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Cervical pessaries to prevent preterm birth in women with a multiple pregnancy: a per-protocol analysis of a randomized clinical trial

Short running title: ProTWIN trial

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Abstract

Introduction. We recently showed that a cervical pessary prevents preterm birth and reduces poor neonatal outcomes in women with a twin pregnancy and a short-cervix (<38 mm). The objective of this study was to evaluate the full potential treatment effect of the pessary in the whole group and in women with a short-cervix. *Material and methods.* We performed a per-protocol analysis of a multicenter randomized controlled trial (ProTWIN trial, NTR1858) where we excluded women who were allocated to the pessary but never had it placed. Women who had the pessary removed before 36 gestational weeks and did not deliver within seven days after removal, were censored. Analyses were performed on all women and in those with a cervical length <38 mm. *Results.* In 23 (6%) women the pessary was not placed. In women with a cervical length <38 mm (25th percentile) the pessary reduced poor perinatal outcome (RR 0.32, 95%CI 0.13-0.78) and birth at <32 weeks (RR 0.41, 95%CI 0.20-0.87). After censoring 47 (12%) women, the time to delivery was longer in the pessary group than in the control group (whole group: hazard ratio 0.68, 95%CI 0.55-0.82, cervical length < 38 mm: hazard ratio 0.35, 95%CI 0.22-0.57). *Conclusions.* The analysis confirms the principal findings of the intention-to-treat analysis. Time to delivery was longer in the pessary group compared to the control group when censored data were used. This implies the pessary should not be removed until labor is evident.

Keywords

Preterm birth, multiple pregnancies, cervical pessaries, delivery, pregnancy

Abbreviations

CI: confidence interval

HR: hazard ratio

IQR: interquartile range

RR: relative risk

Key Message

The per protocol analysis of the ProTWIN trial suggests potential treatment effect of the pessary to be stronger than previously reported in the intention-to-treat analysis.

Introduction

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 and 9% even prior to 32 weeks. In comparison, for women with a singleton pregnancy these rates are 6-10% and 1%, respectively (1;2). Reduction of preterm birth in multiple pregnancies is therefore a major challenge in obstetrical care.

One of the potential strategies to reduce preterm birth in multiple pregnancies is the use of a cervical pessary. We published a multicenter randomized controlled trial (ProTWIN trial) in which we randomized 813 women to treatment with a pessary from 16-20 weeks onwards or no intervention. Although we found that in women with a multiple pregnancy a pessary did not reduce preterm birth or poor perinatal outcomes, in a pre-specified subgroup of women with a cervical length below the 25th percentile (38 mm) the pessary reduced both poor perinatal outcome and birth before 32 weeks of gestation (3).

Analysis in the trial was according to the intention-to-treat principle, which is the universally favored method for data analysis in randomized controlled trials, as it reflects the performance of the treatment in clinical practice (4). The intention-to-treat principle ensures treatment groups with a comparable prognostic profile due to randomisation, and prevents bias in analysis that could be created by post randomisation exclusions. While intention-to-treat does so, it may underestimate the true treatment effect by analysis of all participants, including those that did not receive the treatment they were randomized for. In a per protocol analysis, only those who received an acceptable amount of the test treatment randomized for and who had a minimal amount of follow-up are analysed (5;6).

In our randomized study, several women allocated to the pessary group never had the pessary placed. Furthermore, a substantial part of the women had their pessary removed before the intended 36 weeks of gestation due to reasons not related to preterm birth. This article expands on the first ProTWIN trial report. Our objective was to estimate the potential treatment effect of the cervical pessary by performing a per protocol analysis and to separately analyse the data of women in whom the pessary was removed before 36 weeks of gestation.

