Pessaries for the prevention of preterm birth in multiple pregnancies
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CHAPTER 7

An economic analysis of the use of a pessary to prevent preterm birth in women with a multiple pregnancy (ProTWIN trial)

Submitted
Abstract

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

Design An economic analysis alongside a randomised clinical trial evaluating cervical pessaries (ProTWIN).

Setting Obstetric departments of 40 hospitals in The Netherlands.

Population Women with a multiple pregnancy.

Methods Economic evaluation from a societal perspective. Costs were estimated between randomisation and 6 weeks postpartum. We separately analysed the prespecified subgroup of women with a cervical length (CL) below the 25th percentile (<38 mm).

Main outcome measures Primary endpoint was poor perinatal outcome until 6 weeks postpartum. We estimated direct medical costs and health outcomes. We calculated incremental cost-effectiveness ratios for costs to prevent one poor outcome.

Results Mean costs in the pessary group (n = 401) were €21884 versus €22030 in the no-pessary group (n= 407) (difference -€146 (95% confidence interval (CI) €-5648 to €4718)). In the prespecified subgroup of women with a CL <38 mm we demonstrated a significant reduction of poor perinatal outcome (12% vs 29%, RR 0.40; 95% CI 0.19-0.83). The mean costs in the pessary group (n=78) were €25142 versus €30577 in the no-pessary group (n=55) (difference -€5436 (95% CI €-11001 to €1456). In women with CL <38 mm, pessary treatment is the dominant strategy (more effective and less costly) with a probability of 94%.

Conclusion In unselected women with a multiple pregnancy treatment with a cervical pessary generates comparable costs as in women without treatment. However, using a pessary in women with a CL <38 mm results in better outcomes and lower costs.
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, handicaps and developmental disorders later in life. Women with a multiple pregnancy are at increased risk for preterm delivery. In The Netherlands, approximately 50% of women with a multiple pregnancy deliver before 37 weeks of gestation, of whom 9% even prior to 32 weeks.

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-randomised studies suggest that the pessary could prevent preterm birth. A recently published randomised study among women with a singleton pregnancy and a cervical length (CL) ≤25 mm demonstrated that the pessary is effective in preventing preterm birth.

In view of the absence of effective measures to prevent preterm birth in women with a multiple pregnancy, we recently conducted a multicentre randomized controlled trial to evaluate the effectiveness of a pessary in these women (ProTWIN trial, NTR1858). This study demonstrated that prophylactic use of a cervical pessary did neither increase duration of pregnancy nor reduces poor perinatal outcome in women with a multiple pregnancy. However, in women with a relative short cervix (CL <38 mm) at 16-22 weeks, a pessary significantly reduced both very preterm birth rates and subsequent poor perinatal outcome.

Besides these beneficial clinical outcomes, knowledge on the cost of treatment with a pessary is also important in the decision to introduce this treatment. We performed an economic analysis comparing costs and effects of treatment with a pessary versus no-pessary in women with a multiple pregnancy. Furthermore we investigated the costs in the prespecified subgroup of women with a CL <25th percentile (<38 mm).

Methods

Trial design

We performed an economic evaluation alongside the ProTWIN trial. Full details of the ProTWIN trial have been reported previously. The study was approved by the research ethics committee of the Academic Medical Centre in Amsterdam (MEC 09-107, NTR1858). In short, the study was a multicentre randomised controlled clinical trial conducted between September 2009 and March 2012 in the obstetric departments of six university and 34 teaching and district hospitals in The Netherlands that collaborate in a nationwide research consortium for women's health research (www.studies-obsgyn.nl). The participating hospitals are listed in Appendix S1. Women with a multiple pregnancy between 12-20 weeks of gestation were allocated to either treatment with a cervical pessary or no-pessary. Cervical length was measured by an obstetrician or sonographer between 16 and 22 weeks of gestation, either prior to or shortly after randomisation 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 in case of premature rupture of the membranes, active vaginal bleeding, other signs of preterm labour or severe patient discomfort. Both the pessary and the no-pessary group received otherwise similar obstetrical care.8

Primary outcome of this trial was a composite for poor perinatal outcome, and contained stillbirth, periventricular leukomalacia (PVL) grade II or worse, severe respiratory distress syndrome (RDS) grade II or worse, broncho-pulmonal dysplasia (BPD), intraventricular haemorrhage grade II B or worse (IVH), necrotizing enterocolitis (NEC), proven sepsis and neonatal death before discharge from the nursery. Analysis of the clinical endpoint showed that poor perinatal outcome of at least one of the children occurred in 53 (13%) pregnancies in the pessary group and in 55 (14%) pregnancies in the no-pessary group (RR 0.98; 95% CI 0.69-1.4). In the prespecified subgroup of women with a CL <25th percentile (<38 mm) poor perinatal outcome occurred in 9 (12%) pregnancies in the pessary group and in 16 (29%) pregnancies in the no-pessary group (RR 0.40; 95% CI 0.19-0.83, p-value for interaction 0.011). In this subgroup median gestational age at delivery was 36+3 (IQR 35+0-37+2) weeks in the pessary group and 35+0 (IQR 30+5-36+5) weeks in the no-pessary group (HR 0.49; 95% CI 0.32-0.77). Treatment with a pessary reduced delivery before 28 (4% versus 16%, (RR 0.23; 95% CI 0.06-0.87)) and before 32 weeks (14% versus 29% (RR 0.49; 95% CI 0.24-0.97)).7

Economic evaluation

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 randomisation and 6 weeks postpartum. Discounting of costs was not necessary since all costs occurred within 1 year. We compared costs and effects for the whole group and for the subgroup of women with a CL <25th percentile (<38 mm), according to the published protocol and in line with the presentation of the clinical results.

