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INDUCTION OF LABOR COMPARED WITH EXPECTANT MANAGEMENT FOR PRELABOR RUPTURE OF THE MEMBRANES AT TERM

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Abstract *Background.* As the interval between rupture of the fetal membranes at term and delivery increases, so may the risk of fetal and maternal infection. It is not known whether inducing labor will reduce this risk or whether one method of induction is better than another.

Methods. We studied 5041 women with prelabor rupture of the membranes at term. The women were randomly assigned to induction of labor with intravenous oxytocin; induction of labor with vaginal prostaglandin E_2 gel; or expectant management for up to four days, with labor induced with either intravenous oxytocin or vaginal prostaglandin E_2 gel if complications developed. The primary outcome was neonatal infection. Secondary outcomes were the need for cesarean section and women's evaluations of their treatment.

Results. The rates of neonatal infection and cesarean section were not significantly different among the study groups. The rates of neonatal infection were 2.0 percent for the induction-with-oxytocin group, 3.0 percent for the induction-with-prostaglandin group, 2.8 percent for the expectant-management (oxytocin) group, and 2.7 percent for the expectant-management (prostaglandin) group. The rates of cesarean section ranged from 9.6 to 10.9 percent. Clinical chorioamnionitis was less likely to develop in the women in the induction-with-oxytocin group than in those in the expectant-management (oxytocin) group (4.0 percent vs. 8.6 percent, $P<0.001$), as was postpartum fever (1.9 percent vs. 3.6 percent, $P=0.008$). Women in the induction groups were less likely to say they liked "nothing" about their treatment than those in the expectant-management groups.

Conclusions. In women with prelabor rupture of the membranes at term, induction of labor with oxytocin or prostaglandin E_2 and expectant management result in similar rates of neonatal infection and cesarean section. Induction of labor with intravenous oxytocin results in a lower risk of maternal infection than does expectant management. Women view induction of labor more positively than expectant management. (N Engl J Med 1996;334: 1005-10.)

IN approximately 8 percent of women with pregnancies at term, the fetal membranes rupture before labor begins.[1] If labor is not induced, over 60 percent of these women begin labor spontaneously within 24 hours and over 95 percent begin labor spontaneously within 72 hours.[1,2]

As the time between the rupture of the membranes and the onset of labor increases, so may the risk of maternal and fetal infection. For this reason, many physicians recommend that labor be induced if the pregnancy is at term and labor does not begin spontaneously shortly after the membranes rupture.[3,4] Others believe that waiting for labor to begin spontaneously is preferable for mothers if there is no evidence of fetal or maternal compromise, since the risk of cesarean section may be lower.[5,6] There is limited information about which approach is better.[7,8]

For labor that is induced, the timing of the induction is controversial. Indeed, the decision to induce labor often depends more on the convenience of the physicians, nurses, or midwives than on the actual time that has elapsed after rupture of the membranes.[6] If labor is induced, the method of induction is usually by intravenous administration of oxytocin. More recently, prostaglandins, followed by an infusion of oxytocin if necessary, have been used. It is not known which is the better method.[9]

The Term Prelabor Rupture of the Membranes (TERMPROM) Study was undertaken to determine whether a practice of inducing labor in women with prelabor rupture of the membranes at term is preferable to a practice of waiting for labor to begin spontaneously if there is no evidence of fetal or maternal compromise (expectant management). In this study we compared these two approaches both when labor was induced with intravenous oxytocin and when labor was induced with vaginal prostaglandin E_2 gel, followed by

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*The participants in the Term Prelabor Rupture of the Membranes (TERMPROM) Study Group are listed in the Appendix.

oxytocin if necessary. The study was also designed to compare the two methods of inducing labor.

METHODS

The study was approved by the research-ethics committees at all the participating centers, and the women gave informed consent before being enrolled in the study.

Randomization was centrally controlled at the Perinatal Clinical Epidemiology Unit at Women's College Hospital in Toronto with the use of a computerized randomization program, accessible by means of a touch-tone telephone. To ensure that the four groups were comparable, randomization was done in blocks of four and eight and stratified according to center and parity.

Eligibility Criteria

Women were eligible for entry into the study if they had ruptured membranes, were at ≥37 weeks' gestation, and had a single fetus in a cephalic presentation. Rupture of the membranes was determined clinically and confirmed by positive litmus (Nitrazine) or ferning tests. If necessary, a vaginal examination was performed with a speculum to determine whether the membranes had ruptured. Digital vaginal examinations were avoided.