Material and methods

We performed a secondary analysis on data from the ProTWIN trial. The ProTWIN trial was approved by the research ethics committee of the Academic Medical Center in Amsterdam (MEC 09-107, NTR1858) and the boards of each participating hospital provided local approval for execution of the study. The study was conducted in 40 hospitals in the Netherlands that collaborate in a nationwide consortium for women's health research (www.studies-obsgyn.nl). Women with a multiple pregnancy between 12 and 20 weeks of gestation were eligible for participation. Exclusion criteria were known serious congenital defects, fetal death(s), twin-to-twin transfusion syndrome and known placenta previa. Gestational age and chorionicity were sonographically determined. Cervical length was measured by an obstetrician or sonographer between 16 and 22 weeks of gestation before placement of the pessary, either prior to or shortly after randomization 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. Primary outcome was a composite for poor perinatal condition, 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 diagnosed within six weeks after the expected term date. Secondary outcome measures were time to delivery, preterm birth before 32 and 37 weeks, days of admission to a neonatal intensive care unit, maternal morbidity, and maternal admission days for preterm labor. We performed pre-specified subgroup analysis for women with a cervical length below the 25th percentile (<38 mm) and above the 25th percentile (≥38 mm). We analysed the data on the maternal level; women with a least one child with the poor perinatal outcome were considered to have the poor perinatal outcome. In unselected

women with a multiple pregnancy prophylactic use of a cervical pessary did not reduce poor perinatal outcome (relative risk (RR) 0.98; 95% confidence interval (CI) 0.69-1.4 (intention-to-treat analysis)). However, in women with a cervical length <38 mm, a pessary significantly reduced both poor perinatal outcome and preterm birth <32 weeks of gestation (RR 0.40; 95%CI 0.19-0.83 and RR 0.49; 95%CI 0.24-0.97 (intention-to-treat analysis)) (3).

Statistical analysis

The present analysis was performed according to the per protocol principle. Women who were allocated to the pessary group but who never used the pessary were excluded from this analysis. Moreover, in women who had the pessary removed before 36 weeks of gestation, we evaluated duration of treatment, time interval from removal till delivery, reason for removal, and birth before 32 and 37 weeks of gestation or occurrence of poor perinatal outcome. Women in whom the pessary was removed before 36 weeks of gestation and who did not deliver within seven days after removal were censored at the moment the pessary was removed. Women who delivered within seven days after the removal of the pessary were kept in the analysis and considered to have had an event in the analysis of preterm delivery. In the analysis of neonatal outcome, the condition of the baby was considered to be healthy after removal of the pessary when the woman did not deliver within seven days after removal of the pessary, whereas the condition of the child (poor neonatal outcome or not) was considered when the woman delivered within seven days after removal of the pessary. By censoring individuals from the analyses we attempted to create an unbiased estimate of time to event, thus providing insight into the potential of the pessary (7).

The potential effectiveness of the pessary as compared to no treatment was assessed by calculating the ratio of the primary outcome rates in the two groups. Hence, the measure of association was a RR with a 95% CI. This RR was calculated by using a log-binomial mixed model, which accounted for the stratified randomization by hospital by fitting a random intercept for each hospital. We evaluated time to delivery by Cox proportional hazard analysis and Kaplan-Meier estimates. A log rank test was used to assess statistical differences in the Kaplan-Meier estimates. All statistical analyses were conducted in R for Windows, version 2.15.2 (The R Foundation for Statistical Computing, https://www.r-project.org/).

Results

Between September 2009 and March 2012 a total of 813 women were randomly assigned to the cervical pessary (n=403) or no-pessary (n=410) groups. In 23 (6%) of the 403 women randomized to the pessary group, the pessary was not placed for the following reasons: withdrawal from the study (n=10), cerclage (n=4), placenta previa (n=4), second trimester miscarriage (n=1), or an unspecified reason (n=4). Baseline characteristics for the women compared in the intention-to-treat and per protocol analysis were comparable (Table 1).

Table 2 shows the reasons for removal, duration of treatment, interval between removal and delivery, gestational age at delivery, and occurrence of poor perinatal outcome for three different gestational age categories (<28 weeks, between 28 and 32 weeks, and between 32 and 36 weeks). In the whole study population the pessary was removed before 28 weeks in 57 (31%) women, between 28 and 32 weeks in 21 (11%) women, and between 32 and 36 weeks in 107 (58%) women. Of these, seven (12%), 14 (67%), and 72 (67%) women, respectively, delivered within 48 hours after removal of the pessary. The most prevalent reason for pessary removal at these gestational ages were symptoms of preterm labor, such as pain (16 (28%)), contractions (10 (45%)), and premature rupture of the membranes (29 (27%)), respectively. Poor perinatal outcome occurred in 21 (37%), 10 (45%), and 11 (10%) pregnancies, respectively. The median number of days between removal and delivery was 92 (interquartile range (IQR) 41-112) days for removal <28 weeks, 0 (IQR 0-13) days for removal between 28 and 32 weeks and 1 (IQR 0-4) day for removal between 32 and 36 weeks.

