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Economic analysis of use of pessary to prevent preterm birth in women with multiple pregnancy (ProTWIN trial)

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KEYWORDS: cost-effectiveness; pessary; poor perinatal outcome; preterm birth; randomized controlled trial

ABSTRACT

Objective *To assess the cost-effectiveness of a cervical pessary to prevent preterm delivery in women with a multiple pregnancy.*

Methods *The study design comprised an economic analysis of data from a randomized clinical trial evaluating cervical pessaries (ProTWIN). Women with a multiple pregnancy were included and an economic evaluation was performed from a societal perspective. Costs were estimated between the time of randomization and 6 weeks postpartum. The prespecified subgroup of women with a cervical length (CL) < 25th centile (< 38 mm) was analyzed separately. The primary endpoint was poor perinatal outcome occurring up to 6 weeks postpartum. Direct medical costs and health outcomes were estimated and incremental cost-effectiveness ratios for costs to prevent one poor outcome were calculated.*

Results *Mean costs in the pessary group* (n = *401) were* €*21 783* vs €*21 877 in the group in which no pessary was used* (n = *407) (difference,* −€*94; 95% CI,* −€*5975 to* €*5609). In the prespecified subgroup of women with a CL < 38 mm we demonstrated a significant reduction in poor perinatal outcome (12%* vs *29%; RR, 0.40; 95% CI, 0.19–0.83). Mean costs in the pessary group* (n = *78) were* €*25 141* vs €*30 577 in the no-pessary group* (n = *55) (difference,* −€*5436 (95% CI,* −€*11 001 to* €*1456). In women with a CL < 38 mm, pessary treatment was the dominant strategy (more effective and less costly) with a probability of 94%.*

Conclusion *Cervical pessaries in women with a multiple pregnancy involve costs comparable to those in women without pessary treatment. However, in women with a CL < 38 mm, treatment with a cervical pessary appears to be highly cost-effective.*

INTRODUCTION

Preterm birth is a major contributing factor to perinatal morbidity and mortality. Prematurity requires intensive medical care for the neonate and is associated with a higher risk of mortality, disability and developmental disorders later in life[1]. Women with multiple pregnancy are at increased risk of preterm delivery. In The Netherlands, approximately 50% of women with a multiple pregnancy deliver before 37 weeks of gestation, of whom 9% deliver prior to 32 weeks[2].

In 1959, the cervical pessary was introduced to prevent preterm birth. The Arabin pessary is a silicone device that is non-invasive and can be easily placed or removed in an outpatient clinic. It is flexible and fits high around the cervix, so that the smaller inner diameter encompasses the cervix. Several relatively small and non-randomized studies suggest that the pessary could prevent preterm birth[3–5]. A recently published randomized study among women with a singleton pregnancy and a cervical length (CL) ≤ 25 mm demonstrated that the pessary is effective in preventing preterm birth[6].

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In view of the absence of effective measures to prevent preterm birth in women with a multiple pregnancy, we recently conducted a multicenter randomized controlled trial to evaluate the effectiveness of a pessary (ProTWIN trial, NTR1858). This study demonstrated that prophylactic use of a cervical pessary did not increase duration of pregnancy nor did it reduce poor perinatal outcome in women with a multiple pregnancy. However, in women with a relatively short cervix (CL < 38 mm) at 16–22 weeks of gestation, use of a pessary significantly reduced both very preterm birth rates and subsequent poor perinatal outcome[7].

In addition to these beneficial clinical outcomes, awareness of the cost of treatment with a pessary is also important in the decision to employ this treatment. We performed an economic analysis comparing costs and effects of treatment with and without a pessary in women with a multiple pregnancy. Furthermore we investigated costs in the prespecified subgroup of women with a CL < 25th centile (< 38 mm).

METHODS

We performed an economic evaluation alongside the ProTWIN trial. Full details of the ProTWIN trial have been reported previously[7]. The ProTWIN trial was approved on 14 May 2009 by the Ethics Committee of the Academic Medical Centre in Amsterdam (MEC 09-107) and had local approval from the boards of participating hospitals. The trial was registered in the Dutch trial registry (NTR1858). In brief, the study was a multicenter randomized controlled clinical trial conducted between September 2009 and March 2012 in the obstetric departments of six universities and 34 teaching and district hospitals in The Netherlands that collaborate in a nationwide research consortium for women's health (www.studies-obsgyn.nl). Participating hospitals are listed in Appendix S1. Women with a multiple pregnancy between 12 and 20 weeks of gestation were allocated to one of two groups (treatment with or without a cervical pessary).

