

ORIGINAL ARTICLE

## Amnioinfusion for the Prevention of the Meconium Aspiration Syndrome

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### ABSTRACT

#### BACKGROUND

It is uncertain whether amnioinfusion (infusion of saline into the amniotic cavity) in women who have thick meconium staining of the amniotic fluid reduces the risk of perinatal death, moderate or severe meconium aspiration syndrome, or both.

#### METHODS

We performed a multicenter trial in which 1998 pregnant women in labor at 36 or more weeks of gestation who had thick meconium staining of the amniotic fluid were stratified according to the presence or absence of variable decelerations in fetal heart rate and then randomly assigned to amnioinfusion or to standard care. The composite primary outcome measure was perinatal death, moderate or severe meconium aspiration syndrome, or both.

#### RESULTS

Perinatal death, moderate or severe meconium aspiration syndrome, or both occurred in 44 infants (4.5 percent) of women in the amnioinfusion group and 35 infants (3.5 percent) of women in the control group (relative risk, 1.26; 95 percent confidence interval, 0.82 to 1.95). Five perinatal deaths occurred in the amnioinfusion group and five in the control group. The rate of cesarean delivery was 31.8 percent in the amnioinfusion group and 29.0 percent in the control group (relative risk, 1.10; 95 percent confidence interval, 0.96 to 1.25).

#### CONCLUSIONS

For women in labor who have thick meconium staining of the amniotic fluid, amnioinfusion did not reduce the risk of moderate or severe meconium aspiration syndrome, perinatal death, or other major maternal or neonatal disorders.

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\*The participants in the Amnioinfusion Trial Group are listed in the Appendix.

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**M**ECONIUM-STAINED AMNIOTIC FLUID occurs in 7 to 22 percent of term deliveries,<sup>1,2</sup> and the meconium aspiration syndrome complicates 1.7 to 35.8 percent of these deliveries.<sup>3-8</sup> The case fatality rate of the meconium aspiration syndrome is reported to range from 5 to 40 percent.<sup>4,9-11</sup> The meconium aspiration syndrome is believed to result from aspiration of meconium during intrauterine gasping or at the first breath. Prophylactic pharyngeal suctioning and tracheal aspiration have not been shown to reduce the risk of the meconium aspiration syndrome.<sup>4</sup>

Amnioinfusion, or transcervical infusion of saline into the amniotic cavity, has been proposed as a method to reduce the risk of the meconium aspiration syndrome. Potential mechanisms include dilution of meconium, thus reducing its mechanical and inflammatory effects, and cushioning of the umbilical cord, thus correcting recurrent umbilical-cord compressions that lead to fetal acidemia (a condition predisposing to the meconium aspiration syndrome).

A systematic review of randomized trials found that amnioinfusion was associated with an overall reduction in the meconium aspiration syndrome and cesarean section.<sup>8</sup> However, most previous trials had small sample sizes, and in some, outcome measures were not clearly defined.<sup>8,12</sup> The largest study, which showed a clear benefit associated with amnioinfusion, was carried out in a setting where routine intrapartum fetal heart-rate monitoring and neonatal resuscitation were not available.<sup>13</sup>

Amnioinfusion may not be without risk. The combined sample size of all previous trials is too small to assess adequately the possibility of rare but serious complications such as umbilical-cord prolapse, amniotic-fluid embolism, and uterine rupture.<sup>14-16</sup>

The objective of this international, randomized, controlled trial was to determine whether amnioinfusion reduces the risk of the composite outcome of perinatal death, moderate or severe meconium aspiration syndrome, or both. We also assessed the effect of the intervention on the risk of cesarean delivery and other major indicators of neonatal and maternal disorders.

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#### METHODS

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We conducted the trial from April 1999 to August 2003 in 56 centers in 13 countries. Women were enrolled during labor if they had all of the follow-

ing: thick meconium staining of the amniotic fluid; a single fetus in the cephalic presentation with a gestational age of 36 weeks or more; ruptured membranes; cervical dilatation between 2 and 7 cm; and no indication for urgent delivery (e.g., loss of fetal heart-rate variability and late decelerations on a 30-minute prandomization fetal heart-rate tracing). Women were ineligible if there was a suspected major fetal anomaly, chorioamnionitis, placenta previa or vaginal bleeding, known or suspected seropositivity for the human immunodeficiency virus, hepatitis B or C, active genital herpes, polyhydramnios, a previous uterine incision other than low transverse, an urgent indication for delivery, or an inability to comprehend the consent form. The study was approved by the ethics review board of each center. Written informed consent was obtained from all participants.

