Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial

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Summary

Background In women with a multiple pregnancy, spontaneous preterm delivery is the leading cause of perinatal morbidity and mortality. Interventions to reduce preterm birth in these women have not been successful. We assessed whether a cervical pessary could effectively prevent poor perinatal outcomes.

Methods We undertook a multicentre, open-label randomised controlled trial in 40 hospitals in the Netherlands. We randomly assigned women with a multiple pregnancy between 12 and 20 weeks' gestation (1:1) to pessary or control groups, using a web-based application with a computer-generated list with random block sizes of two to four, stratified by hospital. Participants and investigators were aware of group allocation. For women in the pessary group, a midwife or obstetrician inserted a cervical pessary between 16 and 20 weeks' gestation. Women in the control group did not receive the pessary, but otherwise received similar obstetrical care to those in the pessary group. The primary outcome was a composite of poor perinatal outcome: stillbirth, periventricular leucomalacia, severe respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, necrotising enterocolitis, proven sepsis, and neonatal death. Analyses were by modified intention to treat. This trial is registered in the Dutch trial registry, number NTR1858.

Findings Between Sept 21, 2009, and March 9, 2012, 813 women underwent randomisation, of whom 808 were analysed (401 in the pessary group; 407 in the control group). At least one child of 53 women (13%) in the pessary group had poor perinatal outcome, compared with 55 (14%) in the control group (relative risk 0·98, 95% CI 0·69–1·39).

Interpretation In unselected women with a multiple pregnancy, prophylactic use of a cervical pessary does not reduce poor perinatal outcome.

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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 an increased risk of mortality, disability, and developmental disorders later in life.[1,2] Women with a multiple pregnancy are at increased risk of preterm delivery. In the Netherlands, about 50% of women with a multiple pregnancy deliver before 37 weeks' gestation, of whom 9% deliver before 32 weeks.[3] In the USA, 60% deliver before 37 weeks, of whom 12% deliver before 32 weeks.[4] By contrast, 6–10% of women with a singleton pregnancy deliver before 37 weeks, of whom 1% deliver before 32 weeks.[3,4]

Therefore, reduction of preterm birth in women with multiple pregnancies is a major challenge in obstetrical care. Studies have shown that 17α-hydroxyprogesterone caproate and vaginal progesterone reduce the frequency of preterm birth in women with singleton pregnancies who have a history of spontaneous preterm birth or a short cervix.[5–10] However, vaginal progesterone and 17α-hydroxyprogesterone caproate are not effective in prevention of preterm birth in women with multiple pregnancies,[11–13] and neither are other interventions, such as routine hospital admission with bed rest and prophylactic use of a cervical cerclage.[14,15]

However, treatment with a cervical pessary might prevent preterm birth. Pessaries of different types and sizes are available. Although exactly how cervical pessaries act is unknown, they surround the cervix and therefore might change the inclination of the cervical canal. By relieving direct pressure on the internal cervical ostium, pessaries could distribute the weight of the uterus onto the vaginal floor, retrosymphyseal osteomuscular structures, and Pouch of Douglas. Hence, they might prevent premature dilatation of the cervix and rupture of the membranes.[16] Alternatively, the cervical canal could be compressed, which might prevent deterioration or loss of the cervical mucus plug. During pregnancy, the cervix normally stays tightly closed, with a cervical mucus plug sealing the opening. The role of the cervical mucus plug as an immunological gatekeeper might prevent ascending infections that lead to preterm delivery.[17,18]

Previous studies of pessaries for prevention of preterm birth have been fairly small and non-randomised.[19–23] The PECEP trial[24] showed that a cervical pessary reduced

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For the **ProTWIN protocol** see http://www.studies-obsgyn.nl/protwin/page.asp?page_id=770

For more on the **nationwide consortium** see http://www.studies-obsgyn.nl

preterm birth in women with a singleton pregnancy and a cervical length of less than 25 mm.[24] Because no effective measures exist to prevent preterm birth in women with a multiple pregnancy, we assessed the effectiveness of a pessary in these women.

Methods

Study design and participants

We undertook the multicentre, open-label randomised ProTWIN trial in 40 hospitals in the Netherlands that collaborate in a nationwide consortium for women's health research. Women with a multiple pregnancy between 12 and 20 weeks' gestation were eligible. Exclusion criteria were known serious congenital defects, fetal death, twin-to-twin transfusion syndrome, and known placenta praevia. Gestational age and chorionicity were established sonographically. Women were counselled about the trial by research nurses and midwives, or by their own obstetrician.

All participants provided written informed consent. The study was approved by the research ethics committee of the Academic Medical Centre in Amsterdam (MEC 09-107, NTR1858) and by the boards of each participating hospital.

