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Economic analysis comparing induction of labor and expectant management in women with preterm prelabor rupture of membranes between 34 and 37 weeks (PPROMEXIL trial)

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Key words
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Conflict of interest
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Abstract

Objective. To compare the costs of induction of labor and expectant management in women with preterm prelabor rupture of membranes (PPROM). *Design.* Economic analysis based on a randomized clinical trial. *Setting.* Obstetric departments of eight academic and 52 non-academic hospitals in the Netherlands. *Population.* Women with PPROM near term who were not in labor 24 h after PPROM. *Methods.* A cost-minimization analysis was done from a health care provider perspective, using a bottom-up approach to estimate resource utilization, valued with unit-costs reflecting actual costs. *Main outcome measures.* Primary health outcome was the incidence of neonatal sepsis. Direct medical costs were estimated from start of randomization to hospital discharge of mother and child. *Results.* Induction of labor did not significantly reduce the probability of neonatal sepsis [2.6% vs. 4.1%, relative risk 0.64 (95% confidence interval 0.25–1.6)]. Mean costs per woman were €8094 for induction and €7340 for expectant management (difference €754; 95% confidence interval −335 to 1802). This difference predominantly originated in the postpartum period, where the mean costs were €5669 for induction vs. €4801 for expectant management. Delivery costs were higher in women allocated to induction than in women allocated to expectant management (€1777 vs. €1153 per woman). Antepartum costs in the expectant management group were higher because of longer antepartum maternal stays in hospital. *Conclusions.* In women with pregnancies complicated by PPROM near term, induction of labor does not reduce neonatal sepsis, whereas costs associated with this strategy are probably higher.

Abbreviations: EM, expectant management; IoL, induction of labor; PPROM-EXIL, Preterm Prelabour Rupture Of the Membranes Expectant management or Induction of Labor study; PPROM, preterm prelabor rupture of membranes; RR, relative risk.

Introduction

The estimated incidence of preterm prelabor rupture of the membranes (PPROM) between 34 and 37 weeks of gestation is 1.5%, which corresponds to about 3000 pregnancies per year in the Netherlands. PPROM is an important clinical problem, and a dilemma for both patient and gynecologist. While awaiting spontaneous labor PPROM may lead to an increase in infectious disease for both mother and child and to stillbirth; induction of labor (IoL) may lead to preterm birth with an increase in neonatal morbidity (such as respiratory distress syndrome) and a possible rise in the number of instrumental deliveries (1).

Guidelines concerning this clinical dilemma are not straightforward. The American Congress of Obstetricians and Gynecologists guideline recommends IoL if PPROM occurs at or beyond 34 weeks of gestation (2). The British Royal College of Obstetricians and Gynaecologists guideline states that delivery should be considered at 34 weeks of gestation (3). The Dutch Society of Obstetrics and Gynecology (NVOG) guideline advised, until the results of our trial were known, expected management until 35 gestational weeks (if there were no maternal or fetal indications for immediate delivery), whereas labor could be induced from 35 weeks onwards, and IoL has been advocated beyond 37 weeks of gestational age (4).

In view of this lack of consensus on the management of women with PPROM between 34 and 37 weeks, we recently performed a randomized clinical trial on the subject, called the Preterm Prelabour Rupture Of the Membranes Expectant management or Induction of Labour study (PPROMEXIL) (5). At present, information on the costs and cost-effectiveness of IoL and expectant management (EM) in women with PPROM between 34 and 37 weeks of gestation is lacking. A cost-minimization analysis was performed alongside the PPROMEXIL trial, comparing the costs generated by IoL with the costs of EM in pregnancies complicated by PPROM.

Material and methods

Full details of the PPROMEXIL trial were reported previously (5). This study has been approved by the ethics committee of the University Hospital Maastricht (ref. no. MEC 05-240). The trial is registered in the controlled trial register under number: IS-RCTN29313500. Briefly, the study was a multicenter, parallel, open-labeled randomized controlled trial in the Netherlands, in which 60 of 90 hospitals (eight academic and 52 non-academic) in the Netherlands participated. Women with a singleton or twin pregnancy presenting with PPROM between 34^{+0} and 36^{+6} weeks of gestation who had not delivered within 24 h after rupture of membranes were allocated to either IoL (n = 266) or EM (n = 266).

