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Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial

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In the print issue of the Journal we wish to publish Table 2

Condensation

Results of a randomized clinical trial comparing expectant management versus cervical pessary show that this intervention does not reduce the rate of early preterm birth

Short version of article title

RCT of cervical pessary in twin gestations

STRUCTURED ABSTRACT

Background: Preterm birth is the leading cause of neonatal death and handicap in survivors. Although twins are found in 1.5% of pregnancies they account for about 25% of preterm births. Randomized controlled trials in singleton pregnancies reported that the prophylactic use of progestogens, cervical cerclage and cervical pessary reduce significantly the rate of early preterm birth. In twin pregnancies, progestogens and cervical cerclage have been shown to be ineffective in reducing preterm birth.

Objective: The objective of this study was to test the hypothesis that the insertion of a cervical pessary in twin pregnancies would reduce the rate of spontaneous early preterm birth.

Study design: This was a multicenter, randomized controlled trial in unselected twin pregnancies of cervical pessary placement from 20^{+0} - 24^{+6} weeks' gestation until elective removal or delivery vs. expectant management. Primary outcome was spontaneous birth <34 weeks. Secondary outcomes included perinatal death and a composite of adverse neonatal outcomes (intraventricular haemorrhage, respiratory distress syndrome, retinopathy of prematurity or necrotizing enterocolitis) or need for neonatal therapy (ventilation, phototherapy, treatment for proven or suspected sepsis, or blood transfusion). Analysis was by intention to treat. This trial is registered in the ISRCTN registry, number 01096902.

Results: A total of 1,180 (56.0%) of the 2,107 eligible women agreed to take part in the trial; 590 received cervical pessary and 590 had expectant management. Two of the former and one of the latter were lost to follow up. There were no

significant differences between the pessary and control groups in rates of spontaneous birth <34 weeks (13.6% vs. 12.9%; relative risk 1.054, 95% confidence interval [CI] 0.787-1.413; p=0.722), perinatal death (2.5% vs. 2.7%; relative risk 0.908, 95% CI 0.553-1.491; p=0.702), adverse neonatal outcome (10.0 vs. 9.2%; relative risk 1.094, 95% CI 0.851-1.407; p=0.524) or neonatal therapy (17.9% vs. 17.2%; relative risk 1.040, 95% CI 0.871-1.242; p=0.701). A *post hoc* subgroup analysis of 214 women with short cervix (≤25 mm) showed no benefit from the insertion of a cervical pessary.

Conclusions: In women with twin pregnancy, routine treatment with cervical pessary does not reduce the rate of spontaneous early preterm birth.

Key words: Arabin pessary, cervical length, neonatal morbidity, prematurity, preterm birth, sonographic short cervix, twins

INTRODUCTION

Preterm birth is responsible for more than 70% of all neonatal and infant deaths.[1] Additionally, children born preterm, compared to those born at term, have a 10-fold increase in risk of cerebral palsy.[2] Twins, with a prevalence of 1.5% of pregnancies,[3] account for about 25% of preterm births.[1] Mortality and morbidity are inversely related to gestational age at delivery and are therefore more common in cases with early preterm birth.[1,4,5] Randomized controlled trials (RCT) in singleton pregnancies with short cervical length reported that the prophylactic use of progesterone reduces significantly the rate of preterm birth and neonatal morbidity.[6-9] Cervical cerclage in singleton pregnancies with short cervix is beneficial only in the subgroup with history of previous preterm birth.[10,11] In twin pregnancies, progestogens and cervical cerclage have been shown to be ineffective in reducing preterm birth.[11-15]

An alternative approach for prevention of preterm birth is transvaginal placement of a silicone pessary around the cervix; this is thought to support the cervix and change its direction towards the sacrum, thereby reducing the direct pressure from the uterine contents on the cervical cana.[16,17] Two RCTs, published after the start of this study, in singleton pregnancies with short cervix provided contradictory results on the effect of cervical pessary on the rate of spontaneous birth at <34 weeks; in one study, the pessary reduced the rate from 27% to 6%,[18] but in the second study of 108 pregnancies there was no significant effect (5.5% vs. 9.4%).[19] A RCT in 813 unselected multiple pregnancies, published after the start of this study, reported that cervical pessary did not

reduce significantly the rate of birth at <32 weeks (12% vs. 10%), but in an unplanned subgroup analysis of 133 women with cervical length <38 mm the rate was reduced (29% vs 14%).[20]

The objective of this multicentre RCT is to test the hypothesis that the insertion of a cervical pessary in twin pregnancies, compared to expectant management, would reduce the rate of spontaneous birth at <34 weeks' gestation.