Randomisation and masking

We randomly assigned women (1:1) to the pessary or control groups, using a web-based application with a computer-generated list with random block sizes of two or four, stratified by hospital, and rendered by an independent data manager. Participants and investigators were aware of allocation; masking was impossible because of the nature of the intervention.

Procedures

An obstetrician or sonographer measured cervical length between 16 and 22 weeks' gestation, either before or shortly after randomisation. A transvaginal probe with a 5 MHz transducer was placed in the anterior fornix of the vagina, after which a sagittal view of the cervix, with the echogenic endocervical mucosa along the length of the canal, was obtained. Callipers were used to measure the distance between the triangular area of echodensity at the external ostium and the V-shaped notch at the internal ostium. Presence or absence of funnelling at the internal ostium was recorded.

For women in the pessary group, an experienced research midwife or obstetrician inserted an Arabin pessary between 16 and 20 weeks' gestation in an outpatient clinic. The pessary (CE0482, MED/CERT ISO 9003/EN 46003; Dr Arabin GmbH and Company, KG; Witten, Germany) is made of soft flexible silicone and available in six different sizes. A vaginal speculum examination was done to establish the appropriate size. The site with the smallest diameter was placed upwards to surround the cervix. Participating hospitals received instructions about how to place the pessary, but because placement was straightforward, no specific training was provided. The pessary was 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. Women in the control group did not receive the pessary, but otherwise received similar obstetrical care to those in the pessary group.[25]

The primary outcome was a composite of poor perinatal outcome: stillbirth, periventricular leucomalacia of grade 2 or worse, severe respiratory distress syndrome of grade 2 or worse, bronchopulmonary dysplasia, intraventricular haemorrhage of grade 2B or worse, necrotising enterocolitis, proven sepsis, and neonatal death within 6 weeks after the expected term date. Periventricular leucomalacia, respiratory distress syndrome, intraventricular haemorrhage, and necrotising enterocolitis were defined according to previously described classifications.[26–30] Secondary outcome measures were time to delivery, preterm birth before 32 and 37 weeks, days of admission to a neonatal intensive care unit, days of maternal admission for preterm labour, and maternal morbidity (defined as thromboembolic complications, urinary tract infection treated with antibiotics, pneumonia, endometritis, eclampsia, HELLP syndrome [ie, haemolysis, elevated liver enzymes, and low platelets], death, or other). Additionally, we did a post-hoc analysis of preterm birth before 28 weeks.

Statistical analysis

Statistical analyses were by modified intention to treat. We assessed the differences between the two groups by calculating the relative risk (RR) of the primary outcome with a log-binomial mixed model. Stratification by hospital was accounted for with a random intercept for each hospital.

We assessed time to delivery by Cox proportional hazard analysis and Kaplan-Meier estimates, and compared results with a log-rank test. We assessed differences in continuous outcomes that did not follow a normal distribution with a linear quantile mixed model, with adjustment for stratified randomisation.[31]

We initially planned a subgroup analysis in women with a cervical length of less than 25 mm. During the assessment of the distribution of midpregnancy cervical length before analysis, we noted that only nine women had a cervical length of less than 25 mm (three in the pessary group and six in the control group). Therefore, before the comparative analysis, we altered the cutoff of cervical length to the 25th percentile, which was approved by the ethics committee. We did a subgroup analysis for women with a cervical length lower than the 25th percentile and of the 25th percentile or higher, and added an interaction term between the treatment and the subgroup variable to the regression model. When an interaction term was significant ($p<0·05$), we estimated the treatment effect within strata on the basis of the subgroup variable. We planned exploratory subgroups analyses for

parity, chorionicity, and number of fetuses. To investigate the effect of missing cervical length measurements on any effect recorded in the subgroups, we did a sensitivity analysis in which the missing measurements were imputed with multiple imputation.[32]

We calculated expected frequencies of poor perinatal outcome of 12·4% per pregnancy in the control group and 6·7% in the pessary group, on the basis of the probability that a woman delivers at a specific gestational age combined with the probability of poor perinatal outcome at that gestational age. We used these expected frequencies to calculate sample size. Women who had at least one child with a poor perinatal outcome were deemed to have a poor perinatal outcome. Using a two-sided test with a type I error of 0·05 and a type II error of 0·2, we calculated that we would need a sample size of 800 women (400 per group). This sample size calculation was different from that in our original protocol (660 women).[33] The initial sample size was based on the expected proportion of bad perinatal outcome for each neonate. However, because randomisation and intervention were done for mothers, we decided during the study that the analysis would be done on maternal level. This adjustment was recommended by the data safety monitoring committee before the end of recruitment, and was approved by the medical ethics committee.[34] Additionally, we report data on the child level, assessed with generalised estimating equations to account for clustering of children within one mother.[35] We also analysed data for the first 660 enrolled patients (original sample size).

