ORIGINAL ARTICLE

A Randomized Trial of a Cervical Pessary to Prevent Preterm Singleton Birth

Kypros H. Nicolaides, M.D., Argyro Syngelaki, Ph.D., Liona C. Poon, M.D., Gemma Picciarelli, M.D., Natasa Tul, M.D., Aikaterini Zamprakou, M.D., Evdoxia Skyfta, M.D., Mauro Parra-Cordero, M.D., Ricardo Palma-Dias, M.D., Ph.D., and Jesus Rodriguez Calvo, M.D.

ABSTRACT

From the Harris Birthright Research Center for Fetal Medicine, King's College, London (K.H.N., A.S., L.C.P., A.Z., E.S., J.R.C.), and the Department of Fetal Medicine, Medway Maritime Hospital, Gillingham (G.P.) — both in the United Kingdom; Department of Perinatology, University Medical Center Ljubljana, Slovenia (N.T.); Fetal Medicine Unit, Hospital Clinico Universidad de Chile, Santiago, Chile (M.P.-C.); and Pregnancy Research Center, Royal Women's Hospital, Melbourne, VIC, Australia. (R.P.-D.). Address reprint requests to Dr. Nicolaides at the Harris Birthright Research Center for Fetal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS, United Kingdom, or at kypros@fetalmedicine.com.

BACKGROUND

Preterm birth is the leading cause of neonatal and infant death and of disability among survivors. It is unclear whether a pessary inserted around the cervix reduces the risk of preterm singleton birth.

METHODS

We conducted a multicenter, randomized, controlled trial comparing pessary placement with expectant management (control) in girls and women who were pregnant with singletons (singleton pregnancies) and who had a cervical length of 25 mm or less at 20 weeks 0 days to 24 weeks 6 days of gestation. Participants in either group who had a cervical length of 15 mm or less, at randomization or at subsequent visits, received treatment with vaginal progesterone. The primary outcome was spontaneous delivery before 34 weeks of gestation.

RESULTS

In an intention-to-treat analysis, there was no significant difference between the pessary group (465 participants) and the control group (467 participants) in the rate of spontaneous delivery before 34 weeks (12.0% and 10.8%, respectively; odds ratio in the pessary group, 1.12; 95% confidence interval, 0.75 to 1.69; P=0.57). There were no significant differences in the rates of perinatal death (3.2% in the pessary group and 2.4% in the control group, P=0.42), adverse neonatal outcome (6.7% and 5.7%, respectively; P=0.55), or neonatal special care (11.6% and 12.9%, respectively; P=0.59). The incidence of new or increased vaginal discharge was significantly higher in the pessary group than in the control group.

CONCLUSIONS

Among girls and women with singleton pregnancies who had a short cervix, a cervical pessary did not result in a lower rate of spontaneous early preterm delivery than the rate with expectant management. (Funded by the Fetal Medicine Foundation; Current Controlled Trials number, ISRCTN01096902.)

PRETERM BIRTH IS RESPONSIBLE FOR more than 70% of all neonatal and infant deaths.[1] In addition, the risk of cerebral palsy among children born preterm is 10 times as high as that among those born at term.[2] The risks of perinatal death and illness are inversely related to gestational age at delivery.[1,3,4] The risk of preterm birth is inversely related to cervical length as measured by ultrasonography at mid-gestation.[5,6] Randomized, controlled trials involving women who were pregnant with singletons (singleton pregnancies) and who had a short cervical length have shown that the prophylactic use of progesterone results in a significantly lower rate of preterm delivery and neonatal death than the rate with placebo.[7-10] Meta-analyses of trials of cervical cerclage in women with singleton pregnancies who had a short cervix have not shown a significantly lower rate of preterm delivery overall than the rate with no cerclage, although they have shown benefit in the subgroup of women who had a previous preterm delivery.[11,12]