Induction of labor or elective cesarean section was planned within 24 h after randomization. The method of induction was according to local policy. Women randomized for EM were also treated according to local policy. This was in either an outpatient or inpatient setting. If a patient in this group reached 37^{+0} weeks of gestation age, IoL was performed according to local policy.

The primary outcome measure used in the clinical trial was proven or suspected neonatal sepsis, defined as a positive blood or amniotic fluid culture or a combination of clinical symptoms (apnea, temperature instability, lethargy, feeding intolerance, respiratory distress, hemodynamic instability, positive surface culture or rise in C-reactive protein >20 mg/L) in combination with antibiotic treatment during admission (6–8). A power analysis was performed for this primary outcome measure. This required 260 women per treatment arm to statistically demonstrate a 66% risk reduction with 80% power and a 5% type one error probability. We assumed that this sample size also provided sufficient power for the cost analysis.

Between 1 May 2007 and 9 September 2009, a total of 776 women were asked to participate in the PPROMEXIL trial, of whom 536 women (69%) gave informed consent. Four had to be excluded after randomization, due to violation of protocol. We allocated 266 women to IoL and 266 to EM. Of the remaining 240 women, 13 (5.4%) did not give informed consent because they preferred IoL,

Key Message

For women with PPROM near term, induction of labor is equally effective as expectant management in terms of neonatal sepsis, but probably generates more short-term medical costs.

194 (81%) women preferred EM and 33 (13.8%) did not want to participate in this study at all (6). This study found that in pregnancies complicated by PPROM between 34 and 37 weeks of gestation, IoL did not reduce the incidence of neonatal sepsis [relative risk (RR) 0.64 (95% confidence interval, CI 0.25–1.6)] but increased the risk of hypoglycemia [RR 2.2 (95% CI 1.4–3.5)] and hyperbilirubinemia [RR 1.5 (95% CI 1.1–1.9)] (9).

Economic evaluation

Economic evaluations investigate the economic impact of interventions in health care, often as a comparative analysis of alternative courses of action in terms of both their costs and consequences. Therefore, the basic tasks of any economic evaluation are to identify, measure, value, and compare the costs and consequences of the alternatives being considered (10). Full economic evaluations (the evaluation that concerns the comparison of both costs and effects) can be divided into four types of analysis depending on how the difference in effectiveness is presented: cost-effectiveness analysis (costs per clinical outcome measure or per life year gained), cost-utility analysis (costs per quality-adjusted life years), cost-benefit analysis (both costs and effects are expressed in monetary values) and cost-minimization analysis. A cost-minimization analysis is used when both interventions are equivalent in terms of health outcomes and only costs have to be considered (10). Because no significant difference was found on primary outcome in the PPROMEXIL trial, our study solely reports on costs. We used a health care provider perspective, in which direct medical costs are included (10). We differentiated between three phases of the clinical process in which costs were generated: antepartum costs (between randomization and onset of labor), delivery costs, and postpartum costs (between childbirth and hospital discharge). In economic evaluations when cost and/or effect are incurred at substantially different times, we need to adjust for time preference (discounting). Discounting refers to our differential valuation of a good or service, depending on when the good or service is consumed (11). Discounting is only necessary in economic evaluations with a time horizon of over 1 year. Therefore no discounting was applied in this study because all costs occurred within 1 year.