Cervical length was measured by an obstetrician or sonographer between 16 and 22 weeks of gestation, either prior to or shortly after randomization and before placement of the pessary. Women allocated to the pessary group had the pessary inserted between 16 and 20 weeks of gestation. The pessary was placed around the cervix with the smaller diameter upwards, and removed in the 36th week of gestation or when there was premature rupture of the membranes, active vaginal bleeding, other signs of preterm labor or severe patient discomfort. Both the pessary group and the group not treated with a pessary (no-pessary group) received otherwise similar obstetric care[8].

Primary outcome of this trial was a composite of poor perinatal outcome and contained stillbirth, periventricular leukomalacia Grade II or worse, severe respiratory distress syndrome Grade II or worse, broncho-pulmonary dysplasia, intraventricular hemorrhage Grade II B or worse, necrotizing enterocolitis, proven sepsis or neonatal death before discharge. Analysis of the clinical endpoint showed that poor perinatal outcome of at least one of the infants occurred in 53 (13%) cases in the pessary group and in 55 (14%) cases in the no-pessary group (relative risk (RR), 0.98; 95% CI, 0.69–1.4). In the prespecified subgroup of women with a CL < 25th centile (< 38 mm) poor perinatal outcome occurred in nine (12%) cases in the pessary group and in 16 (29%) cases in the no-pessary group (RR, 0.40; 95% CI, 0.19–0.83, *P* for interaction, 0.011). In this subgroup, median gestational age at delivery was 36 + 3 (interquartile range (IQR), 35 + 0 to 37 + 2) weeks in the pessary group and 35 + 0 (IQR, 30 + 5 to 36 + 5) weeks in the no-pessary group (hazard ratio (HR), 0.49; 95% CI, 0.32–0.77). Treatment with a pessary reduced the incidences of delivery before 28 weeks of gestation (4% *vs* 16%, (RR, 0.23; 95% CI, 0.06–0.87)) and before 32 weeks of gestation (14% *vs* 29% (RR, 0.49; 95% CI, 0.24–0.97))[7].

The economic evaluation was set up as a cost-effectiveness analysis with poor perinatal outcome as effectiveness measure[9,10]. We used a societal perspective, including effects and direct medical costs between time of randomization and 6 weeks postpartum, and costs pertaining to travel and productivity loss. Discounting of costs was not necessary since all costs occurred within 1 year. We compared costs and effects for the entire group and for the subgroup of women with a CL < 25th centile (< 38 mm), according to published protocol and in line with the presentation of clinical results. This economic evaluation, including estimation of unit costs, is based on Dutch guidelines for economic evaluations[11].

We collected data concerning resource use in the extended Case Record Form with specific items concerning healthcare use during the antenatal/delivery and postpartum phases. In the antenatal/delivery phase we included the use of pessaries, medication, ultrasound, laser treatment for twin-to-twin transfusion syndrome, amnion drainage, antepartum maternal care (home or ward; medium, high or intensive), mode of delivery and transfusions. Obstetric procedures, e.g. induction methods, vaginal delivery, Cesarean section and instrumental attempts, were counted separately to allow differentiation in resource use between both groups. For the postpartum phase, we included maternal and neonatal care (home or ward; medium, high or intensive), medication (surfactant), neonatal intubation, days of continuous positive airway pressure (CPAP), number of neonatal computed tomography (CT) scans, neonatal ultrasound examinations, neonatal X-rays, travel costs and maternal productivity loss. For each maternal or neonatal admission, hospital stay was differentiated according to the level of care: home or ward; medium, high or intensive. Duration of neonatal admission was calculated as the number of days between birth and hospital discharge. Extra costs for neonatal admission to the maternal ward were not calculated since it was assumed that these costs were already included in those for the mother.

We used different methods and sources to estimate unit costs as valuations for documented volumes of resource use (Table 1)[11]. Unit costs were expressed in € (2011

Table 1 Cost analysis considering units of resource use, unit costs, valuation method and volume source