METHODS

Study design and participants

This was an open-label randomized study of cervical pessary vs. expectant management in twin pregnancies in 23 maternity hospitals in England, Spain, Germany, Austria, Slovenia, Portugal, Italy, Belgium, Albania, Hong Kong, Brazil and Chile.

All women with twin pregnancies undergoing routine ultrasound examination at 20^{+0}-24^{+6} weeks' gestation for assessment of fetal anatomy and measurement of cervical length, were eligible for the study. Exclusion criteria were maternal age <16 years, fetal death, major fetal defect, severe twin-to-twin transfusion syndrome or selective fetal growth restriction, cervical cerclage *in situ*, painful regular uterine contractions and history of ruptured membranes diagnosed before randomization.

Women agreeing to participate in the study gave written informed consent. The study was approved by the National Research Ethics Committee in the

United Kingdom, as well as the local ethics committees of the participating hospitals outside of the United Kingdom. The trial was registered in the ISRCTN registry, number N01096902.

Randomization

Eligible women were randomized in a 1:1 ratio to either cervical pessary or expectant management, using a web-based application with a computer-generated random-number list. In the random-sequence generation there were no restrictions, such as block size or stratification by site. At each centre the patients agreeing to participate in the study were registered with a central computer which then instructed the operator as to whether the patient should receive a cervical pessary or managed expectantly. Consequently, there was no way for study personnel to know or guess the group assignment prior to allocation.

Procedures

Gestational age was determined from the menstrual history and confirmed from the measurement of the crown–rump length of the bigger fetus at 11-13 weeks' gestation.[21] At the same scan chorionicity was determine from examination of the junction between the inter-twin membrane and the placenta.[22]

Cervical length was measured by transvaginal ultrasound examination at 20-24 weeks with women, who had emptied the bladder, placed in the dorsal lithotomy position as previously described,[23] by operators with certification of competence in the technique (Fetal Medicine Foundation Certificate of Competence in Cervical Assessment).

Cervical pessaries (CE0482, MED/CERT ISO 9003 / EN 46003), which consist of flexible silicone, were purchased from the manufacturer (Dr. Arabin GmbH & Co, Witten, Germany). Speculum examination was carried out to inspect the cervix for any pathology and obtain a high vaginal swab for bacteriological examination. If there was offensive vaginal discharge antibiotic therapy was given and insertion of the pessary was delayed until the discharge subsided. The pessary was inserted through the vagina with the woman in the recumbent position and placed upwards around the cervix.[16,18] The research team members introducing the cervical pessaries received instruction on selecting the appropriate size and introducing the device.

Women in the control group received the same obstetrical care as those in the pessary group. Follow-up visits for ultrasound assessment of fetal growth and cervical length were carried out every four weeks until 34 weeks' gestation. If after 26 weeks the cervical length was <10 mm, steroids were administered for fetal lung maturation. At the time of randomization, the participants were informed that a symptom related to the insertion of the pessary could include increased vaginal discharge. At each follow-up visit we asked the participants in both arms of the study and recorded their answer as to whether they had noted an increase in severity or frequency of this symptom and whether they had developed any new symptoms since the beginning of treatment. Women reporting increased vaginal discharge were examined by a doctor for evidence of infection, bacterial swabs were taken and antibiotic therapy was given without removal of the pessary.

The cervical pessary was removed by a simple vaginal examination at 37 weeks' gestation in asymptomatic patients. Earlier removal of the pessary was undertaken if firstly, there was medically indicated induction of labor or elective caesarean section, secondly, preterm labor not responding to tocolytic therapy or preterm prelabor rupture of the membranes or active vaginal bleeding and thirdly, at the patient request because of discomfort.

Quality control of screening, handling of data, and verification of adherence to protocols at the different centers were performed on a regular basis by the trial coordinators. Data on pregnancy outcomes were obtained from hospital maternity records or the patients' general medical practitioners. The records of all patients delivering at <34 weeks were examined to determine whether the birth was medically indicated or spontaneous. Spontaneous births included those with spontaneous onset of labor and those with rupture of membranes before labor.