A total of 1998 women were randomly assigned at a ratio of 1:1 to either amnioinfusion or standard care with the use of a single, centralized computer-randomization service. Randomization was stratified according to the study center. Because variable decelerations in fetal heart rate were of potential prognostic significance, we also stratified according to the absence or presence of three or more variable decelerations during the 30-minute period before randomization. Randomization was according to block, with block size randomly varying between two and four patients.

Women assigned to amnioinfusion underwent the procedure immediately after randomization. A sterile catheter was introduced transcervically to a depth of 30 cm, and a bolus of 800 ml of sterile saline at room temperature was infused under the force of gravity at a rate of 20 ml per minute over a period of 40 minutes. The infusion was then continued at a rate of 2 ml per minute to a maximum of 1500 ml. Women were assessed by continuous monitoring of intrauterine pressure or by uterine palpation at 15-minute intervals for signs of uterine overdistention or hypertonic contractions. Amnioinfusion was discontinued if the baseline intrauterine pressure increased by more than 15 mm Hg, if on palpation the uterus did not relax between contractions, or if polyhydramnios was confirmed on ultrasonographic evaluation. Continuous electronic fetal heart-rate monitoring was performed in both groups. The use of oxytocin was permitted if there was a delay in the progress of labor, provided that the fetal heart-rate tracing did not indicate that urgent delivery was necessary.

Careful suctioning of the oropharynx and nasopharynx was performed before presentation of the shoulders and again immediately after delivery. Laryngoscopy and tracheal intubation and suctioning were reserved for infants with respiratory depression requiring positive-pressure ventilation.

The composite primary outcome measure was the occurrence of perinatal death, moderate or severe meconium aspiration syndrome, or both. In accordance with clinical criteria previously described,<sup>7</sup> the meconium aspiration syndrome was defined as respiratory distress in the first four hours after birth and categorized as severe (requiring assisted mechanical ventilation) or moderate (requiring oxygen for at least 48 hours or at a concentration of 40 percent or greater but without mechanical ventilation). A team of three neonatologists who were blinded to the treatment groups determined which infants met the criteria for moderate or severe meconium aspiration syndrome.

Secondary outcomes included perinatal death, serious morbidity, or both, defined as the presence of at least one of the following: perinatal death; moderate or severe meconium aspiration syndrome; hypotonia; assisted ventilation or intubation of more than five minutes' duration; a five-minute Apgar score below 7; an umbilical-artery blood pH value below 7.05; abnormal consciousness; the need for tube feeding; convulsions; a blood or lumbar culture positive for bacteria; major trauma including basal skull or long-bone fracture, spinal cord injury, or facial or brachial palsy; and maternal death or serious morbidity (defined as the presence of any of the following: uterine rupture, amniotic-fluid embolism, antepartum hemorrhage requiring urgent delivery, postpartum hemorrhage requiring transfusion, hysterectomy, admission to the intensive care unit, or disseminated intravascular coagulation). Acidosis and severe acidosis were defined as umbilical-artery blood pH values below 7.15 and below 7.05, respectively.

Study centers were asked to send films of neonatal chest radiographs to the trial coordinating center, where they were interpreted by a single experienced radiologist who was blinded to the treatment group. When films could not be obtained for blinded interpretation, results were abstracted from the hospital record. A chest radiograph was considered abnormal if one or more of the following was noted: hyperinflation; coarse, patchy infiltrates; atelectasis; interstitial emphysema; pneumomediastinum or pneumopericardium; and pleural effusion.

Fetal heart-rate tracings were interpreted by a single obstetrician who was blinded to the study group. Tracings were categorized as normal, as having abnormalities of insufficient severity to justify clinical intervention, or as having abnormalities requiring clinical intervention. The presence of decreased heart-rate variability with late or prolonged decelerations was considered reason for intervention.