Women were excluded from the study if they were in active labor, if there had been a previous, failed attempt to induce labor, or if there was a contraindication to either induction of labor (such as placenta previa) or expectant management (such as meconium staining of the amniotic fluid or chorioamnionitis). Before entering the study, women were given a nonstress test and introital or vaginal swabs were taken for the culture of group B streptococcus.

Treatment Protocol

Women were randomly assigned to one of four groups. In two of the groups, labor was induced immediately, either with oxytocin (in the induction-with-oxytocin group) or prostaglandin E_2 gel (Prostin E_2 Vaginal Gel; in the induction-with-prostaglandin group). In the other two groups, women waited for labor to begin spontaneously unless there was evidence of fetal or maternal compromise, or until four days had elapsed, in which case labor was induced with either oxytocin or prostaglandin E_2 gel in the expectant-management (oxytocin) and the expectant-management (prostaglandin) groups, respectively.

For women assigned to the induction-with-oxytocin group, an infusion of oxytocin was initiated and the infusion rate was titrated to contractions, according to local hospital practice. For women assigned to the induction-with-prostaglandin group, 1 or 2 mg of prostaglandin E_2 gel was inserted into the posterior vaginal fornix. This application was repeated six hours later if labor had not started and was followed by an infusion of oxytocin four or more hours later if labor still had not started.

Women assigned to the expectant-management (oxytocin) group were either admitted to the hospital or cared for as outpatients. Women checked their temperatures twice daily and reported any fever, changes in the color or odor of the amniotic fluid, or other complications. Some women underwent additional monitoring tests. If complications developed or if labor had not started after four days, labor was induced with oxytocin as for women in the induction-with-oxytocin group. For women assigned to the expectant-management (prostaglandin) group, the approach was the same except that if labor was induced, the method used was the same as that used for women in the induction-with-prostaglandin group.

Decisions about other aspects of fetal and maternal care, including the use and timing of antibiotics and the mode of delivery, were made by the nurse, midwife, or attending physician. At delivery, cord-blood gases were measured and Apgar scores were determined. Babies of mothers in the study had blood samples taken for culture and white-cell counts performed within 24 hours of birth and before treatment with antibiotics. Other tests and treatments administered to the babies were determined by the attending physicians. After delivery, women evaluated their experiences by completing structured questionnaires to indicate what they liked and disliked about their care.

Table 1. Base-Line Characteristics of the Women in the Induction and Expectant-Management Groups.*

Characteristic	Induction/ Oxytocin (N = 1258)	Expectant/ Oxytocin (N = 1263)	Induction/ Prostaglandin (N = 1259)	Expectant/ Prostaglandin (N = 1261)
Maternal age (yr)	28.3±5.2	28.5±5.2	28.5±5.4	28.4±5.3
Gestational age (wk)	38.9±1.2	38.9±1.2	38.9±1.2	39.0±1.2
Interval from membrane rupture to delivery (hr)				
Median	5.1	5.2	5.5	5.3
5th and 95th percentiles	1.3, 29.5	1.3, 27.4	1.5, 27.8	1.3, 28.8
			percent	
Parity				
0	59.1	59.4	59.7	60.0
≥1	40.9	40.6	40.4	40.1
Ultrasound to confirm gestational age	93.6	92.9	92.6	93.4
Method of confirming rupture of membranes				
Litmus test alone	77.2	75.7	77.4	75.1
Ferning test alone	5.2	5.2	5.6	4.4
Litmus and ferning tests	17.7	19.2	16.9	20.5
Vaginal examination with a speculum				
None	35.8	34.4	33.0	35.1
Cervix unripe	49.4	50.8	54.0	52.2
Cervix ripe	14.6	14.5	12.8	12.4
Digital vaginal examination				
None	61.1	62.6	64.6	63.4
Cervix unripe	32.8	29.4	29.7	30.1
Cervix ripe	5.9	7.9	5.6	6.4
Group B streptococcus on vaginal or introital culture				
Present	9.6	11.8	10.6	9.1
Absent	85.6	83.8	86.0	87.1
Unknown	4.8	4.4	3.4	3.8
Previous cesarean delivery	3.8	3.8	3.3	3.1
Smoking during pregnancy	24.9	25.8	24.2	27.4

*Plus–minus values are means ±SD. For any comparison between groups, there was a small number of missing values. Because of this and rounding, percentages do not always total 100. "Cervix unripe" denotes a cervix that is dilated <3 cm and <80 percent effaced. "Cervix ripe" denotes a cervix that is dilated ≥3 cm or ≥80 percent effaced. The results of the culture for group B streptococcus were not known before delivery for most women.