A planned interim analysis was done after 300 women had been enrolled. The data safety monitoring committee noted no conditions to stop the trial at interim analysis. All analyses were adjusted for the interim analyses with the O'Brien-Fleming alpha spending function.[36] As a result, a nominal p value of less than 0·049 was deemed to indicate statistical significance. All statistical analyses were done in R for Windows (version 2.15.2).

This trial is registered in the Dutch trial registry, number NTR1858.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SL and ES had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Between Sept 21, 2009, and March 9, 2012, 813 women underwent randomisation (figure 1). More cervical length measurements were missing in the control group than in the pessary group (table 1). Mean cervical length was slightly higher in the control group than in the pessary group (table 1). The pessary was not inserted in 23 women (6%) assigned to the pessary group: ten (2%) withdrew from the study, four (1%) had cerclage, four (1%) had placenta praevia, one (<1%) delivered before placement of the pessary, and four (1%) for an unspecified reason. In the pessary group, insertion before 16 weeks' gestation occurred in 18 patients (4%) and after 20 weeks' gestation in two (<1%).

Five women in the pessary group had a surgical cerclage, one of whom died. At 19·3 weeks' gestation, after randomisation but before insertion of the pessary, she presented with contractions indicating preterm labour. After transvaginal sonography showed a cervical length of 27 mm and funnelling, the local investigator

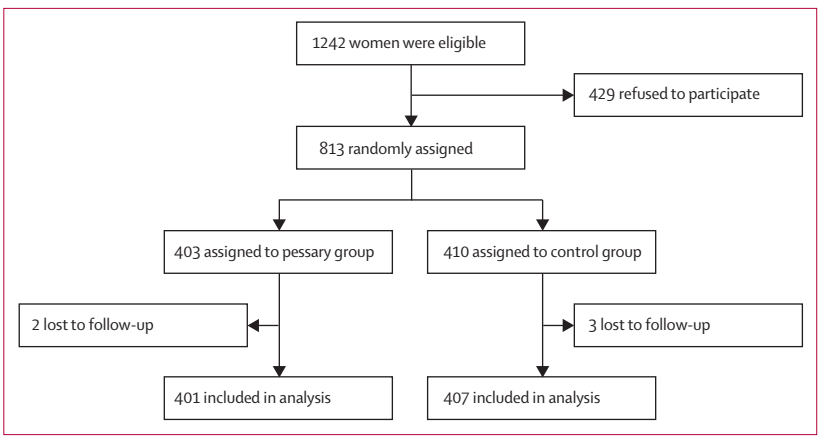

Figure 1: **Trial profile**

	Pessary group (n=403)	Control group (n=410)
Maternal characteristic		
Age at randomisation (years)	33·1 (4·6)	32·7 (4·5)
Body-mass index (kg/m²)	23·7 (21·5–26·3)	22·9 (21·0–25·8)
Ethnic origin*		
White European	352 (91%)	347 (90%)
Non-white European	35 (9%)	38 (10%)
University or higher vocational education	153 (38%)	156 (38%)
Nulliparous	222 (55%)	225 (55%)
Previous preterm delivery	29 (7%)	26 (6%)
Smoking during pregnancy	16 (4%)	25 (6%)
Pregnancy characteristics		
Pregnant after fertility treatment†	150 (37%)	141 (34%)
Triplets	9 (2%)	9 (2%)
Monochorionic pregnancy	87 (22%)	100 (24%)
Gestational age at randomisation (weeks)	16·9 (2·0)	17·0 (2·0)
Gestational age at pessary placement (weeks)	18·7 (1·5)	..
Measurement of cervical length at 16–22 weeks' gestation	328 (81%)	293 (71%)
Gestational age at cervical length measurement (weeks)	18·4 (1·7)	18·6 (2·3)
Cervical length overall (mm)	43·6 (8·1)	44·2 (8·5)
Funnelling at randomisation	5 (1%)	4 (1%)

Data are mean (SD), median (IQR), or n (%). *Known for 387 women in pessary group and 385 in control group. †Ovarian hyperstimulation, in-vitro fertilisation, intracytoplasmic sperm injection, or intrauterine insemination.

Table 1: **Baseline characteristics**

decided not to place the pessary but to do a McDonald cerclage. During this procedure, the membranes of one twin ruptured; the woman subsequently received antibiotics. After 6 days, she developed severe sepsis and died a few hours after transfer to intensive care. The other four women who had a cerclage delivered at 21·6 weeks, 23·1 weeks, 26·4 weeks, and 36·7 weeks of gestation. Three of them had poor perinatal outcomes. In the control group, no women had a cerclage.

