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Vaginal progesterone, cerclage or cervical pessary for preventing preterm birth in asymptomatic singleton pregnant women with a history of preterm birth and a sonographic short cervix

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KEYWORDS: cervical cerclage; cervical pessary; preterm birth; progesterone; transvaginal ultrasound; uterine cervix

ABSTRACT

Objective *To compare the outcome of pregnancy in cohorts of women with singleton pregnancy and history of preterm birth and sonographic short cervix managed with different treatment protocols, namely cerclage, vaginal progesterone or cervical pessary.*

Methods *This was a comparison of three management protocols for women with singleton pregnancy and a high risk of preterm birth because of a prior spontaneous preterm birth before 34 weeks and a shortened cervical length detected by transvaginal ultrasound. The study included 142 women who were initially treated with cerclage (USA), 59 with vaginal progesterone (UK) and 42 with cervical pessary (Spain). Perinatal outcomes were compared between the three cohorts.*

Results *There were no statistically significant differences in perinatal losses, neonatal morbidity and preterm births among the three groups, apart from a higher rate of preterm birth before 34 weeks' gestation after treatment with vaginal progesterone in comparison with treatment with cervical pessary (32% vs 12%; relative risk (RR) = 2.70; 95% CI, 1.10–6.67). When only the subgroups of women with cervical length < 25 mm, irrespective of gestational age, were compared, the difference between these two cohorts was not statistically significant (RR = 2.21; 95% CI, 0.83–5.89).*

Conclusion *Cerclage, vaginal progesterone and pessary appear to have similar effectiveness as management strategies in women with singleton pregnancy, previous spontaneous preterm birth and short cervix. Direct randomized comparisons of these strategies, or combinations thereof, are needed to determine optimal management.* *Copyright © 2012 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Preterm birth remains the leading cause of perinatal morbidity and mortality worldwide[1], and effective preventative strategies are required to minimize the burden of prematurity. Multiple pregnancy and iatrogenic preterm birth caused by pre-eclampsia and fetal growth restriction remain important causes of prematurity; however, the prevention of recurrent spontaneous preterm birth in singletons has been highlighted recently by the USA Food and Drug Administration approving, and the American College of Obstetricians and Gynecologists endorsing[2], the use of 17α-hydroxyprogesterone caproate for this indication. The indication for 17α-hydroxyprogesterone caproate has been restricted to pregnant women with prior spontaneous preterm births, consistent with the evidence that these women have a particularly high risk of preterm birth in subsequent pregnancies[3].

Shortened cervical length, measured by transvaginal ultrasound, has also emerged as a consistently powerful predictor of spontaneous preterm birth[4–6] and several treatment strategies have been proposed. A recently published individual patient data meta-analysis of five randomized trials provided evidence that, when compared with placebo, vaginal progesterone reduces both the preterm birth rates before 33 weeks' gestation (relative risk (RR) = 0.58; 95% CI, 0.42–0.80) and neonatal mortality/morbidity (RR = 0.57; 95% CI, 0.40–0.81) when

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prescribed to asymptomatic pregnant women with a short cervix (≤ 25 mm)[7]. These results were not replicated in a study in which 17α-hydroxyprogesterone caproate was used in nulliparas with cervical length less than 30 mm[8]. A Cochrane review of cerclage for preterm birth prevention in singleton pregnancy reported a less marked, but statistically significant, reduction in preterm birth when cerclage was compared with no treatment[9]. The reduction in preterm births after cerclage was consistent across commonly reported gestational cut-off periods (< 37, < 34 and < 28 weeks' gestation) and for all prespecified clinical subgroups, including ultrasound-indicated cerclage for high-risk women. The benefit of cerclage for women with singleton pregnancy, short cervix and previous preterm birth was also highlighted in the meta-analysis by Berghella *et al.*[10]. Cervical pessary is another treatment option that has been proposed as a treatment for sonographically detected short cervix[11]. In a recent multicenter study in Spain, 380 pregnant women, some of whom had a history of previous preterm birth, who had cervical length ≤ 25 mm were randomized to cervical pessary or expectant management. The investigators found significant reductions in preterm birth before 34 weeks' gestation (6.3% *vs* 26.8%) and in composite neonatal morbidity (4.2% *vs* 22.1%) in the pessary cohort[12].