An alternative approach for the prevention of preterm birth is the transvaginal placement of a silicone pessary around the cervix; this device is thought to support the cervix and change its direction toward the sacrum, thereby reducing the direct pressure from the uterine contents on the cervical canal.[13,14] Two randomized trials involving women with singleton pregnancies who had a short cervix, both of which were published after the start of the current trial, provided contradictory results regarding the effect of a pessary on the rate of spontaneous delivery before 34 weeks; in one trial, involving 380 women, the rate of this outcome was significantly lower with a pessary than with no pessary (6% vs. 27%),[15] but in the second trial, involving 108 women, there was no significant effect (9.4% and 5.5%, respectively).[16]

We performed this trial to test the hypothesis that among girls and women with singleton pregnancies who have a short cervix, the insertion of a cervical pessary would result in a lower rate of spontaneous delivery before 34 weeks of gestation than the rate with expectant management.

METHODS

TRIAL DESIGN AND PARTICIPANTS

This was an open-label, randomized trial comparing pessary placement with expectant management (control) in girls and women with singleton pregnancies. We conducted the trial at 16 maternity hospitals in England, Slovenia, Portugal, Chile, Australia, Italy, Albania, Germany, and Belgium. All females 16 years of age or older who were pregnant with singletons, who underwent routine ultrasonographic examination at 20 weeks 0 days to 24 weeks 6 days of gestation, and who were found to have a cervical length of 25 mm or less were eligible for the trial. Exclusion criteria were a maternal age of less than 16 years, fetal death, major fetal defect, cervical cerclage in situ, painful regular uterine contractions, and ruptured membranes diagnosed before randomization. All participants in the trial provided written informed consent. The trial was approved by the National Research Ethics Committee in the United Kingdom and by the local ethics committee at each participating hospital.

A Quick Take is available at NEJM.org

Neither the trial sponsor (the Fetal Medicine Foundation) nor the company that makes the pessary had any role in the design of the trial, the collection, analysis, or interpretation of the data, or the writing of the manuscript. The first author takes responsibility for the accuracy and completeness of the data and for the fidelity of the trial and this report to the protocol, available with the full text of this article at NEJM.org.

RANDOMIZATION

Participants were randomly assigned in a 1:1 ratio to either the pessary group or the control group, with the use of a Web-based application. In the random-sequence generation, there were no restrictions, such as block size or stratification according to site. At each center, those who agreed to participate in the trial were registered with a central computer program, which then instructed the operator as to whether the participant should receive a cervical pessary or the pregnancy should be managed expectantly. Consequently, the trial personnel had no role in the random assignment.

PROCEDURES

Gestational age was determined from the measurement of fetal crown–rump length at 11 to 13 weeks.[17] Cervical length was measured by transvaginal ultrasonographic examination at 20 to 24 weeks as described previously,[18] by operators with certification of competence in the technique (Fetal Medicine Foundation Certificate of Competence in Cervical Assessment).

At randomization, participants underwent a speculum examination, and a high vaginal swab was obtained for bacteriologic examination; if the results showed infection, appropriate antibiotic therapy was given. A pessary certified by European Conformity (CE0482, MED/CERT ISO 9003/EN 46003; Dr. Arabin, Witten, Germany) was inserted through the vagina with the woman in the recumbent position and was placed upward around the cervix.[13,15] The research-team members who inserted the pessaries had received practical training in the placement of the device.

Participants in the control group received the same obstetrical care as those in the pessary group. All the participants had follow-up visits every 4 weeks until 34 weeks of gestation for ultrasonographic measurement of cervical length, assessment of adverse events, and collection of vaginal swabs. If after 26 weeks the cervical length was less than 10 mm, glucocorticoids were administered for fetal lung maturation. At the time of randomization, the participants were informed that increased vaginal discharge was a possible symptom related to insertion of the pessary. At each follow-up visit, we asked the participants in both groups whether they had noted an increase in the severity or frequency of vaginal discharge and whether any other symptoms had developed since the beginning of treatment. If bacterial culture showed pathogenic results, the appropriate antibiotic therapy was given without removal of the pessary. Participants in either group who had a cervical length of 15 mm or less at randomization or at subsequent visits were given capsules containing natural progesterone (200 mg) and were instructed to introduce one capsule into the vagina before going to sleep every night up to 33 weeks 6 days of gestation.[7]

The cervical pessary was removed by vaginal examination at 37 weeks of gestation in asymptomatic participants. Earlier removal was undertaken in the following circumstances: medically indicated induction of labor or elective cesarean section; preterm labor, prelabor rupture of membranes, or active vaginal bleeding; or at the participant's request.