We needed 984 women in each group in order to detect a reduction in the rate of meconium aspiration syndrome from 5.0 percent in the control group to 2.5 percent in the amnioinfusion group with a power of 80 percent and a two-tailed alpha level of 0.05. All women except those lost to follow-up were analyzed according to the group to which they had been randomly assigned. We used Student's *t*-test to compare continuous variables and the chi-square test or Fisher's exact test for categorical variables. The effects of the intervention were expressed as relative risks with their 95 percent confidence intervals. We used the SAS statistical software package (version 8.0). The industry sponsor had no role in the design of the study, data collection, data management, analysis, or the writing of the manuscript.

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## RESULTS

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A total of 1998 women (81.3 percent of whom did not have recurrent variable decelerations in fetal heart rate on monitoring) underwent randomization, 995 to the amnioinfusion group and 1003 to the control group. Nineteen women (7 in the amnioinfusion group and 12 in the control group) were lost to follow-up. In addition, four women (two in the amnioinfusion group and two in the control group) did not meet the eligibility criteria and were excluded from the analysis. Of these women, three had breech presentations and one had a twin pregnancy. Thus, 1975 women were included in the analysis. Major congenital anomalies were diagnosed in two infants of women (one in each group) who were included in the analysis.

The study groups were balanced with respect to sociodemographic and anthropometric variables, as well as baseline obstetrical characteristics and several cointerventions that could influence the primary outcome (Table 1). However, continuous fetal heart-rate monitoring was performed in slightly more women in the amnioinfusion group than in the control group (95.0 percent vs. 92.4 percent,  $P=0.02$ ).

**Table 1. Baseline Demographic and Obstetrical Characteristics of the Women, According to Study Group.\***

| Characteristic   | Amnioinfusion (N=986) | Control (N=989) | P Value |
|--|-----------------------|-----------------|---------|
| Maternal age — yr  | 26.6±6.3              | 26.4±6.3        | 0.45    |
| Maternal education — yr  | 10.6±3.7              | 10.7±3.7        | 0.67    |
| Maternal body-mass index†  | 30.2±5.6              | 30.2±5.8        | 0.97    |
| Gestational age — no. (%)  |                       |                 | 0.90    |
| 35–36 wk   | 28 (2.8)              | 30 (3.0)        |         |
| 37–40 wk   | 526 (53.3)            | 524 (53.0)      |         |
| 41–42 wk   | 409 (41.5)            | 407 (41.2)      |         |
| >42 wk   | 23 (2.3)              | 28 (2.8)        |         |
| Nulliparous — no. (%)‡   | 543 (55.4)            | 567 (57.6)      | 0.31    |
| Cervical dilatation at admission — no. (%)                               |                       |                 | 0.99    |
| 2 cm   | 98 (9.9)              | 98 (9.9)        |         |
| 3–5 cm   | 602 (61.1)            | 607 (61.4)      |         |
| >5 cm  | 285 (28.9)            | 283 (28.6)      |         |
| Induced labor — no. (%)  | 153 (15.5)            | 166 (16.8)      | 0.44    |
| Interval between randomization and delivery — min                        | 254.6±198.4           | 253.3±215.4     | 0.91    |
| Oxytocin — no. (%)§  | 195 (19.8)            | 220 (22.2)      | 0.35    |
| Regional anesthesia — no. (%)  | 518 (52.5)            | 505 (51.1)      | 0.51    |
| Artificial membrane rupture — no. (%)‡                                   | 546 (55.4)            | 536 (54.4)      | 0.65    |
| Continuous electronic fetal heart-rate monitoring during labor — no. (%) | 937 (95.0)            | 914 (92.4)      | 0.02    |
| Fetal-scalp blood-gas assessment — no. (%)                               | 33 (3.3)              | 39 (3.9)        | 0.48    |
| Birth weight of infant — g   | 3345.7±509.5          | 3346.3±474.3    | 1.00    |

\* Plus-minus values are means ±SD. Because of rounding, percentages may not total 100.

† Maternal body-mass index was the predelivery weight in kilograms divided by the square of the height in meters.

‡ Data were missing for less than 1 percent of the participants.

§ Oxytocin was administered after randomization but before delivery.