Costs were calculated as the product of resource use and unit costs. Resource use during the study period was documented in Case Report Forms. The following resource items were collected: maternal and neonatal admissions, method of delivery, type of induction, outpatient visits, medication, maternal laboratory tests, neonatal monitoring. Maternal admissions were differentiated into three levels of care (intensive, medium, ward). Neonatal admissions were divided into four levels of care (intensive, high, medium, ward). Ward admissions of newborns were not calculated, as such additional costs were assumed to be already incorporated in costs of maternal ward admissions. Use of the labor room was calculated as hours between admission to labor room and birth plus 1 h extra for extended recovery care. As IoL takes place inside the labor room, we expected that use of the labor room would be higher in the induction group due to the time needed for induction. Where a cesarean section was performed, use of the operating room (in hours) was estimated as well.

Unit cost estimates were based on several sources: top-down calculations provided by the financial departments in one participating academic and one participating general hospital [for maternal and neonatal admissions to ward, medical care, obstetric high care (N)ICU and neonatal monitoring]; bottom-up calculation (1 h use of the labor room and operating theatre); Dutch standardized prices (visits to primary health care providers and outpatient visits) (12), and market prices (medication) (13). In Table 1, unit costs together with valuation methods and sources are presented. All unit costs were expressed in €2009 using the consumer pricing index (14). Top-down unit costs associated with vaginal delivery did not take into account differences in use of the labor room. Therefore we also estimated unit costs associated with 1 h of labor room use and incorporated this differentiation in the analyses. Where a cesarean section was performed, hours in the operating room were estimated as well.

Data analysis

Group differences in volumes of resource use were tested using the non-parametric Mann–Whitney test because these volumes are never normally distributed. Resource use per patient was multiplied by unit costs, and total costs per patient were estimated. Mean and median total costs per woman were estimated, and differences in total costs between study groups were tested using the non-parametric Mann–Whitney test. The 95% CI around the differences in mean (sub) total costs were determined by bootstrapping. The following subgroup analyses were performed to find out the robustness of the findings: (i) gestational age at randomization (three subgroups AD 34^{+0}–34^{+6} weeks, AD 35^{+0}–35^{+6} weeks and AD 36^{+0}–36^{+6} weeks); (ii) maternal age at randomization (<21 years, 21–30 years, 31–40 years, >40 years); (iii) nulliparous or multiparous; (iv) maternal ethnic origin (Caucasian or other ethnic origin); (v) educational level of mother (low = primary or secondary school or lower professional school, medium = medium professional school, high = higher professional school or university); and (vi) maternal smoking. Statistical, economic and simulation analyses were performed

Table 1. Cost-analyses: units of resource use, unit costs and valuation.

Medical costs	Unit	Unit cost[a] (€)	Valuation method (source)
Admission mother[b]			
Hospital stay – ward	Day	359	Top-down calculation
Hospital stay – medium care	Day	546	Top-down calculation
Hospital-stay – intensive care	Day	1742	Top-down calculation
Admission child[b]			
Hospital stay – medium care	Day	546	Top-down calculation
Hospital stay – high care	Day	1462	Top-down calculation
Hospital-stay – NICU	Day	1514	Top-down calculation
Specialist care	Hour	72	Dutch costing guidelines
Outpatient visit[b]	Visit	85	Top-down calculation
Midwife	Hour	35	Dutch costing guidelines
General practitioner	Visit	22	Dutch costing guidelines
Paramedical	Visit	25	Dutch costing guidelines
Home care	Hour	33	Dutch costing guidelines
Induction methods[c]	Gift	16	Pharmacotherapeutic website
Medication[c]	Dose per day	7	Pharmacotherapeutic website
Analgesics during labor[c]	Procedure	167	Top-down calculation
Neonatal monitoring[c]	Procedure	39	Top-down calculation
Operation room[b]	Hour	145	Bottom-up calculation
Labor room[b]	Hour	84	Bottom-up calculation
Laboratory test	Procedure	2	Tariff

NICU, neonatal intensive care unit.
[a]Depreciation and overhead costs are integrated in the unit costs of admission, outpatient visit and labor/operation room costs.
[b]Mean of the unit cost for an academic hospital and for a general hospital.
[c]Mean of several methods/medications.

using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA) and EXCEL (Microsoft, Redmond, WA, USA).