Resource use

We collected resource use in the extended Case Record Form with specific items on healthcare use during the antenatal delivery and postpartum phases. In the antenatal/delivery phase we included the use of pessaries, medication, ultrasounds, laser treatments for twin-to-twin transfusion syndrome, amnion drainage, antepartum maternal admissions (home, ward, medium, high and intensive care), mode of delivery and transfusions. Obstetric procedures, like induction methods, vaginal delivery, caesarean 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 admissions (home, ward, medium, high and intensive care), medication use (surfactant), neonatal intubation, days of continuous positive airway pressure (CPAP), number of neonatal CT scans, neonatal ultrasounds, 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: intensive care, medium care,
maternal ward or home care. Duration of neonatal admission was calculated as the number of days between birth and hospital discharge. No extra costs for neonatal admission to the maternal ward were calculated since it was assumed that these costs were already included in those for the mother.

**Unit costs**
We used different methods and sources to estimate unit costs as valuations for documented volumes of resource use (Table 1). Unit costs were expressed in 2011 Euros using the consumer pricing index. For maternal and neonatal admissions and obstetric procedures we used unit cost estimates retrieved from the financial department of one participating academic hospital and one participating non-academic hospital. We subtracted the costs that did not apply for our population (top-down approach). National standardised prices were used for some cost units (outpatient visit, specialist care, nurse care and home care). Medication prices were obtained from the Dutch Pharmacotherapeutic Compass. Unit costs for diagnostic interventions (including ultrasounds, CT scans, and X-rays), as well as for intubation and continuous positive airway pressure (CPAP) were obtained from Dutch Health Authority Tariff.

**Analyses**
All analyses were according to the intention-to-treat principle. The nonparametric Mann–Whitney U test was used to test differences in resource use. We calculated costs by multiplying the quantity of resource use and unit costs. Mean and median total costs per woman were calculated for the total trial period. We then calculated incremental cost-effectiveness ratios (ICER) for the composite poor perinatal outcome rate. In this analysis the ICER reflects the costs needed to prevent one poor perinatal outcome by using the pessary. We used bootstrapping to determine the 95% CI around the difference in mean costs and ICERs. In accordance with the guidelines on costing of healthcare services we used 1000 non-parametric bootstraps replications with replacement generating multiple data sets from the original data. In each dataset the statistic of interest (mean costs and effects, and ICER) were calculated. Uncertainty in main results of the economic evaluation was visualised by plotting the cost-effectiveness plane and cost-effectiveness acceptability curves.

**Sensitivity, scenario and subgroup analysis**
To evaluate the robustness of our findings we performed multiple sensitivity analyses. In four univariate analyses we examined the influence of assumptions and unit costs estimates. In model 1 and 2 we estimated cost differences in an academic and a non-academic setting. There was large variation of costs in the postpartum phase for the neonate. Therefore we calculated the cost of preterm birth at each week of gestational age from our database. We used these standardized prices for preterm birth according to gestational age at delivery (model 3). In model 4 we included extra cost for neonatal admissions on the maternal ward. Furthermore, we performed all these analyses 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.
Table 1: Cost-analysis: units of resource use, unit costs, valuation method and volume source (2011 €)

<table>
<thead>
<tr>
<th>Unit</th>
<th>Unit cost</th>
<th>Valuation method (source)</th>
</tr>
</thead>
<tbody>
<tr>
<td>admission mother</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ward*</td>
<td>day</td>
<td>372 Top-down calculation</td>
</tr>
<tr>
<td>medium care*</td>
<td>day</td>
<td>565 Top-down calculation</td>
</tr>
<tr>
<td>ICU*</td>
<td>day</td>
<td>1,804 Top-down calculation</td>
</tr>
<tr>
<td>admission child</td>
<td></td>
<td></td>
</tr>
<tr>
<td>maternal ward*</td>
<td>day</td>
<td>372 Top-down calculation</td>
</tr>
<tr>
<td>medium care*</td>
<td>day</td>
<td>565 Top-down calculation</td>
</tr>
<tr>
<td>high care*</td>
<td>day</td>
<td>1,514 Top-down calculation</td>
</tr>
<tr>
<td>neonatal intensive care*</td>
<td>day</td>
<td>1,568 Top-down calculation</td>
</tr>
<tr>
<td>specialist care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gynaecologist</td>
<td>hour</td>
<td>75 Dutch costing guideline</td>
</tr>
<tr>
<td>neonatologist</td>
<td>hour</td>
<td>75 Dutch costing guideline</td>
</tr>
<tr>
<td>paediatrician</td>
<td>hour</td>
<td>75 Dutch costing guideline</td>
</tr>
<tr>
<td>other health care providers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>midwife</td>
<td>hour</td>
<td>36 Dutch costing guideline</td>
</tr>
<tr>
<td>home care</td>
<td>hour</td>
<td>34 Dutch costing guideline</td>
</tr>
<tr>
<td>nurse</td>
<td>hour</td>
<td>33 Dutch costing guideline</td>
</tr>
<tr>
<td>room occupation + overhead</td>
<td></td>
<td></td>
</tr>
<tr>
<td>labour room*</td>
<td>hour</td>
<td>87 Bottom-up calculation</td>
</tr>
<tr>
<td>theatre*</td>
<td>hour</td>
<td>150 Bottom-up calculation</td>
</tr>
<tr>
<td>medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tocolysis**</td>
<td>gift</td>
<td>50 Dutch Pharmacotherapeutic Compass</td>
</tr>
<tr>
<td>infection treatment (incl. diagnostics)</td>
<td>treatment</td>
<td>33 Dutch Pharmacotherapeutic Compass</td>
</tr>
<tr>
<td>surfactant</td>
<td>treatment</td>
<td>1,031 Dutch Pharmacotherapeutic Compass</td>
</tr>
<tr>
<td>transfusion</td>
<td>gift</td>
<td>208 Dutch costing guideline</td>
</tr>
<tr>
<td>delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxytocin</td>
<td>gift</td>
<td>1 Dutch Pharmacotherapeutic Compass</td>
</tr>
<tr>
<td>prostaglandin E2 gel</td>
<td>unit</td>
<td>79 Probaat trial</td>
</tr>
<tr>
<td>foley catheter</td>
<td>unit</td>
<td>15 Probaat trial</td>
</tr>
<tr>
<td>vaginal delivery*</td>
<td>procedure</td>
<td>1,142 Top-down calculation</td>
</tr>
<tr>
<td>caesarean section*</td>
<td>procedure</td>
<td>2,014 Top-down calculation</td>
</tr>
<tr>
<td>instrumental attempt*</td>
<td>procedure</td>
<td>207 Top-down calculation</td>
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Table 1: (continued)

