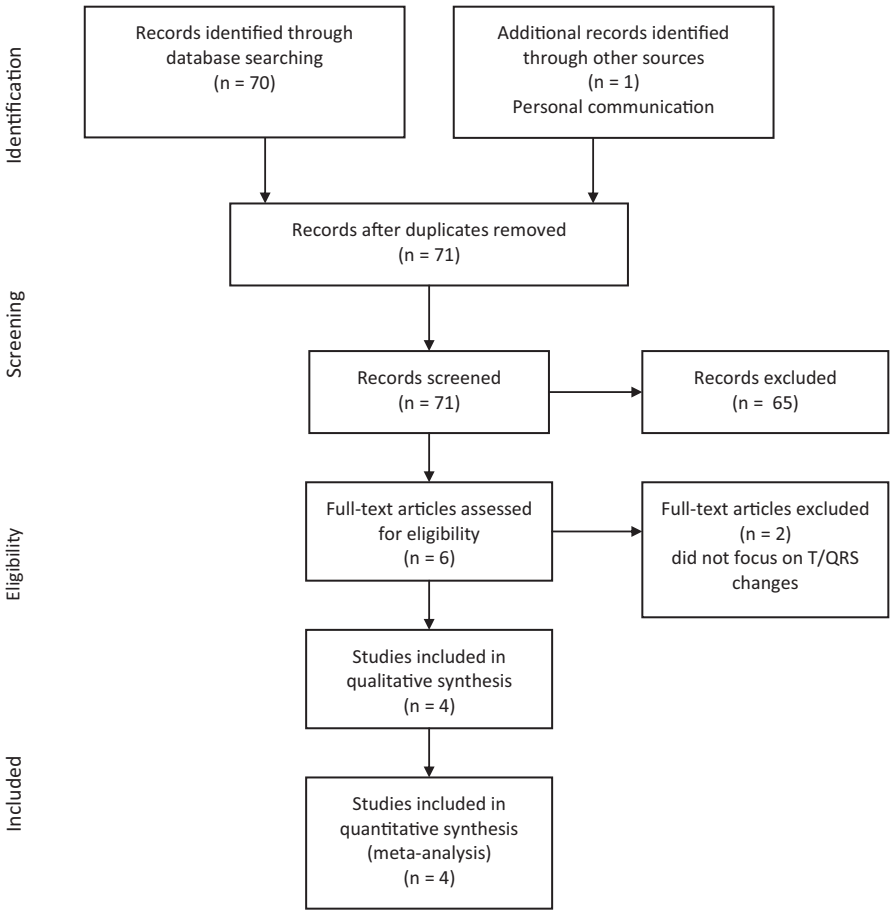
term singleton in cephalic presentation with an indication for internal EFM. The analyses were conducted on an intention-to-treat basis (ie, according to the treatment assigned by randomization, regardless of treatment actually received).

Descriptive comparisons between studies were conducted to assess between-study differences. Treatment effects on the primary and secondary outcomes were estimated by means of a random effects log-binomial model. The measure of association was the risk ratio (RR), with an RR <1 indicating treatment benefit. Both heterogeneity across studies and dependency between data that originated from the same study were taken into account by fitting a random intercept for each original study by means of a random effects model. The presence of heterogeneity in outcomes across trials was assessed using the I^2 measure, and the values were interpreted as follows: 0% indicates no observed heterogeneity; 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively.[18] If necessary, analyses were adjusted for variables that were used in stratified randomization (eg, center and/or parity) by including them as covariates in the regression model. Additionally, we calculated the number needed to test (NNT) with 95% CI when an association was found to be statistically significant. The NNT is comparable with the numbers needed to treat but refers to the number of tests (in this case the number of laboring women who need to be monitored with EFM + ST analysis) to prevent 1 case of metabolic $acidosis_{BDecf}$.

To investigate subgroup effects, the treatment effects were investigated with an interaction term between the allocation and the subgroup in the regression model defined earlier. When a significant interaction was present, the treatment effect was then estimated within strata based on that subgrouping variable. For the primary outcome, metabolic $acidosis_{BDecf}$, which is a stratified analysis across the predefined subgroups, was performed despite the presence of a significant interaction in the regression model to investigate the direction of the additional effect of ST analysis in different strata of the subgroups.

The 4 RCTs had different proportions of missing values for the primary outcome that ranged from 2.4–14.5% (Table 1). Because these missing values are often selectively missing, which was also the case in these RCTs (Appendix; Supplementary Tables 1-3; and Appendix 3 of Westerhuis et al[10]), a complete case analysis is likely to yield biased results.[19] To avoid this bias, we used observed patient characteristics to impute missing data by means of multiple imputations. Missing data were imputed (10 times) with the use of a logistic regression model that included the following variables: center, allocation, parity, neonatal sex, Apgar score at 1 and 5 minutes, arterial pH, arterial BD_{blood}, arterial BD_{ecf}, arterial pCO2, venous pH, venous pCO2, birthweight, and indication for the intervention. The primary outcome was included in the imputation model to

FIGURE
Flow diagram of study selection



The figure shows the process from the identification to the inclusion of studies in this individual patient data metaanalysis.

T/QRS, T-wave in relation to the QRS-complex.

Schuit. Individual participant data metaanalysis of fetal ST analysis. Am J Obstet Gynecol 2013.

improve imputations for missing data on other variables of interest. Missing data were imputed within each individual study before pooling the studies.[20] Analyses were performed individually on each of the 10 imputed data sets and results were pooled using standard methods (Rubin's rule).[21]

Statistical analyses and multiple imputations were performed with the use of R software (version 2.15.0; The R Foundation for Statistical Computing, 2012).