The aim of our study was to compare the outcome of pregnancy in cohorts of women with singleton pregnancy and a history of preterm birth and sonographic short cervix, managed with different treatment protocols, namely cerclage, vaginal progesterone or cervical pessary.

METHODS

We identified three different cohorts of asymptomatic women with singleton pregnancy, a history of at least one spontaneous preterm birth before 34 weeks and short cervix on ultrasonography: 142 women (USA) were initially treated with cerclage (with or without 17α-hydroxyprogesterone caproate), 59 with vaginal progesterone followed by cerclage in cases of progressive cervical shortening (UK) and 42 with cervical pessary (Spain). For all three cohorts, we obtained permission from the relevant local authorities to use the data for analysis. The cerclage trial was approved by the human use committees at all participating centers in the USA; the ethics committees for all participating hospitals in Spain approved the cervical pessary protocol; and for the UK vaginal progesterone protocol, Liverpool Women's Hospital Research and Development Committee declared the study exempt from research ethics committee approval.

Cerclage

This cohort represents the intervention arm of a randomized study carried out by a consortium of 15 clinical centers in the USA between 2003 and 2007[13]. In brief, we included the data from women with singleton pregnancies who had at least one prior spontaneous preterm birth between $17 + 0$ and $33 + 6$ weeks' gestation and who received cerclage when the cervical length was found to be less than 25 mm. Serial transvaginal examinations commenced between $16 + 0$ and $21 + 6$ weeks' gestation and were continued fortnightly, or weekly if the cervical length was observed to be 25–29 mm, using the method as described by Owen *et al*[14]. As part of routine obstetric care, women were screened for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, and treatment was prescribed for those who were culture positive. We included only women in whom, irrespective of allocated treatment by randomization, the McDonald or the Shirodkar procedure with a non-absorbable suture was performed within 96 h of the qualifying scan – the 'on treatment' cohort. Postcerclage management included the recommendation for pelvic rest, described as abstinence from any sexual activity involving penetration of the vagina, no use of tampons and no douching. Recommended physical activity restrictions consisted of no prolonged standing for > 4 h; no heavy physical work involving lifting > 20 pounds or straining; exercise only in moderation with no impact aerobics or other activity that involves straining or Valsalva, such as weight training; and avoidance of any activity that brings on symptoms of pelvic pressure or discomfort. In the absence of pregnancy complications requiring earlier removal (e.g. chorioamnion rupture, labor or hemorrhage), the cerclage suture was removed at 37 weeks' gestation.

Vaginal progesterone

This dataset was derived from the database for continuous service evaluation of the Preterm Labour Clinic at Liverpool Women's Hospital, UK. Women with singleton pregnancies are referred to the weekly outpatient clinic if they have a history of spontaneous preterm birth, preterm rupture of membranes before 34 weeks or significant cervical surgery. Serial transvaginal scans of the cervix start at 16 weeks' gestation and are continued at 1- to 4-weekly intervals, depending on the initial cervical length and the gestational age of previous preterm births. Short cervix, in the absence of previous surgery, was measured as described by Iams *et al.*[4], and was defined as $< 3^{rd}$ centile, which corresponds to 30.5 mm at 16 weeks' gestation and 24.5 mm at 23 weeks' gestation[15]. Between January 2008 and December 2011, 354 high-risk women attended the clinic, of whom 59 (16.6%) fulfilled the study criteria (i.e. at least one preterm birth before 34 weeks' gestation and a short cervix on transvaginal scan). These women were prescribed 200 mg of vaginal progesterone to be inserted at night. The women were advised to avoid strenuous physical exercise or prolonged standing, but no formal advice was given in terms of physical or sexual activity restrictions. Vaginal swabs were taken only in the presence of symptoms indicating possible vaginal infection. If further significant cervical shortening was observed after the treatment was commenced, ultrasound-indicated cerclage was carried out. Progressive cervical

shortening was defined as a cervical length of < 15 mm in women who had a cervical length of > 15 mm when treatment was commenced, or further shortening of > 50% if the cervical length was < 15 mm when treatment was initiated.