Vaginal discharge was frequent in the pessary group (table 2). The pessary was removed before 28 weeks' gestation in 57 (14%) of 401 women in the pessary group included in analyses, seven (12%) of whom delivered within 48 h of removal. The reason for pessary removal before 28 weeks was preterm premature rupture of the membranes in nine women (16%), vaginal bleeding in eight (14%), contractions in five (9%), pain in 17 (30%), increased discharge in seven (12%), induction of labour in two (4%), spontaneous loss of the pessary in seven (12%), and not specified in two (4%). The pessary was removed between 28 and 32 weeks' gestation in 22 women (5%), of whom 13 (59%) delivered within 48 h after removal. The reason for removal between 28 and 32 weeks was preterm premature rupture of the membranes in six women (27%), vaginal bleeding in one (5%), contractions in ten (45%), pain in two (9%), induction of labour in two (9%), and spontaneous loss of the pessary in one (5%). The pessary was removed between 32 and 36 weeks' gestation in 107 women (27%), of whom 70 (65%) delivered within 48 h after removal. The reason for removal between 32 and 36 weeks was preterm premature rupture of the membranes in 29 women (27%), vaginal bleeding in two (2%), contractions in 31 (29%), pain in four (4%), increased discharge in two (2%), induction of

	Pessary group (n=401)	Control group (n=407)
Vaginal discharge	104 (26%)	0
Pain	16 (4%)	1 (<1%)
Discharge and pain	13 (3%)	0
Fever or signs of infections	9 (2%)	5 (1%)
Other	5 (1%)	2 (<1%)

Data are n (%).

Table 2: **Adverse events**

	Maternal level			Child level		
	Pessary group (n=401)	Control group (n=407)	RR (95% CI)	Pessary group (n=811)	Control group (n=823)	RR (95% CI)
Neonatal outcome						
Composite poor perinatal outcome	53 (13%)	55 (14%)	0·98 (0·69 to 1·39)	81 (10%)	87 (11%)	0·95 (0·65 to 1·38)
Stillbirth	10 (2%)	10 (2%)	1·02 (0·41 to 2·59)	10 (1%)	14 (2%)	0·72 (0·30 to 1·77)
Periventricular leucomalacia	0	5 (1%)	NA	0	5 (1%)	NA
Respiratory distress syndrome	27 (7%)	18 (4%)	1·52 (0·85 to 2·72)	36 (4%)	29 (4%)	1·26 (0·67 to 2·35)
Bronchopulmonary dysplasia	2 (<1%)	6 (1%)	0·34 (0·07 to 1·67)	2 (<1%)	9 (1%)	0·23 (0·04 to 1·17)
Intraventricular haemorrhage	6 (1%)	5 (1%)	1·22 (0·37 to 3·98)	8 (1%)	7 (1%)	1·16 (0·33 to 4·07)
Necrotising enterocolitis	8 (2%)	6 (1%)	1·35 (0·47 to 3·88)	8 (1%)	7 (1%)	1·16 (0·39 to 3·43)
Sepsis	16 (4%)	18 (4%)	0·89 (0·45 to 1·77)	19 (2%)	25 (3%)	0·77 (0·38 to 1·55)
Death before discharge	16 (4%)	18 (4%)	0·90 (0·46 to 1·77)	23 (3%)	28 (3%)	0·83 (0·41 to 1·68)
Birthweight						
<2500 g	271 (68%)	275 (68%)	0·99 (0·90 to 1·09)	442 (55%)	466 (57%)	0·96 (0·86 to 1·06)
<1500 g	49 (12%)	53 (13%)	0·93 (0·65 to 1·35)	82 (10%)	86 (10%)	0·95 (0·65 to 1·41)
Congenital anomalies	18 (4%)	27 (7%)	0·68 (0·38 to 1·24)	22 (3%)	33 (4%)	0·68 (0·37 to 1·26)
5-min Apgar score <7	39 (10%)	47 (12%)	0·84 (0·56 to 1·25)	50 (6%)	60 (7%)	0·85 (0·55 to 1·30)
Admission to neonatal intensive care unit	60 (15%)	76 (19%)	0·80 (0·57 to 1·13)	102 (13%)	124 (15%)	0·83 (0·60 to 1·15)
Length of admission (days)	11 (5 to 33)	14 (6 to 26)	0·00 (–9·57 to 9·57)*	9 (4 to 21)	9 (3 to 17)	–1·00 (–5·12 to 3·16)*
Delivery						
Gestational age at delivery (weeks)†	36·7 (34·7 to 37·4)	36·4 (34·3 to 37·6)	0·91 (0·76 to 1·09)‡	..	..	..
<28 weeks§	16 (4%)	21 (5%)	0·79 (0·50 to 1·27)	..	..	..
<32 weeks	41 (10%)	49 (12%)	0·86 (0·65 to 1·15)	..	..	..
<37 weeks	222 (55%)	233 (57%)	0·94 (0·87 to 1·07)	..	..	..
Labour induction	175 (44%)	179 (44%)	1·00 (0·85 to 1·16)	..	..	..
Fetal indication	31 (8%)	37 (9%)	0·85 (0·55 to 1·32)	..	..	..
Maternal indication	63 (16%)	59 (14%)	1·10 (0·81 to 1·41)	..	..	..
Combined	16 (4%)	12 (3%)	1·36 (0·65 to 2·83)	..	..	..
Elective	65 (16%)	71 (17%)	0·96 (0·74 to 1·23)	..	..	..