Outcomes

The primary outcome was definite or probable neonatal infection. Definite neonatal infection was defined as the presence of clinical signs of infection and one or more of the following: a positive culture of blood, cerebrospinal fluid, urine, tracheal aspirate, or lung tissue; a positive Gram's stain of cerebrospinal fluid; a positive antigen-detection test with blood, cerebrospinal fluid, or urine; a chest radiograph compatible with pneumonia; or a histologic diagnosis of pneumonia. Probable neonatal infection was defined as the presence of clinical signs of infection and one or more of the following: a high or low blood neutrophil count, a high immature-to-total neutrophil ratio, a high actual immature neutrophil count,[10] or abnormal cerebrospinal fluid findings showing an elevated white-cell count, a high level of protein, or a low level of glucose.

An adjudication committee, unaware of the women's group assignments and of whether labor was induced or spontaneous, determined whether neonatal infection was present.

The secondary outcome was the need for cesarean section. Other outcomes involved other measures of maternal, fetal, and neonatal health and the women's evaluations of the care they received.

Statistical Analysis

The sample size was chosen to provide a power of 80 percent to detect a reduction of 50 percent or more, from ≥4 percent to

Table 2. Methods of Inducing Labor and Use of Oxytocin during Labor in the Induction and Expectant-Management Groups.*

Variable	Induction/ Oxytocin (N = 1258)	Expectant/ Oxytocin (N = 1263)	Induction/ Prostaglandin (N = 1259)	Expectant/ Prostaglandin (N = 1261)
			percent	
Method of induction				
Oxytocin only	88.4	20.3	1.2	5.3
Prostaglandin only	0.4	1.8	79.2	12.7
Prostaglandin and oxytocin	0.2	0.6	9.1	3.1
Other method	—	0.1	0.2	—
Not induced				
Spontaneous labor	10.7	77.0	10.2	78.5
No labor	0.2	0.2	0.2	0.4
Use of oxytocin in labor	91.9	49.9	43.1	43.8

*Because of rounding, percentages do not always total 100.

⩽2 percent, in the rate of neonatal infection in each treatment comparison.

The results were analyzed according to the intention to treat, and all the women who underwent randomization and for whom outcome data were available were included in the analysis. Because we anticipated the possibility of differences between the methods of induction,[9] we planned, a priori, three principal treatment comparisons among the four study groups: induction-with-oxytocin versus expectant-management (oxytocin), induction-with-prostaglandin versus expectant-management (prostaglandin), and induction-with-prostaglandin versus induction-with-oxytocin. Perinatal deaths were excluded from the analysis of measures of neonatal morbidity. One interim analysis was conducted after 2500 women were enrolled, comparing the study groups with respect to neonatal infection.

The groups were compared by means of contingency-table chi-square analyses for categorical and binary variables and by means of the Wilcoxon rank-sum test for continuous data that were not normally distributed.[11]

Two-sided P values are reported for all significance tests: a P value of less than 0.045, to account for the one interim analysis,[12] was considered to indicate statistical significance for differences in the rates of neonatal infection, and a P value of less than 0.05 for differences in the rates of cesarean section. To allow for the large number of multiple comparisons, a P value of less than 0.01 was considered to indicate statistical significance for differences in all other outcomes.[12]

Results

The study enrolled 5042 women between January 1, 1992, and May 31, 1995, at 72 hospitals in Canada, the United Kingdom, Australia, Israel, Sweden, and Denmark. Data were received for 5041 women, of whom 1263 were assigned to the expectant-management (oxytocin) group, 1258 to the induction-with-oxytocin group, 1259 to the induction-with-prostaglandin group, and 1261 to the expectant-management (prostaglandin) group. Base-line characteristics were similar in the four groups (Table 1).

Management of Pregnancy

Labor was induced in 1120 women (89.0 percent) in the induction-with-oxytocin group and 1129 women (89.7 percent) in the induction-with-prostaglandin group. Labor began spontaneously in 972 women (77.0 percent) in the expectant-management (oxytocin) group and 990 women (78.5 percent) in the expectant-management (prostaglandin) group. The methods of and primary reasons for induction and the use of oxytocin are shown in Tables 2 and 3.