Table 3 demonstrates the primary outcome for the intention-to-treat and per protocol analyses at the maternal level. For the whole group, in the intention-to-treat analysis poor perinatal outcome of at least one of the newborns occurred in 53 (13%) women in the pessary group and in 55 (14%) women in the control group (RR 0.98, 95%CI 0.69-1.4). When analysed per protocol poor perinatal outcome occurred in 44 (12%) women in the pessary group and in 55 (14%) women in the control group (RR 0.86, 95%CI 0.59-1.3).

For the subgroup of women with a cervical length <38 mm the pessary was removed before 28 weeks in 15 (37%), between 28 and 32 weeks in five (12%), and between 32 and 36 weeks in 21 (51%) women (Table 2). Of these, one (7%), three (60%), and 13 (62%) women delivered within 48

hours after removal of the pessary, respectively. The most prevalent reasons for pessary removal before 28 weeks were both discharge and pain (3 (20%) and 3 (20%)). Premature rupture of the membranes (2 (40%) and 7 (33%)) was the most prevalent reason for pessary removal between 28 and 32 weeks, and between 32 and 36 weeks, respectively. Poor perinatal outcome occurred in six (40%) women in whom the pessary was removed before 28 weeks of gestation and did not occur in the group of women in whom the pessary was removed after 28 weeks of gestation. The median number of days between removal and delivery were 89 (IQR 22-111) days for removal <28 weeks, three (IQR 0-28) days for removal between 28 and 32 weeks and one (IQR 0-6) day for removal between 32 and 36 weeks.

In the subgroup of women with a cervical length <25th percentile (<38 mm), in the intention-to-treat analysis poor perinatal outcome occurred in at least one of the children in nine (12%) women in the pessary group compared to in 16 (29%) in the no-pessary group (RR 0.40, 95%CI 0.19-0.83) (Table 4). When analysed per protocol, poor perinatal outcome occurred in seven (9%) women in the pessary group and in 16 (29%) in the no-pessary group (RR 0.32, 95%CI 0.13-0.78). The point estimate for reduction of preterm birth <32 weeks of gestation was lower in the per protocol analysis compared to the intention-to-treat analysis, although not substantially different.

Figure 1 shows Kaplan Meier curves for time to delivery with and without censoring for all women (A) and women with a cervical length < 38 mm (B). Time to delivery was censored at 37 weeks of gestation. Furthermore, we censored 47 (12%) women, of whom 15 (4%) had a cervical length <38 mm, because delivery did not occur within seven days after removal of the pessary. The baseline characteristics for this group demonstrated no difference. Time to delivery was longer in the pessary group compared to the control group, with the censored data demonstrating a larger treatment effect for both the whole group and the short cervix group in the per protocol analysis compared to the intention-to-treat analysis using uncensored data (whole group: hazard ratio (HR) 0.68, 95%CI 0.55-0.82 vs. HR 0.88, 95%CI 0.73-1.1, cervical length < 38 mm: HR 0.35, 95%CI 0.22-0.57 vs. HR 0.45, 95%CI 0.29-0.70). Similar results were found when we censored all women in whom the pessary was removed and delivery did not occur within 48 hours (whole group: HR 0.60, 95%CI 0.49-0.74 vs. HR 0.88, 95% CI 0.73-1.1, cervical length < 38 mm: HR 0.33, 95%CI 0.21-0.54 vs. HR 0.45, 95%CI 0.28-0.70).

Discussion

In this per protocol analysis, we confirmed the principal findings of the ProTWIN trial, i.e. that use of a cervical pessary did not prevent poor perinatal outcome in an unselected group of women with a multiple pregnancy. The treatment effect in women with a cervical length <38 mm was already statistically significant in the intention-to-treat analysis. However, the per-protocol analysis showed a lower point estimate for the risk of poor perinatal outcome in these women.

We censored 47 (12%) women from the analysis; the results imply that treatment with a pessary as compared to no pessary caused a prolongation of pregnancy for all women with a multiple pregnancy. Our censoring technique allowed us to assess the maximal potential benefit of pessary use. In the original study, some women allocated to pessary never got the pessary in place, while other women had the pessary removed for no clear medical reason while their pregnancy continued. In our present and new analysis, we evaluated only the period in which the woman indeed had the pessary in place. This indicates that there is a potential benefit of the pessary for the prolongation of pregnancy when consistently applied in women with a multiple pregnancy.