<table>
<thead>
<tr>
<th>Unit</th>
<th>Unit cost</th>
<th>Valuation method (source)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiology</strong></td>
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<td></td>
</tr>
<tr>
<td>Ultrasound procedure</td>
<td>31</td>
<td>Dutch Health Authority Tariff</td>
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<tr>
<td>CT scan procedure</td>
<td>192</td>
<td>Dutch Health Authority Tariff</td>
</tr>
<tr>
<td>X-ray procedure</td>
<td>48</td>
<td>Dutch Health Authority Tariff</td>
</tr>
<tr>
<td><strong>Extra care</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intubation day</td>
<td>107</td>
<td>Dutch Health Authority Tariff</td>
</tr>
<tr>
<td>Cpap day</td>
<td>34</td>
<td>Dutch Health Authority Tariff</td>
</tr>
<tr>
<td><strong>Travel/productivity loss</strong></td>
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<td></td>
</tr>
<tr>
<td>Travel cost km</td>
<td>0.20</td>
<td>Dutch costing guideline</td>
</tr>
<tr>
<td>Productivity loss hour</td>
<td>40</td>
<td>Dutch costing guideline</td>
</tr>
</tbody>
</table>

* the mean of the unit cost for an academic hospital and a general hospital is presented
** the mean of several methods/medication is presented

Results

Resource use
We randomised 813 women, of whom 403 were allocated to the pessary group and 410 to the no-pessary group. Five women were lost to follow up, leaving a total of 808 women included for the cost analysis (401 women in the pessary group and 407 women in the no-pessary group). Average volumes of resources used and total costs in each group are demonstrated in Appendix S2 (all women) and S3 (subgroup of women with a CL <38 mm) (see Supporting Information).

There were no statistically significant differences in resource use between the pessary and no-pessary group neither in the total study population nor in the subgroup of women with a CL <38 mm.

Costs
A summary of mean and median costs per woman is presented in Table 2. The mean costs in the antepartum/delivery phase were €4297 in the pessary group and €4393 in the no-pessary group. The costs for maternal antepartum admission were lower in the pessary group. The average postpartum costs were €17587 in the pessary and €17637 in the no-pessary group. In this phase we observed comparable mean costs from neonatal admissions (ward, medium care, high care and intensive care) in the pessary group compared to the no-pessary group (€14939 versus €14889 respectively). The mean productivity loss costs were higher in the no-pessary group compared to the pessary group (€549 versus €432 respectively). The mean total costs in the pessary group (n = 401) were €21884 versus €22030 in the no-pessary group (n= 407), with an average difference of -€146 in favour of the pessary group (95% CI €-5648 to €4718).
Table 2: Costs per women (all women) (2011€)

<table>
<thead>
<tr>
<th></th>
<th>Pessary (n = 401)</th>
<th>No pessary (n =407)</th>
<th>Diff*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>median</td>
<td>mean</td>
</tr>
<tr>
<td></td>
<td>cost</td>
<td>cost</td>
<td>cost</td>
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<tr>
<td>Pessary</td>
<td>38</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Tocolysis</td>
<td>98</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Coticosteroids</td>
<td>1,30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ultrasounds antepartum</td>
<td>65</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Laser treatment TTTS</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amnion Drainage</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Admission antepartum</td>
<td>2463</td>
<td>1235</td>
<td>309</td>
</tr>
<tr>
<td>Delivery **</td>
<td>1612</td>
<td>1984</td>
<td>1053</td>
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<tr>
<td>Antepartum + delivery</td>
<td>4297</td>
<td>4393</td>
<td>-96</td>
</tr>
<tr>
<td>Packet cells</td>
<td>59</td>
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<td>0</td>
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<tr>
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<td>1824</td>
<td>1544</td>
<td>927</td>
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<tr>
<td>post-partum</td>
<td>14939</td>
<td>1587</td>
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</tr>
<tr>
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<td>0</td>
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<td>18</td>
<td>13</td>
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<tr>
<td>radiology</td>
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<td>0</td>
</tr>
<tr>
<td>Total postpartum and</td>
<td>17587</td>
<td>17637</td>
<td>-50</td>
</tr>
<tr>
<td>direct follow-up (admissions)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total costs</td>
<td><strong>21884</strong></td>
<td><strong>22030</strong></td>
<td><strong>-146</strong></td>
</tr>
<tr>
<td>95%CI***</td>
<td>-5648 to 7718</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Pessary minus no pessary.
** Including instrumental attempts, caesarean and induction of labour
*** Nonparametric confidence interval based on 1000 bootstrap replications