Variable	*Unit*	*Unit cost (€)**	*Valuation method/volume source*
Admission (mother)			
Ward	Day	372†	Top-down calculation
Medium care	Day	565†	Top-down calculation
ICU	Day	1804†	Top-down calculation
Admission (child)			
Maternal ward	Day	372†	Top-down calculation
Medium care	Day	565†	Top-down calculation
High care	Day	1514†	Top-down calculation
Neonatal intensive care	Day	1568†	Top-down calculation
Specialist care			
Gynecologist	Hour	75	Dutch costing guideline
Neonatologist	Hour	75	Dutch costing guideline
Pediatrician	Hour	75	Dutch costing guideline
Other healthcare providers			
Midwife	Hour	36	Dutch costing guideline
Home care	Hour	34	Dutch costing guideline
Nurse	Hour	33	Dutch costing guideline
Room occupation (incl. overheads)			
Labor room	Hour	87†	Bottom-up calculation
Theater	Hour	150†	Bottom-up calculation
Medication			
Tocolysis	Gift	50‡	Dutch Pharmacotherapeutic Compass
Infection treatment (incl. diagnostics)	Treatment	33	Dutch Pharmacotherapeutic Compass
Surfactant	Treatment	1031	Dutch Pharmacotherapeutic Compass
Transfusion	Gift	208	Dutch costing guideline
Delivery			
Oxytocin	Gift	1	Dutch Pharmacotherapeutic Compass
Prostaglandin E2 gel	Unit	79	PROBAAT trial[13]
Foley catheter	Unit	15	PROBAAT trial[13]
Vaginal delivery	Procedure	1142†	Top-down calculation
Cesarean section	Procedure	2014†	Top-down calculation
Instrumental attempt	Procedure	207†	Top-down calculation
Radiology			
Ultrasound	Procedure	31	Dutch Health Authority Tariff
CT scan	Procedure	192	Dutch Health Authority Tariff
X-ray	Procedure	48	Dutch Health Authority Tariff
Extra care			
Intubation	Day	107	Dutch Health Authority Tariff
CPAP	Day	34	Dutch Health Authority Tariff
Travel/productivity loss			
Travel cost	km	0.20	Dutch costing guideline
Productivity loss	Hour	40	Dutch costing guideline

*€ values are those of 2011. †Mean of the unit cost for an academic hospital and a general hospital. ‡Mean of several methods or medications. CPAP, continuous positive airway pressure; CT, computed tomography; ICU, intensive care unit; incl., including.

value) using the consumer pricing index[12]. For maternal and neonatal admissions and for obstetric procedures we used unit cost estimates retrieved from the financial department of one participating academic hospital and one participating non-academic hospital. Costs that did not apply to our population were subtracted (top-down approach). National standardized prices were used for some cost units (travel, outpatient visit, specialist care, nurse fees and home care)[11,13,14]. Medication prices were obtained from the Dutch Pharmacotherapeutic Compass[15]. Unit costs for diagnostic interventions (including ultrasound examinations, CT scans and X-rays), as well as for intubation and CPAP, were obtained from the Dutch Health Authority Tariff. The value of productivity loss was calculated using the friction cost method which assumes that workers who are withdrawn from work because of ill health will be replaced after an adaptation period, i.e. the friction period. Thus, the costs of productivity loss are limited to a period of 10 weeks. Standard costs per hour from Dutch guidelines for economic evaluations were used[11].

All analyses were done according to the intention-to-treat principle. The non-parametric Mann–Whitney *U*-test was used to assess differences in resource use. Costs were calculated by multiplying the quantity of resource use by unit costs. Mean and median total costs per woman were calculated for the total trial period. Incremental cost-effectiveness ratios (ICERs) were then calculated to determine the composite poor perinatal outcome rate. In this analysis ICERs reflect the costs needed to prevent one poor perinatal outcome by using the pessary[9,12,15,16].

Non-parametric bootstrapping was used to determine the 95% CI around the difference in mean costs and ICERs[17]. In accordance with guidelines for costing of healthcare services we used 1000 non-parametric bootstrap replications with replacement generating multiple data sets from the original data[17]. In each dataset the statistic of interest (mean costs and effects, and ICERs) was calculated. Uncertainty in main results of the economic evaluation was visualized by plotting the cost-effectiveness plane and cost-effectiveness acceptability curves[18].

To evaluate the robustness of our findings we performed multiple sensitivity analyses. In four univariate analyses we examined the influence of assumptions and unit cost estimates. In Models 1 and 2 we estimated cost differences in an academic and a non-academic setting. The variation in costs for the neonate in the postpartum phase was large. Therefore, we calculated the cost of preterm birth at each week of gestational age from our database, using these standardized prices for preterm birth according to gestational age at delivery (Model 3). In Model 4 we included the extra cost of neonatal admission to the maternal ward. These analyses were performed for women with a CL < 38 mm. All statistical, economic and simulation analyses were performed using SPSS version 18.0 (Chicago, IL, USA) and Microsoft Excel 2003.