Outcome measures

The primary outcome was spontaneous birth from randomization to <34 weeks (237 days) of gestation. The secondary outcome measures were: birth weight (mean, <2.5 Kg and <1.5 Kg), perinatal death, composite of major adverse events for the neonate before discharge from the hospital (intraventricular hemorrhage, respiratory distress syndrome, retinopathy of prematurity, or necrotizing enterocolitis), composite of neonatal therapy (ventilation, phototherapy, treatment for proven or suspected sepsis, or blood transfusion) and major maternal complication attributable to the pessary.

Statistical analysis

The sample-size calculation was based on detecting a treatment effect that produces a one-third reduction in the incidence of spontaneous delivery between randomization and 33^{+6} weeks from an anticipated 13% in the expectant management group. In the computer simulations it was assumed that the distribution of cervical lengths and risks in the expectant group were the same as previously reported in our population.[24] Using logistic regression analysis, with adjustment for cervical length, a total sample of 1,180 patients has 85% power of detecting this difference at a (two-tailed) significance level of 5%.

Statistical analyses were by intention to treat and no interim analyses were performed. Baseline data for the cervical pessary and expectant groups were summarized by the median and the interquartile range (IQR). Comparisons between groups were performed with the use of the Mann–Whitney U test. Univariate comparisons of dichotomous data were performed with the use of Fisher's exact test. The P values for all hypothesis tests were two-sided and $P < 0.05$ was considered to indicate statistical significance. The risk of spontaneous preterm birth before 34 weeks was quantified by the relative risk and 95% confidence interval (CI). The risk of spontaneous birth from randomization until 34 weeks was assessed using Kaplan–Meier analysis,[25] where gestational age was the time scale, spontaneous birth was the event, and elective deliveries were treated as censored. For the purposes of this analysis, all pregnancies were considered to be no longer at risk for the event at the start of the 34th week. Hazard ratios were estimated with the use of the Cox proportional-hazards

model, with a formal test of the proportional-hazards assumption.[25,26] Odds ratios were converted to relative risks with the use of the method of Zhang and Yu.[27] Results on perinatal and neonatal outcome were examined both at the pregnancy and fetal / neonatal level because of the potential of non-independence of outcomes from the two twins arising from the same pregnancy.

***Post hoc* analysis**

We conducted a *post hoc* analysis to examine the effect of cervical pessary in women with short cervix (≤25 mm). The reason for undertaking this analysis is that a recent RCT in multiple pregnancies reported that although the pessary was not beneficial in the total population, in an unplanned subgroup analysis of those with cervical length <38 mm the rate of early preterm birth was halved.[20] The cut-off of 38 mm was selected because only 1% of the patients had cervical length <25 mm, which was the cut-off selected for a pre-planned subgroup analysis. However, in our study the cervical length was <25 mm in 18% of cases.

Role of the funding source

Funding for the study was provided by the Fetal Medicine Foundation (UK charity No: 1037116), which had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Study population

A total of 1,180 of the 2,107 eligible pregnant women agreed to take part in the trial (Figure 1). The participants were recruited between August 2008 and May 2011. There were 600 women from England, 391 from Spain, 145 from other European countries and 44 from non-European countries. There were no important differences in baseline characteristics between the pessary and the expectant groups (Table 1). Two pregnancies in the pessary group and one in the controls were lost to follow up. Two of the patients in the control group were treated with vaginal progesterone from 26 and 28 weeks' gestation, respectively, because of cervical shortening; in both cases delivery was >34 weeks.

Outcomes

There was no significant difference between the cervical pessary and control groups in rates of spontaneous birth at <34 weeks, perinatal death, adverse neonatal event or neonatal therapy (Table 2). Logistic regression analysis, with adjustment for cervical length, demonstrated no significant effect of the cervical pessary in the rate of spontaneous birth at <34 weeks (odds ratio 1.058, 95% CI 0.740-1.511; p=0.7584). The cumulative percentage of women who did not give birth spontaneously at <34 weeks was not significantly different between the two groups (hazard ratio, 1.061; 95% CI, 0.776-1.453; P = 0.709, Figure 2).

There were no cases of maternal death or serious vaginal trauma either during insertion or removal of the pessary. There was one case where the pessary was associated with cervical oedema requiring removal under general anesthesia. There were four cases of chorioamnionitis, three in the pessary and one in the control groups, including two in women with miscarriage and two in

those with preterm prelabor rupture of membranes.

***Post hoc* subgroup analysis**

The median cervical length at randomization was 32 mm in both the pessary group and controls and in both groups there was an inverse correlation between cervical length and rate of spontaneous birth at <34 weeks, which was not significantly different between the two groups (Figure 3).