RESULTS

Included studies

Six studies on ST analysis in laboring women with a term singleton pregnancy that was in cephalic presentation were identified, of which 4 women met the inclusion criteria (Figure; Table 1).[7-10] The study of Strachan et al[22] was excluded because it studied the PR waveform of the fetal electrocardiogram rather than the ST segment. Even though the study of Westgate et al[6] focused on T/QRS changes, the study was excluded because the ST-analysis method that was used was different than the methods used in more recent studies. In the study by Westgate et al, the STAN 8801 recorder (Neoventa Medical) was used; the other studies used the STAN S21 and/or S31. Although investigating T/QRS changes, the threshold for performance of an intervention was based on the absolute T/QRS ratio and not a change in T/QRS ratio. Furthermore, biphasic ST changes were not incorporated in the guideline. Another important difference was that ST changes were identified by visual analysis. The STAN S21 and S31 monitors provide an automatic assessment of the ST changes and give an automatic warning in case of significant changes. Datasets that contained IPD were obtained for 4 RCTs: Amer-Wahlin et al[7], Ojala et al[8], Vayssière et al,[9] and Westerhuis et al.[10]

The characteristics of the included studies are shown in Table 1. In general, all studies had similar inclusion and exclusion criteria. The only exception was the study of Vayssière et al, which included only women who had an abnormal EFM or thick meconium-stained amniotic fluid during labor. Because all studies also used similar interventions and controls, these studies can be considered to have a high degree of homogeneity. The study of Westerhuis et al[10] stratified the randomization of participants to EFM + ST analysis or EFM alone by center and parity (nulli- vs multiparous).

All trials used adequate methods to generate allocation sequences and adequate methods for allocation concealment (Table 1). Because of the nature of the intervention, the blinding of participants and medical professionals was not possible. Blinding the assessors to the outcome was adequate in all trials. The number of women with incomplete primary outcome data differed per study but could be accounted for with multiple imputations. No other problems were found that could lead to bias.

Individual data from 6524 participants who were allocated to EFM + ST analysis of the fetal electrocardiogram and 6463 participants who were allocated to EFM alone were included in this IPDMA. The baseline characteristics of combined participants by treatment groups were similar (Table 2).

Overall effects of ST analysis of the fetal electrocardiogram

Table 3 shows the effect of ST analysis + EFM compared with EFM alone for the primary and secondary outcomes. The primary outcome, metabolic acidosis$_{BDecf}$, was present in 57 women (0.9%) in the EFM with additional ST-analysis

TABLE 2
Baseline characteristics of participants in each trial and in the overall treatment group

Characteristic	Study				Combined treatment groups	
	Amer-Wahlin et al (Sweden) 2001[7]	Ojala et al (Finland) 2006[8]	Vayssiere et al (France) 2007[9]	Westerhuis et al (The Netherlands) 2010[10]	ST analysis + EFM	EFM alone
n	5049	1472	799	5667	6524	6463
Mean maternal age, y[a]	NA	28.0 ± 5.5	30.0 ± 5.7	32.0 ± 4.8	31.0 ± 5.3	31.0 ± 5.3
Nulliparous, n (%)	3105 (61)	757 (51)	575 (72)	3236 (57)	3851 (59)	3823 (59)
Previous cesarean delivery, n (%)	NA	NA	49 (6)	716 (13)	370 (11)[b]	395 (12)[b]
Diabetes mellitus, n (%)	104 (2)	115 (8)	41 (5)	169 (3)	261 (4)	168 (3)
Female sex of the newborn infant, n (%)	2388 (47)	733 (50)	NA	2668 (47)	2860 (47)[c]	2929 (48)[c]
Gestational age, wk[a]	39.6 ± 1.6	40.1 ± 1.3	40.0 ± 1.9	40.2 ± 1.4	39.9 ± 1.5	40.0 ± 1.6
Induced onset of labor, n (%)	866 (17)	277 (19)	257 (36)	2341 (41)	1879 (29)	1862 (29)
Meconium-stained amniotic fluid, n (%)	1143 (23)	260 (18)	121 (15)	1471 (26)	1476 (23)	1519 (24)
Epidural anesthesia, n (%)	1957 (39)	793 (54)	725 (91)	2389 (42)	2898 (44)	2966 (46)
Birthweight (g)[a]	3567 ± 531	3605 ± 503	3243 ± 500	3544 ± 518	3546 ± 527	3536 ± 525

All numbers are based on the data as shared by the individual research groups.
EFM, electronic fetal monitoring; *NA*, not available.
[a] Data are presented as mean ± SD; [b] Percentage based on studies of Vayssiere et al[9] and Westerhuis et al[10]; [c] Percentage is based on studies of Amer-Wahlin et al,[7] Ojala et al,[8] and Westerhuis et al.[10]
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group and 73 women (1.1%) in the EFM alone group (RR, 0.76; 95% confidence interval [CI], 0.53–1.10). Using a 2-step approach (ie, analysis like an ADMA), we found a moderate amount of heterogeneity for the primary outcome between the studies (I^2 = 42%; 95% CI, 0–81%; Tau^2 = 0.09).

The frequency of fetal blood samplings (RR, 0.49; 95% CI, 0.44–0.55; NNT, 13; 95% CI, 12–16) and of instrumental vaginal deliveries (RR, 0.90; 95% CI, 0.83–0.99; NNT, 69; 95% CI, 38–357) were reduced significantly by EFM + ST analysis. ST analysis + EFM did not reduce the incidence of any other secondary outcome. The results were similar even after correction for stratified randomization.

Subgroup analyses

EFM + ST analysis did not show a significant effect for metabolic acidosis$_{BDecf}$ (Table 4), composite neonatal outcome, instrumental vaginal delivery, cesarean delivery, need for intubation, and hypoxic-ischemic encephalopathy according to gestational age, parity, previous cesarean delivery, maternal diabetes mellitus, induced onset of labor, meconium-stained amniotic fluid, epidural anesthesia, or birthweight below the tenth percentile. It must be noted that information regarding previous cesarean delivery was not available from Amer-Wahlin et al[7] and Ojala et al.[8]

Significant subgroup effects were found for 2 secondary outcomes: fetal blood sampling and NICU admission according to gestational age at delivery and epidural anesthesia (Table 5). EFM + ST analysis reduced the fetal blood sampling more in women with epidural anesthesia than in women without anesthesia (RR, 0.46; 95% CI, 0.40–0.52 vs RR, 0.61; 95% CI, 0.49–0.75; probability value of interaction, .03). This is rather uninformative, however, because both benefit from additional ST analysis. Furthermore, EFM + ST analysis reduced the frequency of NICU admissions in women with a gestational age at delivery of >41 weeks (RR, 0.61; 95% CI, 0.39–0.95).