Quality control of screening, handling of data, and verification of adherence to protocols at the various centers were performed by the trial coordinators. Data on pregnancy outcomes were obtained from hospital maternity records or the participants' general medical practitioners. The records of all participants who delivered before 34 weeks of gestation 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 delivery before 34 weeks (238 days) of gestation. Secondary outcome measures were birth weight (mean, <2.5 kg and <1.5 kg), perinatal (fetal or neonatal) death, a composite of major adverse events in the neonate before discharge from the hospital (any grade of intraventricular hemorrhage, the respiratory distress syndrome, any retinopathy of prematurity, or necrotizing enterocolitis), a composite of indicators of neonatal special care (admission to the neonatal intensive care unit, mechanical ventilation, phototherapy, treatment for proven or suspected sepsis, or blood transfusion), and major maternal complication attributable to the pessary (maternal death, serious cervical or vaginal trauma, or chorioamnionitis).

STATISTICAL ANALYSIS

The trial was one of two randomized trials that used essentially the same protocol: one involving participants with singleton pregnancies who had a short cervix and the other involving participants with twin pregnancies, irrespective of cervical length. Calculation of the sample size assumed a logistic-regression analysis of the probability of spontaneous delivery before 34 weeks. After adjusting for the effect of cervical length, on the assumption that the pessary would have an effect equivalent to an odds ratio of 0.5, we calculated that enrollment of 1600 participants with singleton pregnancies would give the study a power of 85% to show a treatment effect at a two-sided alpha level of 5%. In the computer simulations for the singleton-pregnancy trial, it was assumed that 7% of the participants would have a cervical length of 1 to 10 mm, 7% would have a cervical length of 11 to 15 mm, and 86% would have a cervical length of 16 to 25 mm and that the risks of spontaneous delivery before 34 weeks in the control group would be 44%, 23%, and 3.6%, respectively, with an overall rate of 6%; these values were obtained from our unpublished research involving more than 50,000 pregnant women.

Enrollment in the singleton-pregnancy trial

was lower than expected and declined after completion of the twin-pregnancy trial, which showed no significant benefit from placement of a cervical pessary.[19] The trial was therefore terminated after recruitment of 935 participants.

Statistical analyses were performed on an intention-to-treat basis, and no interim analyses were performed. Baseline data for the pessary group and the control group were summarized with the use of medians and interquartile ranges. 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 risk of spontaneous delivery before 34 weeks was quantified as the odds ratio and 95% confidence interval and was assessed with the use of Kaplan–Meier analysis,[20,21] in which gestational age was the time scale, spontaneous delivery was the event, and elective deliveries were excluded. All the participants were considered to be no longer at risk for the event at the start of the 34th week. Hazard ratios were estimated.[22] Time-

to-event curves were compared with the use of a log-rank test. Cox regression analysis was used to analyze the association of cervical length, participating center, obstetrical history, progesterone use, and antibiotic treatment with the effect of a cervical pessary on spontaneous delivery before 34 weeks. Post hoc subgroup analyses were performed to examine the effect of a cervical pessary according to progesterone therapy (yes vs. no), antibiotic therapy (yes vs. no), obstetrical history (nulliparous vs. parous with previous delivery at <37 weeks vs. parous with previous delivery at ≥37 weeks), and country of participating center (England vs. other countries). The statistical software packages SPSS (version 22.0) and Medcalc were used for all data analyses.

