Ultrasound Obstet Gynecol 2013; **42**: 426–433
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.12507

Arabin cervical pessary in women at high risk of preterm birth: a magnetic resonance imaging observational follow-up study

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KEYWORDS: Arabin pessary; cervical pessary; magnetic resonance imaging; observational study; preterm birth

ABSTRACT

Objective *To help elucidate the mechanism of action of the Arabin cervical pessary in pregnancies at high risk for preterm delivery.*

Methods *Cervical length and uterocervical angle were evaluated in relation to gestational age in 198 pregnancies not at high risk for preterm birth that underwent clinical fetal magnetic resonance imaging (MRI). Additionally, in 73 singleton pregnancies at high risk for preterm birth, an Arabin cervical pessary was placed at 14–33 weeks' gestation. We performed MRI of the cervix immediately before and after placement and at monthly follow-up until removal of the pessary. In a subgroup of 54 pregnancies with a short cervix and pessary placement at 17–31 weeks' gestation, the uterocervical angle and cervical length at follow-up were compared with the preplacement values.*

Results *In pregnancies not at high risk for preterm birth, the uterocervical angle did not vary, but cervical length showed a significant decrease with gestational age ($r = -0.15$, $P < 0.05$). Among the high-risk patients, the cervical pessary was successfully placed at first attempt in 60 (82.2%) and by the second attempt in 66 (90.4%), remaining well positioned until removal. In five patients we failed to place the pessary after two attempts, in one patient the pessary dislodged during follow-up and in one case the pessary was partly placed in the external cervical canal and triggered labor the next day. Among the subgroup of 54 patients, the median uterocervical angle immediately after pessary placement was significantly more acute than that prior to placement in the 46 (85.2%) who delivered after 34 weeks (132° vs 146°, $P < 0.01$), but was unchanged in the eight patients who delivered before 34 weeks (143° vs 152°, $P > 0.05$).*

Conclusion *In patients at high risk for preterm delivery, correct placement of the Arabin cervical pessary should be checked immediately; this can be performed quickly and easily using MRI. This study provides some evidence that, in singleton pregnancies with a short cervix, a cervical pessary delays birth through a mechanical effect on the uterocervical angle. Copyright © 2013 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Prematurity is responsible for more than half of all neonatal deaths[1], and while advances in neonatal care have dramatically improved the survival of extremely premature infants, there remains a significant risk of neurodevelopmental and physical disability in survivors[2–4]. Despite advances in recent decades in knowledge of the risk factors and mechanisms related to preterm labor, efforts to reduce prematurity have made limited progress[5]. This is mainly because of the lack of a sufficiently effective screening test for identifying women at high risk and the lack of an effective subsequent intervention to prevent preterm delivery. Because most of the morbidity caused by preterm birth occurs in infants delivered before 34 weeks' gestation, this cut-off has been used as an outcome in recent studies testing preventive methods[2,3,6,7].

It has been shown that an effective strategy for identifying pregnant women at high risk of preterm birth before 34 weeks' gestation should not only rely on a history of previous preterm birth, but also include sonographic screening of all pregnant women at mid-gestation. Asymptomatic women found to have a short cervix ($\leq$ 25 mm) are at increased risk of spontaneous preterm birth[8–10]. Women with a cervical length of 1–25 mm account for about 40% of all spontaneous early preterm deliveries, while only about 10% of spontaneous deliveries before 34 weeks occur in women with a history of preterm birth[11]. The use of 17-alpha-hydroxyprogesterone caproate has

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Accepted: 3 May 2013

been shown to reduce the rate of spontaneous early preterm delivery by about 50% in patients with previous preterm birth, and the use of vaginal progesterone has been shown to lead to a reduction of about 45% in asymptomatic patients found to have a short cervix at mid-trimester (≤ 15 mm at the 20–24-week scan or 10–20 mm at the 19–23-week scan)[7,12,13].

A recent randomized controlled trial (RCT) of asymptomatic singleton pregnancies with a short cervix (≤ 25 mm) at the 18–22-week scan found that use of the Arabin cervical pessary reduces the occurrence of spontaneous delivery before 34 weeks by about four-fold, and this therefore seems to be the most effective treatment available[6]. Unfortunately, the precise mechanism by which the Arabin pessary confers a benefit remains unclear. Thus, the purpose of this study was to help elucidate the mechanism of action of this device.

METHODS

This was a single-institution study, conducted at the Departments of Radiology and Fetal Medicine Unit of the University Hospital Brugmann, Brussels, Belgium, from July 2010 to September 2012. The study comprised two parts: a retrospective, cross-sectional component and a longitudinal prospective component. None of the pregnancies included in the study has been previously reported on. The study was approved by the local ethics committee. For the prospective part, all patients gave written informed consent and for the retrospective part, the need for informed consent was waived.