Results

For 528 women, sufficient data were available to be included in the economic analysis. Average volumes of resource utilization and total costs as well as average costs per woman for each study group are presented in Table 2. In the antepartum phase, women in the EM group were found to have longer hospital stays for maternal ward care (IoL: 2.5 days vs. EM: 5.0 days, $p < 0.05$) and more scheduled outpatient visits (IoL: 1.8 visits vs. EM: 4.9 visits, $p < 0.05$). During delivery, differences were seen in mean number of hours in the labor room for spontaneous deliveries (IoL: 14.8 h vs. EM: 6.9 h, $p < 0.05$) and in mean numbers of hours in the labor room and operation theater for cesarean sections (IoL: 27.6 h vs. EM: 18.3 h, $p < 0.05$). Furthermore, in the IoL-group more children were admitted to medium care (64% vs. 54%) for a longer time period (IoL: 10.2 days vs. EM: 8.9 days, $p < 0.05$).

A summary of the mean and median total costs per woman is provided in Table 3. In the antepartum period, total costs per woman appeared to be higher in the EM group, mainly due to longer duration of maternal admissions (difference: −€738; 95% CI: −967 to −535). On the other hand, in the IoL group women appeared to generate more costs during delivery than women in the expectant group (difference: €624; 95% CI: 261–1006) due to a longer duration in the labor room because of IoL. Until 6 weeks postpartum, women in the IoL group again generated higher costs than those in the EM group (difference: €868; 95% CI: −41 to 1929), mainly because of more neonatal medium care admissions of longer duration. Overall, mean costs per patient were €8094 (95% CI: €1083–25 932) for IoL and €7340 (95% CI: €627–30 874) in the EM group (difference €754: 95% CI: −335 to 1802).

The results of the subgroup analysis dividing the patients in three groups according to gestational age at randomization are presented in Table 4. As can be seen from this table the differences in total costs per woman are almost zero for women between 36 and 37 weeks of pregnancy (−€45). On the other hand, IoL generates much greater costs in women with gestational age between 35 and 36 weeks (€3417). Although patients with gestational age between 34 and 35 weeks generate more mean costs per person, the difference between IoL and EM is comparable with the total group difference (€795 vs. €754). In several other subgroup analyses we examined the impact of several demographic characteristics on the final results. From those results it can be seen that in all examined subgroups, IoL generated more per patient costs than expectant monitoring did. There was one exception, in the age groups above 30 years, where expectant monitoring became the more expensive strategy.

Discussion

In this study, we report that in women whose pregnancy is complicated by PPROM between 34 and 37 weeks of gestational age, EM generated fewer costs than IoL,

Table 2. Resource use, mean costs per woman and total costs, medical care (€2009).