(Continues on next page)

	Maternal level			Child level		
	Pessary group (n=401)	Control group (n=407)	RR (95% CI)	Pessary group (n=811)	Control group (n=823)	RR (95% CI)
(Continued from previous page)						
Mode of delivery						
Spontaneous	134 (33%)	179 (44%)	0·77 (0·65 to 0·92)	..	..	..
Planned caesarean delivery	105 (26%)	83 (20%)	1·30 (1·01 to 1·67)	..	..	..
Emergency caesarean delivery	104 (26%)	97 (24%)	1·09 (0·87 to 1·39)	..	..	..
Forceps or ventouse	54 (13%)	51 (13%)	1·09 (0·76 to 1·55)	..	..	..
All livebirths at any gestational age	388 (97%)	392 (96%)	1·01 (0·87 to 1·16)	796 (98%)	803 (98%)	1·01 (0·99 to 1·02)
Pregnancy						
Tocolytic drugs	74 (18%)	92 (23%)	0·82 (0·62 to 1·07)	..	..	..
Corticosteroids	94 (23%)	113 (28%)	0·83 (0·65 to 1·04)	..	..	..
Cerclage placement	5 (1%)	0	NA	..	..	..
Preterm prelabour rupture of membranes	35 (9%)	34 (8%)	1·06 (0·68 to 1·66)	..	..	..
Gestational age (weeks)	32·7 (27·1 to 35·1)	33·9 (31·0 to 36·3)	1·92 (1·00 to 3·70)‡	..	..	..
Hypertensive disorder	65 (16%)	53 (13%)	1·22 (0·88 to 1·72)	..	..	..
Chorioamnionitis	13 (3%)	14 (3%)	0·93 (0·43 to 2·01)	..	..	..
Intrauterine fetal death <24 weeks	3 (1%)	4 (1%)	0·89 (0·43 to 1·90)	3 (<1%)	7 (1%)	0·44 (0·10 to 1·98)
Maternal morbidity	38 (9%)	32 (8%)	1·22 (0·77 to 1·92)	..	..	..
Thromboembolic complications	3 (1%)	2 (<1%)	1·56 (0·26 to 9·37)	..	..	..
Urinary tract infection treated with antibiotics	4 (1%)	0	NA	..	..	..
Pneumonia	1 (<1%)	0	NA	..	..	..
Endometritis	2 (<1%)	2 (<1%)	1·11 (0·13 to 9·67)	..	..	..
Eclampsia or HELLP syndrome	8 (2%)	7 (2%)	1·20 (0·41 to 3·54)	..	..	..
Death	1 (<1%)	0	NA	..	..	..
Other	19 (5%)	21 (5%)	0·95 (0·51 to 1·77)	..	..	..
Length of maternal admission for preterm labour (days)	3 (1 to 5)	2 (1 to 6)	0·00 (–1·17 to 1·69)*	..	..	..

Data are presented as n (%) or median (IQR), unless otherwise stated. RR=relative risk. NA=not applicable. *Difference in median, not RR. †Only four women with an interval between deliveries >1 day; gestational age at delivery was not assessed at the child level. ‡Hazard ratio instead of RR. §Post-hoc analysis.

Table 3: **Outcomes by study group**

labour in 21 (20%), spontaneous loss of the pessary in one (1%), logistical reasons in 14 (13%; clinic visit in 35th week), and was not specified in three (3%).

In analysis at the maternal level, frequency of poor perinatal outcome for at least one of the neonates did not differ between groups (table 3). Additionally, frequency of the individual components of the composite poor perinatal outcome did not differ (table 3). Median gestational age at delivery was similar in the two groups (figure 2, table 3). Frequencies of delivery before 28, 32, and 37 weeks did not differ (table 3). Frequency and length of admission to neonatal intensive care unit were also similar (table 3). Maternal morbidity occurred at similar frequencies in the two groups (table 3). Analysis on child level showed that frequency of poor perinatal outcome did not differ between groups (table 3). Analysis of the data for the original sample size of 660 women also showed no difference (data not shown).

The 25th percentile of cervical length for the subgroup analysis was 38 mm. Baseline characteristics did not differ between women with a cervical length of less than 38 mm and those with a cervical length of at least 38 mm (data not shown). In women with a cervical length of less than 38 mm, median cervical length was 35 mm (IQR 32–36) in the pessary group and 34 mm (32–35) in the control group. In analysis at the maternal level for these women, poor perinatal outcome was less frequent in the pessary group ($p_{interaction}$=0·0106; table 4). Additionally, median gestational age at delivery was longer in the pessary group than in the control group ($p_{interaction}$=0·0437; figure 2, table 4). The pessary reduced risk of delivery before 28 ($p_{interaction}$=0·0158) or 32 weeks ($p_{interaction}$=0·0476), but not delivery before 37 weeks ($p_{interaction}$=0·5739; table 4). Analysis at the child level also showed that the composite poor perinatal outcome was less frequent in the pessary group than in the control group (table 4).