Cervical pessary

This cohort consisted of 21 women with singleton pregnancy and prior preterm birth before 34 weeks who participated in the 'Pesario Cervical para Evitar Prematuridad' (PECEP) trial conducted in Spain from June 2007 to June 2010[12]. In addition, we included a cohort of 21 women who were monitored at one of the participating hospitals (Hospital Universitari Vall d'Hebron) because of a history of spontaneous preterm birth or preterm rupture of membranes before 34 weeks. Serial transvaginal scans of the cervix started at 16 weeks' gestation and were continued at 1- to 4-weekly intervals, depending on the initial cervical length and the gestational age of previous preterm births. In all women, cervical length was measured according to the criteria of The Fetal Medicine Foundation[16]. Patients were given detailed instructions on the subsequent management, with special emphasis on the need to report any adverse symptoms immediately. Cervical and vaginal swabs were taken in all patients for bacteriological study. If visual evidence existed of obvious infection, appropriate treatment was given and pessary insertion was delayed by 1 week. The pessary was not removed in cases in which there was evidence of bacterial infection after pessary insertion; however, appropriate antibiotic therapy was given.

The pessary was removed during the 37th week of gestation. Indications for pessary removal before the 37th week were active vaginal bleeding, threat of preterm labor with persistent contractions, despite tocolysis, or severe patient discomfort.

Statistical analysis

Demographic characteristics are given as *n* (%), and categorical and quantitative measures are given as mean ± SD. Data on the number of prior preterm births are given as median (interquartile range). The outcomes of interest included preterm births before 37, 34 and 28 weeks' gestation, Cesarean section, perinatal losses and serious neonatal morbidity (ultrasound evidence of intracranial hemorrhage, respiratory distress syndrome, clinical diagnosis of necrotizing enterocolitis or retinopathy of prematurity). The differences in proportions between the groups were compared by calculation of RR and 95% CI. Any result for which the 95% CI did not include unity (1) was considered to be statistically significant. The proportions and heterogeneity between the three cohorts were compared using the random effects DerSimonian–Laird method (StatsDirect Version 2.6.8; StatsDirect Ltd, Altrincham, UK). As this was a purposive sample, there was no prespecified sample-size calculation.

RESULTS

The demographic characteristics of the three cohorts are shown in Table 1. In the USA cohort of 142 women treated with cervical cerclage, the majority of women were Afro-Caribbean (53%), whilst the vaginal progesterone and cervical pessary cohorts consisted mainly of Caucasian women, with a relatively high proportion of Hispanic ethnicity in the cervical pessary cohort (19%). There were no other clinically important differences in the demographic characteristics among the three groups.

In the cerclage cohort, 38% of women at randomization also indicated an intent to receive weekly injections of 17α-hydroxyprogesterone caproate, and five (3.5%) received antibiotics because of positive *Chlamydia* swabs.

Table 1 Demographic characteristics of three cohorts of women with prior preterm birth and short cervix on transvaginal ultrasound, treated with different management protocols: cerclage (USA), vaginal progesterone (UK) or cervical pessary (Spain)

	Primary treatment for short cervix		
Group characteristic	*Cerclage (n = 142)*	*Vaginal progesterone (n = 59)*	*Cervical pessary (n = 42)*
Maternal age (years)	26 ± 5	30 ± 6	31 ± 7
Racial origin			
Afro-Caribbean	75 (53)	3 (5)	1 (2)
Caucasian	51 (36)	53 (89)	35 (83)
Other	16 (11)	3 (5)	6 (14)
Smoker	23 (16)*	21 (36)	11 (26)
Body mass index	30 ± 8	25 ± 6	27 ± 6
Prior births before 34 weeks	2 (1–3)	1 (1–3)	1 (1–3)
Gestational age (weeks) when treatment started	19 ± 2	21 ± 3	21 ± 2
Cervical length (mm) when treatment started	18.4 ± 6.3	21.1 ± 8.1	19.3 ± 5.1
Cerclage	142 (100)	6 (10)	0
Progesterone	54 (38)†	59 (100)‡	0
Cervical pessary	0	1 (2)	42 (100)

Data are given as mean ± SD, *n* (%) or median (interquartile range). *Data missing for one woman. †17α-hydroxyprogesterone caproate. ‡Natural vaginal progesterone.