RESULTS

A total of 813 women were randomized, of whom 403 were allocated to the pessary group and 410 to the no-pessary group. Five women were lost to follow-up, leaving 808 women for the cost analysis (401 women in the pessary group and 407 in the no-pessary group). Average volumes of resources used and total costs in each group are presented in Table S1 (all women) and Table S2 (subgroup of women with a CL < 38 mm).

There were no statistically significant differences in resource use between the pessary and no-pessary groups, nor between the total study population and the subgroup of women with a CL < 38 mm.

A summary of mean and median costs per woman is presented in Table 2. Mean costs in the antepartum/delivery phase were €4337 in the pessary group and €4414 in the no-pessary group. Costs for maternal antepartum admission were lower in the pessary group. Average postpartum costs were €17 445 in the pessary group and €17 464 in the no-pessary group. In this phase we observed comparable mean costs of neonatal care (ward; medium, high or intensive) in the pessary group compared to those in the no-pessary group (€14 865 *vs* €14 780, respectively). Mean costs of productivity loss were higher in the no-pessary group compared to those in the pessary group (€545 *vs* €429 respectively). Mean total costs in the pessary group ($n = 401$) were €21 783 *vs* €21 877 in the no-pessary group ($n = 407$), with an average difference of −€94 in favor of the pessary group (95% CI, −€5975 to €5609).

Table 3 summarizes mean and median costs per woman for the subgroup of women with a CL < 38 mm. Mean costs in the antepartum/delivery phase were €3901 in the pessary group and €4017 in the no-pessary group. Costs for maternal antepartum admission were lower in the pessary group (€1985 *vs* €2185). Mean postpartum

Table 2 Costs per woman (all women)

	Pessary (n = *401*)		*No pessary* (n = *407*)		*Difference*
Variable	*Mean cost*	*Median cost (IQR)*	*Mean cost*	*Median cost (IQR)*	*(P − NP)**
Antepartum costs					
Pessary	38	38 (38–38)	0	0 (0–0)	38
Tocolysis	98	0 (0–0)	118	0 (0–0)	−20
Corticosteroids	1	0 (0–0)	1	0 (0–372)	0
Antibiotics	11	0 (0–0)	11	0 (0–0)	0
Ultrasound examinations	65	31 (31–62)	66	31 (31–94)	−1
Laser treatment (TTTS)	7	0 (0–0)	7	0 (0–0)	0
Amniodrainage	1	0 (0–0)	1	0 (0–0)	0
Admission	2451	1235 (309–3089)	2636	1235 (330–2813)	−185
Delivery†	1609	1984 (1053–2043)	1530	1257 (1045–2043)	79
Packed cells	56	0 (0–0)	44	0 (0–0)	12
Total antepartum (incl. delivery)	4337		4414		−77
Postpartum costs					
Maternal admission	1819	1544 (927–2178)	1840	1544 (927–2178)	−21
Neonatal admission	14 865	1550 (0–12 698)	14 780	2357 (0–13 214)	85
Extra neonatal care/radiology	297	0 (0–0)	263	0 (0–62)	34
Travel costs	35	18 (13–41)	36	18 (13–41)	−1
Productivity loss	429	0 (0–0)	545	0 (0–0)	−116
Total postpartum and direct follow-up (admissions)	17 445		17 464		−19
Total costs	21 783		21 877		−94
(95% CI)‡					−5975 to 5609

All cost data are given as €, with values being those of 2011. *Cost of pessary group minus cost of no-pessary group. †Includes instrumental attempts, Cesarean section and induction of labor. ‡Non-parametric confidence interval based on 1000 bootstrap replications. incl., including; IQR, interquartile range; TTTS, twin-to-twin transfusion syndrome.

Table 3 Costs per woman (subgroup with cervical length < 38 mm)

Variable	*Pessary (n = 78)*		*No pessary (n = 55)*		*Difference (P – NP)**
	Mean cost	*Median cost (IQR)*	*Mean cost*	*Median cost (IQR)*	
Antepartum costs					
Pessary	38	38 (38–38)	0	0 (0–0)	38
Tocolysis	114	0 (0–0)	144	0 (0–0)	−30
Corticosteroids	2	0 (0–4)	2	0 (0–4)	0
Antibiotics	11	0 (0–0)	10	0 (0–0)	1
Ultrasound examinations	70	31 (31–94)	64	62 (31–94)	6
Laser treatment (TTTS)	0	0 (0–0)	0	0 (0–0)	0
Amniodrainage	0	0 (0–0)	2	0 (0–0)	−2
Admission	1985	927 (309–2614)	2185	1313 (309–3706)	−200
Delivery†	1628	1984 (1048–2043)	1533	1257 (1045–2043)	95
Packed cells	53	0 (0–0)	77	0 (0–0)	−24
Total antepartum (incl. delivery)	3901		4017		−116
Postpartum costs					
Maternal admission	1780	1743 (1158–2178)	2394	1881 (927–2614)	−614
Neonatal admission	18 300	1852 (0–12 264)	22 948	5050 (0–26 195)	−4648
Extra neonatal care/radiology	300	0 (0–62)	437	0 (0–167)	−137
Travel costs	40	21 (13–39)	45	24 (13–56)	−5
Productivity loss	820	0 (0–0)	736	0 (0–0)	84
Total postpartum and direct follow-up (admissions)	21 240		26 560		−5320
Total costs	25 141		30 577		−5436
(95% CI)‡					−11 001 to 1456