Table 3 summarizes mean and median cost per woman for the subgroup of women with a CL <38 mm. The mean costs in the antepartum/delivery phase were €3901 in the pessary group and €4017 in the no-pessary group. The costs for maternal antepartum admission were lower in the pessary group (€1985 versus €2185). The mean postpartum costs were €21240 in the pessary and €26560 in the no-pessary group. In this phase we observed lower costs from neonatal admissions in the pessary group compared to the no-pessary group (€18300 versus €22948 respectively). Costs for maternal admissions were also lower in the pessary group (€1780 versus €2394). The mean total costs in the pessary group (n=78) were €25142 versus €30577 in the no-pessary group (n=55), with a difference of -€5436 in favour of the pessary group (95% CI €-11001 to €1456).
An economic analysis of the ProTWIN trial

Table 3: Costs per women (subgroup with a CL <38 mm) (2011 €)

<table>
<thead>
<tr>
<th></th>
<th>Pessary (n = 78)</th>
<th>No pessary (n = 54)</th>
<th>Diff *</th>
</tr>
</thead>
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<tr>
<td></td>
<td>mean</td>
<td>median</td>
<td>IQR</td>
</tr>
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<td>38</td>
<td>38</td>
</tr>
<tr>
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<td>0</td>
</tr>
<tr>
<td>Coticosteroids</td>
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<td>0</td>
<td>4</td>
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<tr>
<td>Antibiotics</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>70</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Laser treatment TTTS</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amnion Drainage</td>
<td>1985</td>
<td>927</td>
<td>309</td>
</tr>
<tr>
<td>Admission antepartum</td>
<td>1628</td>
<td>1984</td>
<td>1048</td>
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<td>Packet cells</td>
<td>53</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Antepartum + delivery</td>
<td>3901</td>
<td>4017</td>
<td>-116</td>
</tr>
<tr>
<td>Maternal admission</td>
<td>1780</td>
<td>1743</td>
<td>1158</td>
</tr>
<tr>
<td>Post-partum</td>
<td>1515</td>
<td>1515</td>
<td>62</td>
</tr>
<tr>
<td>Delivery **</td>
<td>300</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Travel costs</td>
<td>40</td>
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<td>13</td>
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<tr>
<td>Productivity loss</td>
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<td>0</td>
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<tr>
<td>Total postpartum</td>
<td>21240</td>
<td>26560</td>
<td>-5320</td>
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<tr>
<td>and direct follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(admissions)</td>
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<td></td>
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<td>-5436</td>
</tr>
<tr>
<td>95% CI***</td>
<td>-11001 to 1456</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Pessary minus no pessary.
** Including instrumental attempts, caesarean and induction of labour
*** Nonparametric confidence interval based on 1000 bootstrap replications

Cost-effectiveness

In the study sample, we could not demonstrate a reduction of poor perinatal outcome (13% in the pessary group versus 14% in the no-pessary group, RR 0.98; 95% CI 0.69 to 1.4), and also total costs were comparable in both groups. Hence, the interpretation of the incremental cost-effectiveness ratio (ICER), being a ratio of the difference in costs and difference in effectiveness, is not very straightforward. In the prespecified subgroup of women with a CL <25th percentile (<38 mm), a lower rate of poor perinatal outcome as well as lower costs were observed for the pessary group, indicating that the non-pessary group is dominated (higher rate of poor outcome and higher costs). In 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 for both cost and effectiveness differences to be plotted in a combined space. Each point in the cost-effectiveness plane represents the additional costs and health gain of treatment with a pessary compared with no-pessary for the whole group (blue dots) and subgroup <25th percentile (red dots) in each bootstrap sample (Figure 1). The ICER scatter (blue dots) spreads over all four quadrants, around the origin, indicating that our trial did not show significant differences in reduction of poor perinatal outcome rate (x-axis) and in costs (y-axis) for the whole group. The ICER scatter (red dots) for our subgroup demonstrates that there is a significant treatment effect of the pessary, but the cost spreads are mainly in the lower right quadrant (dominance), but also in the upper right quadrant.

**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 with no pessary (multiple samples from original data set). (dots: whole group, squares: subgroup <25th percentile, white dot and black square: base case ICERs both groups)

**Figure 2:** Cost-acceptability plot for the whole group (dashed line) and the subgroup with a CL <25th percentile (solid line). Probability of pessary to be cost-effective to prevent poor perinatal outcome. The probability increases as result of an increase in willingness-to pay.
Results located in the lower right quadrant reflect dominance, indicating that the 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-to-pay for these health gains. Cost-effectiveness acceptability curves visualise the probability that an intervention is considered cost-effective when increasing the willingness-to-pay threshold. For the total study sample, the probability that pessary treatment is cost-effective ranges from 25%, to a maximum of 50% for the highest WTP values. 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 15000 euro per additional case of poor neonatal outcome prevented (Figure 2).