For the 3333 women enrolled between January 15, 1994, and May 31, 1995, we collected information about whether the women stayed in the hospital or went home after randomization. More women in the induction groups than the expectant groups stayed in the hospital: induction-with-oxytocin group, 815 of 837 (97.4 percent); induction-with-prostaglandin group, 769 of 826 (93.1 percent); expectant-management (oxytocin) group, 516 of 834 (61.9 percent); and expectant-management (prostaglandin) group, 501 of 836 (59.9 percent).

Cesarean Section and Maternal Outcomes

The rate of cesarean section did not differ significantly between the induction-with-oxytocin and the expectant-management (oxytocin) groups (127 of 1258 [10.1 percent] vs. 123 of 1263 [9.7 percent]; odds ratio, 1.0; 95 percent confidence interval, 0.8 to 1.4), between the induction-with-prostaglandin and the expectant-management (prostaglandin) groups (121 of 1259 [9.6 percent] vs. 138 of 1261 [10.9 percent]; odds ratio, 0.9; 95 percent confidence interval, 0.7 to 1.1), or between the induction-with-prostaglandin and the induction-with-oxytocin groups (odds ratio, 1.0; 95 percent confidence interval, 0.7 to 1.2). The modes of delivery for women in the induction and expectant-management groups are shown in Table 4 according to parity.

Clinical chorioamnionitis was less likely to develop in the women in the induction-with-oxytocin group than in those in the expectant-management (oxytocin) group (50 of 1258 [4.0 percent] vs. 109 of 1263 [8.6 percent], $P<0.001$). Women in the induction-with-oxytocin group were less likely to receive antibiotics before or during labor than those in the expectant-management (oxytocin) group (94 of 1258 [7.5 percent] vs. 150 of 1263 [11.9 percent], $P<0.001$). Women in the induction-with-oxytocin group were less likely to have postpartum fever (temperatures >38°C) than those in the expectant-management (oxytocin) group (24 of 1258 [1.9 percent] vs. 46 of 1263 [3.6 percent], $P=0.008$) (Table 5).

Women in the induction-with-oxytocin group had fewer digital vaginal examinations, went into active labor sooner, had shorter labors, had a shorter interval between membrane rupture and delivery, and spent less time in the hospital before delivery than those in the expectant-management (oxytocin) or the induction-with-prostaglandin group (Table 5). Although women in the induction-with-prostaglandin group went into active labor sooner and had a shorter interval between membrane rupture and delivery than those in the expectant-man-

Table 3. Principal Reasons for Inducing Labor in the Expectant-Management Groups.*

Reason	Expectant/ Oxytocin (N = 1263)	Expectant/ Prostaglandin (N = 1261)
	percent	
Obstetrical complication	2.5	2.7
Chorioamnionitis	1.4	0.8
Rupture of membranes ⩾4 days previously	3.6	4.6
Request by patient	10.6	9.4
Request by physician	4.8	3.7
No induction	77.2	78.9

*Because of rounding, percentages do not always total 100.

agement (prostaglandin) group, they had more vaginal examinations (Table 5). Other maternal outcomes are shown in Table 5.

There were two cases of cord prolapse during labor, one in the induction-with-oxytocin group and one in the expectant-management (oxytocin) group. Both babies had Apgar scores ≥7 at one and five minutes. The frequency of other complications during labor, including vomiting or diarrhea, hypertonus, ruptured uterus, abruptio placentae, and shoulder dystocia, was low and did not differ significantly among the groups (data not shown).

Women's Evaluations of Treatment

Fewer women in the induction-with-oxytocin group indicated that there was nothing they liked about their treatment than in the expectant-management (oxytocin) group (74 of 1258 [5.9 percent] vs. 173 of 1263 [13.7 percent], P<0.001). Similarly, fewer women in the induction-with-prostaglandin group indicated that there was nothing they liked about their treatment than in the expectant-management (prostaglandin) group (64 of 1259 [5.1 percent] vs. 147 of 1261 [11.7 percent], P<0.001). When asked, "If you had to do it all over again, would you participate in the study?" more women said "yes" in the induction-with-oxytocin group than in the expectant-management (oxytocin) group (847 of 1258 [67.3 percent] vs. 756 of 1263 [59.9 percent], P<0.001). Similarly, more women said "yes" to this question in the induction-with-prostaglandin group than in the expectant-management (prostaglandin) group (837 of 1259 [66.5 percent] vs. 746 of 1261 [59.2 percent], P<0.001). Responses to the other questions either did not differ significantly among the groups or favored the induction groups (data not shown). There were no significant differences in women's evaluations of treatment between the two induction groups.