COMMENT

Principal findings of the study

This metaanalysis that is based on IPDMA from 4 randomized clinical trials of ST analysis showed that EFM + ST analysis of the fetal electrocardiogram does not reduce metabolic acidosis$_{BDecf}$ and cesarean delivery rates but reduces the frequency of fetal blood sampling and instrumental vaginal deliveries compared with EFM alone. Subgroup analyses showed an additional advantage of ST analysis for women with a gestational age of >41 weeks in the reduced frequency of NICU admissions.

Comparison of the findings with previous studies

The results of this study are in line with the 3 previously published ADMAs.[11-13] The slight differences in the point estimates for the primary outcome between the metaanalyses and this IPDMA are explained by the inclusion of the trial of Westgate et al[6] in the ADMAs. First, Westgate et al showed that additional ST analysis significantly decreases

TABLE 3
Primary and secondary outcomes per study and the overall effect of ST analysis + EFM compared with EFM alone

Outcome	Study sample size, n (%)				Combined treatment groups, n (%)		Relative risk (95% CI)[a]	*P* value	No. needed to test (95% CI)	I^2: percentage (95% CI)
	Amer-Wahlin et al[7]	Ojala et al[8]	Vayssiere et al[9]	Westerhuis et al[10]	ST analysis + EFM	EFM alone				
n	5049	1472	799	5667	6524	6463	—	—	—	—
Primary outcome										
Metabolic acidosis BD_{ecf} (pH<7.05; BD_{ecf} >12 mmol/L)	54 (1)	10 (1)	19 (2)	46 (1)	57 (0.9)	73 (1.1)	0.76 (0.53–1.10)	.13	NC	42 (0–81)
Secondary outcomes										
Metabolic acidosis BD_{blood} (pH<7.05 & BD_{blood}>12 mmol/L)	NA	23 (2)	NA	107 (2)	58 (1.6)[a]	72 (2.0)[a]	0.82 (0.58–1.16)	.25	NC	83 (56–93)
Arterial pH <7.15	997 (20)	218 (15)	159 (20)	861 (15)	1118 (17)	1117 (17)	0.99 (0.91–1.08)	.79	NC	0 (0–84)
Arterial pH <7.05	178 (4)	28 (2)	29 (2)	117 (2)	165 (2.5)	187 (2.9)	0.87 (0.70–1.09)	.20	NC	68 (6–89)
Arterial pH <7.00	67 (1)	7 (0)	14 (2)	50 (1)	65 (1.0)	72 (1.1)	0.89 (0.62–1.26)	.48	NC	57 (0–86)
BD_{ecf} >12 mmol/L	150 (3)	34 (2)	123 (15)	204 (4)	266 (4)	246 (4)	1.07 (0.90–1.29)	.42	NC	0 (0–27)
BD_{blood} >12 mmol/L	NA	83 (6)	NA	413 (7)	244 (7)[a]	251 (7)[a]	0.98 (0.82–1.16)	.80	NC	0 (0–44)
Apgar at 5 minutes <7	61 (1)	17 (1)	13 (2)	76 (1)	89 (1.4)	78 (1.2)	1.14 (0.84–1.54)	.41	NC	0 (0–0)
Admitted to a neonatal intensive care unit	387 (8)	49 (3)	10 (1)	86 (2)	258 (4)	274 (4)	0.92 (0.78–1.09)	.32	NC	0 (0–0)
Hypoxic-ischemic encephalopathy	7 (0)	1 (0)	NA	2 (0)	3 (0.1)	7 (0.2)	0.42 (0.11–1.64)	.21	NC	0 (0–68)
Need for intubation	NA	12 (1)	8 (1)	22 (3)	16 (1.1)	26 (1.7)	0.64 (0.35–1.20)	.16	NC	18 (0–92)
Seizures	NA	2 (0)	2 (0)	9 (1)	4 (0.3)	9 (0.6)	0.46 (0.14–1.51)	.20	NC	0 (0–65)
Perinatal death	3 (0)	0 (0)	1 (0)	5 (0.1)	5 (0.1)	4 (0.1)	1.24 (0.33–4.61)	.75	NC	0 (0–75)
Composite perinatal outcome[c]	75 (1)	28 (2)	33 (4)	91 (2)	101 (1.6)	125 (1.9)	0.80 (0.62–1.05)	.10	NC	0 (0–82)
Fetal blood sampling	NA	166 (11)	356 (45)	879 (16)	460 (12)	941 (24)	0.49 (0.44–0.55)	< .0001	13 (12–16)	9 (0–91)
Cesarean delivery	447 (9)	82 (6)	209 (26)	796 (14)	768 (12)	766 (12)	0.99 (0.91–1.09)	.91	NC	18 (0–87)
Fetal distress	194 (4)	30 (2)	119 (15)	164 (3)	253 (4)	254 (4)	0.99 (0.83–1.17)	.87	NC	42 (0–81)
Failure to progress	217 (4)	37 (3)	NA	509 (9)	388 (6)	375 (6)	1.03 (0.90–1.18)	.70	NC	55 (0–87)
Instrumental vaginal delivery	542 (11)	149 (10)	226 (28)	815 (14)	823 (13)	909 (14)	0.90 (0.83–0.99)	.02	69 (38–357)	0 (0–77)
Fetal distress	239 (5)	84 (6)	161 (20)	337 (6)	393 (6)	428 (7)	0.91 (0.80–1.05)	.19	NC	1 (0–85)
Failure to progress	261 (5)	30 (2)	NA	361 (6)	305 (5)	347 (6)	0.87 (0.75–1.01)	.07	NC	0 (0–87)
Operative delivery	989 (20)	231 (16)	435 (55)	1611 (28)	1591 (24)	1675 (26)	0.94 (0.88–1.01)	.10	NC	0 (0–79)
Because of fetal distress	433 (9)	114 (8)	280 (35)	501 (9)	646 (10)	682 (11)	0.94 (0.84–1.05)	.26	NC	50 (0–84)
Because of failure to progress	478 (9)	67 (5)	NA	870 (15)	694 (11)	722 (12)	0.95 (0.86–1.05)	.31	NC	65 (0–90)

All numbers are based on the data as shared by the individual research groups.
BD_{blood}, base deficit calculated in blood; *BD_{ecf}*, base deficit calculated in the extra cellular fluid compartment; *CI*, confidence interval; *EFM*, electronic fetal monitoring; *NA*, not available, *NC*, not calculated.