In order to describe the normal anatomy of the cervix and the uterocervical angle, we first conducted a retrospective chart review of all pregnancies that had undergone clinical fetal magnetic resonance imaging (MRI) in our center between July 2008 and March 2012. A total of 749 of the 947 available examinations were excluded because of inappropriate images for cervical measurements, incompleteness of data, multiple pregnancy or polyhydramnios ($n = 644$), or induced ($n = 76$) or spontaneous ($n = 29$) preterm birth before 37 weeks' gestation. This left 198 singleton pregnancies with a gestational age between 23.1 and 40.9 weeks at MRI that all delivered at term. Indications for fetal MRI were central nervous system anomalies ($n = 90$), facial anomalies ($n = 4$), gastrointestinal anomalies ($n = 12$), renal anomalies ($n = 18$), thoracic anomalies ($n = 46$), skeletal anomalies ($n = 10$), multiple anomalies ($n = 9$) and extrafetal anomalies ($n = 9$).

The prospective component of the study was initiated in July 2010 to investigate the anatomical changes associated with pessary placement. In this part of the study, 74 patients aged 18 years or older with a singleton pregnancy and considered to be at high risk for preterm birth were given the option of receiving an Arabin cervical pessary and participating in a longitudinal MRI follow-up study. High risk for preterm birth was indicated by a short cervix (≤ 25 mm) on transvaginal ultrasound examination (using a RIC 5–9 probe and a Voluson 730 Expert or E8 machine; GE Medical Systems, Zipf, Austria) at 17–33 weeks' gestation ($n = 63$) or a history of cervical cone biopsy or previous spontaneous preterm birth and/or a short cervix at ultrasound ($n = 11$)[14]. Exclusion criteria were major fetal abnormalities, presence of persistent painful regular uterine contractions, active vaginal bleeding, ruptured membranes, placenta previa, cervical cerclage *in situ* or signs of infection. All patients except one (who had a short cervix at ultrasound) consented to participate in the study.

An Arabin cervical pessary (Cerclage Pessar; CE0482, MED/CERT ISO 9003/EN 46003; Dr. Arabin GmbH & Co., Witten, Germany) was used with the following dimensions: lower larger diameter 65 mm, height 21 mm and upper smaller diameter 32 mm. By September 2012, pessary placement had been attempted in a total of 73 patients. MRI of the cervix was performed prior to pessary placement and immediately after, within hours of placement. Subsequently, the patient was followed-up longitudinally and we aimed to perform MRI of the cervix every 4 weeks. In pregnancies with a short cervix, the pessary was placed when the patient was referred. For the second group of high-risk patients, we aimed to place the pessary in the early second trimester at 14–16 weeks, unless the patient was referred later. We aimed to remove the pessary during the 37th week of pregnancy.

MRI examination

MRI was performed using a clinical 1.5-T whole-body unit (Magnetom Avanto; Siemens, Erlangen, Germany) with gradient field strength of 45 mT/m. For the prospective part of the study, no maternal sedation was administered. Patients were scanned in the supine position, with a combination of a six-channel phased-array body coil and six elements of the spine coil positioned over the lower pelvic area. The MRI protocol consisted of T2-weighted images with geometric parameters as follows: 19 adjacent slices with a 4-mm slice thickness, an intersection gap of 0.8 mm, a field of view of 400×400 mm^2, matrix 200×256, TR (repetition time)/TE (echo time) = 4.65 ms/2.33 ms, resulting voxel resolution of $2.0 \times 1.6 \times 4.0$ mm^3 and a bandwidth of 399 Hz/pixel.

Except for the first two patients, T2-weighted images were obtained using fast imaging with steady-state free precession (TrueFISP) sequences on sagittal planes of the mother, who was not requested to hold her breath. The radiologist adjusted the image orientation for the pregnant patient as required for optimal acquisition of images and measurements. Total time for the localizer and the TrueFISP sequence acquisition was 29 s. None of the patients showed discomfort during the MRI examination, probably because the examination time was kept short.

For the retrospective part of the study, T2-weighted imaging was performed using a single-shot Half-Fourier TSE (HASTE) sequence in sagittal planes using geometric parameters, as described previously[15,16].

MRI measurements

For both the retrospective and the prospective parts of the study, the uterocervical angle was measured as the angle formed by the anterior lower uterine segment with respect to the cervical canal using PACS (picture archiving and communication system) software (Impax; Agfa-Gevaert, Mortsel, Belgium) (Figures 1a and 1b)[17]. Cervical length was measured as the straight-line distance between the internal and external ostia (Figure 1c). For the prospective part of the study, the cervix was noted as being edematous if its diameter was larger than the upper smaller diameter of the pessary (Figure 2).

For the prospective component of the study, all measurements were performed by a single trained operator (M.C., with 11 years' experience in fetal MRI and planimetric measurements). For the retrospective part of the study, measurements were performed by one of five operators with limited experience in planimetric measurements (maternal–fetal medicine specialists: O.D., L.G. and B.S.; specialists in training: S.Z. and E.S.); they were, however, always supervised by a single trained operator (M.C.).