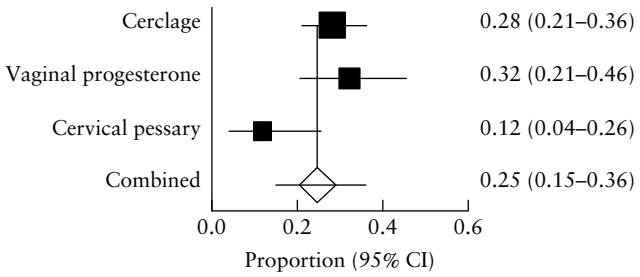

Figure 1 Proportion meta-analysis plot (random effects) for preterm birth before 34 weeks in three cohorts of women with short cervix and previous preterm birth, treated with cerclage (USA), vaginal progesterone (UK) or cervical pessary (Spain).

Table 2 Clinical outcomes for three cohorts of women with prior preterm birth and short cervix on transvaginal ultrasound, treated with different management protocols: cerclage (USA), vaginal progesterone (UK) or cervical pessary (Spain)

	Primary therapy for short cervix			*Relative risk (95% CI)*		
Clinical outcome	*Cerclage (A) (n = 142)*	*Vaginal progesterone (B) (n = 59)*	*Cervical pessary (C) (n = 42)*	*A* vs *B*	*A* vs *C*	*B* vs *C*
Pregnancy outcome						
Birth < 37 weeks	63 (44)	27 (46)	19 (45)	0.97 (0.69–1.35)	0.98 (0.67–1.43)	1.01 (0.66–1.56)
Birth < 34 weeks	40 (28)	19 (32)	5 (12)	0.87 (0.56–1.38)	2.37 (1.00–5.61)	2.70 (1.10–6.67)
Birth < 28 weeks	20 (14)	8 (14)	3 (7)	1.04 (0.48–2.22)	1.97 (0.62–6.31)	1.90 (0.53–6.74)
Cesarean section	43 (30)	12 (20)	10 (24)	1.49 (0.85–2.61)	1.23 (0.70–2.31)	0.85 (0.41–1.79)
Neonatal outcome						
Perinatal loss	12 (8)	5 (8)	1 (2)	0.99 (0.37–2.71)	3.55 (0.47–26.51)	3.56 (0.43–29.37)
Serious ICH	0	1 (2)	0	—	—	—
Serious respiratory morbidity	12 (8)	6 (10)	2 (4)	0.83 (0.33–2.11)	1.77 (0.41–7.62)	2.14 (0.45–10.07)
Necrotizing enterocolitis	2 (1)	0	1 (2)	—	—	—
Retinopathy of prematurity	3 (2)	0	0	—	—	—

Data are given as *n* (%) or relative risk (95% CI). ICH, intracranial hemorrhage.

Table 3 Subgroup analysis including only women who had cervical length < 25 mm, irrespective of gestational age

	Primary therapy for short cervix			*Relative risk (95% CI)*		
Clinical outcome	*Cerclage (A) (n = 142)*	*Vaginal progesterone (B) (n = 38)**	*Cervical pessary (C) (n = 42)*	*A* vs *B*	*A* vs *C*	*B* vs *C*
Birth < 34 weeks	40 (28)	10 (26)	5 (12)	1.07 (0.59–1.94)	2.37 (0.99–5.61)	2.21 (0.83–5.89)
Perinatal loss	12 (8.5)	5 (13)	1 (2)	0.64 (0.24–1.71)	3.55 (0.47–26.51)	5.53 (0.68–45.21)

Data are given as *n* (%) or relative risk (95% CI). *Fifteen women had cervix < 3rd centile but ≥ 25 mm, and for six women with cervical length < 3rd centile the actual cervical length was not recorded.

Seven (12%) women in the UK cohort had 'rescue' treatment because of progressive cervical shortening despite vaginal progesterone therapy; six had cerclage and one had a cervical pessary because cerclage was declined. There was no significant difference in number of preterm births before 37 weeks between the three groups (Table 2). There were fewer preterm births before 34 and 28 weeks' gestation in the cervical pessary group, but the differences were not statistically significant apart from births before 34 weeks in the vaginal progesterone group compared with the cervical pessary group (32% *vs* 12%; RR = 2.70; 95% CI, 1.10–6.67) (Table 2). When only the subgroups of women with cervical length < 25 mm, irrespective of gestational age, were compared, the difference between these two cohorts was not statistically significant (RR = 2.21; 95% CI, 0.83–5.89) (Table 3). Comparison of rates of preterm birth before 34 weeks' gestation among the three groups revealed significant heterogeneity (Figure 1). Neonatal deaths and serious neonatal morbidity were relatively rare events and there was no statistically significant difference among the three groups (Table 2).