[a] Estimated with the use of a random effects model in which a random intercept was fitted for each individual study; [b] Percentage is based on studies of Ojala et al[8] and Westerhuis et al[10]; [c] Composite of intrapartum fetal death, neonatal death, Apgar score of ≤3 at 5 minutes, seizure(s), cord artery pH of ≤7.05 and BD_{ecf} of ≥12 mmol/L, intubation for ventilation at delivery, or presence of neonatal encephalopathy.

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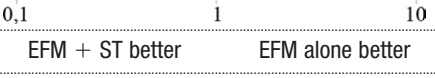
the incidence of metabolic acidosis$_{BDecf}$. Therefore, exclusion of this study from the IPDMA gives a conservative result on the added value of ST analysis. Second, the IPDMA accounted for missing data. Imputation of missing values resulted in 7 additional cases (15%) of metabolic acidosis$_{BDecf}$ in the EFM + ST-analysis group and 6 additional cases (9%) in the

TABLE 4
Risk of neonatal metabolic acidosis$_{BDecf}$ in relevant subgroups

Variable	ST analysis + EFM (event/n)[a]	EFM alone (event/n)[b]	Relative risk (95% CI)	Relative risk (95% CI)[c]	*P* value
Gestational age, wk					
≤37	1/326 (0.3%)	1/325 (0.3%)		1.00 (0.07–14.8)	Reference
37-40	25/3262 (0.8%)	38/3167 (1.2%)		0.65 (0.38–1.09)	.75
40-41	18/1575 (1.1%)	13/1508 (0.9%)		1.32 (0.63–2.78)	.84
>41	12/1356 (0.9%)	21/1454 (1.4%)		0.62 (0.30–1.29)	.73
Parity					.17
Nulliparous	46/3850 (1.2%)	52/3823 (1.4%)		0.88 (0.57–1.34)	
Multiparous	10/2674 (0.4%)	21/2640 (0.8%)		0.49 (0.22–1.07)	
Previous cesarean delivery[d]					.91
Yes	4/370 (1.1%)	5/395 (1.3%)		0.83 (0.22–3.17)	
No	26/2853 (0.9%)	29/2844 (1.0%)		0.89 (0.51–1.56)	
Maternal diabetes mellitus					.81
Yes	4/261 (1.5%)	3/168 (1.8%)		0.98 (0.21–4.49)	
No	52/6215 (0.8%)	70/6253 (1.1%)		0.75 (0.51–1.09)	
Induced onset of labor					.90
Yes	14/1879 (0.7%)	17/1862 (0.9%)		0.78 (0.38–1.62)	
No	41/4580 (0.9%)	55/4534 (1.2%)		0.75 (0.49–1.14)	
Meconium-stained amniotic fluid					.23
Yes	13/1476 (0.9%)	25/1519 (1.6%)		0.56 (0.28–1.11)	
No	43/5005 (0.9%)	47/4902 (1.0%)		0.89 (0.58–1.37)	
Epidural anesthesia					.75
Yes	30/2898 (1.0%)	38/2966 (1.3%)		0.81 (0.49–1.33)	
No	26/3626 (0.7%)	35/3497 (1.0%)		0.72 (0.43–1.23)	
Birthweight					.35
<10th percentile	4/667 (0.6%)	9/641 (1.4%)		0.29 (0.03–2.37)	
≥10th percentile	48/5728 (0.8%)	62/5691 (1.1%)		0.78 (0.41–1.47)	



CI, confidence interval; *EFM*, electronic fetal monitoring.

[a] n = 6524; [b] n = 6463; [c] Estimated with the use of a random effects model in which a random intercept was fitted for each individual study; [d] Percentage based on studies of Vayssiere et al[9] and Westerhuis et al.[10]

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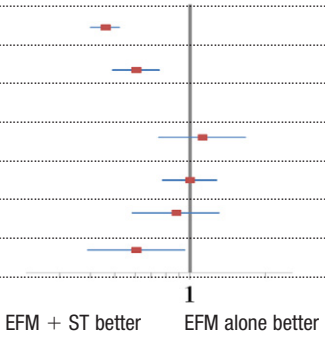
EFM-only group. Because of the increase in numerator (more cases of metabolic acidosis$_{BDecf}$) and the denominator (no participants with missing outcome values, so all participants were included in the analyses), the estimated effect of ST analysis was expected to be different from the ADMAs.

The point estimate of metabolic acidosis$_{BDecf}$ in this study is consistent with only 2 of the 4 included studies and was opposite to the effects found by Ojala et al[8] and Vayssiere et al.[9] It is unclear what might have caused this difference. Vayssière et al used slightly different inclusion criteria (Table 1), which may have led to the inclusion of women who were at higher risk (Table 2) and potentially may have influenced the effect of ST analysis on metabolic acidosis$_{BDecf}$. However, the inclusion criteria of Ojala et al were very similar to the studies of Amer-Wahlin et al[7] and Westerhuis et al.[10] It must be noted that the studies by Ojala et al and Vayssière et al were not powered to find a difference in metabolic acidosis$_{BDecf}$. Despite these differences, the baseline characteristics were comparable. However, there was a moderate degree of heterogeneity among the primary outcomes

TABLE 5
Risk of an instrumental vaginal delivery in relevant subgroups

Outcome	Subgroup	ST analysis + EFM (event/)[a]	EFM alone (event/n)[b]	Relative risk (95% CI)	Relative risk (95% CI)[c]	No. needed to test (95% CI)	*P* value
Fetal blood sampling	Epidural anesthesia						.03
	Yes	323/2898 (11%)	715/2966 (24%)		0.46 (0.40–0.52)	8 (7–9)	
	No	137/3626 (4%)	226/3497 (6%)		0.61 (0.49–0.75)	37 (27–60)	
Admitted to neonatal intensive care unit	Gestational age, wk						
	≤37	52/326 (16%)	46/325 (14%)		1.12 (0.75–1.66)	NC	Reference
	37-40	129/3262 (4%)	124/3167 (4%)		1.00 (0.78–1.27)	NC	.62
	40-41	48/1575 (3%)	53/1508 (4%)		0.88 (0.59–1.30)	NC	.36
	>41	29/1356 (2%)	51/1454 (4%)		0.61 (0.39–0.95)	73 (39–669)	.038



CI, confidence interval; *EFM*, electronic fetal monitoring; *NC*, not calculated.