Data and statistical analysis

For the retrospective part of the study, linear regression analysis using least-squares estimation was performed to assess the relationship between gestational age and uterocervical angle and that between gestational age and cervical length.

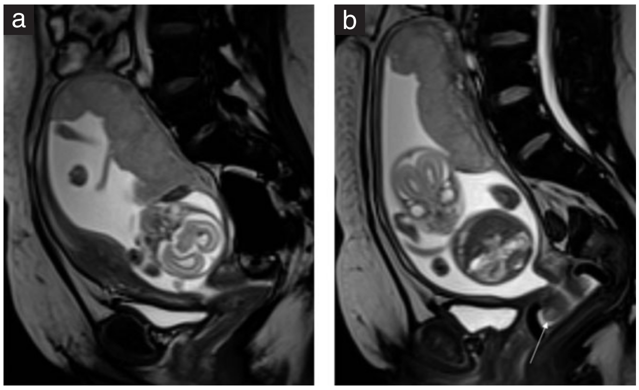

Figure 2 Sagittal T2-weighted magnetic resonance images at level of cervix: (a) before cervical pessary placement at 19.0 weeks' gestation and (b) 1 week later, showing cervical edema (arrow).

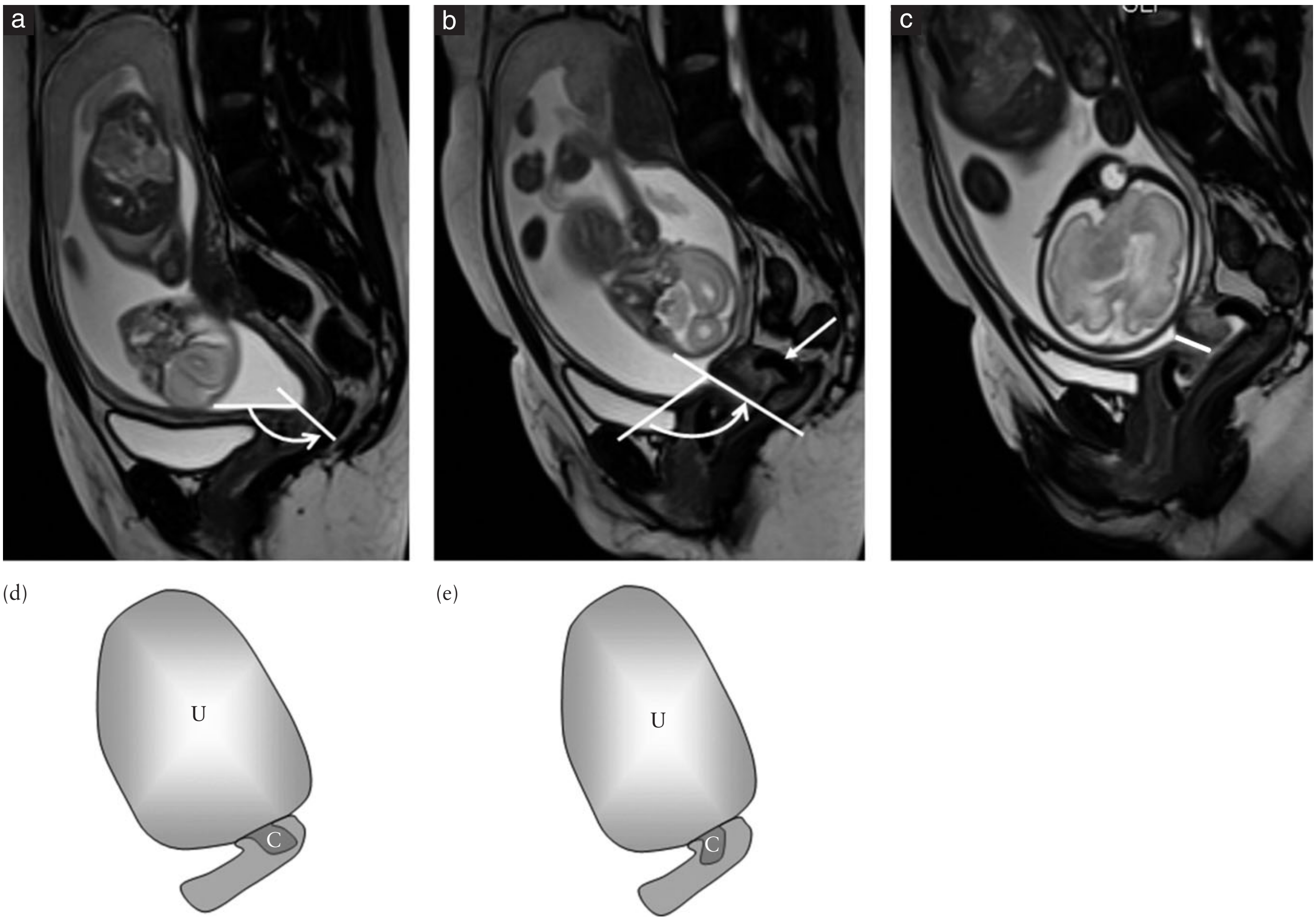

Figure 1 Sagittal T2-weighted magnetic resonance images at level of cervix: (a) before cervical pessary placement at 23 weeks' gestation and (b) immediately after successful pessary placement (straight arrow), showing change in uterocervical angle (curved arrows). (c) Same pregnancy after pessary placement showing measurement of cervical length at 30.2 weeks' gestation (white line). Schematic drawings illustrate change in uterocervical angle from before (d) to after (e) pessary placement. C, cervix; U, uterus.