DISCUSSION

Our results suggest similar effectiveness of currently available treatment strategies for women with singleton pregnancy who have at least one prior preterm birth and a shortened cervical length detected by transvaginal ultrasound examination (Figure 1). Apart from the higher incidence of preterm birth before 34 weeks' gestation in the vaginal progesterone group compared with the cervical pessary group, no other comparisons were statistically significant. We restricted our analysis to include only high-risk women with singleton pregnancy and at least one prior preterm birth before 34 weeks, who were found to have a short cervical length detected on transvaginal ultrasound examination. We did not include cohorts treated with intramuscular 17α-hydroxyprogesterone caproate as the primary intervention for short cervix because of the recent evidence that this treatment may be less effective[8].

A potential source of bias is that the cerclage cohort from the USA consisted of mainly Afro-Caribbean women, whilst the UK and Spanish cohorts had relatively high proportions of smokers; both Afro-Caribbean race and smoking are confounders known to be associated with an increased risk of preterm birth. However, in women with a short cervix the impact of smoking and ethnicity is relatively low[5] and would be unlikely to explain any difference in effectiveness. The definition of short cervical length differed slightly in the three cohorts, reflecting modest differences in the definition of shortened cervical length in different countries. However, a subgroup analysis that compared only women with cervix < 25 mm (Table 3) showed very similar results.

There were also some differences in the protocols for infection screening between the three cohorts. The USA cohort was screened for *N. gonorrhoeae* and *C. trachomatis* and the Spanish cohort was screened for bacterial vaginosis, whilst the UK cohort was screened only if women were symptomatic. Despite the different screening protocols, the proportion of women who received antibiotics was very low. Given that the effectiveness of antibiotics to prevent preterm birth remains unproven[17], it is unlikely that this was an important source of bias.

The UK protocol for the use of vaginal progesterone included ultrasound-indicated cerclage when progressive cervical shortening was noted on follow-up scans. We suggest that this protocol represents the pragmatic summary of the best, currently available evidence related to vaginal progesterone as a preventative intervention in women with short cervical length. It is noteworthy that most protocols from published clinical trials of vaginal progesterone for a sonographic short cervix included only physical examination-indicated ('rescue') cerclage; however, the majority of women included in these studies (78%) did not have a history of previous preterm birth and did not undergo serial ultrasound scans[7]. Faced with a finding of short cervical length in a woman with a prior preterm birth, it is reasonable to continue to monitor cervical length even after treatment with progesterone has been initiated. Given the evidence from the study of Owen *et al.*[13], that cervical cerclage is likely to be of increased benefit when the cervix is particularly short (< 15 mm), cervical cerclage seems to be an appropriate choice for progressive cervical shortening despite treatment with progesterone.

Another potential source of bias is that the cerclage cohort had a significant proportion of women who were prescribed intramuscular 17α-hydroxyprogesterone caproate. The compliance was not monitored, and given that recent evidence suggests that this drug does not appear to be effective for women with short cervical length, we did not exclude this subgroup from our analysis.

Faced with the finding of short cervical length on transvaginal ultrasound, clinicians have a choice of expectant management with possible administration of antenatal corticosteroids[18], use of vaginal progesterone[7] with an option of cerclage in cases of progressive cervical shortening, cerclage[9,10] or cervical pessary[12,13]. Ideally, these treatments should be compared in randomized trials with neonatal and childhood morbidity as the primary outcome on which sample-size calculations are based. Our data suggest that, in the high-resource setting, the composite outcome of mortality and serious prematurity-related morbidity may not exceed 10%. Therefore, even the most optimistic randomized trials looking for an added treatment benefit in excess of 25% will need to include several-thousand high-risk women with short cervical length. In fact, these trials should be designed to confirm the non-inferiority of less invasive and cheaper treatments and, as such, need to be even larger. In the absence of such studies, we have considered performing network meta-analysis of the currently available evidence[19]. Given that the possible sources of bias described above would not be eliminated with this complex and evolving methodological approach, we felt that, until well-designed randomized trials are reported, cohort comparison would be a methodologically valid study design.