[a] n = 6524; [b] n = 6463; [c] Estimated with the use of a random effects model in which a random intercept was fitted for each individual study.

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in the 4 studies. This heterogeneity is likely a result of different directions of the effect of ST analysis in the individual studies, with the studies of Ojala et al[8] and Vayssière et al[9] that showed RRs >1 (harmful) and those of Amer-Wahlin et al[7] and Westerhuis et al[10] that found RRs <1 (beneficial). Given the amount of heterogeneity, a fixed effect assumption was considered unrealistic for the outcomes; we therefore used random effects models that were similar to the ADMAs to account for this heterogeneity.

Strengths and limitations

A potential problem in ADMA is that primary outcomes of clinical trials and subgroup definitions can differ between trials, which makes it difficult to pool the results of different studies. An IPDMA overcomes this problem because it involves synthesis of individual level data from clinical trials, which allows for more flexibility in the choice of endpoints, subgroups, potential harms, data analysis, and handling of missing data. Furthermore, IPDMA allows standardization of inclusion and exclusion criteria across studies, which is independent of bias that may arise through selective reporting.[23] Therefore, an IPDMA offers a more reliable conclusion on the effectiveness of ST analysis.

To put our results into context, a few limitations must be addressed. All studies that were included in the IPDMA that registered information on fetal blood sampling showed a clear effect of ST analysis on the use of fetal blood sampling.[8-10] Fetal blood sampling is a relatively invasive procedure and is used as an adjunct test whenever the fetal heart rate monitoring is indeterminate. The results of the studies and our IPDMA indicate that ST analysis replaced fetal blood sampling as the adjunct test. Because fetal blood sampling was available in the countries that were included in the study, it might be difficult to generalize these results to countries where fetal blood sampling is not used. Comparison with the results of the ongoing NICHD trial in the United States will be particularly interesting.

To investigate the effect of the algorithm that was used to calculate the BD_{blood} and to be able to use umbilical cord gas acid-base data from the studies of Amer-Wahlin et al[7] and Vayssiere et al,[9] which did not record BD_{blood}, a sensitivity analysis was performed. In this sensitivity analysis, the BD_{blood} was calculated by the Corning and the Roche algorithms, which use a fixed value for the hemoglobin concentration (9.3 mmol/L).[24] Including metabolic acidosis$_{BDblood}$ calculated with these algorithms in the sensitivity analysis, the effect of additional ST analysis was found to be similar to the results in Table 3 (data not shown).

Ojala et al[8] excluded 11 women and Westerhuis et al[10] excluded14 women after randomization because it was discovered later that they did not fulfill the inclusion criteria. Technically, this means that analyses in the studies, and therefore also in this IPDMA, were not performed according to the intent-to-treat principle. However, because the excluded women did not fulfill the inclusion criteria, it was justified to leave them out of the analyses.

Clinical implications

EFM + ST analysis leads to a reduction in the frequency of operative vaginal deliveries and fetal blood samples. Although the incidence of metabolic acidosis$_{BDecf}$ was reduced by 25%, this reduction was not statistically significant, which might be due to its low incidence of 1.0%. This incidence in the control group was much lower than anticipated by the sample size calculations that were used by Amer-Wahlin et al[7] (1.3%) and Westerhuis et al[10] (3.5%).[7,10] This might be the result of a better interpretation of the EFM in the

EFM-alone group because of the specific STAN clinical guidelines training (Hawthorne effect). It is important to note that, although adverse neonatal outcome might be a more clinically relevant outcome, additional ST analysis did not lead to a significant reduction. Therefore, results of the ongoing RCT that is being carried out by the NICHD in the United States in which the primary outcome is adverse neonatal outcome will be of crucial importance in guiding future management.[17]

Given the results of our IPDMA, we believe that ST analysis has added value in EFM, especially in hospitals where fetal blood samples are performed. STAN should be introduced into practice carefully, taking into account the learning curve. The favorable effect of ST analysis in the study by Amer-Wahlin et al[7] was observed mainly in the second part of the trial. The interim analysis showed several avoidable protocol violations in participants who gave birth to babies with metabolic acidosis$_{BDecf}$. These cases resulted in structured feedback and renewed training.[25] Recent observational studies that have investigated the effects of long-term use of ST analysis have shown a decrease in the incidence of metabolic acidosis$_{BDecf}$ over time.[25-27] Furthermore, the cases of adverse neonatal outcome that are described in the literature mainly are due to problems with the interpretation of the EFM or violation of guidelines,[28,29] which further supports the hypothesis that the real impact of ST analysis is still unknown.

Implications for research

As mentioned by Neilson,[30] little information about the long-term development of the infants who participated in the studies exists. A short follow-up in the Swedish RCT showed a decreased number of neonates with moderate or severe neonatal encephalopathy in the ST analysis arm.[31] A long-term follow-up study of the Dutch RCT is currently ongoing. Follow-up studies should provide more insight into long-term behavioral and neurologic outcomes, which in turn will allow for the investigation of long-term cost-effectiveness. However, because there already seems to be a clear association between neonatal acidosis and long-term poor neurologic outcome,[2] we believe that neonatal asphyxia, which is defined as metabolic acidosis in the umbilical artery, is the best available surrogate marker.