For the prospective part of the study, in patients with successful pessary placement and follow-up with at least three postplacement measurements, the median uterocervical angle and cervical length at different time points were compared with the preplacement values using the Wilcoxon signed-rank test. The proportions of patients with cervical edema were compared using Fisher's exact test. The median initial uterocervical angle before cervical pessary placement was compared with the median uterocervical angle of pregnancies included in the retrospective part of the study using the Mann–Whitney *U*-test, and the same was done for cervical length.

For the prospective part of the study, in patients with a short cervix at 17–31 weeks as assessed on ultrasound and with successful pessary placement and follow-up, the median uterocervical angle immediately after pessary placement was compared with the preplacement value in patients who delivered after 34 weeks' gestation and in patients who delivered before 34 weeks using the Wilcoxon signed-rank test. The change in the uterocervical angle immediately after pessary placement was defined with respect to the preplacement value as follows: (preplacement uterocervical angle – postplacement uterocervical angle) × 100/postplacement uterocervical angle. Regression analysis was used to investigate associations between the change in the uterocervical angle and the patient's age, body mass index (BMI), gestational age at placement and cervical length on MRI as continuous variables and parity as a categorical variable.

Data were analyzed using the statistical software packages SPSS 16.0 (SPSS Inc., Chicago, IL, USA), MedCalc 7.4 (MedCalc Software, Mariakerke, Belgium) and Excel 9.0 (Microsoft, Redmond, WA, USA). Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Retrospective analysis in term pregnancies

Among the 198 pregnancies included in the retrospective part of the study, the uterocervical angle did not vary significantly with gestational age: uterocervical angle (degrees) = 136.12 – (0.2823 × gestational age (weeks)) ($r = -0.05$, $P > 0.05$) (Figure 3a). However, cervical length was negatively correlated with gestational age and decreased significantly according to the following linear fit: cervical length (mm) = 46.103 – (0.3964 × gestational age (weeks)) ($r = -0.15$, $P < 0.05$) (Figure 3b).

Prospective analysis of high-risk pregnancies

Median maternal age at pessary placement was 29 (range, 18–42) years, 30 (41.1%) patients were nulliparous and median BMI was 25 (range, 17–40) kg/m^2. Median cervical length on MRI was 19.1 (range, 0–45.4) mm. Twelve patients (16.4%) had a cervical length below 4 mm, including 10 with a cervical length of 0 mm and with membranes bulging into the vagina (Figure 4). Five

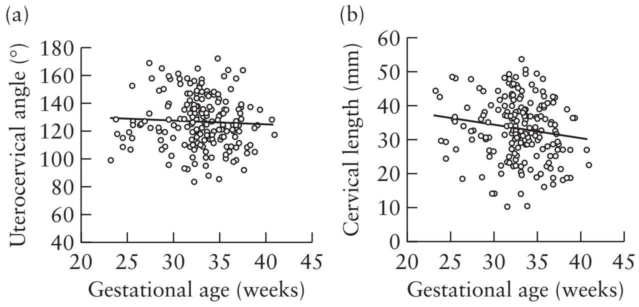

Figure 3 Scatterplots showing: (a) relationship between uterocervical angle and gestational age, with no significant correlation, and (b) relationship between cervical length and gestational age, with a significant negative correlation, in retrospective component of study that included review of magnetic resonance images of singleton pregnancies that delivered at term ($n = 198$). Linear regression lines are shown.

women had a history of cervical cone biopsy, including one with an open cervix and membranes bulging into the vagina. Among the 73 pregnancies, 60 (82.2%) delivered after 34 weeks' gestation.

Success of pessary placement

The cervical pessary was placed successfully at the first attempt in 60 (82.2%) out of 73 pregnant women and remained correctly positioned until removal. In six pregnancies the cervical pessary was correctly repositioned at a second attempt (Figure 5). In these women, the pessary remained correctly placed around the cervix at MRI follow-up examinations until removal at 37 weeks, all six patients delivering at term.

In one pregnancy, with a cervical length of 16 mm on ultrasound at 29 weeks, the cervical pessary was partly placed in the external cervical canal rather than around the cervix and was not immediately repositioned. The patient delivered prematurely the next day. In another pregnancy, with a cervical length of 8 mm at 28 weeks, the pessary was observed to be dislodged into the vagina at each MRI follow-up examination despite being repositioned around the cervix on each occasion. The patient delivered at 39 weeks.