The initial trial analysis was performed according to the intention-to-treat principle. A minority of women (23/403) never had the pessary inserted, while in almost half of the women the pessary was removed prior to 36 weeks, mainly due to signs of preterm delivery. Several pessaries were removed for other reasons than signs of preterm delivery. Equipoise towards or maybe even disbelief in the effectiveness of the pessary among obstetricians might have influenced the decision to discontinue the use of the pessary. In most cases the pessaries were removed due to patient discomfort like increased vaginal discharge or pain. We believe that caregivers as well as women with a multiple pregnancy would consider continuing treatment with a pessary despite discomfort if they were aware of the potential benefit. The pessary should only be removed when labor is evident.

The exact mechanism of action of the cervical pessary remains unknown. It has been hypothesized that the pessary encompasses the cervix and changes the inclination of the cervical canal. By relieving direct pressure on the internal cervical ostium, it distributes the weight of the pregnant uterus onto the vaginal floor, retro-symphyseal osteomuscular structures and towards the pouch of

Douglas. Hence, it may prevent premature dilatation of the cervix and premature rupture of the membranes (8). Another possible explanation is that, due to the encompassed cervix, the cervical canal is compressed and this might prevent deterioration or loss of the cervical mucus plug. During pregnancy the cervical internal os normally stays closed with a mucus plug sealing the opening. The role of the cervical mucus plug as an immunological gatekeeper, protecting the fetoplacental unit against infection from the vagina, may potentially play an important role in preventing ascending infections leading to preterm delivery (9;10).

We performed a secondary analysis of a randomized controlled trial, investigating the effect of the use of a cervical pessary in women with a multiple pregnancy. To our knowledge this is the first study investigating the effect of the removed pessaries in women with a multiple pregnancy. Our results are in line with the results of a randomized trial (PECEP) evaluating the effectiveness of the pessary in women with a singleton pregnancy and a short cervical length (≤25 mm) (11). That trial demonstrated a substantial reduction in the preterm birth rate before 34 weeks, which resulted in a reduction of poor neonatal outcome. Recently the PECEP-twins demonstrated that the insertion of a cervical pessary reduces the rate of spontaneous early preterm delivery in women with a multiple pregnancy and a short cervix (abstract only) (12).

Our study has several limitations. First of all, this is a secondary analysis of the data of the ProTWIN trial. By including only women who received the pessary, the per protocol analysis reflected the effects of the intervention unaffected by protocol deviations or non-adherence. It might introduce bias because participants may be excluded after randomisation. The original comparability of the groups in baseline characteristics achieved by randomisation might not have been maintained. Therefore, differences between treatment groups at the end of the study might not have been due to differences in treatment received, but be a result of differences between treatment groups in their baseline characteristics (13). Since the baseline characteristics between both groups showed no differences we believe we did not introduce this bias. Furthermore it could be questioned whether censoring women in whom the pessary was removed and did not deliver within one week is justified. Since these women did not deliver within seven days after removal of the pessary, we concluded that in these women the pessary was not removed for the correct reason. This might overestimate the treatment effect of the pessary and might introduce an unforeseeable direction of bias. The cut-

off for the interval between removal and delivery was seven days and even when the interval cut-off was two days the similar effects were found.

In summary, we demonstrated that a per protocol analysis does not change the principal findings of the ProTWIN trial. However, the per protocol analysis demonstrated an potentially larger reduction of poor perinatal outcome and very preterm delivery rates than the intention-to-treat analysis for women with a cervical length below <38 mm. Time to delivery was longer in the pessary group compared to the control group when censored data were used. This indicates that the treatment effect of the pessary in the prevention of preterm birth and poor perinatal outcome in women with a multiple pregnancy might be larger when consistently applied. This also implies that it is better not to remove the pessary until labor is evident.

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Table 1: Baseline characteristics per protocol.