Metabolic acidosis, which is related to perinatal and long-term outcomes such as neonatal mortality, hypoxic ischemic encephalopathy, intraventricular hemorrhage or periventricular leukomalacia, and cerebral palsy,[2] is considered to be an intermediate outcome (ie, a proxy for other outcomes). The incidence of metabolic acidosis hardly tops 1%, which means that trials will need substantial sample sizes to prove a statistically significant treatment effect. It is therefore debatable whether future studies should use this outcome. Instead, we would like to suggest the use of a neonatal outcome that is composed of clinical outcomes that include moderate and severe perinatal asphyxia as defined by the American College of Obstetricians and Gynecologists[32] and perinatal death. Moreover, long-term outcomes (eg, neurodevelopmental delay) should be of interest in future studies, especially because the long-term effects of EFM alone and EFM + ST analysis are currently unknown. Furthermore, maternal outcomes are clinically important as well, especially a cesarean delivery that may have both short- and long-term consequences.

This IPDMA did not show a reduction of metabolic acidosis for those pregnancies that were monitored with ST analysis compared with EFM alone but did show a reduced frequency of operative deliveries and fetal blood sampling. Consequently, such discrepancies call for formal cost-effectiveness assessment of ST analysis compared with EFM alone. Two up-to-date formal cost-effectiveness studies have been performed.[33,34] One study, a long-term cost-effectiveness study based on a probabilistic decision model with the use of Swedish maternity ward data, showed that ST analysis is cost-effective in comparison with EFM alone.[33] The other study, a cost-effectiveness study based on the study of Westerhuis et al,[10] concluded that the additional costs of monitoring by ST analysis are very limited when compared with monitoring with EFM only and very low compared with the total costs of delivery.[34] Because the results in this IPDMA are comparable with the results of the study on which the latter cost-effectiveness analysis was based, we believe that the results of this cost-effectiveness analysis can be translated to this IPDMA. To reach a final conclusion on the cost-effectiveness of ST analysis, it may be necessary to perform a formal and extensive cost-effectiveness study with the use of all the available IPDMA that were collected in this metaanalysis. However, this fell outside the scope of the current IPDMA study.

In conclusion, this large IPDMA adds to the literature that the addition of ST analysis to cardiotocography in fetal monitoring does not reduce the incidence of metabolic acidosis$_{BDecf}$, but does reduce the frequency of instrumental vaginal deliveries and the need for fetal blood sampling. ■

REFERENCES

1. Lavrijsen SW, Uiterwaal CS, Stigter RH, de Vries LS, Visser GH, Groenendaal F. Severe umbilical cord acidemia and neurological outcome in preterm and full-term neonates. Biol Neonate 2005;88:27-34.

2. Malin GL, Morris RK, Khan KS. Strength of association between umbilical cord pH and perinatal and long-term outcomes: systematic review and meta-analysis. BMJ 2010;340:c1471.

3. van de Riet JE, Vandenbussche FP, Le CS, Keirse MJ. Newborn assessment and long-term adverse outcome: a systematic review. Am J Obstet Gynecol 1999;180:1024-9.

4. Westgate JA, Bennet L, Brabyn C, Williams CE, Gunn AJ. ST waveform changes during repeated umbilical cord occlusions in near-term fetal sheep. Am J Obstet Gynecol 2001;184:743-51.

5. Widmark C, Lindecrantz K, Murray H, Rosen KG. Changes in the PR, RR intervals and ST waveform of the fetal lamb electrocardiogram with acute hypoxemia. J Dev Physiol 1992;18:99-103.

6. Westgate J, Harris M, Curnow JS, Greene KR. Plymouth randomized trial of cardiotocogram only versus ST waveform plus cardiotocogram for intrapartum monitoring in 2400 cases. Am J Obstet Gynecol 1993;169:1151-60.

7. Amer-Wahlin I, Kjellmer I, Marsal K, Olofsson P, Rosen KG. Swedish randomized controlled trial of cardiotocography only versus cardiotocography plus ST analysis of fetal electrocardiogram revisited: analysis of data according to