In five pregnancies we failed to place the pessary around the cervix in two attempts and decided not to make another attempt. Three out of the five patients had a history of posterior cervical cone biopsy (Figure 6). Two of these patients miscarried, at 19 and at 20 weeks, respectively, and three delivered at term.

In none of our patients in whom the pessary dislodged were there any clinical symptoms, besides vaginal discharge as common to all patients, nor was this suspected by the clinician. However, we did not ask the patients to stand up in order to check whether the pessary still surrounded the cervical lips.

Pregnancies with at least three follow-up examinations

Among the 73 singleton pregnancies, 44 patients had successful pessary placement and normal follow-up with

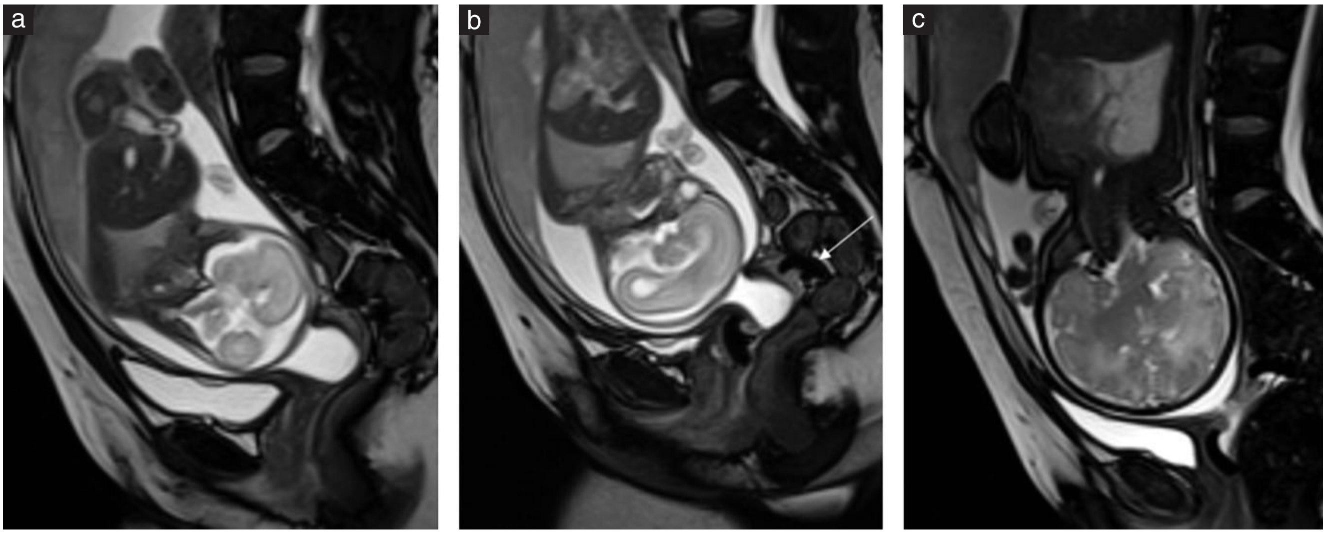

Figure 4 Sagittal T2-weighted magnetic resonance images at level of cervix showing: (a) an open cervix with bulging membranes prior to cervical pessary placement at 24.3 weeks' gestation, (b) membranes still bulging immediately after successful pessary placement (arrow) and (c) a closed cervix 12 weeks later, at 36.4 weeks.