Our data suggest that, for women with singleton pregnancy and a history of prior preterm birth who are found to have a short cervix on ultrasound, cervical pessary, vaginal progesterone or cerclage are reasonable treatment options. In the absence of randomized cohorts and long-term safety data, the decision regarding which treatment options to choose should take into account women's and clinicians' preferences. Hopefully our findings will stimulate other groups to publish their results of large cohorts with clearly agreed-upon, and reproducible, protocols and complete follow-up that will complement the data presented here. We also hope that international collaborations will be set up to test these treatments in adequately powered randomized trials, involving both low-risk and high-risk women.

REFERENCES

1. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008; **371**: 75–84.
2. U.S. Food and Drug Admistration. FDA statement Makena. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm249025.htm [Accessed 27 December 2011].
3. Ananth CV, Getahun D, Peltier MR, Salihu HM, Vintzileos AM. Recurrence of spontaneous versus medically indicated preterm birth. *Am J Obstet Gynecol* 2006; **195**: 643–650.
4. Iams JD, Goldberg RL, Meis PJ, Mercer BM, Moawad A, Das A, Thom E, McNellis D, Copper RL, Johnson F, Roberts JM. The length of the cervix and the risk of spontaneous premature delivery. *N Engl J Med* 1996; **334**: 567–572.
5. Celik E, To M, Gajewska K, Smith GC, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. 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**: 549–554.
6. Owen J, Yost N, Berghella V, Thom E, Swain M, Dildy GA 3rd, Miodovnik M, Langer O, Sibai B, McNellis D. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. *JAMA* 2001; **286**: 1340–1348.
7. Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien JM, Cetingoz E, Da Fonseca E, Creasy G, Klein K, Rode L, Soma-Pillay, Fusey S, Cam C, Alfirevic Z, Hassan SS. 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**: 124.e1–19.
8. Grobman W for the Eunice Kennedy Shriver NICHD, MFM Units Network. Randomized controlled trial of progesterone treatment for preterm birth prevention in nulliparous women with cervical length less than 30 mm. *Am J Obstet Gynecol* 2012; **206**: S367.
9. Alfirevic Z, Stampalija T, Roberts D, Jorgensen AL. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. *Cochrane Database Syst Rev* 2012; **4**: CD008991.

10. 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**: 663–671.
11. 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**: 122–133.
12. Goya M, Pratcorona L, Merced C, Rodó C, Valle L, Romero A, Juan M, Rodríguez A, Muñoz B, Santacruz B, Bello-Muñoz JC, Llurba E, Higueras T, Cabero L, Carreras E; Pesario Cervical para Evitar Prematuridad (PECEP) Trial Group. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. *Lancet* 2012; **379**: 1800–1806.
13. Owen J, Hankins G, Iams JD, Berghella V, Sheffield JS, Perez-Delboy A, Egerman RS, Wing DA, Tomlinson M, Silver R, Ramin SM, Guzman ER, Gorddon M, How HY, Knudtson EJ, Szychowski JM, Cliver S, Hauth JC. Multicenter randomized trial of cerclage for preterm birth prevention in high risk women with shortened midtrimester cervical length. *Am J Obstet Gynecol* 2009; **201**: 375.e1–8.
14. Owen J, Yost N, Berghella V, Thom E, Swain M, Dildy GA 3rd, Miodovnik M, Langer O, Sibai B, McNellis D; National Institute of Child Health and Human Development, Maternal-Fetal Medicine Units Network. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. *JAMA* 2001; **286**: 1340–1348.
15. Salomon LJ, Diaz-Garcia C, Bernard JP, Ville Y. Reference range for cervical length throughout pregnancy: non-parametric LMS-based model applied to a large sample. *Ultrasound Obstet Gynecol* 2009; **33**: 459–464.
16. To MS, Skentou CA, Chan C, Zagaliki A, Nicolaides KH. Cervical assessment at the routine 23-week scan: standardizing techniques. *Ultrasound Obstet Gynecol* 2001; **17**: 217–219.
17. McDonald HM, Brocklehurst P, Gordon A. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev* 2007; **1**: CD000262.
18. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2006; **3**: CD004454.
19. Li T, Puhan MA, Vedula SS, Singh S, Dickerson K. Network meta-analysis-highly attractive but more methodological research is needed. *BMC Med* 2011; **9**: 79.