RESULTS

TRIAL POPULATION
A total of 935 of the 1829 eligible pregnant girls and women agreed to take part in the trial (Fig. 1). The participants were recruited during
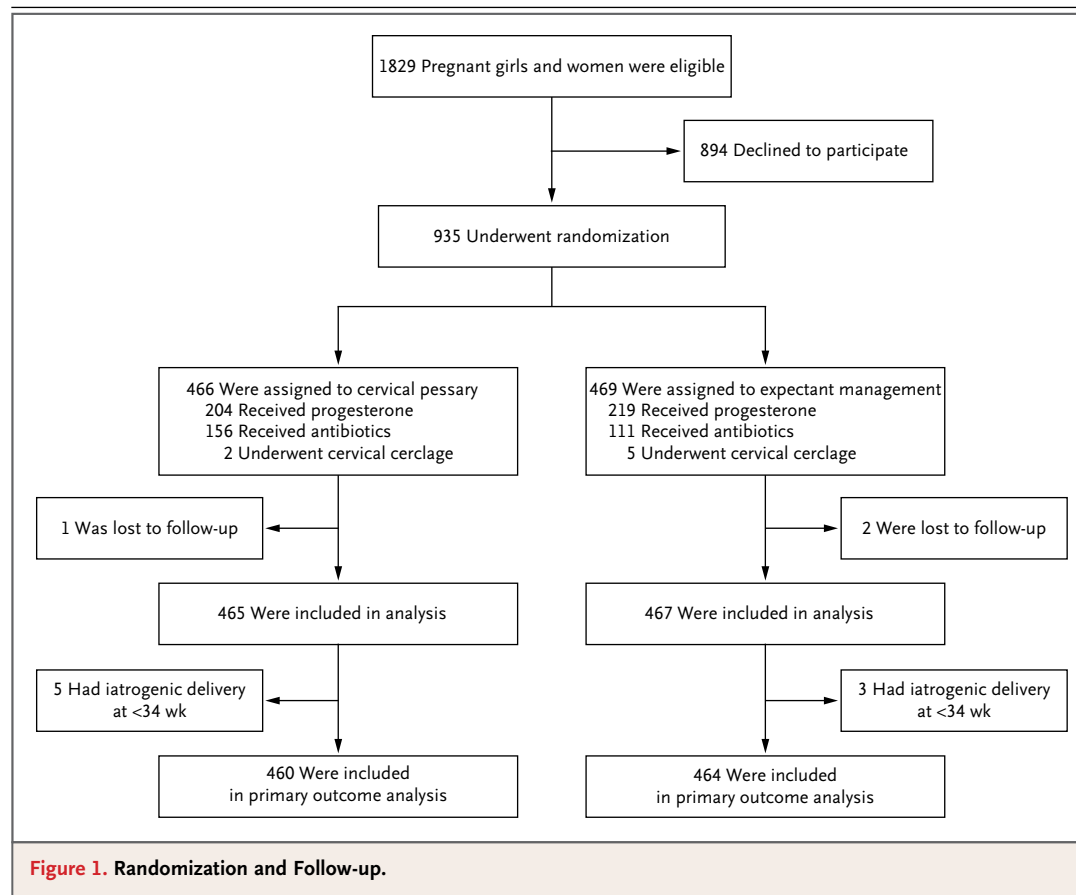

Figure 1. Randomization and Follow-up.