Post hoc subgroup analysis of 214 women with short cervix showed no benefit from the insertion of a cervical pessary (Table 3). The cumulative percentage of women who did not give birth spontaneously at <34 weeks was not significantly different between the two treatment groups in either those with cervical length ≤25 mm (hazard ratio 1.256, 95% CI 0.760-2.074, P=0.374) or those with length >25 mm (hazard ratio 0.975, 95% CI 0.652-1.458, P=0.902) (Figure 4).

Adverse events

At recruitment to the trial, in the cervical pessary compared to control group, there was no significant difference in reported vaginal discharge (10.9% vs. 10.2%, p=0.705) or pelvic discomfort (1.2% vs. 1.5%, p=0.802). In any one of the follow up visits, cervical pessary was associated with significantly higher rate of vaginal discharge (42.1% vs. 20.4%, p<0.0001), but not pelvic discomfort (5.8% vs. 5.1%, p=0.695).

In the cervical pessary group, vaginal swabs demonstrated an infection, most commonly with Candida albicans, group B Streptococcus or Gardnerella vaginalis, in 14.0% (82/585) of cases at recruitment to the trial and in 20.9%

(116/555) in any one of the follow up visits. The respective values in the control group were 13.4% (76/567) and 16.8% (86/511) and these were not significantly different from the pessary group (p=0.797 and p=0.100).

Removal of the pessary at <34 weeks' gestation

The cervical pessary was removed at <34 weeks in 22.3% (131/588) of pregnancies, including 18 for iatrogenic delivery, 34 for preterm labor, 48 for preterm prelabor rupture of membranes and 31 for patient request. Subsequently, there was birth at <34 weeks in 94.4% (17/18) of the iatrogenic group, 90.2% (74/82) of those with preterm labor or rupture of membranes and 22.7% (7/31) of the patient request group. In the latter group, the rate of spontaneous birth at <34 weeks was not significantly higher to that in the total group treated with pessary placement (16.1% vs 13.6%, p=0.589).

COMMENT

Main findings

The findings of this trial demonstrate that in unselected twin pregnancies, or in the subgroup with cervical length ≤25 mm, placements of a cervical pessary at 20-24 weeks' gestation does not reduce the rate of spontaneous early preterm birth, perinatal death, adverse neonatal outcome or need for neonatal therapy.

The cervical pessary was well tolerated by most women and only 5% requested that this is removed. The pessary doubled the rate of vaginal discharge but did not increase the rate of cervico-vaginal infection.

In this randomized twins cohort, the median cervical length at 20-24 weeks' gestation, the overall rate of spontaneous birth at <34 weeks was 13% and this rate was inversely related to cervical length. These findings are consistent with our previous study involving 1,163 twin pregnancies, which was the basis for the power calculations of this trial.[24]

Strengths and limitations

The strengths of the study are first, RCT with central randomization and recruitment of the desired number of patients with nearly complete follow up, second, there were no changes to the protocol after commencement of the trial, no outcomes were selectively dropped post-hoc and the person who performed the statistical analysis was blinded to the allocated interventions, third, measurement of cervical length by appropriately trained sonographers, and fourth, the rate of spontaneous birth at <34 weeks was the same as the one estimated for the power calculations.

A potential limitation of the study is that many research team doctors were involved in the insertion of the pessary and, unlike measurement of cervical length, they did not receive supervised training in doing so. It is therefore not possible to be certain that there was appropriate insertion in all cases. Another potential limitation arises from the inevitable open-label nature of the trial that could have affected medical decision making.

Comparison with results of previous studies

A multicentre RCT in 813 unselected multiple pregnancies, including 795 with twins, reported that cervical pessary inserted at a median gestational age of 19

weeks, compared to expectant management, did not reduce significantly the rate of poor perinatal outcome (13% vs. 14%) or birth at <32 weeks (10% vs. 12%).[20] However, in a subgroup of 133 women with cervical length below the 25th percentile (<38 mm), the pessary group (n=78) compared to controls (n=55) significantly reduced the rate of both poor perinatal outcome (12% vs. 29%) and birth at <32 weeks (14% vs. 29%).[20] In this trial the median cervical length was 44 mm and it was <25 mm, which was the originally planned cut-off for the subgroup analysis, in only 1% of cases. The respective values in our study, in which all measurements of cervical length were carried out by doctors with extensive experience in the technique, were 32 mm and 18%, respectively.