All cost data are given as €, with values being those of 2011. *Cost of pessary group minus cost of no-pessary group. †Includes instrumental attempts, Cesarean section and induction of labor. ‡Non-parametric confidence interval based on 1000 bootstrap replications. incl., including; IQR, interquartile range; TTTS, twin-to-twin transfusion syndrome.

costs were €21 240 in the pessary group and €26 560 in the no-pessary group. In this phase costs for neonatal admissions were lower in the pessary group compared to those in the no-pessary group (€18 300 *vs* €22 948, respectively). Costs for maternal admissions were also lower in the pessary group (€1780 *vs* €2394). Mean total costs in the pessary group ($n = 78$) were €25 141 *vs* €30 577 in the no-pessary group (n = 55), with a difference of −€5436 in favor of the pessary group (95% CI, −€11 001 to €1456).

In the study sample, we could not demonstrate a reduction in poor perinatal outcome (13% in the pessary group *vs* 14% in the no-pessary group; RR, 0.98; 95% CI, 0.69–1.4) and total costs were also comparable in both groups. Hence, interpretation of the ICER, i.e. a ratio of the difference in costs and difference in effectiveness, is not entirely straightforward. In the prespecified subgroup of women with a CL < 25th centile (< 38 mm), the rate of poor perinatal outcome and costs was lower in the pessary group, indicating that the no-pessary group was dominated (higher rate of poor perinatal outcome and higher costs). In the case of dominance, the ICER itself is not very informative, but its location and associated uncertainty are better reported in a cost-effectiveness plane.

The cost-effectiveness plane allows point estimates and associated uncertainty so that differences in both cost and effectiveness can be plotted in a combined space. Each point in the cost-effectiveness plane represents the additional costs and health gain of treatment with or without a pessary for the entire group (circles) and subgroup < 25th centile (squares) in each bootstrap sample (Figure 1). The ICER scatter (circles) spreads over all four

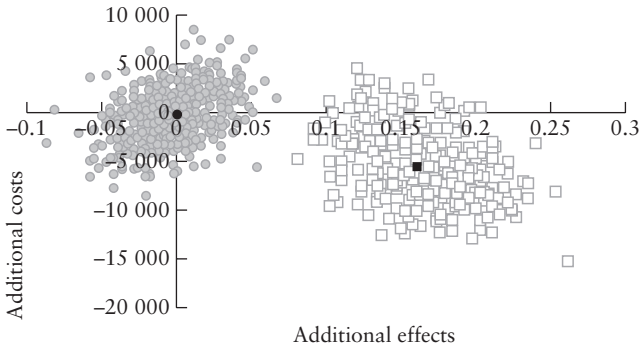

Figure 1 Cost-effectiveness plane. Each point in the cost-effectiveness plane represents the additional costs and health gain of treatment with a pessary compared to no treatment (multiple samples from original dataset). ○, entire group of women recruited for the cost analysis; □, subgroup of women with cervical length < 25th centile; ● and ■, base case incremental cost-effectiveness ratios (both groups).

quadrants, around the origin, indicating that our trial did not show significant differences in reduction of the poor perinatal outcome rate (*x*-axis) nor of costs (*y*-axis) for the entire group. The ICER scatter for our subgroup (squares) demonstrates that there is a significant treatment effect of the pessary. Although the cost spreads are mainly in the lower right quadrant (dominance), they are also in the upper right quadrant.