standard versus modified intention-to-treat principle. Acta Obstet Gynecol Scand 2011; 90:990-6.
8. Ojala K, Vaarasmaki M, Makikallio K, Valkama M, Tekay A. A comparison of intrapartum automated fetal electrocardiography and conventional cardiotocography: a randomised controlled study. BJOG 2006;113:419-23.
9. Vayssiere C, David E, Meyer N, et al. A French randomized controlled trial of ST-segment analysis in a population with abnormal cardiotocograms during labor. Am J Obstet Gynecol 2007;197:299-6.
10. Westerhuis ME, Visser GH, Moons KG, Zuithoff N, Mol BW, Kwee A. Cardiotocography plus ST analysis of fetal electrocardiogram compared with cardiotocography only for intrapartum monitoring: a randomized controlled trial. Obstet Gynecol 2011;117:406-7.
11. Becker JH, Bax L, Amer-Wahlin I, et al. ST analysis of the fetal electrocardiogram in intrapartum fetal monitoring: a meta-analysis. Obstet Gynecol 2012;119:145-54.
12. Neilson JP. Fetal electrocardiogram (ECG) for fetal monitoring during labour. Cochrane Database Syst Rev 2006;3:CD000116.
13. Potti S, Berghella V. ST waveform analysis versus cardiotocography alone for intrapartum fetal monitoring: a meta-analysis of randomized trials. Am J Perinatol 2012;29:657-64.
14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.
15. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343:d5928.
16. Siggaard-Andersen O. An acid-base chart for arterial blood with normal and pathophysiological reference areas. Scand J Clin Lab Invest 1971;27:239-45.
17. Belfort MA, Saade GR. ST segment analysis (STAN) as an adjunct to electronic fetal monitoring: part II, clinical studies and future directions. Clin Perinatol 2011;38:159-67, vii.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
19. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087-91.
20. Koopman L, van der Heijden GJ, Grobbee DE, Rovers MM. Comparison of methods of handling missing data in individual patient data meta-analyses: an empirical example on antibiotics in children with acute otitis media. Am J Epidemiol 2008;167:540-5.
21. Rubin DB. Multiple imputation for nonresponse in surveys. New York: Wiley; 1987.
22. Strachan BK, van Wijngaarden WJ, Sahota D, Chang A, James DK. Cardiotocography only versus cardiotocography plus PR-interval analysis in intrapartum surveillance: a randomised, multicentre trial: FECG study group. Lancet 2000;355:456-9.
23. Riley RD, Lambert PC, bo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010;340:c221.
24. Mokarami P, Wiberg N, Olofsson P. An overlooked aspect on metabolic acidosis at birth: blood gas analyzers calculate base deficit differently. Acta Obstet Gynecol Scand 2012; 91:574-9.
25. Amer-Wahlin I, Kallen K, Herbst A, Rydhstroem H, Sundstrom AK, Marsal K. Implementation of new medical techniques: experience from the Swedish randomized controlled trial on fetal ECG during labor. J Matern Fetal Neonatal Med 2005;18:93-100.
26. Noren H, Blad S, Carlsson A, et al. STAN in clinical practice: the outcome of 2 years of regular use in the city of Gothenburg. Am J Obstet Gynecol 2006;195:7-15.
27. Noren H, Carlsson A. Reduced prevalence of metabolic acidosis at birth: an analysis of established STAN usage in the total population of deliveries in a Swedish district hospital. Am J Obstet Gynecol 2010;202:546-7.
28. Westerhuis ME, Kwee A, van Ginkel AA, Drogtrop AP, Gyselaers WJ, Visser GH. Limitations of ST analysis in clinical practice: three cases of intrapartum metabolic acidosis. BJOG 2007;114:1194-201.
29. Westerhuis ME, Porath MM, Becker JH, et al. Identification of cases with adverse neonatal outcome monitored by cardiotocography versus ST analysis: secondary analysis of a randomized trial. Acta Obstet Gynecol Scand 2012;91:830-7.
30. Neilson JP. Fetal electrocardiogram (ECG) for fetal monitoring during labour. Cochrane Database Syst Rev 2012;4:CD000116.
31. Noren H, Amer-Wahlin I, Hagberg H, et al. Fetal electrocardiography in labor and neonatal outcome: data from the Swedish randomized controlled trial on intrapartum fetal monitoring. Am J Obstet Gynecol 2003;188:183-92.
32. American College of Obstetricians and Gynecologists. ACOG Committee Opinion no. 326. Inappropriate use of the terms fetal distress and birth asphyxia. Obstet Gynecol 2005;106:1469-70.
33. Heintz E, Brodtkorb TH, Nelson N, Levin LA. The long-term cost-effectiveness of fetal monitoring during labour: a comparison of cardiotocography complemented with ST analysis versus cardiotocography alone. BJOG 2008;115: 1676-87.
34. Vijgen SM, Westerhuis ME, Opmeer BC, et al. Cost-effectiveness of cardiotocography plus ST analysis of the fetal electrocardiogram compared with cardiotocography only. Acta Obstet Gynecol Scand 2011;90:772-8.
35. Rosen KG, Lynch P. Intrapartum fetal monitoring: its basis and current developments. Prenatal and Neonatal Medicine 2000;5:155-68.

Appendix

SUPPLEMENTARY TABLE 1
Distribution of missing values for Finnish trial

Variable	Complete cases: all variables completely observed (n = 1308)	Patients with at least 1 missing value (n = 164)	*P* value[a]
Patient age at delivery, y[b]	27.8 ± 5.5	27.8 ± 5.2	.97
Gestational age at delivery, wk[b]	40.1 ± 1.3	40.1 ± 1.1	.76
Nulliparous, n (%)	628 (48)	86 (53)	.29
Previous cesarean delivery, n (%)	NA	NA	NA
Prolonged pregnancy: at least 42 wk, n (%)	56 (4)	4 (3)	.40
Maternal diabetes mellitus, n (%)	99 (8)	16 (10)	.32
Meconium-stained amniotic fluid, n (%)	233 (18)	27 (19)	.90
Epidural anesthesia, n (%)	718 (55)	75 (46)	.03
Induction of labor, n (%)	245 (19)	32 (22)	.46
Birthweight, g[b]	3611 ± 502[c]	3561 ± 513[c]	.24[c]
Birthweight <2500 g, n (%)	22 (2)	5 (3)	.31
Neonatal female sex, n (%)	654 (50)	69 (48)	.76
Cord-artery pH <7.05; BD_{ecf} >12 mmol/L, n (%)	14 (1)	2 (2)	.95
Cord-artery pH <7.05; BD_{blood} >12 mmol/L, n (%)	21 (2)	2 (2)	.74
Cord-artery pH <7.15, n (%)	192 (15)	23 (18)	.39
Cord-artery pH <7.05, n (%)	25 (2)	3 (2)	1.00
Cord-artery pH <7.00, n (%)	6 (0.5)	1 (1)	.87
Cord-artery BD_{ecf} >12, n (%)	68 (5)	9 (8)	.38
Cord-artery BD_{blood} >12, n (%)	73 (6)	8 (7)	.72
Apgar score at 5 min, <7, n (%)	13 (1)	4 (3)	.16
Fetal blood sampling, n (%)	151 (12)	15 (9)	.43
Cesarean delivery, n (%)	73 (6)	9 (6)	.88
Instrumental vaginal delivery, n (%)	128 (10)	21 (13)	.27
Admission to neonatal intensive care unit, n (%)	47 (4)	2 (2)	.35
Moderate or severe hypoxic ischemic encephalopathy: Sarnat grade 2 or 3, n (%)	1 (<0.1)	0	.22
Seizures, n (%)	2 (<0.1)	0	.53
Intubation, n (%)	6 (0.5)[c]	6 (4)[c]	< .001[c]
Perinatal death, n (%)	0	0	NA
Allocation to index group, n (%)	646 (49)	87 (53)	.42

BD_{blood}, base deficit calculated in blood; *BD_{ecf}*, base deficit calculated in the extra cellular fluid compartment; *NA*, not available.

[a] Calculated with the χ^2 test or the Student *t* tests for dichotomous or continuous variables, respectively; [b] Data are presented as mean ± SD; [c] Missing data were not completely at random but were related to other subject characteristics, which indicates not to perform a complete case analysis but rather apply multiple imputation first.