Conclusions and implications

Twin pregnancies are at substantially higher risk of early preterm birth than singleton pregnancies and this risk is inversely related to sonographically measured cervical length at 20-24 weeks' gestation. Insertion of cervical pessary at around 22 weeks in both unselected twins and in those with short cervix does not reduce the rate of spontaneous early preterm birth. The extent to which cervical pessary inserted before 20 weeks in twins with short cervix reduces the rate of early preterm birth may require further investigation. However, before such study is undertaken it is important that the technique for measuring cervical length is standardized and the operators demonstrate their competence in undertaking such measurements.

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Table 1. Characteristics of the study participants.

Characteristics	**Pessary group (n=590)**	**Control group (n=590)**
Age in years, median (IQR)	33.1 (29.5-36.7)	33.2 (29.1-36.6)
Weight in kg, median (IQR)	67.0 (60.0-76.3)	68.0 (60.0-79.0)
Height in cm, median (IQR)	165 (160-170)	164 (160-169)
Racial origin		
Caucasian, n (%)	497 (84.2)	483 (81.9)
Afro-Caribbean, n (%)	43 (7.3)	54 (9.2)
South Asian, n (%)	19 (3.2)	20 (3.4)
East Asian, n (%)	19 (3.2)	22 (3.7)
Mixed, n (%)	12 (2.0)	11 (1.9)
Past obstetric history		
Nulliparous, n (%)	363 (61.5)	360 (61.0)
Parous, n (%)	227 (38.5)	230 (39.0)
Delivery at 24-33 weeks, n (%)	9 (4.0)	15 (6.5)
Delivery at 34-36 weeks, n (%)	11 (4.8)	18 (7.8)
Delivery at ≥37 weeks, n (%)	207 (91.2)	197 (85.7)
Conception		
Spontaneous, n (%)	373 (63.2)	366 (62.0)
Ovulation drugs, n (%)	21 (3.6)	20 (3.4)
In-vitro fertilization, n (%)	196 (33.2)	204 (34.6)
Cigarette smoking during pregnancy, n (%)	45 (7.6)	53 (9.0)
Previous cervical surgery		
Loop excision of transformation of zone, n (%)	14 (2.4)	17 (2.9)
Cone biopsy, n (%)	5 (0.8)	4 (0.7)
Chorionicity		
Dichorionic, n (%)	479 (81.2)	479 (81.2)
Monochorionic, n (%)	111 (18.8)	111 (18.8)
GA at randomization in weeks, median (IQR)	22.6 (21.4-23.9)	22.7 (21.4-23.9)
GA at pessary insertion in weeks, median (IQR)	22.7 (21.7-23.9)	-
Cervical length at randomization		
Median in mm (IQR)	32.0 (27.0-36.0)	32.0 (27.0-37.0)
≤ 25 mm, n (%)	107 (18.1)	108 (18.3)

IQR = interquartile range; GA = Gestational age

Table 2. Outcomes according to study group.