Results located in the lower right quadrant reflect dominance, indicating that treatment with a pessary is the better strategy (more effective at lower costs). For results located in the upper right quadrant, whether a pessary is considered cost-effective depends on the willingness

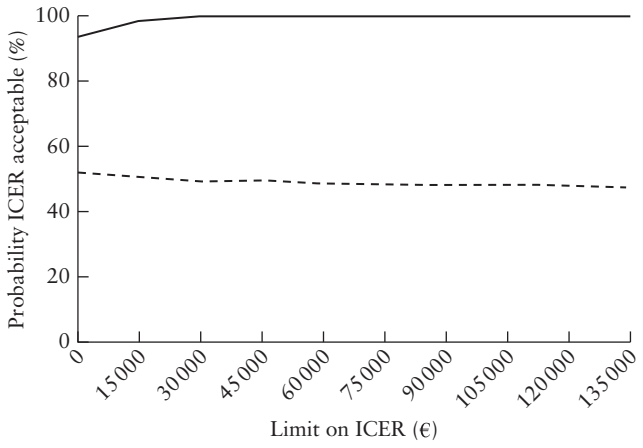

Figure 2 Cost-acceptability plot for the entire group of women recruited for the cost analysis (- - - -) and the subgroup with a cervical length < 25th centile (——), showing the probability of pessary treatment to be cost-effective in preventing poor perinatal outcome. The probability increases as a result of an increase in willingness to pay. ICER, incremental cost-effectiveness ratio.

to pay (WTP) for these health gains. Cost-effectiveness acceptability curves visualize the probability that an intervention is considered cost-effective when increasing the WTP threshold. In women with a CL < 38 mm, due to dominance, the probability that a pessary is cost-effective is at least 98% at a WTP value of €15 000 per additional case of poor neonatal outcome prevented (Figure 2).

Table 4 summarizes results of the sensitivity analyses. For the total study sample, the difference in mean total costs increased to −€187 (95% CI, −€6400 to €6094) when only unit prices for academic settings were used (Model 1), in favor of the pessary. When unit prices for general hospitals were used the difference in mean costs decreased to −€11 (95% CI, −€5115 to €4979) (Model 2). If costs according to gestational age at delivery were used, a cost difference of €1957 (95% CI, −€3193 to €6914) would be demonstrated (Model 3). Including neonatal ward admissions revealed an increased difference in mean costs of −€359 (95% CI, −€6124 to 5020) (Model 4).

In the subgroup of women with a CL < 38 mm, pessary treatment consistently generated lower costs in all four models. Differences were not statistically significant, indicating robustness against varying estimates in resource use and unit prices.

DISCUSSION

This study assessed the cost-effectiveness of using a cervical pessary to prevent poor perinatal outcome in women with a multiple pregnancy. The analysis was performed from a societal perspective according to the ProTWIN trial. The results demonstrate that mean costs per woman are not significantly lower in women treated with a cervical pessary compared to women not treated with a cervical pessary (mean difference, −€94; 95% CI, −€5975 to €5609). The primary clinical measure, poor perinatal outcome, was also comparable in both groups.

In the prespecified subgroup of women with a CL < 38 mm, treatment with a pessary compared to treatment without a pessary was associated with comparable costs (−€5436; 95% CI, −€11 001 to €1456). Differences in cost originated predominantly at the postpartum phase. Cost-effectiveness analyses showed that treatment with a pessary in women with a CL < 38 mm is likely to be cost-effective (94% probability at a WTP threshold of €0). The probability is higher when the WTP threshold is increased. Sensitivity analyses demonstrate that our analyses are robust against varying estimates in resource use and unit prices.

The strengths of the study include the fact that it was based on data from a randomized controlled trial enabling prospective registration of resource uses. Furthermore, the large sample size, the diversity of participating hospitals and the well-organized structure for data collection within

Table 4 Sensitivity analyses to evaluate the robustness of findings in the total study sample and those with cervical length (CL) < 38 mm

	*Cost (€)**			
Variable	*Pessary*	*No pessary*	*Difference (P − NP)†*	*95% CI*
All women				
Base case	21 783	21 877	−94	−5975 to 5609
Model 1: Value admissions by using academic unit prices only	27 186	27 373	−187	−6400 to 6094
Model 2: Value admissions by using general unit prices only	19 717	19 728	−11	−5115 to 4979
Model 3: Value admissions by using prices according to gestational age at delivery	24 427	22 471	1957	−3193 to 6914
Model 4: Including neonatal ward admissions	23 161	23 520	−359	−6124 to 5020
Women with CL < 38 mm				
Base case	25 141	30 577	−5436	−11 001 to 1456
Model 1: Value admissions by using academic unit prices only	31 509	34 900	−3391	−11 333 to 3 854
Model 2: Value admissions by using general unit prices only	24 051	27 675	−3624	−9681 to 3062
Model 3: Value admissions by using prices according to gestational age at delivery	29 319	32 241	−2922	−9795 to 2929
Model 4: Including neonatal ward admissions	26 343	31 892	−5549	−13 045 to 464

*€ values are those of 2011. †Cost of pessary group minus cost of no-pessary group.

the Dutch Obstetric Consortium are likely to extend the internal and external validity of our results. As the results of extensive sensitivity analyses were similar, we conclude that the cost-effectiveness model is robust against the most influential uncertainties[9,16,18].