**Sensitivity, scenario and subgroup analysis**

Table 4 summarizes the results of the sensitivity analyses. For the total study sample, the difference in mean total costs increases to -€146 (95% CI €-5648 to €4718) when only unit prices for academic settings are used (model 1), in favour of the pessary. When unit prices for general hospitals are used the difference in mean costs increases to -€187 (95% CI €-6400 to €6094) (model 2). If costs according to gestational age of delivery were used, a costs difference of €1957 (95% CI €-3193 to €6914) is demonstrated (model 3). Including neonatal ward admissions showed an increased difference in mean costs to -€ 359 (95% CI €-6124 to 5020) (model 4).

**Table 4: Sensitivity analyses (2011 €)**

<table>
<thead>
<tr>
<th>Model</th>
<th>Model Pes</th>
<th>No pess</th>
<th>diff</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALL WOMEN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base case</td>
<td>0</td>
<td>21884</td>
<td>-146</td>
<td>-5648 to 4718</td>
</tr>
<tr>
<td>Model 1: Value admissions by using academic unit prices only</td>
<td>1</td>
<td>27186</td>
<td>-187</td>
<td>-6400 to 6094</td>
</tr>
<tr>
<td>Model 2: Value admissions by using general unit prices only</td>
<td>2</td>
<td>19717</td>
<td>-11</td>
<td>-5115 to 4979</td>
</tr>
<tr>
<td>Model 3: Value admissions by using prices according to gestational age at delivery</td>
<td>3</td>
<td>24427</td>
<td>1957</td>
<td>-3193 to 6914</td>
</tr>
<tr>
<td>Model 4: Including neonatal ward admissions</td>
<td>4</td>
<td>23161</td>
<td>-359</td>
<td>-6124 to 5020</td>
</tr>
<tr>
<td><strong>WOMEN WITH CL &lt; 25 PERCENTILE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base case</td>
<td>0</td>
<td>25142</td>
<td>-5435</td>
<td>-11001 to 1456</td>
</tr>
<tr>
<td>Model 1: Value admissions by using academic unit prices only</td>
<td>1</td>
<td>31509</td>
<td>-3391</td>
<td>-11333 to 3854</td>
</tr>
<tr>
<td>Model 2: Value admissions by using general unit prices only</td>
<td>2</td>
<td>24051</td>
<td>-3624</td>
<td>-9681 to 3062</td>
</tr>
<tr>
<td>Model 3: Value admissions by using prices according to gestational age at delivery</td>
<td>3</td>
<td>29319</td>
<td>-2922</td>
<td>-9795 to 2929</td>
</tr>
<tr>
<td>Model 4: Including neonatal ward admissions</td>
<td>4</td>
<td>26343</td>
<td>-5549</td>
<td>-13045 to 464</td>
</tr>
</tbody>
</table>
In the subgroup of women with a CL <38 mm, pessary treatment consistently generates lower costs in all four models. Differences were not statistically significant, indicating robustness against varying estimates in resource use and unit prices.

Discussion

Main findings
This study assessed the cost-effectiveness of a cervical pessary in the prevention of poor perinatal outcome in women with a multiple pregnancy. Our analysis was performed from a societal perspective along the ProTWIN trial. Our results demonstrated that the mean costs per woman were not significantly lower in women with a cervical pessary compared to women without a cervical pessary (mean difference -€146; 95% CI €-5648 to €4718). The primary clinical outcome, poor perinatal, was also comparable in both groups.

In the prespecified subgroup of women with a CL <38 mm treatment with a pessary compared to no pessary was associated with lower costs (-€5436; 95% CI €-11001 to €1456)). Costs differences predominantly originated from the postpartum phase. Treatment with a pessary in women with a CL 38 mm also resulted in a lower risk of poor perinatal outcome. Cost-effectiveness analyses showed that treatment with a pessary in women with a CL <38 mm is most likely to be cost-effective (94% probability at a WTP threshold of €0). Sensitivity analyses demonstrated that our analyses are robust against varying estimates in resource use and unit prices.

Strengths and limitations
Strengths of our study are the fact that it was a randomised controlled trial enabling prospective registration of resource uses. Furthermore the large sample size, diversity of participating hospitals and well-organized structure of the data collection within the Dutch Obstetric Consortium are likely to extend the internal and external validity of our results. As extensive sensitivity analyses showed similar results, we conclude that the model is robust against the most influential uncertainties. 9;16;17 The study has also 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. To calculate QALY’s for this purpose several conceptual points need to be taken into consideration. Currently, neither clinical long-term outcomes nor QALY’s are integrated in studies evaluating perinatal interventions. 18 Hence, a QALY-based analysis probably should encompass a long-term perspective and not only till 6 weeks post partum. To facilitate studies addressing the long-term perspective, a systematic approach is needed to developing prediction models to extrapolate short-term outcomes to a long-term horizon. 19 Since there is little evidence on how this can be achieved, we decided not to include this. A second limitation is the fact that we had a relatively small sample size for our subgroup. This resulted in wide confidence intervals and lack of statistical significance. Also we observed large variation in costs for the neonatal postpartum period, therefore we differentiated costs by delivery.
per week of gestation. This sensitivity analysis also showed results consistent with the main analysis. Furthermore, although our study had a short time horizon, we believe that treatment with a cervical pessary is likely to generate less 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.

Relation to other studies
According to our knowledge this is the first economic evaluation that prospectively compared treatment with a cervical pessary versus no-pessary in women with a multiple pregnancy. The clinical outcomes are in line with the PECEP trial demonstrating a significant reduction of preterm birth in women with a singleton pregnancy and a short CL (<25 mm).