	Intention-to-treat		**Per protocol**	
	Pessary (n=403)	**Control (n=410)**	**Pessary (n=380)**	**Control (n=410)**
Maternal characteristic				
Maternal age	33.1 (4.6)	32.7 (4.5)	33.1 (4.6)	32.7 (4.5)
Body Mass Index [#]	23.7 (21.5-26.3)	22.9 (21.0-25.8)	23.7 (21.5-26.6)	22.9 (21.0-25.8)
Ethnic origin				
Caucasian	352 (91)	347 (90)	334 (91)	347 (90)
Non-caucasian	35 (9)	38 (9)	32 (9)	38 (9)
Higher professional education	153 (38)	156 (38)	147 (39)	156 (38)
Nulliparous	222 (55)	225 (55)	209 (55)	225 (55)
Previous preterm delivery	29 (7)	26 (6)	25 (7)	26 (6)
Smoking during pregnancy	16 (4)	25 (6)	13 (4)	25 (6)
Pregnancy characteristics				
Pregnant after ART[**]	150 (37)	141 (35)	139 (37)	141 (35)
Triplets	9 (2)	9 (2)	9 (2)	9 (2)
Monochorionic pregnancy	87 (22)	100 (25)	84 (22)	100 (25)
CL measurement	328 (81)	293 (71)	315 (83)	293 (71)
GA at randomisation	16.9 (2.0)	17.0 (2.0)	16.9 (2.0)	17.0 (2.0)
GA at pessary placement	18.7 (1.5)	NA	18.7 (1.5)	NA
GA at CL measurement	18.8 (1.1)	18.7 (1.5)	18.7 (1.2)	18.7 (1.5)
Cervical length overall [‡]	43.6 (8.1)	44.2 (8.5)	43.7 (7.8)	44.2 (8.5)
Funnelling at randomisation	5 (1)	4 (1)	4 (1)	4 (1)

Data are presented as mean (SD), median (IQR) of no. (%).

The body mass index is the weight in kilograms divided by the square of the height in meters.

** Ovarian hyperstimulation, IVF, intracytoplasmic sperm injection or intra-uterine insemination.

‡ not all women had a cervical length measurement.

ART, assisted reproductive technology; CL, cervical length; GA, gestational age.

Table 2: Pessary removal and outcome categorized.

GA at removal	**Total Number**	**PPROM**	**Contractions**	**Vaginal bleeding**	**Pain**	**Discharge**	**Other ***	**Duration of treatment days**	**GA at delivery**	**Days removal till delivery**	**Poor perinatal outcome**
All women (n= 186)											
<28 weeks	57 (31)	9 (16)	5 (9)	8 (14)	16 (28)	7 (12)	12 (21)	21 (6-34)	34^{+5} (28^{+5}-37^{+0})	92 (41-112)	21 (37)
≥28 and < 32	22 (11)	6 (27)	10 (45)	1 (5)	2 (9)	0 (0)	3 (14)	75 (66-86)	31^{+3} (29^{+3}-34^{+1})	0 (0-13)	10 (45)
≥32 and <36	107 (58)	29 (27)	28 (26)	2 (1)	3 (3)	2 (1)	43 (40)	113 (102-119)	35^{+2} (34^{+1}-	1 (0-4)	11 (10)

									36^{+1})		
Subgroup women with a CL <38 mm (n=41)											
<28 weeks	15 (37)	2 (13)	1 (7)	2 (13)	3 (20)	3 (20)	4 (27)	20 (13-30)	34^{+6} (29^{+1}-37^{+0})	89 (22-111)	6 (40)
≥28 and < 32	5 (12)	2 (40)	1 (20)	0 (0)	1 (20)	0 (0)	1 (20)	86 (72-88)	31^{+3} (31^{+2}-35^{+4})	3 (0-28)	0 (0)
≥32 and <36	21 (51)	7 (33)	6 (29)	0 (0)	2 (10)	1 (5)	5 (24)	110 (100-114)	35^{+0} (34^{+2}-36^{+0})	1 (0-6)	0 (0)

Data are presented as mean (SD), median (IQR) or no. (%).

*Induction of labor, spontaneous loss of the pessary or reasons no-further specified.

GA, gestational age; PPROM, preterm premature rupture of membranes; CL, cervical length.

Table 3: Outcome per protocol analysis for all women (women in whom the pessary was not placed are not included in this table).