Table 1. Characteristics of the Trial Participants.*

Characteristic	Pessary Group (N = 465)	Control Group (N = 467)
Age — yr		
Median	30.1	29.5
IQR	26.0–34.2	25.4–34.1
Weight — kg		
Median	64.0	64.0
IQR	57.0–74.0	56.0–77.0
Height — cm		
Median	165	164
IQR	160–170	160–169
Race or ethnic group — no. (%)†		
White	297 (63.9)	317 (67.9)
Black	134 (28.8)	123 (26.3)
South Asian	19 (4.1)	17 (3.6)
East Asian	3 (0.6)	3 (0.6)
Mixed	12 (2.6)	7 (1.5)
Obstetrical history — no. (%)		
Nulliparous	248 (53.3)	257 (55.0)
Parous	217 (46.7)	210 (45.0)
Delivery at <37 wk	70 (15.1)	84 (18.0)
Delivery at ≥37 wk	147 (31.6)	126 (27.0)
Conception — no. (%)		
Natural	450 (96.8)	446 (95.5)
Assisted by use of ovulation drugs	5 (1.1)	7 (1.5)
In vitro fertilization	10 (2.2)	14 (3.0)
Cigarette smoker — no. (%)	61 (13.1)	68 (14.6)
Previous cervical surgery — no. (%)		
Loop excision of transformation zone	50 (10.8)	59 (12.6)
Cone biopsy	24 (5.2)	26 (5.6)
Gestation at randomization — wk		
Median	23.4	23.6
IQR	22.6–24.3	22.7–24.4
Cervical length at randomization		
Median (IQR) — mm	20 (14–22)	20 (15–22)
≤15 mm — no. (%)	143 (30.8)	130 (27.8)
Additional therapy — no. (%)		
Progesterone	204 (43.9)	219 (46.9)
At randomization	165 (35.5)	161 (34.5)
At follow-up visits	39 (8.4)	58 (12.4)
Cervical cerclage for cervical shortening	2 (0.4)	5 (1.1)
Antibiotics for positive vaginal swabs		
At any visit	156 (33.5)	111 (23.8)
At randomization	95 (20.4)	69 (14.8)
At follow-up visits	96 (20.6)	64 (13.7)

* There were no significant differences between the two groups. IQR denotes interquartile range.
† Race and ethnic group were self-reported.

the period from September 2008 through January 2013. There were 746 participants from England and 189 from other countries. Additional therapy included vaginal progesterone therapy in 423 participants because of short cervical length at recruitment or subsequent visits, antibiotics in 267 participants because of positive cultures of vaginal swabs at recruitment or subsequent visits, and cervical cerclage in 7 participants (including 2 participants in the pessary group, after removal of the pessary) because of a very short cervix. There were no significant differences between the pessary group and the control group in the baseline characteristics shown in Table 1, including the frequency of use of additional therapies.

OUTCOMES

Spontaneous delivery before 34 weeks of gestation occurred in 55 participants (12.0%) in the pessary group and in 50 participants (10.8%) in the control group (odds ratio in the pessary group, 1.12; 95% confidence interval [CI], 0.75 to 1.69; P=0.57) (Table 2). The cumulative percentage of participants who did not give birth spontaneously before 34 weeks did not differ significantly between the two groups (hazard ratio in the pessary group, 1.13; 95% CI, 0.77 to 1.65; P=0.54) (Fig. 2). The results were materially unchanged when iatrogenic births were included and were similar in an analysis that was adjusted for cervical length, participating center, obstetrical history, progesterone use, and antibiotic treatment (odds ratio for spontaneous preterm delivery in the pessary group, 1.09; 95% CI, 0.73 to 1.61; P=0.68). There were no significant between-group differences in the prespecified secondary outcomes of perinatal death, adverse neonatal event, and neonatal special care (Table 2).

In post hoc subgroup analyses, the risks of the primary outcome or secondary outcomes were not materially affected by status with respect to receipt of progesterone therapy, status with respect to receipt of antibiotics, parity, status with respect to previous preterm delivery, or trial site (England vs. elsewhere) (Tables S1 through S5 in the Supplementary Appendix, available at NEJM.org).

ADVERSE EVENTS

At recruitment to the trial, the pessary group had a higher rate than the control group of