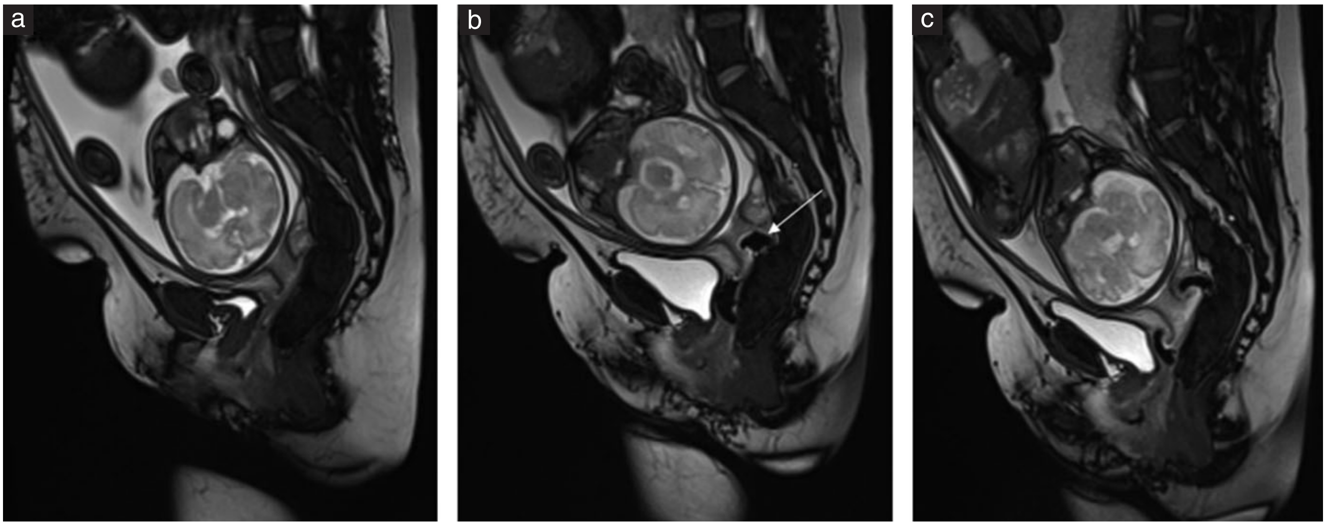

Figure 5 Sagittal T2-weighted magnetic resonance images at level of cervix at 30 weeks' gestation: (a) before cervical pessary placement, (b) immediately after first attempt at pessary placement (arrow), showing pessary partly placed in external cervical canal rather than around cervix and (c) immediately after a second attempt, showing pessary correctly placed around cervix.

at least three MRI examinations available after placement. A first assessment was performed prior to pessary placement at a median of 26.0 (range, 16.0–31.6) weeks, with a second assessment performed immediately after. A third assessment was performed at a median of 29.4 (range, 20.1–35.3) weeks and a fourth assessment at a median of 33.4 (range, 24.1–37.6) weeks. The median uterocervical angle before pessary placement was 148° and it became significantly more acute immediately after pessary placement (median 133°, $P < 0.01$), remaining so at third (median 132°, $P < 0.01$) and fourth assessments (median 128°, $P < 0.01$) (Figure 7a). The median cervical length was 20 (range, 0–53.4) mm and remained unchanged at different time points after pessary placement ($P > 0.05$ for all comparisons) (Figure 7b). Immediately after pessary placement, 4.5% of patients were classified as having cervical edema, this increasing to 20.5% at the third assessment and to 38.6% at the fourth assessment ($P < 0.01$) (Figure 2).

The median initial uterocervical angle before cervical pessary placement in high-risk patients included in the prospective part of the study ($n = 44$) was significantly more obtuse than that of term pregnancies from the retrospective part of the study (148° *vs* 125°, $P < 0.001$). Similarly, the median cervical length before pessary placement was significantly shorter than the median cervical length of pregnancies from the retrospective part of the study (20 *vs* 32.6 mm, $P < 0.001$).

Pregnancies with a short cervix

Of the 54 patients with a short cervix at 17–31 weeks and in whom the pessary was successfully placed

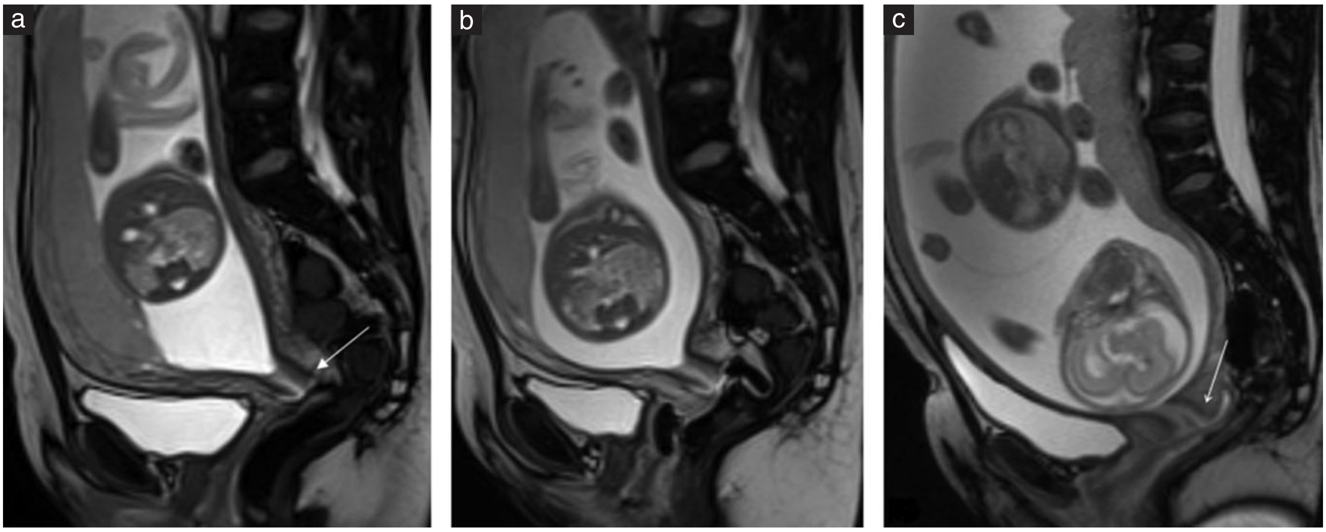

Figure 6 Sagittal T2-weighted magnetic resonance images at level of cervix at 23.7 weeks' gestation in a singleton pregnancy with a history of posterior cone biopsy, showing absence of a posterior cervical lip (a) (arrow), which prevented correct placement of a cervical pessary (b). (c) Comparable image from a twin pregnancy at 22.9 weeks, showing a clear posterior cervical lip (arrow).