Of the 986 women assigned to amnioinfusion, 907 (92.0 percent) actually underwent the procedure (Table 2). Reasons for failure to perform amnioinfusion in this group included delivery that was too rapid (44 women), inability to insert the catheter (8), absence of return of fluid in the proximal port (5), and error in inscription at randomization (1). The reason was not documented in 21 women. In the control group, 20 women (2.0 percent) underwent amnioinfusion on the basis of a physician's decision or the patient's request. There was satisfactory compliance with the amnioinfusion protocol among women in the amnioinfusion group.

The composite primary outcome — perinatal death, moderate or severe meconium aspiration syndrome, or both — occurred in 44 infants of women in the amnioinfusion group (4.5 percent) and 35 infants of women in the control group (3.5 percent) (relative risk, 1.26; 95 percent confidence interval, 0.82 to 1.95) (Table 3). Moderate or severe

meconium aspiration syndrome assessed on the basis of clinical criteria occurred in 43 infants of women in the amnioinfusion group (4.4 percent) and 31 in the control group (3.1 percent) (relative risk, 1.39; 95 percent confidence interval, 0.88 to 2.19). There were five perinatal deaths in the amnioinfusion group (0.5 percent) and five in the control group (0.5 percent). The frequency of mild respiratory distress did not differ significantly between infants of women in the amnioinfusion group and those in the control group (2.9 percent and 2.7 percent, respectively). Among the 43 infants in the amnioinfusion group with moderate or severe meconium aspiration syndrome, results of chest radiographs were available for 30; findings were normal in 11 and abnormal in 19. Among the 31 infants in the control group with moderate or severe meconium aspiration syndrome, results of chest radiographs were available for 21; findings were normal in 8 and abnormal in 13.

**Table 2. Characteristics of the Infusion in the 907 Women Who Underwent Amnioinfusion.\***

| Characteristic   | Value       |
|--|-------------|
| Volume of initial bolus — ml                                       | 727.0±170.1 |
| Continuous infusion rate — ml/min                                  | 0.8±1.7     |
| Total volume of saline administered — ml                           | 982.2±365.3 |
| Cervical dilatation at amnioinfusion — cm                          | 5.1±1.6     |
| Interval from randomization to commencement of amnioinfusion — min | 21.4±27.9   |
| Interval from cessation of amnioinfusion to delivery — min         | 57.5±98.4   |
| Intrauterine pressure monitored — no. (%)                          | 668 (73.6)  |
| Volume of amniotic fluid assessed by ultrasonography — no. (%)     | 33 (3.6)    |
| Amnioinfusion temporarily stopped — no. (%)                        | 70 (7.7)    |
| Technical problems encountered — no. (%)                           | 139 (15.3)  |
| Difficulty in obtaining return of meconium-stained amniotic fluid  | 84 (9.3)    |
| Catheter fell out  | 16 (1.8)    |
| Catheter blocked   | 15 (1.7)    |
| Other  | 33 (3.6)    |
| Complications diagnosed during amnioinfusion — no. (%)             | 70 (7.7)    |
| Bleeding   | 10 (1.1)    |
| Uterine hypertonicity, polyhydramnios, or overdistention           | 63 (6.9)    |

\* Plus–minus values are means ±SD.

A stratified analysis showed no significant effect of amnioinfusion on the rate of the primary outcome, regardless of whether decelerations in fetal heart rate at randomization were present (3.4 percent in the amnioinfusion group vs. 3.2 percent in the control group; relative risk, 1.05; 95 percent confidence interval, 0.62 to 1.78) or absent (9.3 percent vs. 5.1 percent; relative risk, 1.83; 95 percent confidence interval, 0.84 to 3.99). However, the study was underpowered to detect effects within strata. We did not find evidence of heterogeneity when we stratified according to decelerations in fetal heart rate ( $P=0.24$ ) or when we stratified according to the region of the study center (northern vs. southern hemisphere) ( $P=0.96$ ) (data not shown).

The rates of oropharyngeal suctioning, laryngoscopy, and intubation in the delivery room were similar between the groups, as were the proportion of infants with meconium seen below the vocal cords. There were no differences between the groups in the occurrence of the combined outcome of perinatal death, serious morbidity, or both (Table 3).

Fetal umbilical-artery blood pH was assessed in 512 participants in the amnioinfusion group (51.9 percent) and 471 in the control group (47.6 percent). Abnormal results (pH value below 7.15) were noted in 69 participants in the amnioinfusion group

(13.5 percent) and 57 in the control group (12.1 percent) (relative risk, 1.11; 95 percent confidence interval, 0.80 to 1.55).