The study also has several limitations. Interpretation of a composite clinical outcome is difficult and a possible solution is to use the quality-adjusted lifeyear (QALY) which is an aggregate health metric. However, quality of life would also have been a relevant outcome parameter during pregnancy and the first weeks postpartum. To calculate QALYs for this purpose several conceptual points must be taken into consideration. Currently, neither clinical long-term outcomes nor QALY's are integrated into studies evaluating perinatal interventions[19]. Hence, a QALY-based analysis probably should encompass a long-term perspective beyond 6 weeks postpartum. To facilitate studies addressing the long-term perspective, a systematic approach to developing prediction models to extrapolate short-term outcomes to a long-term horizon is needed[20]. Since there is little evidence on how this can be achieved, we decided not to include this approach.

A second limitation is the relatively small sample size of our subgroup which resulted in wide confidence intervals and absence of statistical significance. Also, we observed a large variation in costs for the neonatal postpartum period; therefore, we differentiated costs by delivery per week of gestation. The results of this sensitivity analysis were consistent with those of the main analysis. Furthermore, although our study had a short-term horizon, we believe that treatment with a cervical pessary is likely to generate fewer medical and societal costs after discharge by reducing preterm birth and poor perinatal outcome. In view of the long-term costs associated with preterm birth, it would be even more cost-effective in the long term.

To our knowledge this is the first economic evaluation that prospectively compared treatment with and without a cervical pessary in women with a multiple pregnancy. The clinical outcomes are in line with the PECEP trial[6] which demonstrated a significant reduction in preterm birth in women with a singleton pregnancy and a short CL (< 25 mm).

Since preterm birth is the major contributing factor to perinatal morbidity and mortality, reduction of preterm birth in multiple pregnancies is a major goal in obstetrics. Our study showed comparable costs in the pessary and no-pessary groups. Cost-effectiveness acceptability curves suggest that the probability that treatment with a pessary is cost-effective is low, even at high WTP thresholds. In women with a multiple pregnancy and a CL < 38 mm, significant differences in costs and effects were in favor of pessary treatment, resulting in a very high probability that this treatment is cost-effective in this subgroup of women.

Concerning future research, our study suggests that treatment with a pessary reduces perinatal mortality and morbidity and reduces costs in women with a relatively short CL (< 38 mm). These results should be confirmed in appropriately powered studies to detect differences in preterm birth rates and poor perinatal outcomes.

Progesterone has been found to be effective in women with a singleton pregnancy and a short cervix[21]. A recent meta-analysis with individual patient data concerning women with a multiple pregnancy and a CL ≤ 25 mm showed a reduction in poor neonatal outcome in women treated with vaginal progesterone[22]. Future studies should investigate the comparison of treatment with a pessary and with progesterone in women with a relatively short cervix.

Cervical pessaries in women with a multiple pregnancy involve costs comparable to those in women without pessary treatment. However, in women with a CL < 38 mm treatment with a cervical pessary appears to be highly cost-effective. In light of the potential benefit that we observed in a group of women in whom the prognosis without intervention is so poor, it is our view that, until findings from new randomized controlled trials indicate otherwise, placement of a pessary should be considered in women with a multiple pregnancy and a CL < 38 mm.

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REFERENCES

1. Hille ET, Weisglas-Kuperus N, van Goudoever JB, Jacobusse GW, Ens-Dokkum MH, de Groot L, Wit JM, Geven WB, Kok JH, de Kleine MJ, Kollée LA, Mulder AL, van Straaten HL, de Vries LS, van Weissenbruch MM, Verloove-Vanhorick SP; Dutch Collaborative POPS 19 Study Group. Functional outcomes and participation in young adulthood for very preterm and very low birth weight infants: the Dutch Project on Preterm and Small for Gestational Age Infants at 19 years of age. *Pediatrics* 2007; **120**: e587–e595.
2. Schaaf JM, Mol BW, Abu-Hanna A, Ravelli AC. Trends in preterm birth: singleton and multiple pregnancies in the Netherlands, 2000-2007. *BJOG* 2011; **118**: 1196–1204.
3. Acharya G, Eschler B, Gronberg M, Hentemann M, Ottersen T, Maltau JM. Noninvasive cerclage for the management of cervical incompetence: a prospective study. *Arch Gynecol Obstet* 2006; **273**: 283–287.
4. Arabin B, Halbesma JR, Vork F, Hubener M, van EJ. Is treatment with vaginal pessaries an option in patients with a sonographically detected short cervix? *J Perinat Med* 2003; **31**: 122–133.
5. Vitsky M. Simple treatment of the incompetent cervical os. *Am J Obstet Gynecol* 1961; **81**: 1194–1197.
6. Goya M, Pratcorona L, Merced C, Rodó C, Valle L, Romero A, Juan M, Rodríguez A, Muñoz B, Santacruz B, Bello-Muñoz JC, Llurba E, Higueras T, Cabero L, Carreras E; Pesario Cervical para Evitar Prematuridad (PECEP) Trial Group. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomized controlled trial. *Lancet* 2012; **379**: 1800–1806.