Table 5. Maternal Outcomes in the Induction and Expectant-Management Groups.

Outcome	Induction/Oxytocin (N = 1258)	Expectant/Oxytocin (N = 1263)	Induction/Prostaglandin (N = 1259)	Expectant/Prostaglandin (N = 1261)
	number (percent)			
Internal monitoring of fetal heart rate	434 (34.5)	360 (28.5)*	379 (30.1)	368 (29.2)
Fetal distress	130 (10.3)	143 (11.3)	117 (9.3)	126 (10.0)
Meconium-stained amniotic fluid	86 (6.8)	107 (8.5)	101 (8.0)	97 (7.7)
Clinical chorioamnionitis†				
Fever before labor	1 (0.1)	16 (1.3)‡	3 (0.2)	13 (1.0)
Fever during labor	46 (3.7)	93 (7.4)‡	70 (5.6)	84 (6.7)
Other signs of chorioamnionitis	8 (0.6)	28 (2.2)*	9 (0.7)	22 (1.7)
Any sign of chorioamnionitis	50 (4.0)	109 (8.6)‡	78 (6.2)	99 (7.8)
Antibiotics before or during labor	94 (7.5)	150 (11.9)‡	113 (9.0)	146 (11.6)
Postpartum fever†	24 (1.9)	46 (3.6)§	39 (3.1)	38 (3.0)
Analgesia	509 (40.5)	515 (40.8)	581 (46.1)¶	538 (42.7)
No anesthesia or analgesia‖	121 (9.6)	164 (13.0)§	131 (10.4)	162 (12.8)
No. of digital vaginal examinations				
<4	638 (50.7)	560 (44.3)**	470 (37.3)††	558 (44.3)‡‡
4–8	571 (45.4)	636 (50.4)	719 (57.1)	641 (50.8)
>8	49 (3.9)	65 (5.1)	70 (5.6)	61 (4.8)
Unknown	—	2 (0.2)	—	1 (0.1)
	median hours (5th, 95th percentiles)			
Time to active labor	5.0 (1.5, 20.0)	17.3 (2.3, 74.3)‡	8.5 (1.5, 28.0)††	16.0 (2.4, 76.4)§§
Duration of active labor	4.5 (1.0, 12.9)	5.9 (1.2, 16.5)‡	5.3 (1.1, 15.7)††	5.8 (1.1, 17.2)
Interval from membrane rupture to delivery	17.2 (7.7, 47.1)	33.3 (10.3, 94.4)‡	23.0 (8.6, 54.1)††	32.6 (9.9, 106.5)§§
Time in hospital before delivery	12.0 (4.6, 32.1)	16.5 (2.9, 66.8)‡	17.0 (4.8, 38.9)††	16.9 (2.0, 69.7)

*P = 0.001 for the comparison between the induction-with-oxytocin and the expectant-management (oxytocin) groups.

†Fever before or during labor was defined as a temperature >37.5°C on two occasions ≥1 hour apart or a temperature of >38°C. Other signs of chorioamnionitis were a maternal white-cell count >20,000 per cubic millimeter or foul-smelling amniotic fluid. Postpartum fever was defined as a temperature >38°C.

‡P<0.001 for the comparison between the induction-with-oxytocin and the expectant-management (oxytocin) groups.

§P = 0.008 for the comparison between the induction-with-oxytocin and the expectant-management (oxytocin) groups.

¶P = 0.004 for the comparison between the induction-with-oxytocin and the induction-with-prostaglandin groups.

‖This category did not exclude the use of local anesthesia.

**P = 0.004 for the comparison between the induction-with-oxytocin and the expectant-management (oxytocin) groups.

††P<0.001 for the comparison between the induction-with-oxytocin and the induction-with-prostaglandin groups.

‡‡P = 0.002 for the comparison between the induction-with-prostaglandin and the expectant-management (prostaglandin) groups.

§§P<0.001 for the comparison between the induction-with-prostaglandin and the expectant-management (prostaglandin) groups.

