OBSTETRICS

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

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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.

CONCLUSION: 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

Preterm birth is responsible for >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 preterm birth.[10,11] In twin pregnancies, progestogens and cervical cerclage have been shown to be ineffective in reducing preterm birth.[11-15]

EDITORS' CHOICE

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 toward 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 1 study, the pessary reduced the rate from 27–6%,[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 patients with cervical length <38 mm the rate was reduced (29% vs 14%).[20]

The objective of this multicenter RCT was 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.

Materials and Methods

Study design and participants

This was an open-label randomized study of cervical pessary vs expectant management in twin pregnancies in 23

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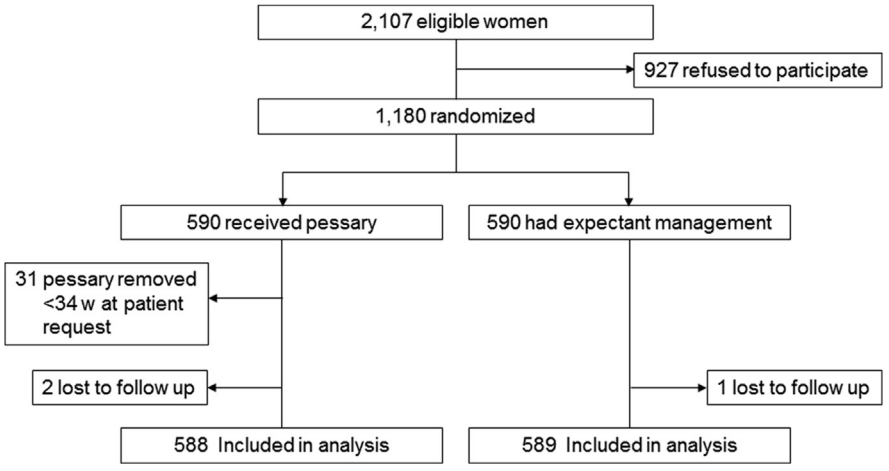
FIGURE 1
Trial profile



Nicolaides et al. RCT of cervical pessary in twin gestations. Am J Obstet Gynecol 2016.

maternity hospitals in the United Kingdom, Spain, Germany, Austria, Slovenia, Portugal, Italy, Belgium, Albania, China, Brazil, and Chile.

All patients 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 International Standard Randomized Controlled Trials registry, number N01096902.

Randomization

Eligible patients were randomized in a 1:1 ratio to either cervical pessary or expectant management, using a World Wide 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 center the patients agreeing to participate in the study were registered with a central computer that then instructed the operator as to whether the patient should receive a cervical pessary or be 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 intertwin membrane and the placenta.[22]

Cervical length was measured by transvaginal ultrasound examination at 20–24 weeks with patients, 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 (Conformite Europeene marking 0482), 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 upward 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 4 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 cesarean delivery; secondly, there was preterm labor not responding to tocolytic therapy or preterm prelabor rupture of the membranes or active vaginal bleeding; and thirdly, at patient request because of discomfort.

Quality control of screening, handling of data, and verification of adherence to protocols at the different centers were