Meaning of the results
Since preterm birth is the major contributing factor of 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 group compared to the no-pessary group. Cost-effectiveness acceptability curves suggest that the probability that treatment with a pessary is cost-effective is low, even at high willingness-to-pay thresholds. In women with a multiple pregnancy and a CL <38 mm, significant differences in costs and effects were observed in favour of pessary treatment, resulting in a very high probability that this treatment is cost-effective in this subgroup of women.

Proposal for future research
Our study suggests that treatment with a pessary is reducing perinatal mortality and morbidity and saving costs in women with a relative short CL (<38 mm). These results should be confirmed in appropriately powered studies to detect differences in preterm birth rates and poor perinatal outcomes. Furthermore progesterone has previously been found to be effective in singleton pregnancies with a short cervix. A recent meta-analysis with individual patient data of women with a multiple pregnancy and a CL ≤25 mm showed a reduction of poor neonatal outcome in women treated with vaginal progesterone. Future studies should investigate the comparison of pessary and progesterone in women with a relative short cervix.

Conclusion
Cervical pessaries in women with a multiple pregnancy generate comparable costs as in women without treatment. However in women with a CL <38 mm treatment with a cervical pessary appears highly cost-effective. In combination with the large benefit that we observed in a group of women were the prognosis without intervention is so poor, in our opinion women with a multiple pregnancy and a CL <38 mm one could consider the use of a pessary as long as new randomised controlled trials on the subject are not available.
Acknowledgements
The authors would like to thank all women who participated in the trial. We would also like to thank all members of the Dutch Obstetrics Consortium (http://www.studiesobsgyn.nl/), especially the research nurses and midwives, who among others made this study possible.

Details of ethics approval
The ProTWIN trial was approved on the 14th of May 2009 by the Ethics Committee of the Academic Medical Centre in Amsterdam (MEC 09-107), and had local approval from the Boards of the other participating hospitals. The trial was registered in the Dutch trial registry (NTR1858).

Additional members of the ProTWIN Study Group
Joke Bais (Medical Centre Alkmaar, The Netherlands), Karin de Boer (Hospital Rijnstate, Arnhem, The Netherlands), Kitty Bloemenkamp (Leiden University Medical Centre, The Netherlands), Jozien Brons (Medical Spectrum Twente, Enschede, The Netherlands), Hans Duvekot (Erasmus Medical Centre, Rotterdam, The Netherlands), Bas Nij Bijvank (Isala Clinics, Zwolle, The Netherlands), Maureen Franssen (University Medical Centre Groningen, The Netherlands), Ingrid Gaugler (Jeroen Bosch Hospital, ’s-Hertogenbosch, The Netherlands), Irene de Graaf (Spaarne Hospital, Hoofddorp, The Netherlands), Martijn Oudijk (University Medical Centre Utrecht, The Netherlands) Dimitri Papatsonis (Amphia Hospital, Breda, The Netherlands) Paula Pernet (Kennemer Gasthuis, Haarlem, The Netherlands), Martina Porath (Maxima Medical Centre, Veldhoven, The Netherlands), Liesbeth Scheepers (Academic Hospital Maastricht, Maastricht, The Netherlands), Marko Sikkema (Hospital Group Twente, Almelo, The Netherlands), Jan Sporken (Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands), Harry Visser (Tergooi Hospital, Blaricum, The Netherlands), Wim van Wijngaarden (Bronovo Hospital, Den Haag, The Netherlands) and Mallory Woiski (Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands).
Appendix S1

In addition to the authors, the following Dutch institutions and gynaecologists participated in the ProTWIN trial:

Medical Centre Alkmaar, Alkmaar – J. Bais MD
Flevo Hospital, Almere – G. Kleiverda MD PhD
Hospital Group Twente, Almelo – M. Sikkema MD PhD
Academic Medical Centre, Amsterdam – B.W. Mol MD PhD
Onze Lieve Vrouwe Gasthuis, Amsterdam – D.J. Bekedam MD PhD
Sint Lucas Andreas, Amsterdam – M.H.B. Heres MD PhD
BovenIJ Hospital, Amsterdam – B. Doekhi MD
Meander Medical Centre, Amersfoort – P.C.M. van der Salm MD
Hospital Rijinstate, Arnhem – K. de Boer MD PhD
Tergooi Hospital, Blaricum – H. Visser MD PhD
Amphia Hospital, Breda – D. Papatsonis MD PhD
Jeroen Bosch Hospital, ’s-Hertogenbosch – I. Gaugler MD PhD
Deventer Hospital, Deventer – R. Stichter MD
Nij Smellinghe Hospital, Drachten – J. Wilpshaar MD
Scheper hospital, Emmen – J.M. Burggraaff MD
Bronovo Hospital, ’s-Gravenhage – W.J. van Wijngaarden MD PhD
Catharina Hospital, Eindhoven – T.H.M. Hasaart MD PhD
Medical Spectrum Twente, Enschede – J. Bronz MD PhD
University Medical Centre Groningen, Groningen – M. Franssen MD PhD
Martini hospital, Groningen – A.J. van Loon MD PhD
Kennemer Gasthuis, Haarlem – P.J.M. Pernet MD
Atrium medical centre, Heerlen – J. Langenveld MD PhD
Elkerliek Hospital, Helmond – F. Delemarre PhD
Midden-Twente Hospital, Hengelo – D. Hoozemans MD
Sparnaar Hospital, Hoofddorp – J. Molkenboer MD PhD
Rijnland Hospital, Leiderdorp – M.J. de Vries MD
Academic Hospital Maastricht, Maastricht – L. Scheepers MD Ph
Sint Antonius Hospital, Nieuwegein – E. van Beek MD PhD
Canisius-Wilhelmina Hospital, Nijmegen – J.M.J. Sporken MD PhD
Radboud University Nijmegen Medical Centre, Nijmegen – M. Woisky MD PhD
Ikazia hospital, Rotterdam – J.W. de Leeuw MD PhD
Erasmus Medical Centre, Rotterdam – J.J. Duvekot MD PhD
Tweedesteden hospital, Tilburg – A. Drogtrop MD PhD
Diakonessen hospital, Utrecht – N. Schuijtemaker MD PhD
University Medical Centre Utrecht, Utrecht – M. Oudijk MD PhD
Maxima Medical Centre, Veldhoven – M. Porath MD PhD
Vie Curie Hospital, Venlo – E.J. Wijnen MD
Zaans Medical Centre, Zaandam – N. Bayram MD PhD
Leids University Medical Centre, Leiden – K. Bloemenkamp MD PhD
Isala Clinics, Zwolle – B. Nij Bijvank MD Ph
# Appendix S2: Average volumes of resources used and total costs in each group (2011 €)