Table 4. Modes of Delivery for Women in the Induction and Expectant-Management Groups, According to Parity.*

Parity and Mode of Delivery	Induction/Oxytocin	Expectant/Oxytocin	Induction/Prostaglandin	Expectant/Prostaglandin
	number (percent)			
Parity, 0				
Cesarean section	105 (14.1)	103 (13.7)	103 (13.7)	115 (15.2)
Operative vaginal delivery	186 (25.0)	212 (28.3)	191 (25.4)	196 (25.9)
Spontaneous vaginal delivery	452 (60.8)	435 (58.0)	457 (60.8)	445 (58.9)
Total	743	750	751	756
Parity, ≥1				
Cesarean section	22 (4.3)	20 (3.9)	18 (3.5)	23 (4.6)
Operative vaginal delivery	47 (9.1)	44 (8.6)	37 (7.3)	30 (5.9)
Spontaneous vaginal delivery	446 (86.6)	449 (87.5)	453 (89.2)	452 (89.5)
Total	515	513	508	505

*Because of rounding, percentages do not always total 100.

Perinatal Mortality

Five babies died of lethal congenital anomalies. Four other babies died — two in the expectant-management (oxytocin) group and two in the expectant-management (prostaglandin) group. The differences between groups in perinatal mortality were not statistically significant. One death, a stillbirth, occurred at 41 weeks' gestation after 14 hours of expectant management in the hospital. Labor was induced after the fetal heart

tones disappeared. The cause of death was asphyxia. The other stillbirth occurred at 38 weeks' gestation after 19 hours of expectant management in the hospital. The fetal heart tones disappeared shortly before the spontaneous onset of labor. Although there were no signs of clinical chorioamnionitis, death was due to group B streptococcal sepsis. One neonatal death, which occurred at 37 weeks' gestation, followed 3 days of expectant management at home. Labor was induced electively. After the cervix had dilated to 7 cm, a difficult cesarean section, which included the use of forceps, was undertaken for fetal distress. The cause of death was birth trauma. The other neonatal death occurred at 40 weeks' gestation. The mother began labor spontaneously after 28 hours of expectant management at home. A cesarean section was undertaken for fetal distress after labor had progressed for five hours in the hospital and the cervix had dilated to 8 cm. The baby died of asphyxia.

Table 6. Neonatal Morbidity in the Induction and Expectant-Management Groups.*

Measure	Induction/Oxytocin (N = 1256)	Expectant/Oxytocin (N = 1259)	Induction/Prostaglandin (N = 1258)	Expectant/Prostaglandin (N = 1259)
	number (percent)			
Apgar score <7 at 1 min	164 (13.1)	166 (13.2)	158 (12.6)	173 (13.7)
Apgar score <7 at 5 min	13 (1.0)	16 (1.3)	25 (2.0)	15 (1.2)
Cord-blood pH <7.10†	28 (2.2)	29 (2.3)	17 (1.4)	24 (1.9)
Resuscitation with oxygen	274 (21.8)	287 (22.8)	253 (20.1)	260 (20.6)
Jitteriness or irritability	20 (1.6)	31 (2.5)	22 (1.7)	17 (1.4)
Seizures	3 (0.2)	5 (0.4)	1 (0.1)	2 (0.2)
Hypotonia	22 (1.8)	22 (1.7)	21 (1.7)	21 (1.7)
Abnormal level of consciousness	3 (0.2)	4 (0.3)	4 (0.3)	3 (0.2)
Apnea	5 (0.4)	3 (0.2)	3 (0.2)	2 (0.2)
Abnormal feeding at ≥48 hr of age	10 (0.8)	17 (1.4)	14 (1.1)	10 (0.8)
Ventilation after initial resuscitation	7 (0.6)	7 (0.6)	13 (1.0)	7 (0.6)
Antibiotics	94 (7.5)	172 (13.7)‡	137 (10.9)§	154 (12.2)
Stay in neonatal intensive care unit >24 hr	83 (6.6)	146 (11.6)‡	116 (9.2)	128 (10.2)

*Group totals exclude perinatal deaths.

†Cord-blood gases were analyzed for most babies: 72.7 percent in the induction-with-oxytocin group, 71.2 percent in the expectant-management (oxytocin) group, 73.1 percent in the induction-with-prostaglandin group, and 72.4 percent in the expectant-management (prostaglandin) group. The pH of the arterial cord blood is given unless it was not known, in which case the pH of the venous cord blood is given.

‡P<0.001 for the comparison between the induction-with-oxytocin and the expectant-management (oxytocin) groups.

§P = 0.003 for the comparison between the induction-with-oxytocin and the induction-with-prostaglandin groups.