		Induction of labor (n = 266)				Expectant management (n = 262)				
	Unit	% women using care	Mean volume[a]	Total costs	Mean costs per patient	% women using care	Mean volume[a]	Total costs	Mean costs per patient	p-value volume difference
Maternal admission MC	Days	3	2.7	5850	30	4	8.6	21 060	108	0.67
Maternal admission ward	Days	75	2.5	116 805	599	75	5.0	234 195	1201	*<0.05*
Home care	Days	2	5.5	585	3	8	6.9	3510	18	0.37
Scheduled outpatient visits	Visit	9	1.8	2145	11	16	4.9	9945	51	*<0.05*
Unscheduled outpatient visits	Visit	2	2.0	585	3	5	1.5	975	5	*<0.05*
Laboratory tests mother	Test	53	1.5	390	2	64	2.1	585	3	*<0.05*
Total antepartum				*208 008*	*648*			*455 994*	*1386*	
Admission because of labor	Day	53	1.4	68 362	257	58	1.4	70 740	270	0.56
Induction PGE gel	Gift	27	2.0	10 906	41	11	1.7	3144	12	0.16
Induction PGE tablets	Gift	9	3.2	1064	4	3	2.1	262	1	0.36
Medication during labor[b]	Unit	46	–	23 408	88	36	–	18 078	69	NA
Spontaneous route of delivery	Hours	80	14.8	261 478	983	78	6.9	117 114	447	*<0.05*
Instrumental delivery	Hours	7	16.3	26 068	98	9	19.3	37 466	143	0.20
Cesarean delivery	Hours	13	27.6	80 066	301	13	18.3	54 234	207	*<0.05*
Episiotomy	Procedure	27	–	1330	5	22	–	1048	4	NA
Total delivery				*570 417*	*1777*			*379 337*	*1153*	
Maternal admission IC	Days	1	2.0	5320	20	0	0	0	0	NA
Maternal admission MC	Days	0	0	0	0	1	3.0	1834	7	NA
Maternal admission ward	Days	89	4.4	329 308	1238	90	4.3	323 570	1235	0.26
Maternal homecare	Days	1	3.5	266	1	2	2.3	262	1	0.81
Neonatal admission IC	Days	9	6.3	212 534	799	6	9.8	237 110	905	0.14
Neonatal admission HC	Days	7	8.6	221 844	834	6	8.3	183 662	701	0.90
Neonatal admission MC	Days	64	10.2	735 756	2766	54	8.9	508 542	1941	*<0.05*
Laboratory tests child	Test	79	1.6	798	3	70	1.6	524	2	0.12
Neonatal monitoring	Procedure	15	1.5	2128	8	13	1.8	2358	9	0.95
Total postpartum				*1 507 954*	*5669*			*1 257 862*	*4801*	
Total costs				*2 598 174*	8094			*2 414 860*	7340	

IC, intensive care; MC, medium care; HC, high care.

[a]Of women using care.

[b]Medication costs are a summation of several medications, therefore no unit and mean volumes are given and no group difference test was performed.

Table 3. Comparison of costs between induction of labour and expectant management.

	Induction (n = 266)		Expectant management (n = 262)		
	Mean	Median (IQR)	Mean	Median (IQR)	Difference in mean cost[a]
Maternal admission and home-care	632	435 (161–720)	1327	739 (345–1561)	−695
Outpatient visits	14	0 (0–0)	56	0 (0–0)	−42
Laboratory tests	2	2 (0–2)	3	2 (0–2)	−1
Total antepartum	*648*	*448 (174–721)*	*1386*	*756 (412–1602)*	*−738*
Admission because of labor	257	298 (0–325)	270	298 (0–325)	−13
Induction material	45	0 (0–94)	13	0 (0–0)	32
Medication during labor	88	32 (0–167)	69	32 (0–167)	19
Mode of delivery	1387	747 (415–1 245)	801	415 (168–814)	586
Total delivery	*1 777*	*1063 (630–1751)*	*1 153*	*750 (458–1227)*	*624*
Maternal admission and home-care	1259	1192 (596–1 680)	1243	1192 (840–1680)	16
Neonatal admission	4399	2287 (0–5 362)	3547	1300 (0–4225)	852
Neonatal monitoring + lab tests	11	2 (2–4)	11	2 (0–4)	0
Total postpartum	*5669*	*3783 (1490–6869)*	*4 801*	*2494 (894–5684)*	*868*
Total cost (95% confidence interval)[b]	8094 (1083–25 932)		7340 (627–30 874)		754 (−335 to 1802)

[a]Induction minus expectant management.
[b]Non-parametric confidence interval based on 1000 bootstrap replications.

Table 4. Comparison of costs between induction of labor (IoL) and expectant management (EM) in subgroups of gestational age at randomization (€2009).