Outcome	Pregnancy level			Fetal / neonatal level		
	Pessary group n=588	**Control group** n=589	**RR (95% CI)**	**Pessary group** n=1,176	**Control group** n=1,178	**RR (95% CI)**
Primary outcome						
Spontaneous birth at <34 weeks, n (%)	80 (13.6)	76 (12.9)	1.054 (0.787-1.413)	-	-	-
Other outcome measures						
Spontaneous birth at <34 weeks, n (%)				-	-	-
Dichorionic twins, n/n (%)	62/477 (13.0)	62/478 (13.0)	1.002 (0.722-1.392)	-	-	-
Monochorionic twins, n/n (%)	18/111 (16.2)	14/111 (12.6)	1.286 (0.673-2.455)	-	-	-
Gestational age at birth, median (IQR)	36.6 (34.9-37.9)	36.7 (35.0-37.9)	-	-	-	-
Any birth at <34 weeks, n (%)	98 (16.7)	92 (15.6)	1.067 (0.822-1.385)	-	-	-
Any birth at <32 weeks, n (%)	52 (8.8)	53 (9.0)	0.983 (0.682-1.416)	-	-	-
Any birth at <30 weeks, n (%)	32 (5.4)	26 (4.4)	1.233 (0.744-2.042)	-	-	-
Any birth at <28 weeks, n (%)	19 (3.2)	15 (2.5)	1.269 (0.651-2.473)	-	-	-
Secondary outcomes						
Birth weight						
Mean in g, (IQR)	-	-	-	2,331 (2,020-2,740)	2,353 (2,050-2,732)	
<2500 g, n (%)	395 (67.2)	407 (69.1)	0.972 (0.899-1.051)	664 (56.5)	670 (56.9)	0.993 (0.925-1.065)
<1500 g, n (%)	60 (10.2)	65 (11.0)	0.925 (0.664-1.288)	100 (8.5)	96 (8.1)	1.043 (0.798-1.364)
Perinatal death, n (%)	20 (3.4)	22 (3.7)	0.911 (0.502-1.651)	29 (2.5)	32 (2.7)	0.908 (0.553-1.491)
Fetal death, n (%)	7 (1.2)	14 (2.4)	0.501 (0.204-1.232)	12 (1.0)	18 (1.5)	0.668 (0.323-1.380)
Neonatal death, n (%)	13 (2.2)	9 (1.5)	1.447 (0.623-3.359)	17 (1.4)	14 (1.2)	1.216 (0.602-2.456)
Secondary outcomes in survivors	n=579	n=579		n=1,147	n=1,146	
Adverse neonatal event	88 (15.2)	69 (11.9)	1.275 (0.951-1.710)	115 (10.0)	105 (9.2)	1.094 (0.851-1.407)
Intraventricular hemorrhage, n (%)	16 (2.8)	12 (2.1)	1.333 (0.636-2.793)	18 (1.6)	15 (1.3)	1.199 (0.607-2.367)
Respiratory distress syndrome, n (%)	84 (14.5)	67 (11.6)	1.254 (0.929-1.692)	109 (9.5)	100 (8.7)	1.089 (0.841-1.411)
Retinopathy of prematurity, n (%)	8 (1.4)	3 (0.5)	2.667 (0.711-10.001)	12 (1.0)	3 (0.3)	3.997 (1.131-14.125)
Necrotizing enterocolitis, n (%)	6 (1.0)	6 (1.0)	1.000 (0.324-3.082)	8 (0.7)	6 (0.5)	1.332 (0.464-3.827)
Neonatal therapy, n (%)	137 (23.7)	127 (21.9)	1.079 (0.873-1.334)	205 (17.9)	197 (17.2)	1.040 (0.871-1.242)
Ventilation, n (%)	80 (13.8)	64 (11.1)	1.250 (0.919-1.701)	114 (9.9)	97 (8.5)	1.174 (0.907-1.520)
Phototherapy, n (%)	86 (14.9)	80 (13.8)	1.075 (0.811-1.425)	111 (9.7)	116 (10.1)	0.956 (0.747-1.224)

Treatment for sepsis, n (%)	41 (7.1)	45 (7.8)	0.911 (0.606-1.369)	66 (5.8)	66 (5.8)	0.999 (0.717-1.392)
Blood transfusion, n (%)	26 (4.5)	25 (4.3)	1.040 (0.608-1.779)	36 (3.1)	36 (3.1)	0.999 (0.634-1.574)

RR = relative risk; CI = Confidence intervals; IQR = interquartile range; percentages for major adverse neonatal events and neonatal therapy were calculated after excluding cases of perinatal deaths.

Table 3. Outcomes according to cervical length at randomization ≤25 mm and >25 mm.

Outcome	Pregnancy level			Fetal / neonatal level		
	Pessary group	**Control group**	**RR (95% CI)**	**Pessary group**	**Control group**	**RR (95% CI)**
Cervical length ≤25 mm (n=214)	n=106	n=108		n=212	n=216	
Primary outcome						
Spontaneous birth at <34 weeks, n (%)	33 (31.1)	28 (25.9)	1.201 (0.784-1.839)	-	-	-
Secondary outcomes						
Birth weight <2500 g, n (%)	82 (77.4)	89 (82.4)	0.939 (0.820-1.074)	149 (70.3)	150 (69.4)	1.012 (0.894-1.146)
Birth weight <1500 g, n (%)	24 (22.6)	21 (19.4)	1.164 (0.692-1.960)	45 (21.2)	36 (16.7)	1.274 (0.858-1.891)
Perinatal death, n (%)	13 (12.3)	6 (5.6)	2.208 (0.872-5.592)	20 (9.4)	12 (5.6)	1.698 (0.852-3.386)
Secondary outcomes in survivors	n=99	n=102		n=192	n=204	
Adverse neonatal event	23 (23.2)	20 (19.6)	1.185 (0.696-2.016)	34 (17.7)	30 (14.7)	1.204 (0.768-1.888)
Neonatal therapy, n (%)	36 (36.4)	31 (30.4)	1.197 (0.808-1.772)	56 (29.2)	52 (25.5)	1.144 (0.829-1.579)
Cervical length >25 mm (n=963)	n=482	n=481		n=964	n=962	
Primary outcome						
Spontaneous birth at <34 weeks, n (%)	47 (9.8)	48 (10.0)	0.977 (0.667-1.432)	-	-	-
Secondary outcomes						
Birth weight <2500 g, n (%)	313 (64.9)	318 (66.1)	0.982 (0.896-1.077)	515 (53.4)	520 (54.1)	0.988 (0.910-1.074)
Birth weight <1500 g, n (%)	36 (7.5)	44 (9.1)	0.817 (0.535-1.245)	55 (5.7)	60 (6.2)	0.915 (0.642-1.304)
Perinatal death, n (%)	7 (1.5)	16 (3.3)	0.437 (0.181-1.052)	9 (0.9)	20 (2.1)	0.449 (0.206-0.981)*
Secondary outcomes in survivors	n=480	n=477		n=955	n=942	
Adverse neonatal event	65 (13.5)	49 (10.3)	1.318 (0.930-1.868)	81 (8.5)	75 (8.0)	1.065 (0.789-1.439)
Neonatal therapy, n (%)	101 (21.0)	96 (20.1)	1.046 (0.815-1.341)	149 (15.6)	146 (15.5)	1.007 (0.816-1.242)