<table>
<thead>
<tr>
<th></th>
<th>Pessary (n = 401)</th>
<th>No pessary (n = 407)</th>
<th>Diff (P-NP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unit</strong></td>
<td>% patients</td>
<td>Mean using care</td>
<td>Mean Volume*</td>
</tr>
<tr>
<td>Pessary unit</td>
<td>100,0%</td>
<td>1,00</td>
<td>1,00</td>
</tr>
<tr>
<td>Adalat days</td>
<td>7,0%</td>
<td>1,75</td>
<td>0,12</td>
</tr>
<tr>
<td>Atosiban days</td>
<td>7,7%</td>
<td>2,30</td>
<td>0,18</td>
</tr>
<tr>
<td>Indocid days</td>
<td>1,0%</td>
<td>1,50</td>
<td>0,02</td>
</tr>
<tr>
<td>Coticosteroids gifts</td>
<td>23,4%</td>
<td>1,54</td>
<td>0,36</td>
</tr>
<tr>
<td>Antibiotics UTI</td>
<td>5,7%</td>
<td>x</td>
<td>0,06</td>
</tr>
<tr>
<td>Antibiotics Bact Vaginosis treatment</td>
<td>7,5%</td>
<td>x</td>
<td>0,07</td>
</tr>
<tr>
<td>Utrasounds anteprtum</td>
<td>100,0%</td>
<td>2,10</td>
<td>2,10</td>
</tr>
<tr>
<td>Laser treatment TTTS</td>
<td>1,5%</td>
<td>x</td>
<td>0,01</td>
</tr>
<tr>
<td>Amnion Drainage unit</td>
<td>0,5%</td>
<td>x</td>
<td>0,00</td>
</tr>
<tr>
<td>Admission Antepartum Home Care days</td>
<td>4,0%</td>
<td>9,25</td>
<td>0,37</td>
</tr>
<tr>
<td>Admission Antepartum Ward days</td>
<td>80,0%</td>
<td>6,45</td>
<td>5,16</td>
</tr>
<tr>
<td>Admission Antepartum Medium Care days</td>
<td>15,0%</td>
<td>5,53</td>
<td>0,83</td>
</tr>
<tr>
<td>Admission Antepartum Intesive Care days</td>
<td>2,7%</td>
<td>5,19</td>
<td>0,14</td>
</tr>
<tr>
<td>Delivery (including instrumental attempts/caesarean/induction)</td>
<td>100,0%</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Antepartum + delivery</td>
<td>1723109</td>
<td>4297</td>
<td>1787898</td>
</tr>
<tr>
<td>Packet cells unit</td>
<td>9,0%</td>
<td>3,11</td>
<td>0,28</td>
</tr>
</tbody>
</table>
**Appendix S2 (continued)**

<table>
<thead>
<tr>
<th>Unit</th>
<th>Pessary (n = 401)</th>
<th>No pessary (n=407)</th>
<th>Diff (P-NP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% patients</strong></td>
<td>using care volume</td>
<td>using care Volume**</td>
<td>Costs (€)</td>
</tr>
<tr>
<td>Maternal Home care days</td>
<td>1,5%</td>
<td>3,33</td>
<td>0,05</td>
</tr>
<tr>
<td>Maternal admission ward</td>
<td>days 84,3%</td>
<td>5,61</td>
<td>4,73</td>
</tr>
<tr>
<td>Maternal admission MC days</td>
<td>4,0%</td>
<td>6,00</td>
<td>0,24</td>
</tr>
<tr>
<td>Maternal admission IC days</td>
<td>days 1,7%</td>
<td>2,94</td>
<td>0,05</td>
</tr>
<tr>
<td>Neonatal Home Care days</td>
<td>days 2,0%</td>
<td>3,37</td>
<td>0,07</td>
</tr>
<tr>
<td>Neonatal admission Ward</td>
<td>days 100,0%</td>
<td>x</td>
<td>3,60</td>
</tr>
<tr>
<td>Neonatal admission MC days</td>
<td>days 46,4%</td>
<td>26,54</td>
<td>12,32</td>
</tr>
<tr>
<td>Neonatal admission HC days</td>
<td>days 7,0%</td>
<td>17,02</td>
<td>2,42</td>
</tr>
<tr>
<td>Neonatal admission IC days</td>
<td>days 14,2%</td>
<td>47,02</td>
<td>3,53</td>
</tr>
<tr>
<td>Surfactant treatment days</td>
<td>7,5%</td>
<td>1,66</td>
<td>0,12</td>
</tr>
<tr>
<td>Intubation days</td>
<td>days 6,7%</td>
<td>8,11</td>
<td>0,54</td>
</tr>
<tr>
<td>CPAP days</td>
<td>days 17,2%</td>
<td>11,80</td>
<td>2,03</td>
</tr>
<tr>
<td>CT scan unit</td>
<td>days 16,5%</td>
<td>4,25</td>
<td>0,70</td>
</tr>
<tr>
<td>Ultrasound post partum</td>
<td>unit 16,5%</td>
<td>4,25</td>
<td>0,70</td>
</tr>
<tr>
<td>X ray unit</td>
<td>days 9,0%</td>
<td>3,82</td>
<td>0,34</td>
</tr>
<tr>
<td>Travel days</td>
<td>days 92,5%</td>
<td>13,60</td>
<td>12,58</td>
</tr>
<tr>
<td>Productivity loss days</td>
<td>days 6,0%</td>
<td>22,61</td>
<td>1,36</td>
</tr>
<tr>
<td><strong>Total postpartum and direct follow-up (admissions)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Appendix S3: Average volumes of resources used and total costs for the subgroup of women with a CL <38 mm (2011 €)