All women	Mother level intention-to-treat			Mother level per protocol		
	Pessary (n=401)	Control (n=407)	Relative Risk (95%CI)	Pessary (n=378)	Control (n=407)	Relative Risk (95%CI)
Neonatal outcome						
Composite poor perinatal outcome	53 (13)	55 (14)	0.98 (0.69-1.4)	44 (12)	55 (14)	0.86 (0.59-1.3)
Stillbirth	10 (2)	10 (2)	1.0 (0.41-2.6)	7 (2)	10 (2)	0.77 (0.27-2.2)
Periventricular leukomalacia	0 (0)	5 (1)	NA	0 (0)	5 (1)	NA
Infant Respiratory distress syndrome	27 (7)	18 (4)	1.5 (0.85-2.7)	25 (7)	18 (4)	1.5 (0.83-2.7)
Bronchopulmonal dysplasia	2 (0)	6 (1)	0.34 (0.07-1.7)	2 (1)	6 (1)	0.36 (0.07-1.8)
Intraventricular hemorrhage IIB	6 (1)	5 (1)	1.2 (0.37-4.0)	6 (2)	5 (1)	1.3 (0.40-4.2)
Necrotizing enterocolitis	8 (2)	6 (1)	1.4 (0.47-3.9)	7 (2)	6 (1)	1.3 (0.42-3.7)
Sepsis	16 (4)	18 (4)	0.89 (0.45-1.8)	15 (4)	18 (4)	0.88 (0.44-1.8)
Death before discharge	16 (4)	18 (4)	0.90 (0.46-1.8)	12 (3)	18 (4)	0.71 (0.34-1.5)

Delivery						
Gestational age at delivery‡	36^{+5} (34^{+5}-37^{+3})	36^{+3} (34^{+2}-37^{+4})	0.91 (0.76-1.1)	36^{+5} (35^{+0}-37^{+3})	36^{+3} (34^{+2}-37^{+4})	0.88 (0.73-1.05)
<28 weeks	16 (4)	21 (5)	0.77 (0.40-1.5)	11 (3)	21 (5)	0.56 (0.27-1.2)
<32 weeks	41 (10)	49 (12)	0.85 (0.57-1.3)	34 (9)	49 (12)	0.75 (0.49-1.1)
<37 weeks	222 (55)	233 (57)	0.95 (0.84-1.1)	206 (54)	233 (57)	0.93 (0.82-1.1)

Data are presented as no. (%) or RR (95% CI).

‡ Hazard ratio.

Table 4: Outcome per protocol analysis for subgroup of women with a cervical length <38 mm (women in whom the pessary was not placed are not included in this table).

Subgroup women with a CL <38	**Mother level intention-to-treat**			**Mother level per protocol**		
	Pessary (n=78)	**Control (n=55)**	**Relative risk (95%CI)**	**Pessary (n=75)**	**Control (n=55)**	**Relative Risk (95%CI)**
Neonatal outcome						
Composite poor perinatal outcome	9 (12)	16 (29)	0.40 (0.19 - 0.83)	7 (9)	16 (29)	0.32 (0.13-0.78)
Stillbirth	3 (4)	2 (4)	1.1 (0.18-6.2)	3 (4)	2 (4)	1.1 (0.19-6.4)
Periventricular leukomalacia	0 (0)	1 (2)	NA	0 (0)	1 (2)	NA
Infant Respiratory distress syndrome	7 (9)	2 (4)	2.5 (0.53-11.5)	6 (8)	2 (4)	2.2 (0.46-10.5)
Bronchopulmonal dysplasia	0 (0)	2 (4)	NA	0 (0)	2 (4)	NA
Intraventricularhemorrhage IIB	0 (0)	3 (5)	NA	0 (0)	3 (5)	NA

Necrotizing enterocolitis	0 (0)	1 (2)	NA	0 (0)	1 (2)	NA
Sepsis	2 (3)	4 (7)	0.38 (0.05-3.1)	2 (3)	4 (7)	0.39 (0.05-3.2)
Death before discharge	2 (3)	10 (18)	0.14 (0.03-0.65)	1 (1)	10 (18)	0.07 (0.01-0.58)
Delivery						
Gestational age at delivery‡	36^{+3} (35^{+0}-37^{+2})	35^{+0} (30^{+5}-36^{+5})	0.49 (0.32-0.77)	36^{+4} (34^{+6}-37^{+3})	35^{+0} (30^{+5}-36^{+5})	0.45 (0.28-0.70)
<28 weeks	3 (4)	9 (16)	0.23 (0.06-0.87)	2 (3)	9 (16)	0.16 (0.04-0.76)
<32 weeks	11 (14)	16 (29)	0.49 (0.24-0.97)	9 (12)	16 (29)	0.41 (0.20-0.87)
<37 weeks	50 (64)	43 (78)	0.82 (0.54-1.2)	47 (63)	43 (78)	0.80 (0.53-1.2)