RR = relative risk; CI = Confidence intervals; IQR = interquartile range; percentages for major adverse neonatal events and neonatal therapy were calculated after excluding cases of perinatal deaths; *significant P-value <0.05

FIGURE LEGENDS

Figure 1. Trial profile.

Figure 2. Kaplan-Meier plot of the proportion of continued pregnancy without delivery in the cervical pessary and control groups.

Figure 3. Association between cervical length at randomization and rate of spontaneous birth at <34 weeks in the pessary (red bars, red interrupted regression curve) and control (white bars, black regression curve) groups.

Figure 4. Kaplan-Meier plot of the proportion of continued pregnancy without delivery in the cervical pessary and control groups in women with cervical length randomization ≤25 mm (left) and >25 mm (right).

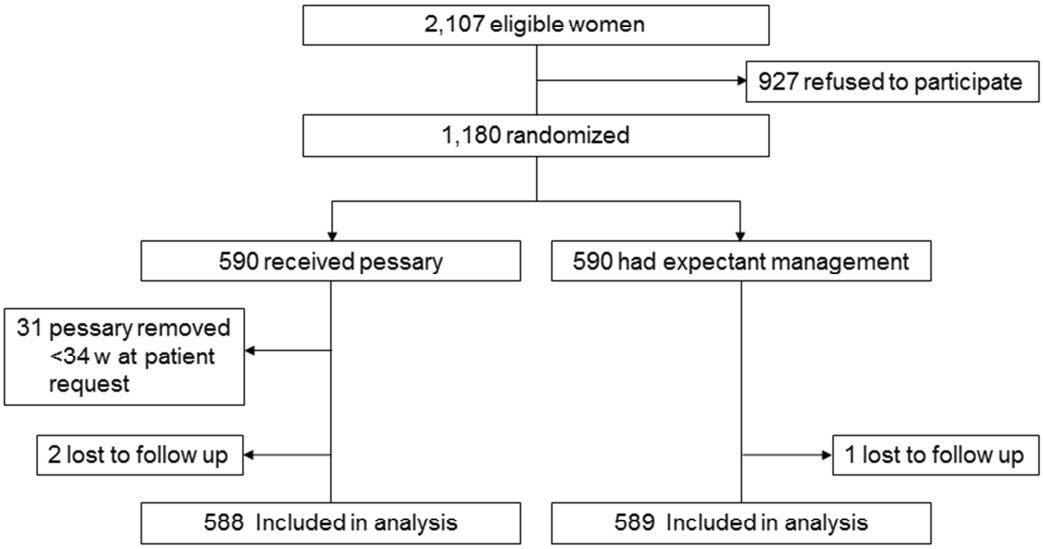


Figure 1.