<table>
<thead>
<tr>
<th>Resource Type</th>
<th>Unit</th>
<th>% Patients (P-NP)</th>
<th>Volume*</th>
<th>Volume**</th>
<th>Costs (€)</th>
<th>Costs pp (€)</th>
<th>Mean</th>
<th>Mean (P-NP)</th>
<th>% Patients (P-NP)</th>
<th>Volume*</th>
<th>Volume**</th>
<th>Costs (€)</th>
<th>Costs pp (€)</th>
<th>Mean</th>
<th>Mean (P-NP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pessary</td>
<td>unit</td>
<td>100,0%</td>
<td>1,00</td>
<td>1,00</td>
<td>2964</td>
<td>38</td>
<td>0,0%</td>
<td>0,00</td>
<td>0,0%</td>
<td>0,00</td>
<td>0,00</td>
<td>0,00</td>
<td>0</td>
<td>0</td>
<td>38</td>
</tr>
<tr>
<td>Adalat</td>
<td>days</td>
<td>3,8%</td>
<td>1,69</td>
<td>0,06</td>
<td>1</td>
<td>0</td>
<td>7,4%</td>
<td>2,50</td>
<td>0,19</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Atosiban</td>
<td>days</td>
<td>11,5%</td>
<td>1,78</td>
<td>0,21</td>
<td>8888</td>
<td>114</td>
<td>13,0%</td>
<td>1,99</td>
<td>0,26</td>
<td>7777</td>
<td>144</td>
<td>-30</td>
<td>-3</td>
<td></td>
<td>-30</td>
</tr>
<tr>
<td>Indocid</td>
<td>days</td>
<td>1,3%</td>
<td>0,98</td>
<td>0,01</td>
<td>0</td>
<td>0</td>
<td>5,6%</td>
<td>1,32</td>
<td>0,07</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Coticosteroids</td>
<td>gifts</td>
<td>26,9%</td>
<td>1,56</td>
<td>0,42</td>
<td>119</td>
<td>2</td>
<td>31,5%</td>
<td>1,56</td>
<td>0,49</td>
<td>93</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Antibiotics UTI</td>
<td>treatment</td>
<td>3,8%</td>
<td>1,05</td>
<td>0,04</td>
<td>257</td>
<td>3</td>
<td>7,4%</td>
<td>0,95</td>
<td>0,07</td>
<td>343</td>
<td>6</td>
<td>-3</td>
<td>-3</td>
<td></td>
<td>-3</td>
</tr>
<tr>
<td>Antibiotics Bact Vaginosis</td>
<td>treatment</td>
<td>9,0%</td>
<td>1,00</td>
<td>0,09</td>
<td>599</td>
<td>8</td>
<td>3,7%</td>
<td>1,08</td>
<td>0,04</td>
<td>171</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Ultrasounds antepartum</td>
<td>unit</td>
<td>100,0%</td>
<td>2,26</td>
<td>2,26</td>
<td>5495</td>
<td>70</td>
<td>100,0%</td>
<td>2,06</td>
<td>0,07</td>
<td>3465</td>
<td>64</td>
<td>6</td>
<td>6</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Laser treatment TTTS</td>
<td>unit</td>
<td>0,0%</td>
<td>0,00</td>
<td>0,00</td>
<td>0</td>
<td>0</td>
<td>0,0%</td>
<td>0,00</td>
<td>0,00</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Amnion Drainage</td>
<td>unit</td>
<td>0,0%</td>
<td>0,00</td>
<td>0,00</td>
<td>0</td>
<td>0</td>
<td>1,9%</td>
<td>1,05</td>
<td>0,02</td>
<td>116,68</td>
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<td>240</td>
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Appendix S3 (continued)

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<th>Unit</th>
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<td>% patients using care</td>
<td>Mean Volume**</td>
<td>Costs (€)</td>
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<td>Maternal admission ward days</td>
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<td>Maternal admission MC days</td>
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<td><strong>Total postpartum and direct follow-up (admissions)</strong></td>
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<td>21 241</td>
<td>143 4254</td>
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<td><strong>Total costs</strong></td>
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*Of patients using care
** Of all patient
Reference List