In women with a cervical length of at least 38 mm, median cervical length was 46 mm (IQR 42–51) in the pessary group and 45 mm (42–50) in the control group. We recorded no differences in analyses of women with cervical lengths of at least 38 mm at either the maternal or child levels (table 5).

Women for whom we did not have a cervical length measurement had a slightly higher risk of poor neonatal

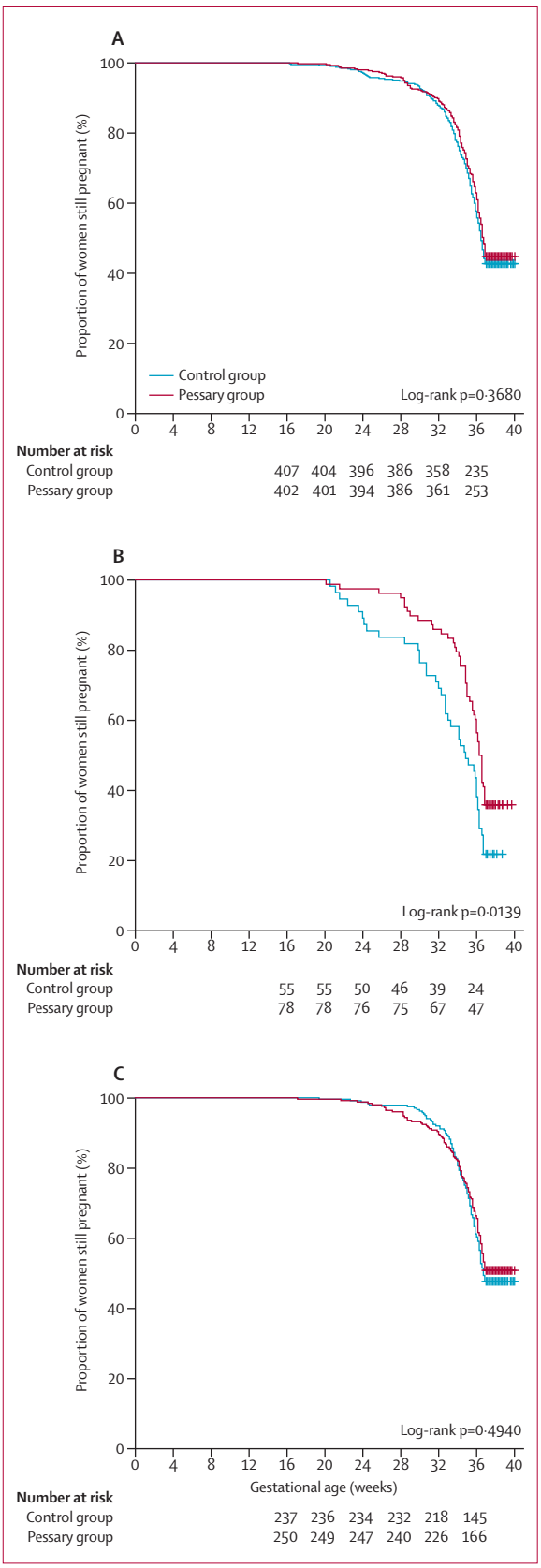

Figure 2: **Kaplan Meier curves of proportion of continued pregnancies in (A) all women, (B) women with a cervical length of less than 38 mm, and (C) women with a cervical length of at least 38 mm**
All curves censored at 37 weeks' gestation. 38 mm is the 25th percentile of cervical length.

outcome in the pessary group than in the control group, although the difference was not significant. However, the sensitivity analysis showed that missing measurements did not change the effect of pessaries (data not shown).

12 (14%) of the 87 women in the pessary group with a monochorionic pregnancy had the composite poor perinatal outcome compared with 26 (26%) of the 100 women in the control group (RR 0·53, 95% CI 0·28–0·99; $p_{interaction}$=0·0149). We recorded no interaction between parity or the number of fetuses and treatment.

Discussion

We have shown that a cervical pessary does not effectively prevent poor perinatal outcome or preterm birth in all women with a multiple pregnancy. However, in a planned subgroup analysis in women with a cervical length of less than the 25th percentile (<38 mm), the pessary significantly reduced frequency of poor perinatal outcome and very preterm delivery.