	Antepartum costs per patient			Delivery costs per patient			Postpartum costs per patient			Total costs per patient		
	IoL	EM	Difference	IoL	EM	Difference	IoL	EM	Difference	IoL	EM	Difference
Total group[a]	648	1386	−738	1777	1153	624	5669	4801	868	8094	7340	754
Gestational age at randomization												
34^{+0}–34^{+6}	904	2656	−1752	2411	1670	741	10 590	8784	1806	13 905	13 110	795
35^{+0}–35^{+6}	702	1319	−617	2020	862	1158	7258	4382	2876	9980	6563	3417
36^{+0}–36^{+6}	538	839	−301	1414	1092	322	3251	3317	−66	5203	5248	−45

[a]See results in Table 3.

although the difference was not significant (€754: 95% CI: −335 to 1802). The difference mainly resulted from more and longer neonatal admissions after IoL, due either to the increased risk of hypoglycemia [RR 2.2 (95% CI 1.4–3.5)] and hyperbilirubinemia [RR 1.5 (95% CI 1.1–1.9)] or to the effects of preterm delivery in general in the IoL group. In the trial no differences were found in maternal morbidity between groups. Postpartum maternal admission costs were comparable as well.

This economic analysis was performed from a health care instead of the societal perspective (10,12). The reason for this was that we did not anticipate any large differences in patient or productivity loss costs. In a previous economic study comparing IoL with expectant monitoring in women with pregnancy-induced hypertension or preeclampsia beyond 36 weeks of gestation, we found no impact of non-medical costs on the final outcome (15).

A limitation of our study might be the short time-horizon we used, from antepartum hospital admission until postpartum hospital discharge, a strategy that was based on the available trial-based data used to estimate both clinical outcomes and costs. For future research, extrapolation of our data to a long-term time-horizon using a decision model is recommended.

Observed cost differences were apparently not significant when we used the boot strap technique. However, the most important cost drivers behind these differences, such as neonatal medium care admission, were significant, providing a reliable fundament under the reported cost difference.

Subgroup analysis of different gestational ages at randomization showed no cost differences between IoL and EM for women with gestational ages between 36 and 37 weeks. The difference in costs for women with a gestational age between 35 and 36 weeks appeared to be much higher. This indicates that IoL does not generate more

costs than EM for women with PPROM beyond 36 weeks of pregnancy.

Overall, the large multicenter PPROMEXIL trial demonstrated that women with PPROM between 34 and 37 weeks of gestational age can be treated expectantly without an increased risk of neonatal sepsis, with less neonatal morbidity due to hyperbilirubinemia or hypoglycemia and equal maternal morbidity (6) and maybe even at lower costs. Due to a lower than expected incidence of neonatal sepsis, more research is needed to support both clinical and economic findings. In a recent updated meta-analysis, we reported on 1090 neonates for the endpoint neonatal sepsis, 1428 neonates for the endpoint respiratory distress syndrome, and 1417 women for the endpoint cesarean section. The RRs of IoL as compared with EM were 0.85 (95% CI 0.48–1.5) for neonatal sepsis, 1.04 (95% CI 0.88–1.3) for respiratory distress syndrome and 1.1 (95% CI 0.88–1.4) for cesarean section (16). These data confirm the assumption of this economic analysis that both the policies of IoL and EM result in similar neonatal and maternal outcomes. Currently, the Australian lead global PROMPT trial is recruiting over 1800 women to address exactly the same dilemma (17). This larger trial will also include an economic analysis alongside the trial. Apart from more accurate estimates of the rates of neonatal sepsis and other neonatal outcomes, which will be provided by PROMPT, the pressing issue in IoL of women with ruptured membranes near term is the risk of long-term neonatal damage in the case of preterm delivery. A recent meta-analysis from our group on this issue (18), as well as a large cohort study from Liverpool (19), indicated a considerably increased risk of pathology in the case of late preterm delivery as compared with term delivery. On the other hand, after PPROM, the fetal risk of umbilical cord prolapse compression resulting in asphyxia or even stillbirth might be increased. As these issues have not been addressed with adequate data, definite conclusions cannot be drawn.

In summary, we found in the PPROMEXIL trial that IoL did not reduce the risk of neonatal sepsis, whereas costs associated with this strategy are probably higher. Although data on stillbirth risk after PPROM and long-term outcome after late preterm delivery are still awaited, it is clear that children born just before term do worse in childhood than those born at 37 weeks. In view of these data, and until additional data are available, we recommend expectant monitoring until 37 weeks in women with PPROM near term.

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