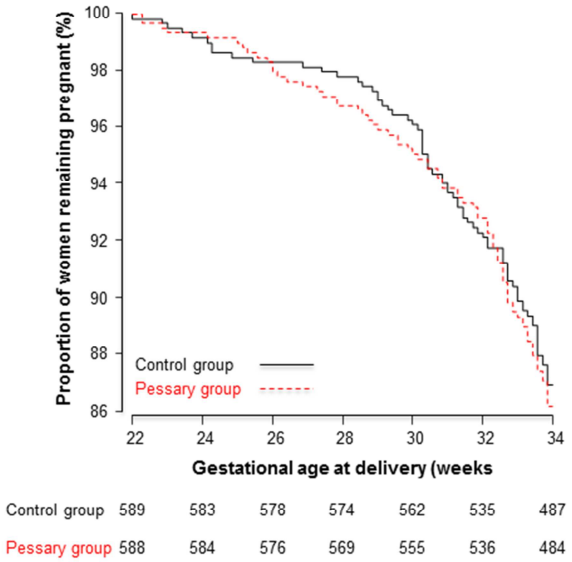
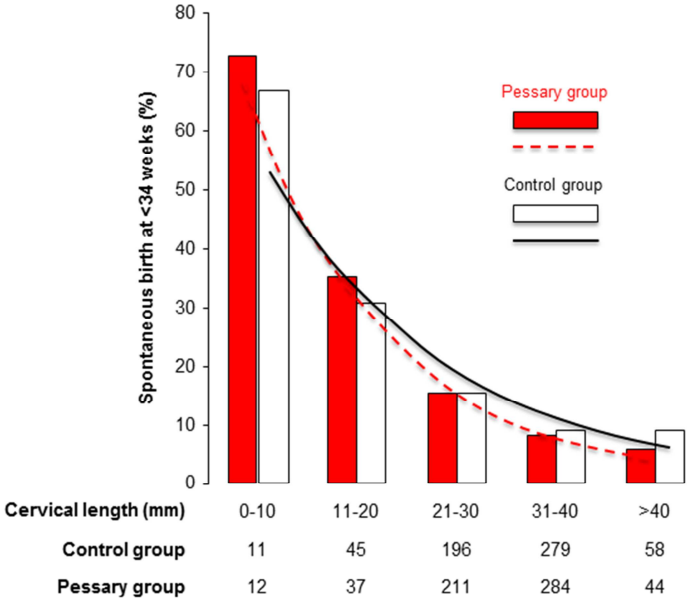


Figure 2.



Cervical length (mm)	0-10	11-20	21-30	31-40	>40
Control group	11	45	196	279	58
Pessary group	12	37	211	284	44

Figure 3.

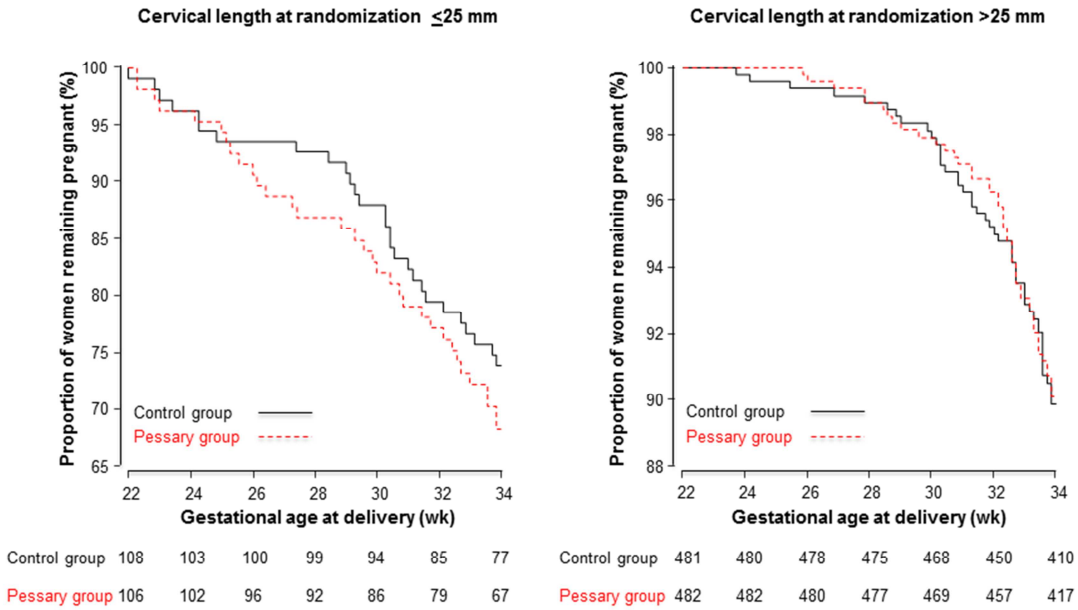


Figure 4.