Table 2. Outcomes According to Trial Group.*

Outcome	Pessary Group	Control Group	Odds Ratio (95% CI)	P Value
Primary outcome				
No. of participants included in analysis	460	464		
Spontaneous delivery at <34 wk — no. (%)	55 (12.0)	50 (10.8)	1.12 (0.75–1.69)	0.57
Other outcome measures				
No. of participants included in analysis	465	467		
Week of gestation at delivery				0.40
Median	38.9	38.7		
IQR	37.0–40.0	37.1–39.9		
Any delivery at <34 wk — no. (%)	60 (12.9)	53 (11.3)	1.16 (0.78–1.72)	0.47
Any delivery at <32 wk — no. (%)	46 (9.9)	35 (7.5)	1.36 (0.86–2.15)	0.20
Any delivery at <30 wk — no. (%)	35 (7.5)	28 (6.0)	1.28 (0.76–2.13)	0.35
Any delivery at <28 wk — no. (%)	25 (5.4)	15 (3.2)	1.71 (0.89–3.29)	0.11
Secondary outcomes				
All fetuses or neonates				
Total no.	465	467		
Birth weight				
Mean (IQR) — g	3120 (2626–3462)	3130 (2760–3510)		0.84
<2500 g — no. (%)	96 (20.6)	86 (18.4)	1.15 (0.83–1.59)	0.39
<1500 g — no. (%)	39 (8.4)	28 (6.0)	1.44 (0.87–2.37)	0.16
Perinatal death — no. (%)	15 (3.2)	11 (2.4)	1.38 (0.63–3.04)	0.42
Fetal death	8 (1.7)	5 (1.1)	1.62 (0.53–4.98)	0.40
Neonatal death	7 (1.5)	5 (1.1)	1.41 (0.45–4.48)	0.56
Termination of pregnancy	0	1 (0.2)	0.33 (0.01–8.22)	0.50
All survivors				
Total no.	450	456		
Adverse neonatal event — no. (%)†	30 (6.7)	26 (5.7)	1.18 (0.69–2.03)	0.55
Intraventricular hemorrhage	9 (2.0)	3 (0.7)	3.08 (0.83–11.46)	0.09
Respiratory distress syndrome	28 (6.2)	25 (5.5)	1.14 (0.66–1.99)	0.64
Retinopathy of prematurity	5 (1.1)	1 (0.2)	5.11 (0.59–43.93)	0.14
Necrotizing enterocolitis	6 (1.3)	3 (0.7)	2.04 (0.51–8.21)	0.32
Neonatal special care — no. (%)†	52 (11.6)	59 (12.9)	0.88 (0.59–1.31)	0.59
Admission to NICU	40 (8.9)	34 (7.5)	1.21 (0.75–1.95)	0.43
Mechanical ventilation	40 (8.9)	33 (7.2)	1.25 (0.77–2.02)	0.36
Phototherapy	25 (5.6)	38 (8.3)	0.65 (0.38–1.09)	0.10
Treatment for sepsis	27 (6.0)	20 (4.4)	1.39 (0.77–2.52)	0.28
Blood transfusion	9 (2.0)	8 (1.8)	1.14 (0.44–2.99)	0.79

* CI denotes confidence interval, IQR interquartile range, and NICU neonatal intensive care unit.
† Percentages for adverse neonatal events and neonatal special care were calculated after cases of perinatal death were excluded.
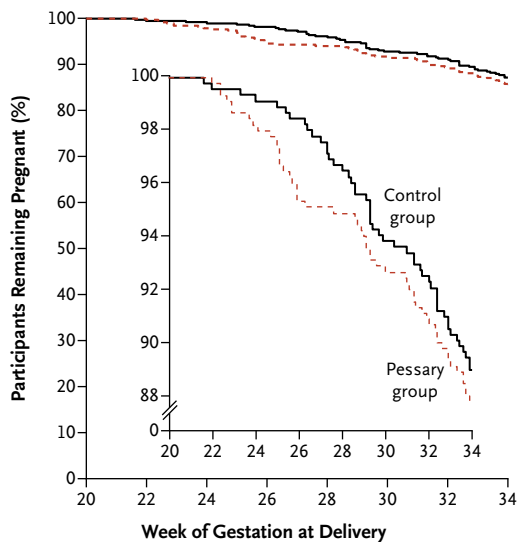
Figure 2. Kaplan–Meier Plot of Continued Pregnancy without Delivery.
Eight participants with iatrogenic delivery before 34 weeks of gestation were excluded from the analysis. The inset shows the same data on an expanded y axis.

reported vaginal discharge (10.5% vs. 6.2%, P=0.02) but not pelvic discomfort (1.9% and 0.6%, respectively; P=0.14). During follow-up, the pessary group had a higher rate than the control group of increased or new vaginal discharge (46.8% vs. 13.8%, P<0.001) and pelvic discomfort (11.4% vs. 3.4%, P<0.001) reported at any of the follow-up visits. Pathogens in the vaginal swabs, most commonly *Candida albicans,* group B streptococcus, or *Gardnerella vaginalis,* were found in a similar percentage of participants in the pessary group and the control group both at recruitment (28.6% and 25.8%, respectively; P=0.39) and at any follow-up visit (31.4% and 30.0%, respectively; P=0.75). Adverse events and the use of antibiotic therapy for participants with positive vaginal swabs are summarized in Tables S6 and S7 in the Supplementary Appendix. There were no cases of maternal death, serious vaginal trauma during insertion or removal of the pessary, or reported chorioamnionitis.