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SUPPLEMENTARY TABLE 2

Distribution of missing values for French trial

Variable	Complete cases: all variables completely observed (n = 633)	Patients with at least 1 missing value (n = 166)	*P* value[a]
Patient age at delivery, y[b]	29.7 ± 5.6[c]	31.0 ± 5.8[c]	.006[c]
Gestational age at delivery, wk[b]	40.0 ± 2.1	39.9 ± 1.4	.30
Nulliparous, n (%)	183 (29)	41 (25)	.33
Previous cesarean delivery, n (%)	41 (6)	8 (5)	.59
Prolonged pregnancy: at least 42 wk, n (%)	2 (<0.1)	1 (1)	.86
Maternal diabetes mellitus, n (%)	32 (5)	9 (5)	.98
Meconium-stained amniotic fluid, n (%)	92 (15)	29 (19)	.23
Epidural anesthesia, n (%)	581 (92)	144 (87)	.07
Induction of labor, n (%)	230 (36)	27 (38)	.88
Birthweight, g[b]	3262 ± 464[c]	3171 ± 615[c]	.038[c]
Birthweight <2500 g, n (%)	28 (4)[c]	19 (11)[c]	.001[c]
Neonatal female sex, , n (%)	NA	NA	NA
Cord-artery pH <7.05 & BD_{ecf} > 12 mmol/L, n (%)	11 (2)	2 (2)	.85
Cord-artery pH <7.05 & BD_{blood} >12 mmol/L, n (%)	14 (2)	2 (1)	.83
Cord-artery pH <7.15, n (%)	113 (18)	32 (24)	.12
Cord-artery pH <7.05, n (%)	16 (3)	5 (4)	.62
Cord-artery pH <7.00, n (%)	5 (1)	2 (2)	.78
Cord-artery BD_{ecf} >12, n (%)	94 (15)	19 (17)	.72
Cord-artery BD_{blood} >12, n (%)	112 (18)	18 (16)	.66
Apgar score at 5 min, <7, n (%)	8 (1)	4 (3)	.40
Fetal blood sampling, n (%)	279 (44)	77 (46)	.66
Cesarean delivery, n (%)	157 (25)	52 (32)	.07
Instrumental vaginal delivery, n (%)	180 (28)	46 (28)	.03
Admission to neonatal intensive care unit, n (%)	26 (4)[c]	22 (14)[c]	< .001[c]
Moderate or severe hypoxic ischemic encephalopathy: Sarnat grade 2 or 3, n (%)	NA	NA	NA
Seizures, n (%)	NA	NA	NA
Intubation, n (%)	3 (<0.1)[c]	5 (3)[c]	.01[c]
Perinatal death, n (%)	0	0	NA
Allocation to index group, n (%)	316 (50)	83 (50)	.95

BD_{blood}, base deficit calculated in blood; *BD_{ecf}*, base deficit calculated in the extra cellular fluid compartment; *NA*, not available.

[a] Calculated by the χ^2 test or the Student *t* tests for dichotomous or continuous variables, respectively; [b] Data are presented as mean ± SD; [c] Missing data were not completely at random but were related to other subject characteristics, which indicates not to perform a complete case analysis but rather apply multiple imputation first.

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SUPPLEMENTARY TABLE 3

Distribution of missing values for Swedish trial

Variable	Complete cases: all variables completely observed (n = 4110)	Patients with at least 1 missing value (n = 939)	*P* value[a]
Patient age at delivery, y[b]	NA	NA	NA
Gestational age at delivery, wk[b]	39.7 ± 1.5[c]	39.4 ± 2.0[c]	< .001[c]
Nulliparous, n (%)	1597 (39)	324 (37)	.36
Previous cesarean delivery, n (%)	NA	NA	NA
Prolonged pregnancy: at least 42 wk, n (%)	35 (1)	7 (1)	.93
Maternal diabetes mellitus, n (%)	88 (2)	16 (2)	.71
Meconium-stained amniotic fluid, n (%)	936 (23)	207 (23)	.73
Epidural anesthesia, n (%)	1627 (40)[c]	330 (35)[c]	.01[c]
Induction of labor, n (%)	709 (17)	157 (17)	.96
Birthweight, g[b]	3585 ± 517[c]	3485 ± 582[c]	< .001[c]
Birthweight <2500 g, n (%)	74 (2)[c]	44 (5)[c]	< .001[c]
Neonatal female sex, , n (%)	1930 (47)	446 (49)	.32
Cord-artery pH <7.05 & BD_{ecf} >12 mmol/L, n (%)	43 (1)	3 (1)	.84
Cord-artery pH <7.05 & BD_{blood} >12 mmol/L, n (%)	NA	NA	NA
Cord-artery pH <7.15, n (%)	788 (19)[c]	72 (33)[c]	< .001[c]
Cord-artery pH <7.05, n (%)	137 (3)	13 (6)	.06
Cord-artery pH <7.00, n (%)	42 (1)[c]	9 (4)[c]	< .001[c]
Cord-artery BD_{ecf} >12, n (%)	62 (2)	3 (5)	.14
Cord-artery BD_{blood} >12, n (%)	NA	NA	NA
Apgar score at 5 min, <7, n (%)	44 (1)	17 (2)	.07
Fetal blood sampling, n (%)	NA	NA	NA
Cesarean delivery, n (%)	367 (9)	80 (9)	.74
Instrumental vaginal delivery, n (%)	410 (10)[c]	132 (14)[c]	< .001[c]
Admission to neonatal intensive care unit, n (%)	282 (7)[c]	105 (11)[c]	< .001[c]
Moderate or severe hypoxic ischemic encephalopathy: Sarnat grade 2 or 3, n (%)	NA	NA	NA
Seizures, n (%)	NA	NA	NA
Intubation, n (%)	NA	NA	NA
Perinatal death, n (%)	NA	NA	NA
Allocation to index group, n (%)	2085 (51)	480 (51)	.86

BD_{blood}, base deficit calculated in blood; *BD_{ecf}*, base deficit calculated in the extra cellular fluid compartment; *NA*, not available.

[a] Calculated by the χ^2 test or the Student *t* tests for dichotomous or continuous variables, respectively; [b] Data are presented as mean ± SD; [c] Missing data were not completely at random but were related to other subject characteristics, which indicates not to perform a complete case analysis but rather apply multiple imputation first.

Schuit. Individual participant data metaanalysis of fetal ST analysis. Am J Obstet Gynecol 2013.