In the analysis of fetal heart-rate monitoring, we included data only from centers that returned at least 80 percent of the tracings performed. Overall, 785 participants in the amnioinfusion group and 769 participants in the control group had interpretable data. Abnormalities classified as justifying clinical intervention were noted in 111 participants in the amnioinfusion group (14.1 percent) and 107 in the control group (13.9 percent) (relative risk, 1.02; 95 percent confidence interval, 0.79 to 1.30). When we repeated the analysis on the basis of participants for whom interpretable data were available, there was minimal change in the effect estimate (relative risk, 1.00; 95 percent confidence interval, 0.78 to 1.28).

Indicators of maternal complications in the two groups are shown in Table 4. There were no significant differences between the groups in the rates of cesarean delivery overall or cesarean delivery for the indication of fetal distress or in the rates of maternal peripartum fever. The rates of maternal death or serious morbidity were also similar in the two groups. One woman in the control group died after massive aspiration of the stomach contents

**Table 3. Distribution of Primary Outcomes and Other Indicators of Perinatal Status, According to Study Group.\***

| Outcome or Indicator  | Amnioinfusion<br>(N=986) | Control<br>(N=989) | Relative Risk<br>(95% CI) |
|---|--------------------------|--------------------|---------------------------|
|   | <i>no. (%)</i>           |                    |                           |
| <b>Primary outcomes</b>   |                          |                    |                           |
| Perinatal death or meconium aspiration syndrome                         | 44 (4.5)                 | 35 (3.5)           | 1.26 (0.82–1.95)          |
| Perinatal death   | 5 (0.5)                  | 5 (0.5)            | 1.00 (0.29–3.45)          |
| Moderate or severe meconium aspiration syndrome                         |                          |                    |                           |
| According to clinical criteria†   | 43 (4.4)                 | 31 (3.1)           | 1.39 (0.88–2.19)          |
| On chest radiography‡   | 19 (1.9)                 | 13 (1.3)           | 1.47 (0.73–2.95)          |
| <b>Neonatal resuscitation</b>   |                          |                    |                           |
| Oropharyngeal suctioning§   | 921 (93.6)               | 941 (95.3)         | 0.98 (0.96–1.00)          |
| Laryngoscopy§   | 236 (24.0)               | 254 (25.8)         | 0.93 (0.80–1.08)          |
| Suctioning of meconium below the cords                                  | 54 (5.5)                 | 70 (7.1)           | 0.77 (0.55–1.09)          |
| Any resuscitation   | 303 (30.7)               | 322 (32.6)         | 0.94 (0.83–1.07)          |
| Oxygen only   | 205 (20.8)               | 213 (21.5)         | —                         |
| Ventilation with bag and mask   | 79 (8.0)                 | 90 (9.1)           | —                         |
| Intubation with ventilation   | 19 (1.9)                 | 19 (1.9)           | —                         |
| Intubation of infant on departure from delivery room                    | 7 (0.7)                  | 7 (0.7)            | 1.00 (0.35–2.84)          |
| <b>Secondary outcomes: perinatal death, serious morbidity, or both¶</b> | 112 (11.4)               | 99 (10.0)          | 1.13 (0.88–1.47)          |
| Hypotonia§  | 32 (3.3)                 | 31 (3.2)           | 1.03 (0.64–1.68)          |
| Assisted ventilation or intubation for >5 min                           | 31 (3.1)                 | 29 (2.9)           | 1.07 (0.65–1.77)          |
| Five-minute Apgar score <7§   | 26 (2.7)                 | 29 (3.0)           | 0.90 (0.53–1.51)          |
| Arterial pH <7.05   | 22 (4.3)                 | 23 (4.9)           | 0.88 (0.50–1.56)          |
| Abnormal consciousness  | 16 (1.6)                 | 15 (1.5)           | 1.07 (0.53–2.15)          |
| Need for tube feeding   | 12 (1.2)                 | 12 (1.2)           | 1.00 (0.45–2.22)          |
| Convulsion  | 7 (0.7)                  | 9 (0.9)            | 0.78 (0.29–2.08)          |
| Blood or lumbar culture positive for bacteria                           | 2 (0.2)                  | 5 (0.5)            | 0.40 (0.08–2.06)          |
| Major fracture or palsy**   | 2 (0.2)                  | 3 (0.3)            | 0.67 (0.11–3.99)          |

\* CI denotes confidence interval, and dashes not assessed.