PESSARY REMOVAL BEFORE 34 WEEKS OF GESTATION
The pessary was removed before 34 weeks of gestation in 114 of the 465 participants (24.5%);

reasons for removal included iatrogenic delivery (6 participants), preterm labor (20), preterm labor or prelabor rupture of membranes (41), and participant request (47; 25 because of discomfort, 19 because of vaginal discharge, and 3 because of vaginal bleeding). After pessary removal, delivery before 34 weeks occurred in 55 of the 67 participants (82%) who had iatrogenic delivery, preterm labor, or prelabor rupture of membranes and in 5 of the 47 participants (11%) who had requested pessary removal. In the latter group, the rate of delivery before 34 weeks was consistent with the rate in the population as a whole.

DISCUSSION

The findings of this trial showed that among girls and women with singleton pregnancies who had a cervical length of 25 mm or less at 20 to 24 weeks of gestation, placement of a cervical pessary did not result in a lower rate of spontaneous early preterm delivery than the rate with expectant management. Pessary placement also did not affect the rates of perinatal death, adverse neonatal outcomes, or the need for neonatal special care.

The pessary had an acceptable side-effect profile in most participants; only 10% requested that it be removed before 34 weeks of gestation, and in this group the rate of spontaneous early preterm delivery was similar to that in the total group treated with pessary placement. Although the rate of new or increased vaginal discharge was more than three times as high in the pessary group as in the control group, rates of cervicovaginal infection did not differ significantly between the groups.

There are several potential limitations to this trial. First, only 935 participants (58%) of the originally planned 1600 underwent randomization; however, the recruited number is considerably higher than the 380 and 108 participants in the two previous randomized trials of pessary placement in women with singleton pregnancies who were at increased risk for preterm delivery.[15,16] Second, the observed distribution of cervical lengths differed from that used for the power calculations (29% and 71% for respective lengths of 1 to 15 mm and 16 to 25 mm, rather than the expected 14% and 86%); correspondingly, the observed rate of spontaneous delivery before 34 weeks was 11%, rather than the expected 6%. This was probably explained by bias to participa-

tion among participants who had a shorter cervix. Third, the open-label nature of the trial could have affected medical decision making, such as the time of the removal of the pessary when the participant presents with contractions.

Post hoc subgroup analysis showed no significant benefit of the pessary with respect to the primary and secondary outcome measures among participants recruited in England or in other centers and among those who received and those who did not receive concomitant therapy with antibiotics or progesterone. Progesterone was administered to most participants who had a cervical length of 15 mm or less, and this therapy could potentially have attenuated any benefit from the cervical pessary in this group. In a previous randomized trial involving women with singleton pregnancies who had a cervical length of 15 mm or less, the rate of spontaneous delivery before 34 weeks was 34% among untreated controls as compared with 19% among those treated with progesterone.[7]

Our results are consistent with those of one previous randomized trial that showed no significant effect of pessary placement on spontaneous early preterm birth[16] but are discordant with those of another trial that showed a significantly lower rate of this outcome with a pessary than with no pessary.[15] The three trials were similar in design and in the median cervical length at randomization (approximately 20 mm), and all included operators who had training in pessary placement.[15,16] The gestational age at randomization was higher in our trial than in the previous trials (23.5 weeks vs. 22.3 weeks[15] and 21.9 weeks[16]), and 45% of the participants in our trial received prophylactic progesterone; data on the use of this therapy were not reported in the other trials.[15,16] The rate of preterm delivery among the controls was substantially higher in the trial that showed benefit from the pessary[15] than in our trial or the other trial that showed no benefit (27% vs. 11% and 6%, respectively).[16] There is no obvious explanation for this difference; participants in our trial were at least as likely as those in the previous positive trial to have major risk factors for preterm delivery, including previous preterm delivery and a very short cervix.[23]

In conclusion, this randomized trial showed that placement of a pessary in girls and women who were pregnant with singletons and who had a short cervix at 20 to 24 weeks of gestation did not result in a lower rate of preterm delivery before 34 weeks of gestation than the rate with expectant management.