Our study has several limitations. First, as previously stated, our sample size calculation was different from that in our original protocol.[33] However, analysis of the data at the child level as well as for the original planned sample size of 660 patients showed similar results as for the total study population of 813 women. Second, we had to alter our initial planned subgroup analysis of women with a cervical length of less than 25 mm to an analysis of women with a cervical length of less than the 25th percentile, because only nine women had a cervical length of less than 25 mm.

Third, the number of missing cervical length measurements differed between the pessary and control groups. The fact that more measurements were missing in the control group was probably because obstetricians were not aware that women in the control group were participating in the trial. Moreover, an additional visit was needed for placement of the pessary in the pessary group, so there was an extra opportunity for cervical length measurement. Women who had a cervical length of at least 38 mm and those with a missing cervical length measurement had a slightly higher risk of poor neonatal outcome with the pessary than without, although these differences were not significant. However, the sensitivity analysis showed that missing measurements did not alter the effect of the pessary.

We included women who did not have the pessary inserted in our analyses. Furthermore, the pessary was removed before 36 weeks' gestation in almost half the women, mainly because of signs of preterm delivery. Indeed, most of these women delivered in a short time after removal of the pessary. Obstetrician ambivalence to or even disbelief in the effectiveness of the pessary might have affected the decision to discontinue use of the pessary. The open-label nature of our trial could also have affected medical decision making. Therefore, the potential benefit of the pessary

	Maternal level			Child level		
	Pessary group (n=78)	Control group (n=55)	RR (95% CI)	Pessary group (n=157)	Control group (n=111)	RR (95% CI)
Neonatal outcome						
Composite poor perinatal outcome	9 (12%)	16 (29%)	0·40 (0·19–0·83)	16 (10%)	27 (24%)	0·42 (0·19–0·91)
Stillbirth	3 (4%)	2 (4%)	1·06 (0·18–6·16)	3 (2%)	2 (2%)	1·06 (0·18–6·18)
Periventricular leucomalacia	0	1 (2%)	NA	0	1 (1%)	NA
Respiratory distress syndrome	7 (9%)	2 (4%)	2·46 (0·53–11·51)	9 (6%)	4 (4%)	1·59 (0·33–7·62)
Bronchopulmonary dysplasia	0	2 (4%)	NA	0	2 (2%)	NA
Intraventricular haemorrhage	0	3 (5%)	NA	0	4 (4%)	NA
Necrotising enterocolitis	0	1 (2%)	NA	0	1 (1%)	NA
Sepsis	2 (3%)	4 (7%)	0·38 (0·05–3·14)	2 (1%)	4 (4%)	0·35 (0·07–1·88)
Death before discharge	2 (3%)	10 (18%)	0·14 (0·03–0·65)	3 (2%)	17 (15%)	0·13 (0·03–0·60)
Delivery						
Gestational age at delivery (weeks)*	36·4 (35·0–37·3)	35·0 (30·7–36·7)	0·49 (0·32–0·77)†	..	..	..
<28 weeks‡	3 (4%)	9 (16%)	0·23 (0·06–0·87)	..	..	..
<32 weeks	11 (14%)	16 (29%)	0·49 (0·24–0·97)	..	..	..
<37 weeks	50 (64%)	43 (78%)	0·82 (0·54–1·24)	..	..	..
Pregnancy						
Tocolytic drugs	16 (21%)	18 (33%)	0·63 (0·35–1·12)	..	..	..
Corticosteroids	21 (27%)	17 (31%)	0·83 (0·49–1·43)	..	..	..

Data are n (%) or median (IQR), unless otherwise stated. RR=relative risk. NA=not applicable.*Only four women with an interval between deliveries of >1 day; gestational age at delivery was not assessed at the child level. †Hazard ratio instead of RR. ‡Post-hoc analysis.