† Moderate or severe meconium aspiration syndrome was determined by a team of blinded neonatologists on the basis of clinical criteria.<sup>7</sup>

‡ This outcome consists of abnormal findings on a chest radiograph. Chest radiographs were available for 30 infants with moderate or severe meconium aspiration syndrome in the amnioinfusion group and for 21 infants with moderate or severe meconium aspiration syndrome in the control group.

§ Data were missing for less than 1 percent of the participants.

¶ Infants could have one or more outcomes, including death or the meconium aspiration syndrome. In the case of missing values, the infant was considered to be negative for the outcome or indicator.

|| Assessment of fetal umbilical-artery blood pH was performed in 512 participants (52.0 percent) in the amnioinfusion group and 471 (47.6 percent) in the control group.

\*\* This outcome includes basal skull or long-bone fracture, spinal cord injury, brachial plexus injury, or facial palsy.

on extubation after general anesthesia for a cesarean section.

## DISCUSSION

This large, multicenter, randomized trial showed that the rate of perinatal death, moderate or severe meconium aspiration syndrome, or both did not

differ according to whether amnioinfusion was or was not performed. We used as the main outcome measure a composite end point of perinatal death, moderate or severe meconium aspiration syndrome, or both. These end points are clinically important and were based on criteria that could be standardized across centers. Although practices with respect to the duration of the use of oxygen and the con-

**Table 4. Distribution of Maternal Disorders and Indicators of Complications, According to Study Group.\***

| Disorder or Indicator                  | Amnioinfusion<br>(N=986) | Control<br>(N=989) | Relative Risk<br>(95% CI) |
|--|--------------------------|--------------------|---------------------------|
|  | no. (%)                  |                    |                           |
| Cesarean delivery†                     | 314 (31.8)               | 287 (29.0)         | 1.10 (0.96–1.25)          |
| Fetal distress                         | 133 (13.5)               | 114 (11.5)         | —                         |
| Dystocia                               | 162 (16.4)               | 164 (16.6)         | —                         |
| Other                                  | 19 (1.9)                 | 9 (0.9)            | —                         |
| Peripartum fever‡                      | 31 (3.1)                 | 33 (3.3)           | 0.94 (0.58–1.53)          |
| Maternal death or serious morbidity§   | 15 (1.5)                 | 15 (1.5)           | 1.00 (0.49–2.04)          |
| Uterine rupture                        | 2 (0.2)                  | 1 (0.1)            | 2.00 (0.18–22.09)         |
| Antepartum hemorrhage¶                 | 3 (0.3)                  | 1 (0.1)            | 3.01 (0.31–28.85)         |
| Hysterectomy                           | 2 (0.2)                  | 0                  | —                         |
| Admission to the intensive care unit   | 3 (0.3)                  | 1 (0.1)            | 3.01 (0.31–28.88)         |
| Maternal death                         | 0                        | 1 (0.1)            | —                         |
| Disseminated intravascular coagulation | 3 (0.3)                  | 1 (0.1)            | 3.01 (0.31–28.91)         |
| Postpartum hemorrhage                  | 11 (1.1)                 | 11 (1.1)           | 1.00 (0.44–2.30)          |

\* CI denotes confidence interval, and dashes not assessed.

† Indications for cesarean delivery included suspected fetal compromise, which was determined on the basis of an abnormal fetal heart-rate tracing or an abnormal fetal-scalp pH, and dystocia, which was defined as failure to progress, cephalopelvic disproportion, or failed forceps or vacuum delivery.

‡ Peripartum fever was defined as intrapartum fever ( $\geq 38.5^{\circ}\text{C}$  on at least one reading between randomization and delivery), postpartum fever ( $\geq 38.5^{\circ}\text{C}$  on at least two readings more than 24 hours apart, excluding the first 24 hours after delivery), or both.

§ Maternal death or serious morbidity was defined as death or at least one maternal complication. In the case of missing values, the mother was considered to be negative for the disorder or indicator.