REFERENCES

1. Office for National Statistics. Gestation-specific infant mortality, 2012 (http://www.ons.gov.uk/ons/rel/child-health/gestation-specific-infant-mortality-in-england-and-wales/2012/stb-gestation-specific-infant-mortality--2012.html).
2. Kodjebacheva GD, Sabo T. Influence of premature birth on the health conditions, receipt of special education and sport participation of children aged 6-17 years in the USA. J Public Health (Oxf) 2015 July 30 (Epub ahead of print).
3. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008; 371:261-9.
4. D'Onofrio BM, Class QA, Rickert ME, Larsson H, Långström N, Lichtenstein P. Preterm birth and mortality and morbid-

ity: a population-based quasi-experimental study. JAMA Psychiatry 2013;70:1231-40.
5. Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous premature delivery. N Engl J Med 1996;334:567-72.
6. Heath VC, Southall TR, Souka AP, Elisseou A, Nicolaides KH. Cervical length at 23 weeks of gestation: prediction of spontaneous preterm delivery. Ultrasound Obstet Gynecol 1998;12:312-7.
7. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007;357:462-9.
8. DeFranco EA, O'Brien JM, Adair CD, et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in

women with a short cervix: a secondary analysis from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2007;30:697-705.
9. Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2011;38:18-31.
10. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and meta-analysis of individual patient data. Am J Obstet Gynecol 2012;206(2):124.e1-19.

11. Berghella V, Odibo AO, To MS, Rust OA, Althuisius SM. Cerclage for short cervix on ultrasonography: meta-analysis of trials using individual patient-level data. Obstet Gynecol 2005;106:181-9.

12. Berghella V, Rafael TJ, Szychowski JM, Rust OA, Owen J. Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: a meta-analysis. Obstet Gynecol 2011;117: 663-71.

13. Arabin B, Halbesma JR, Vork F, Hübener M, van Eyck J. Is treatment with vaginal pessaries an option in patients with a sonographically detected short cervix? J Perinat Med 2003;31:122-33.

14. Dharan VB, Ludmir J. Alternative treatment for a short cervix: the cervical pessary. Semin Perinatol 2009;33:338-42.

15. Goya M, Pratcorona L, Merced C, et al. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. Lancet 2012; 379:1800-6.

16. Hui SY, Chor CM, Lau TK, Lao TT, Leung TY. Cerclage pessary for preventing preterm birth in women with a singleton pregnancy and a short cervix at 20 to 24 weeks: a randomized controlled trial. Am J Perinatol 2013;30:283-8.

17. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. Br J Obstet Gynaecol 1975; 82:702-10.

18. Sonek J, Shellhaas C. Cervical sonography: a review. Ultrasound Obstet Gynecol 1998;11:71-8.

19. Nicolaides KH, Syngelaki A, Poon LC, et al. Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial. Am J Obstet Gynecol 2016;214(1):3.e1-9.

20. Altman DG. Practical statistics for medical research. London: Chapman and Hall, 1991.

21. Hosmer DW Jr, Lemeshow S, May S. Applied survival analysis: regression modeling of time to event data. New York: Wiley, 1999.

22. Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. 2nd ed. New York: Springer, 2003.

23. Celik E, To M, Gajewska K, Smith GCS, Nicolaides KH. Cervical length and obstetric history predict spontaneous preterm birth: development and validation of a model to provide individualized risk assessment. Ultrasound Obstet Gynecol 2008;31:549-54.

Copyright © 2016 Massachusetts Medical Society.