7. Liem S, Schuit E, Hegeman M, Bais J, de Boer K, Bloemenkamp K, Brons J, Duvekot H, Bijvank BN, Franssen M, Gaugler I, de Graaf I, Oudijk M, Papatsonis D, Pernet P, Porath M, Scheepers L, Sikkema M, Sporken J, Visser H, van Wijngaarden W, Woiski M, van Pampus M, Mol BW, Bekedam D. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomized controlled trial. *Lancet* 2013; **382**: 1341–1349.
8. Multiple pregnancy: guideline version 3. Utrecht, the Netherlands: Dutch Society of Obstetrics and Gynaecology (NVOG), 2011. 2012.
9. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes*. (3rd edn). Oxford University Press: Oxford, UK, 2005.
10. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-effectiveness in Health and Medicine*. Oxford University Press: Oxford, UK, 1996.
11. Hakkaart-van Rooijen L, Tan SS, Bouwmans CAM. Handleiding voor kostenonderzoek,methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg (Guidelines for Pharmaco-economic Research). 2010. Diemen, College voor zorgverzekeringen (CvZ) (Health Insurance Board).
12. Statistics Netherlands. Statline Consumer Pricing Index. 2013.
13. Jozwiak M, Oude Rengerink K, Benthem M, van Beek E, Dijksterhuis MG, de Graaf IM, van Huizen ME, Oudijk MA, Papatsonis DN, Perquin DA, Porath M, van der Post JA, Rijnders RJ, Scheepers HC, Spaanderman ME, van Pampus MG, de Leeuw JW, Mol BW, Bloemenkamp KW; PROBAAT Study Group. Foley catheter versus vaginal prostaglandin E2 gel for induction of labour at term (PROBAAT trial): an open-label, randomized controlled trial. *Lancet* 2011; **378**: 2095–2103.
14. Oostenbrink JB, Koopmanschap MA, Rutten FF. Standardisation of costs: the Dutch Manual for Costing in economic evaluations. *Pharmacoeconomics* 2002; **20**: 443–454.
15. College voor zorgverzekeringen (CvZ) (Health Insurance Board). Pharmacotherapeutic Compass 2011 (in Dutch). 2011. Amstelveen.
16. Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. *Stat Med* 2000; **19**: 3219–3236.
17. Nixon RM, Wonderling D and Grieve RD. Non-parametric methods for cost-effectiveness analysis: the central limit theorem and the bootstrap compared. *Health Econ* 2010; **19**: 316–333.
18. Black WC. The CE plane: a graphic representation of cost-effectiveness. *Med Decis Making* 1990; **10**: 212–214.
19. Teune MJ, van Wassenaer AG, Malin GL, Asztalos E, Alfirevic Z, Mol BW, Opmeer BC. Long-term child follow-up after large obstetric randomised controlled trials for the evaluation of perinatal interventions: a systematic review of the literature. *BJOG* 2013; **120**: 15–22.
20. Teune MJ, van Wassenaer AG, Mol BW, Opmeer BC. Long-term health-related and economic consequences of short-term outcomes in evaluation of perinatal interventions. *BMC Pregnancy Childbirth* 2010; **10**: 42.
21. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med* 2007; **357**: 462–469.
22. Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien JM, Cetingoz E, Da Fonseca E, Creasy GW, Klein K, Rode L, Soma-Pillay P, Fusey S, Cam C, Alfirevic Z, Hassan SS. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. *Am J Obstet Gynecol* 2012; **206**: 124.e1–124.19.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Participants in the ProTWIN trial in addition to the authors.

Table S1 Average volumes of resources used and total costs in each group (pessary or no pessary) (2011 €)

Table S2 Average volumes of resources used and total costs for the subgroup of women with a cervical length < 38 mm (2011 €)