¶ Antepartum hemorrhage (without uterine rupture) was defined as that requiring urgent delivery.

|| Postpartum hemorrhage was defined as blood loss of at least 500 ml requiring blood transfusion.

centration of oxygen used among neonates may vary among centers, there was no evidence of heterogeneity of effect across centers.

Compliance with the protocol was satisfactory in both treatment groups. On average, women in the amnioinfusion group underwent amnioinfusion within 20 minutes after randomization, and the intervention continued until approximately 1 hour before delivery. The total volume of saline administered was approximately 1 liter. Continuous electronic fetal heart-rate monitoring was performed in slightly more participants in the amnioinfusion group than in the control group. Although electronic fetal monitoring could lead to earlier detection of fetal acidosis and more frequent obstetrical intervention, its role in the prevention of the meconium aspiration syndrome has not been defined.<sup>17</sup>

We found no evidence that amnioinfusion reduced the risk of serious neonatal or maternal disorders, as defined by several indicators. One published trial showing a significant reduction in the

meconium aspiration syndrome with amnioinfusion was carried out in a setting where electronic fetal heart-rate monitoring and specialized neonatal care were not available.<sup>13</sup> Amnioinfusion is only one of a number of interventions aimed at reducing the risk of the meconium aspiration syndrome. Others include electronic fetal heart-rate monitoring, operative delivery in selected cases, and airway support in the newborn period. The relative benefits of amnioinfusion could depend on the pattern of use of these cointerventions. Our study was designed to determine whether, in centers where electronic fetal monitoring and neonatal resuscitation measures are available, amnioinfusion reduced the risk of the meconium aspiration syndrome. The results of our study can be generalized only to such settings.

We were unable to obtain data from participating centers regarding the proportion of eligible women who did not participate in the study. Although the selection of participants could partially

explain the differences between our findings and those of the investigators in the previously published meta-analyses,<sup>8,12</sup> the overall proportion of newborns with a diagnosis of the meconium aspiration syndrome was similar to that previously reported,<sup>8</sup> indicating that the risk profile of our population was similar to that in previous studies.

Large and simple randomized trials have certain advantages. They evaluate the effects of broadly practicable interventions on clinically important outcomes with the use of sample sizes that are large enough to detect moderate effects.<sup>18</sup> Discordance between the results of meta-analyses of several small trials and the result of a large trial has previously been documented.<sup>19,20</sup> Some studies included in previously published meta-analyses of amnioinfusion have methodologic limitations. In most studies, little information about disease severity was provided. Several studies did not specify whether a calculation of sample size was performed a priori, and some studies excluded from their analysis a substantial number of subjects who had undergone randomization.<sup>21-25</sup>

Recent studies have shown that strategies designed to remove meconium from the airway of the newborn, including routine tracheal intubation and aspiration and oropharyngeal and nasopharyngeal suctioning on the perineum, are not effective in preventing the meconium aspiration syndrome.<sup>26,27</sup> Our findings of a lack of benefit of amnioinfusion extend these observations. Some authors have questioned the long-held belief that meconium is a major cause of respiratory distress and have suggested that chronic or acute asphyxia and intrauterine in-

fection are more likely sources of respiratory compromise in the presence of meconium.<sup>28</sup>

Reports of adverse events occurring in association with amnioinfusion include uterine overdistention and hypertonia, uterine rupture with a previous uterine scar, fetal heart-rate abnormalities, umbilical-cord prolapse, placental abruption, chorioamnionitis, and maternal deaths,<sup>14-16</sup> although serious complications seem to be rare and their relationship to amnioinfusion is, in most cases, uncertain. In our study, 1.1 percent of women in the amnioinfusion group had bleeding. Hypertonicity, polyhydramnios, or uterine overdistention was diagnosed in 6.9 percent. The incidence of other serious complications, such as maternal peripartum fever, uterine rupture, antepartum hemorrhage, hysterectomy, and disseminated intravascular coagulation, did not differ significantly between the groups.

In summary, in clinical settings with standard peripartum surveillance, amnioinfusion in the presence of thick meconium staining of the amniotic fluid did not reduce the risk of perinatal death, moderate or severe meconium aspiration syndrome, or other serious neonatal disorders. We conclude that amnioinfusion should not be recommended for the prevention of the meconium aspiration syndrome in such settings.