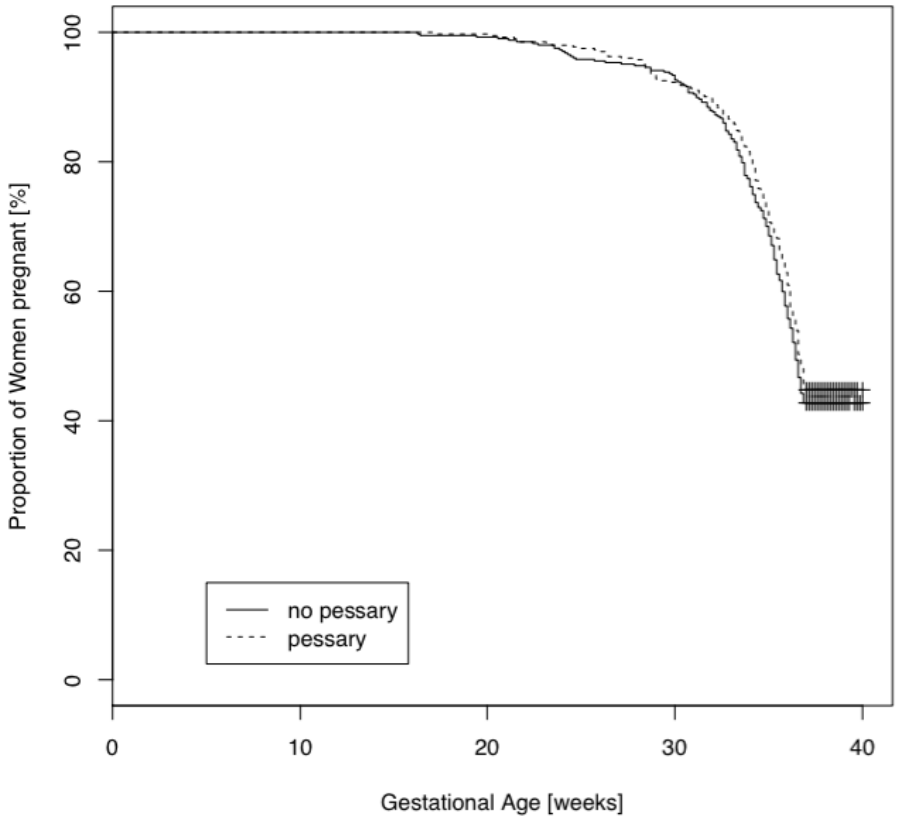
Data are presented as no. (%) or RR (95% CI).

‡ Hazard ratio.