Neonatal Infection

Blood samples were taken for culture and white-cell counts from more than 80 percent of the babies in the four groups. The frequency of neonatal infection did not differ significantly between the induction-with-oxytocin and the expectant-management (oxytocin) groups (25 of 1258 [2.0 percent] vs. 36 of 1263 [2.8 percent]; odds ratio, 0.7; 95 percent confidence interval, 0.4 to 1.2), between the induction-with-prostaglandin and the expectant-management (prostaglandin) groups (38 of 1259 [3.0 percent] vs. 34 of 1261 [2.7 percent]; odds ratio, 1.1; 95 percent confidence interval, 0.7 to 1.8), or between the induction-with-prostaglandin and the induction-with-oxytocin groups (odds ratio, 1.5; 95 percent confidence interval, 0.9 to 2.6).

Neonatal Morbidity

Babies in the induction-with-oxytocin group were less likely to receive antibiotics than those in either the expectant-management (oxytocin) or the induction-with-prostaglandin group (Table 6). Babies in the induction-with-oxytocin group were less likely to stay in an intensive care nursery for more than 24 hours than those babies in the expectant-management (oxytocin) group (Table 6). There were no other significant differences in measures of neonatal morbidity between groups (Table 6).

Discussion

One hundred thirty-three babies born to the women in this study had infection, a rate of 2.6 percent. For those with infection, the mortality rate was less than 1 percent. Neonatal infection did not occur more frequently when rupture of the fetal membranes was managed with a practice of expectant management than when it was managed with a practice of induction of labor. With the care provided to women and their babies in this study, the risk of neonatal infection and its sequelae was low and not influenced by the treatment practices we compared. There was thus no clear advantage to the baby of one practice over another. These results differ from those of other randomized controlled trials that have indicated a lower risk of neonatal infection if labor is induced shortly after membranes rupture.[3,4,13] Previous studies, however, have not taken care to avoid or minimize bias in the search for and determination of neonatal infection. Our study was specifically designed to avoid such bias. A similar number of babies in all groups had blood samples taken for culture and white-cell counts, and the data collected on babies with signs of infection were reviewed by a committee blinded to group assignments and to whether labor was induced or spontaneous, in order to determine whether infection was present. The results of this study are thus more likely to be accurate.

Four normally formed babies in the expectant-management groups and none in the induction groups died. It is possible that expectant management may have contributed to one or more of these deaths. Maternal colonization with group B streptococcus and intrapartum management may also have been contributing factors. If the deaths in the expectant-management groups are combined and compared with those in the induction groups, the differences are not statistically significant and thus may be due to chance (4 of 2524 vs. 0 of 2517, P = 0.125 by Fisher's exact test). A much larger trial than this one (7200 women per group) would be required to detect a reduction in perinatal mortality from 0.16 percent with expectant management to 0.01 percent with induction of labor.

We found no differences among the study groups in

the rates of cesarean section. This finding also contrasts with those of earlier studies.[6,14-17] The centrally controlled approach to randomization (chosen to avoid selection bias), the strict adherence to the treatment protocols in the various treatment groups, and the large number of women evaluated in this study support the conclusion that induction of labor with either intravenous oxytocin or vaginal prostaglandin E_2 gel does not increase the risk of cesarean section, as compared with a practice of expectant management. Women at term with prelabor rupture of the membranes should therefore be reassured that induction of labor is a reasonable option should they prefer this approach.

Other outcomes assessed in this study favored induction of labor with intravenous oxytocin. The differences we found in the use of antibiotics and the frequency of stays in the neonatal intensive care unit may have been influenced by the care givers' greater concern about infection in women whose membranes were ruptured for longer periods. It is less likely that this factor influenced the detection of clinical chorioamnionitis and postpartum fever, since maternal temperatures were usually assessed according to established routines that did not depend on the duration of membrane rupture.

In conclusion, induction of labor with intravenous oxytocin, induction of labor with vaginal prostaglandin E_2 gel, and expectant management are all reasonable options for women and their babies if membranes rupture before the start of labor at term, since they result in similar rates of neonatal infection and cesarean section. Induction of labor with intravenous oxytocin results in a lower risk of maternal infection than expectant management. Women view induction of labor more positively than expectant management.