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## APPENDIX

The following investigators, research nurses, and centers participated in the Amnioinfusion Trial: *Chris Hani Baragwanath Hospital, Bertsham, South Africa* — E. Nicolaou, E. Nguenkeng, C. Parker; *Tembisa Hospital, Midrand, South Africa* — Z. Mlokoti, D. Qolohle, L. Thomas; *Instituto Argentino de Medicina Basada en las Evidencias, Buenos Aires* — N. Barabini; *Hôpital St.-François d'Assise, Quebec, Que., Canada* — V. Morin, J. Bérubé; *Hospital Dr. Jose Penna, Bahia Blanca, Argentina* — J. Castaldi, M. Bertin, S. Mendoza; *Hospital Dr. Jose Maria Penna, Buenos Aires* — E. Aguilera, G. Breccia, E. Werbicki; *Hospital Pereira Rossell, Montevideo, Uruguay* — C. Sosa, L. Godoy, J. Alonso; *Coronation Hospital, Coronationville, Gauteng, South Africa* — C. Nikodem, H. Calvert, U. Benjamin; *Frere Hospital, East London, South Africa* — S. Ferreira, Z. Jafra; *Cecelia Makiwane Hospital, East London, South Africa* — L. Mangesi, M. Singata, N. Makinana; *University of Cincinnati Medical Center, Cincinnati* — H.Y. How, K.R. Recht; *Liverpool Women's Hospital Fetal Centre, Liverpool, United Kingdom* — S. Walkinshaw, B. Yoxall; *Royal Alexandra Hospital, Edmonton, Alta., Canada* — R.S. Chari, N. Demianczuk, E. Pentinnen; *B.C. Children's & Women's Hospital, Vancouver, B.C., Canada* — M.-F. Delisle, V. Popovska; *Centre Hospitalier Universitaire (CHU) Brugmann, Brussels* — A. Vokaer; *ARPEGO (CHRU), Caen, France* — M. Dreyfus, C. Denoual-Ziad; *CHA Hôpital Saint-Sacrement, Quebec, Que., Canada* — S. Bazin, G. Paradis; *Wayne State University Hutzell Hospital, Detroit* — S.C. Blackwell, Y. Sorokin, E. Russel; *St. Joseph's Health Centre, London, Ont., Canada* — R. Gratton, M. Watson; *Joseph's Health Centre, Hamilton, Ont., Canada* — R. Ramanna, S. Kopatch; *Hôpital Erasme, Brussels* — C. Kirkpatrick, C. Lami, A. Petit; *IWK Health Centre, Halifax, N.S., Canada* — C. Craig C. Fanning; *Centre Hospitalier Angrignon, LaSalle, Que., Canada* — M.Y. Arseneault, C. Poirier; *Hospital Santa Marcelina, São Paulo* — M.R. Ymayo, F. Ymayo; *Hôpital Port-Royal, Paris* — V. Tsatsaris; *Complexe Hospitalier de la Sagamie, Chicoutimi, Que., Canada* — S. Dubois, A. Boudreault; *Ottawa Civic Hospital, Ottawa* — G. Tawagi, T. Meeke; *Foothills Medical Centre/Rockyview General Hospital, Calgary, Alta., Canada* — J.K. Pollard, C. Swaby; *St. Boniface Hospital, Winnipeg, Man. Canada* — M.E. Helewa, D. Kenny-Lodevsky; *CHU de Poitiers/Hôpital Jean Bernard, Poitiers, France* — G. Magnin, R. Sarfati; *Mowbray Maternity Hospital, Cape Town, South Africa* — S. Fawcus, L. Linley; *CHU Farat Hached, Sousse, Tunisia* — H. Khaïri, F. Darraggi; *Hôpital Antoine Bécère, Clamart, France* — F. Audibert, B. Simon; *Hospital Garcia de Orta, Almada, Portugal* — M. Meirinho, M.E. Casal; *Royal Victoria Hospital, Montreal* — H. McNamara, A. Benjamin; *Hôpital de Hautepierre, Strasbourg, France* — J. Ritter, A. Treisser, B. Viville, B. Langer; *Hôpital Saint-Pierre, Brussels* — M. Degueldre, P. Barlow; *Centre de Maternité et de Néonatalogie de Tunis, Tunis, Tunisia* — I. Lebbi, H. Chelli; *Maternité*

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