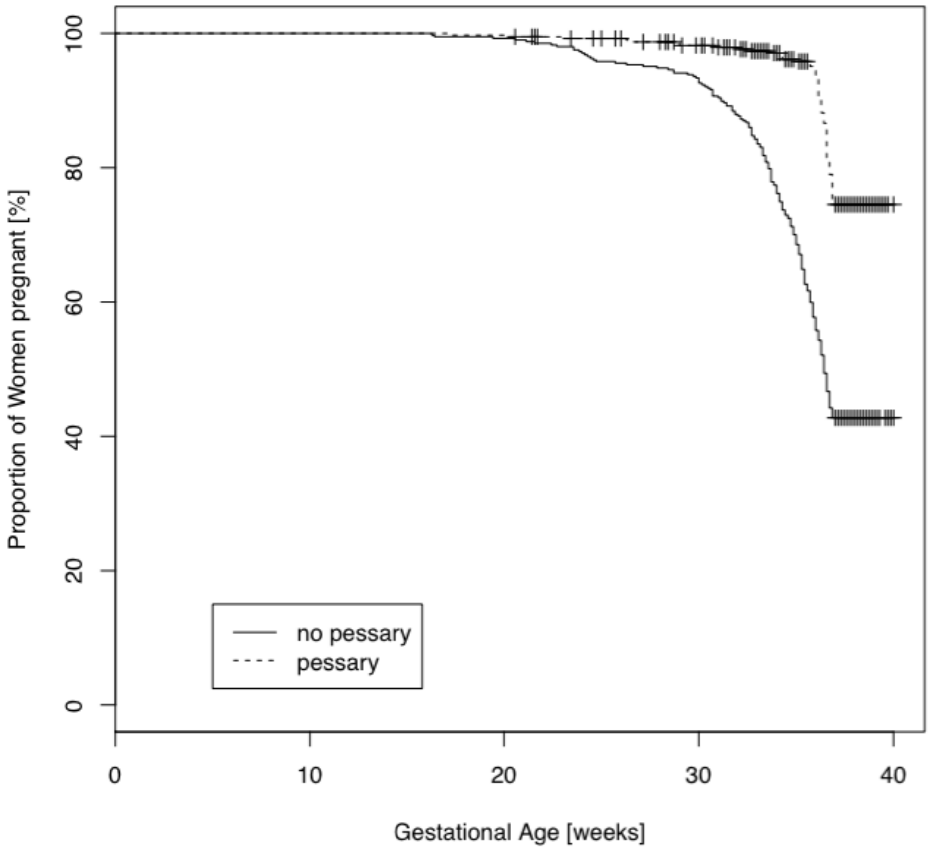
CL, cervical length.

Figure 1: Kaplan Meier curves time to delivery for all women (A) and women with a CL <38 mm (B) with and without censoring of women who did not deliver within seven days after removal of the pessary.

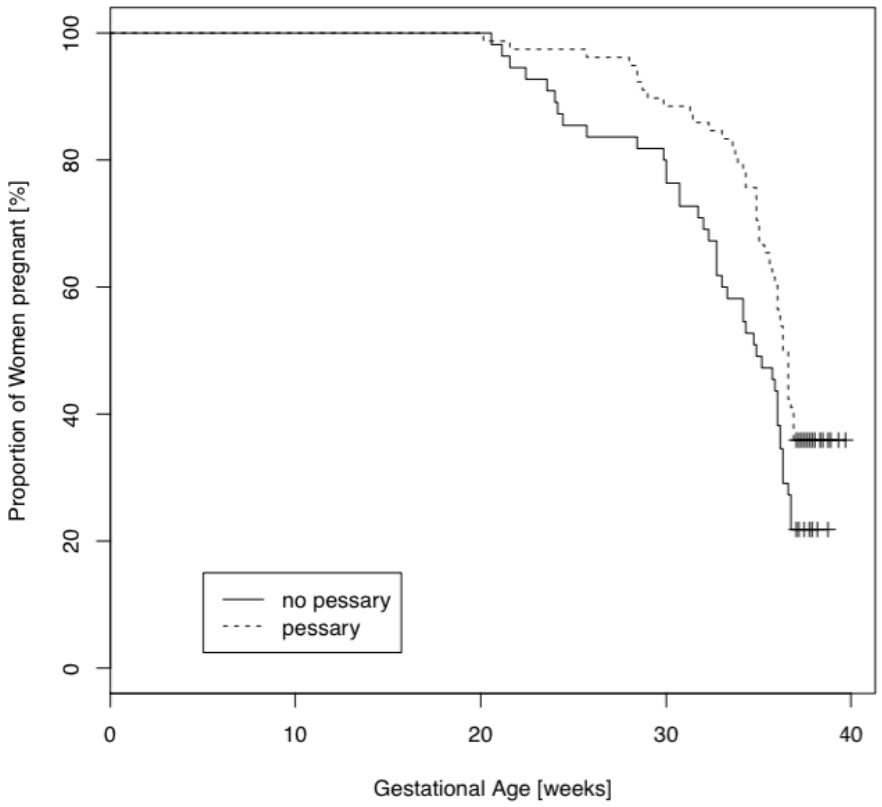
A: all women without censoring (HR 0.88, 95% CI 0.73-1.1)



A: all women with censoring (HR 0.68, 95% CI 0.55-0.82)



B: women with CL <38 mm without censoring (HR 0.45, 95% CI 0.29-0.70)



B: women with CL <38 mm with censoring (HR 0.35, 95% CI 0.22-0.57)