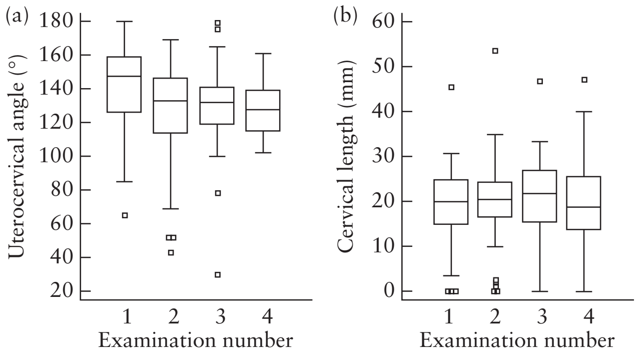

Figure 7 Box plots of uterocervical angle (a) and cervical length (b) in singleton pregnancies before cervical pessary placement (Examination 1, median 26 weeks), immediately after placement (Examination 2), and at first (Examination 3, median 29.4 weeks) and second (Examination 4, median 33.4 weeks) follow-up visits, among patients with successful pessary placement and follow-up with at least three postplacement measurements on magnetic resonance imaging ($n = 44$). A significant decrease in uterocervical angle was observed at all time-points after placement as compared to before ($P < 0.01$ for all pairwise comparisons). No significant change between time points was observed for cervical length ($P > 0.05$). Horizontal line within each box corresponds to median, boxes correspond to first and third quartiles, whiskers indicate smallest and largest observations within 1.5 times interquartile range of the quartiles and squares represent outliers.

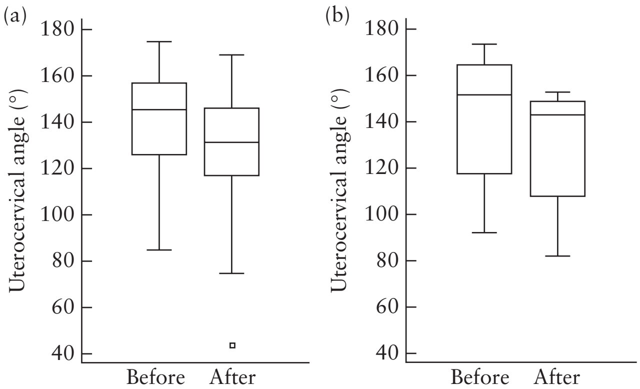

Figure 8 Box plots of uterocervical angle on magnetic resonance imaging before and immediately after pessary placement in singleton pregnancies with a short cervix at ultrasound: (a) that delivered after 34 weeks' gestation ($n = 46$), showing a significant decrease in angle ($P < 0.01$) and (b) that delivered before 34 weeks ($n = 8$), showing no significant change in angle ($P > 0.05$). Horizontal line within each box corresponds to median, boxes correspond to first and third quartiles, whiskers indicate smallest and largest observations within 1.5 times interquartile range of the quartiles and square represents outlier.

and remained correctly positioned at follow-up, 46 (85.2%) delivered after 34 weeks' gestation. Among these women, the median uterocervical angle immediately after pessary placement was significantly more acute than the median uterocervical angle before pessary placement (132° *vs* 146°, $P < 0.01$; Figure 8a). For the remaining eight patients who delivered before 34 weeks, the difference between the median uterocervical angle before and immediately after pessary placement was not statistically significant (143° *vs* 152°, $P > 0.05$; Figure 8b).

Regression analysis including the 54 patients with a short cervix showed that the change in the uterocervical angle was not influenced by the patient's age, parity, BMI, gestational age or cervical length on MRI at initial pessary placement (Table 1).

DISCUSSION

This study has demonstrated that in singleton pregnancies at high risk for preterm birth, the uterocervical angle is significantly less acute and the cervical length shorter than in low-risk patients. Successful placement of the Arabin cervical pessary can be safely monitored using MRI. Excluding patients with a history of cervical cone

Table 1 Results of univariable regression analysis for prediction of change in uterocervical angle as measured by magnetic resonance imaging (MRI) before and immediately after placement of a cervical pessary, among women with a short cervix at 17–31 weeks' gestation ($n = 54$)

Parameter	n *(%) or median (range)*	*Coefficient of regression*	P
Maternal age (years)	29 (18–42)	0.732 (−1.010 to 2.475)	0.403
Body mass index (kg/m^2)	26 (17–40)	−0.427 (−2.986 to 2.133)	0.739
Parity			
Nulliparous	24 (44.4)	—	
Parous	30 (55.6)	2.098 (−19.702 to 23.898)	0.848
Gestational age at pessary placement (weeks)	27.4 (17.7–31.9)	0.937 (−2.125 to 3.999)	0.542
Cervical length on MRI (mm)	18.7 (0–45.4)	−0.898 (−1.935 to 0.140)	0.089

biopsy, failure of cervical pessary placement occurred in fewer than 15% and 6% of patients after a first and second attempt, respectively. At follow-up, pessary dislodgement occurred in less than 2% of patients. After successful placement of the Arabin cervical pessary, a significant and immediate change in the uterocervical angle (which becomes more acute) confers on patients a higher chance of delivery after 34 weeks. However, the magnitude of the change in angle cannot be predicted by patient or pregnancy characteristics.