Table 4: **Outcomes in women with a cervical length of less than 38 mm**

	Maternal level			Child level		
	Pessary group (n=250)	Control group (n=238)	RR (95% CI)	Pessary group (n=506)	Control group (n=479)	RR (95% CI)
Neonatal outcome						
Composite poor perinatal outcome	32 (13%)	24 (10%)	1·26 (0·77–2·09)	48 (9%)	36 (8%)	1·26 (0·74–2·15)
Stillbirth	4 (2%)	4 (2%)	1·13 (0·21–6·09)	4 (1%)	5 (1%)	0·76 (0·18–3·13)
Periventricular leucomalacia	0	4 (2%)	NA	0	4 (1%)	NA
Respiratory distress syndrome	18 (7%)	11 (5%)	1·56 (0·74–3·28)	25 (5%)	17 (4%)	1·40 (0·64–3·04)
Bronchopulmonary dysplasia	2 (1%)	2 (1%)	0·95 (0·13–6·76)	2 (<1%)	3 (1%)	0·63 (0·08–4·74)
Intraventricular haemorrhage	6 (2%)	2 (1%)	2·85 (0·58–14·11)	8 (2%)	3 (1%)	2·52 (0·47–13·67)
Necrotising enterocolitis	4 (2%)	4 (2%)	0·95 (0·24–3·79)	4 (1%)	5 (1%)	0·76 (0·18–3·14)
Sepsis	10 (4%)	8 (3%)	1·19 (0·48–2·98)	11 (2%)	12 (3%)	0·87 (0·33–2·27)
Death before discharge	10 (4%)	4 (2%)	2·52 (0·74–8·62)	15 (3%)	6 (1%)	2·36 (0·70–7·95)
Delivery						
Gestational age at delivery*	37·0 (35·0–38·0)	36·7 (35·0–37·7)	0·93 (0·72–1·19)†	..	..	..
<28 weeks‡	10 (4%)	5 (2%)	2·02 (0·64–6·41)	..	..	..
<32 weeks	24 (10%)	19 (8%)	1·20 (0·67–2·13)	..	..	..
<37 weeks	123 (49%)	124 (52%)	0·94 (0·79–1·12)	..	..	..
Pregnancy						
Tocolytic drugs	41 (16%)	49 (21%)	0·80 (0·55 to 1·17)	..	..	..
Corticosteroids	54 (22%)	64 (27%)	0·78 (0·57 to 1·07	..	..	..

Data are n (%) or median (IQR), unless otherwise stated. RR=relative risk. NA=not applicable. *Only four women with an interval between deliveries of >1 day; gestational age at delivery was not assessed at the child level. †Hazard ratio instead of RR. ‡Post-hoc analysis.

Table 5: **Outcomes in women with a cervical length of at least 38 mm**

in the prevention of preterm birth when used in women with a cervical length of less than 38 mm might even be larger than we reported.

Our results are consistent with those of another randomised trial assessing the effectiveness of the pessary in women with a singleton pregnancy and a

Panel: Research in context

Systematic review

We searched Medline and Embase for reports published in any language before Feb 28, 2013. We used the search terms "preterm birth" and "cervical pessary". We checked reference lists of identified reports for those not identified by electronic searches. We identified reports of four randomised controlled trials[23,24,37,38] and six cohort studies[19,21,22,39–41] of the effectiveness of a cervical pessary to prevent preterm birth. Overall, they showed that cervical pessaries are potentially effective in prevention of preterm birth.

Interpretation

As far as we are aware, ours is the first randomised study of the use of a cervical pessary to prevent preterm birth in women with multiple pregnancies. We showed that a cervical pessary significantly reduces risk of poor perinatal outcome and preterm birth in women with multiple pregnancies and a cervical length of less than 38 mm. Our results are in line with those of the PECEP trial.[24] Our findings need to be confirmed in other trials before definite conclusions can be drawn. However, in view of the large benefit that we recorded in a group of women for whom the outlook without intervention is poor, and in view of the safety and low cost of the pessary, clinicians should consider a cervical pessary in women with a multiple pregnancy and a fairly short cervical length.

short cervical length (≤25 mm; panel).[24] That trial showed a strong reduction in frequency of preterm birth before 34 weeks, which resulted in a reduction in poor neonatal outcome. Another smaller study did not show this effect, but the prevalence of the preterm birth in that study was low.[37]

A meta-analysis of individual patient data for women with a multiple pregnancy and a cervical length of 25 mm or lower showed a reduction in poor neonatal outcome in women given vaginal progesterone.[10] Our finding that the pessary was effective in women with a fairly short cervix (<38 mm) but not in the overall population of women with multiple pregnancies suggests that future studies should compare pessary and progesterone in women with multiple pregnancies and a short cervix.

Other important advantages of the pessary are its low cost (€38 per pessary) and its mechanical working mechanism, which minimises risk of side-effects on the offspring. The low cost means they could be used in developing countries, conditional on the availability of devices to assess cervical length.[42] Furthermore, our data show that the pessary is well tolerated: we did not record differences in maternal morbidity between the pessary and control groups. Similarly, Arabin and colleagues[21] reported that 17 (95%) of 18 women who had a pessary inserted would use a pessary again or even recommend its use to others.

Obviously, the positive treatment effect of the pessary in women with a twin pregnancy and a short cervix needs to be confirmed in future prospective studies before definite conclusions can be drawn. However, in view of the large benefit that we recorded in a group of women for whom the outlook without intervention is poor, and in view of the safety and low cost of the pessary, the question about how to counsel women with multiple pregnancies and short cervixes is an interesting one. In our opinion, a pessary should be considered in the absence of further data.

Contributors

SL, MH, MvP, BWM, and DB designed and coordinated the study. JB, KdB, KB, JB, HD, BNB, MF, IG, IdG, MO, DP, PP, MP, LS, MS, JS, HV, WvW, and MW collected data. SL and ES analysed and interpreted the data. SL wrote the first draft of the report. All authors critically revised the first draft, and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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