APPENDIX

The participants in the TERMPROM Study Group were as follows (for each country, groups are listed in order of the number of women recruited): *Canada* — R. Liston, E. Snelgrove-Clark, K. Rinaldo, P. Jones-Wright (Halifax, N.S.); F. Kyne Woronchak, D. Farquharson, J. Yandel, R. Maclean (Vancouver, B.C.); G. Tawagi, J. Belcher (Ottawa, Ont.); A. Joshi, A. Alcock (Montreal); G. Carson, S. Johnson, D. Overend (Regina, Sask.); D. Lamont, S. Burlock, J. Gardner (Hamilton, Ont.); B. Thomas, J. Downes, L. Peloso (Toronto); D. Farine, J. Telford, C. Pierce (Toronto); M. Sermer, M. Bailey, J. Hillier (Toronto); D. Still, D. Schimeck (Edmonton, Alta.); N. Demianczuk, N. Okun, M. Evans (Edmonton, Alta.); J. Wilkinson, S. Neelands, J. Lowe (Mississauga, Ont.); W. Fraser, J. Flamand, G. Quesnel (Quebec, Que.); F. Morcos, L. Gillespie (Edmonton, Alta.); H. Streeter, G. Hallam, K. Stafford (Victoria, B.C.); R. Turnell, S. Kuling (Saskatoon, Sask.); M. Helewa, S. Fogg (Winnipeg, Man.); P. Beresford, J. Blake (Vancouver, B.C.); S. Scott, B. Ingelson, I. deBruyn (Calgary, Alta.); N. Kainth, L. Ross, S. Fruitman (Scarborough, Ont.); V. Frinton, M. Garrey, M. Jones (Vancouver, B.C.); P. Mohide, G. Hackett-White (Hamilton, Ont.); C. Nimrod, C. Baker (Ottawa, Ont.); S. Wood, J. Currie (Calgary, Alta.); G. Waddell, D. Beaulieu (Sherbrooke, Que.); M. Beatty, D. Brownlee (Oshawa, Ont.); B. Jackson, H. Davis (Toronto); L. Woolford, J. Jackson (Oakville, Ont.); R. Johnston, G. Tinney (Orillia, Ont.); P. Scheufler, K. Jenereaux (Mississauga, Ont.); E. Mocarski (North York, Ont.); L. Hanson (Saskatoon, Sask.); *United Kingdom* — S. Walkinshaw, T. Lavender, S. Rixon (Liverpool); P. Braude, E. Versi, I. Nelson-Ashley, C. Brosnan (London); S. Greenaway, S. Patient (Ipswich); D. McGinlay, A. Cameron, T. Turner (Glasgow); E. Payne, L. Patel, N. Hughes (Birmingham); M. Dooley, J. Hollands (Dorchester); G. Mires, P. Howie, M. MacLeod (Dundee); P. Davies, K. Jones, M. Lobb (Luton); P. Knott, V. Larmond, A. Diffang (Lewisham); J. Haley, S. Jones (Bradford); J. Rymer, K. Mah, J. Rissik (London); M. MacKenzie, I. Greer (Glasgow); A. Moss, J. Scott, D. Shortland (Poole); J. Price, N. Rennison (Uxbridge); S. Bjornsson, J. Johnstone (Glasgow); W. Reid, A. McSkeane (Carlisle); L. Ross, G. Marshall, A. Miller (Carshalton); G. Lang, A. Hourston (Aberdeen); H. Gee, S. Pritchard (Birmingham); J. Walker, J. Gavin (Leeds); M. Austen, A. Warner Smith (Welwyn Garden City); O. Chappatte, H. Thomas (Tunbridge Wells); *Australia* — V. Flenady, J. King, P. Steer (Brisbane); P. Colditz, S. Bloxsom, J. Wilson (Brisbane); R. Watson, K. Tipper, A. Logan (Elizabeth Vale); M. Grehan, P. Davis, S. Brennecke (Carlton); M. Brinsmead, R. Glover, M. Rowley (Newcastle); D. Healy, C. Tippett, N. Taylor (Clayton); C. Crowther, A. Thomas, S. Barton (Adelaide); *Israel* — M. Fejgin, D. Rosen, J. Zausmer (Kfar-Saba); E. Shalev, D. Peleg, J. Hashin (Afula); B. Chayen, L. Harel (Bney Brak); G. Ohel, S. Panski, E. Leshem (Tiberias); Y. Avoulafia, B. Abramov, H. Deevon (Jerusalem); S. Friedman, B. Kaplan (Petah-Tikva); A. Samueloff (Jerusalem); *Sweden* — P. Holmgren, S. Engberg (Umeå); A. Josefsson, G. Berg, A. Johannesson (Linköping); *Denmark* — K. Skajaa, P. Schiøler-Linck, K. Oustrup (Aarhus); B. Bødker, D. Kongsgaard (Glostrup).

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