Two recent RCTs, with similar study designs, have evaluated the effect of the Arabin cervical pessary on preterm birth before 34 weeks in asymptomatic singleton patients with a short cervix at the mid-gestational scan, but have reported contradictory results[6,18]. While the study by Goya *et al.*[6] showed an approximately four-fold reduction in preterm birth after cervical pessary placement, that by Hui *et al.*[18] showed no difference between the treatment and control groups. Interestingly, Goya *et al.* reported that repositioning of the pessary was required in 14.2% of patients, while Hui *et al.* reported that this was needed in only 3.8%. The apparent very low need for pessary repositioning in the latter study coincides with a statistically non-significant but near doubling of the rate of preterm birth in the pessary group. Our MRI follow-up study found that repositioning of the pessary was needed in more than 15% of patients, which is more in line with the results of the study by Goya *et al.*[6].

In contrast to both of the recent RCTs[6,18], we did not exclude patients with a history of cervical cone biopsy or patients with bulging membranes. We did, however, note a higher rate of dislodgement of the pessary in patients who had had a previous cervical cone biopsy. Furthermore, in both RCTs the cervical length was a minimum of 4 mm in the pessary group, while in our study about 16% of patients had a cervical length below 4 mm, most of these being 0 mm. This may explain the relatively high preterm birth rate in our study as compared with that reported by Goya *et al.*[6].

In our study we used MRI rather than ultrasound to monitor the cervical pessary. MRI can provide a large field of view of the cervical region and there is an absence of pessary-induced shadowing. Furthermore, it has been previously shown that probe placement on transvaginal ultrasound can distort the cervical anatomy, thus potentially changing the uterocervical angle during examination[19]. We do not, however, necessarily recommend the use of MRI to monitor cervical pessaries in routine practice. On the other hand, objective measurement and monitoring of the uterocervical angle, the distance of the internal os to the spine and any reduction in the bulging of membranes is difficult to achieve by both digital and ultrasound examination. Future studies should compare the accuracy of clinical examination and/or use of ultrasound with that of MRI in the monitoring of successful placement of cervical pessaries.

Goya *et al.*[6,20] previously hypothesized that the placement of a pessary would rotate the cervix to the posterior vaginal wall. Our study has shown that the change in the uterocervical angle occurs in the opposite direction, resulting in cervical kinking. The study provides some evidence that the mechanism of action of the Arabin cervical pessary is at least partly mechanical. We have further shown that cervical edema often develops with time. Whether the presence of cervical edema confers additional protection against preterm birth needs to be further elucidated. Finally, the cervical pessary could act by the displacement of the internal os towards the spine, which would change how gravity affects the internal os. This might even explain how in some patients there is restoration over time of a cervix with funneling in such a way that the cervical wall is reattached and the endocervical length is even greater than before. Further studies assessing the distance of the internal os to bony landmarks such as the spine would be interesting.

We acknowledge that our study has some limitations. Firstly, we did not include a high-risk control group followed on MRI. We felt uncomfortable with the idea of not proposing the placement of a pessary to patients at risk for preterm birth after learning of the promising results of Goya e*t al.*[6]. However, the recent results of Hui *et al.*[18] have reopened the debate regarding the use of pessaries. Secondly, we included a heterogeneous population at high risk for preterm birth. However, our study was an observational one and was not designed to test the effect of a cervical pessary on preterm birth. Furthermore, a subanalysis including only singleton patients with a short cervix was performed in order to test the association between change in the uterocervical angle and preterm birth.

In conclusion, in patients at high risk for preterm birth, successful placement of the Arabin cervical pessary can be safely monitored using MRI with an examination time of less than a minute. The importance of rigorous teaching for correct pessary placement and continuing follow-up should not be underestimated for maximizing the benefit of the pessary to the patient. Once the cervical pessary has been positioned correctly, its mechanism of action in singleton pregnancies seems to be at least partly mediated by a change in the uterocervical angle, which becomes more acute. Further studies are needed in order to investigate other potential mechanisms of action of this device, the determinants of its success in preventing preterm delivery and whether such findings can be utilized in clinical practice.

ACKNOWLEDGMENTS

We would like to thank Professor Birgit Arabin from the Clara-Angela Foundation, Witten, Germany, who kindly provided advice, recommendations and suggestions for the use of cervical pessaries in pregnant women free of charge.

FUNDING INFORMATION

The Brugmann Foundation partly funded this study by purchasing the cerclage pessaries from Dr. Arabin GmbH & Co. However, they had no role in study design, data gathering, data analysis, data interpretation or writing of the report.

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