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Cervical length screening for prevention of preterm birth in singleton pregnancy with threatened preterm labor: systematic review and meta-analysis of randomized controlled trials using individual patient-level data

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KEYWORDS: cervical length; preterm birth; preterm labor; transvaginal ultrasound

ABSTRACT

Objective *Cervical length screening by transvaginal sonography (TVS) has been shown to be a good predictive test for spontaneous preterm birth (PTB) in symptomatic singleton pregnancy with threatened preterm labor (PTL). The aim of this review and meta-analysis of individual participant data was to evaluate the effect of knowledge of the TVS cervical length (CL) in preventing PTB in singleton pregnancies presenting with threatened PTL.*

Methods *We searched the Cochrane Pregnancy and Childbirth Group's Trials Register and the Cochrane Complementary Medicine Field's Trials Register (May 2016) and reference lists of retrieved studies. Selection criteria included randomized controlled trials of singleton gestations with threatened PTL randomized to management based mainly on CL screening (intervention group), or CL screening with no knowledge of results or no CL screening (control group). Participants included women with singleton gestations at 23 + 0 to 36 + 6 weeks with threatened PTL. We contacted corresponding authors of included trials to request access to the data and perform a meta-analysis of individual participant data. Data provided by the investigators were merged into a master database constructed specifically for the review. The primary outcome was PTB < 37 weeks. Summary measures were reported as relative risk (RR) or as mean difference (MD) with 95% CI.*

Results *Three trials including a total of 287 singleton gestations with threatened PTL between 24 + 0 and 35 + 6 weeks were included in the meta-analysis, of which 145 were randomized to CL screening with knowledge of results and 142 to no knowledge of CL. Compared with the control group, women who were randomized to the known CL group had a significantly lower rate of PTB < 37 weeks (22.1% vs 34.5%; RR, 0.64 (95% CI, 0.44–0.94); three trials; 287 participants) and a later gestational age at delivery (MD, 0.64 (95% CI, 0.03–1.25) weeks; MD, 4.48 (95% CI, 1.18–8.98) days; three trials; 287 participants). All other outcomes for which there were available data were similar in the two groups.*

Conclusions *There is a significant association between knowledge of TVS CL and lower incidence of PTB and later gestational age at delivery in symptomatic singleton gestations with threatened PTL. Given that in the meta-analysis we found a significant 36% reduction in the primary outcome, but other outcomes were mostly statistically similar, further study needs to be undertaken to understand better whether the predictive characteristics of CL screening by TVS can be translated into better clinical management and therefore better outcomes and under what circumstances. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

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INTRODUCTION

Spontaneous preterm birth (PTB) remains the main cause of perinatal morbidity and mortality in many countries, including the USA[1]. Mortality and morbidities, including respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and sepsis, are inversely associated with gestational age at birth[1,2].

Cervical length (CL) measured by transvaginal sonography (TVS) has been shown to be an effective predictor of spontaneous PTB[3,4]. This finding has been confirmed in singleton and multiple gestations, in women with or without risk factors for PTB, and in asymptomatic women as well as women with preterm labor (PTL) or preterm prelabor rupture of membranes (PPROM)[4]. One of the challenges in the management of women who present with PTL is the distinction between true and false PTL. Women with threatened PTL are usually managed according to cervical dilation detected on digital (manual) vaginal examination. However, most women with threatened PTL have minimal cervical dilation (≤ 2 cm) on manual examination and about 75% do not deliver preterm[3,4]. Therefore, in these women, CL on TVS has been suggested as a better screening tool to determine the need for intervention[4]. It has been hypothesized that management of PTL patients with CL measurement leads to treatment of women truly at risk for PTB, and avoids intervention in women not at risk (e.g. those with CL ≥ 30 mm)[4].

It remains controversial whether management of these women based on TVS CL results would decrease the incidence of PTB. The aim of this systematic review and meta-analysis of randomized clinical trials (RCTs) was to evaluate the effectiveness of management of singleton pregnancies with threatened PTL based on knowledge of the CL measurement compared with no knowledge of CL.

METHODS

Search strategy

This meta-analysis was performed according to a protocol recommended for systematic reviews[5]. The review protocol was designed *a priori*, defining methods for collecting, extracting and analyzing data. We searched the Trials Register of the Cochrane Pregnancy and Childbirth Group (PCG) by contacting the PCG Trials Search Co-ordinator.

Briefly, the Cochrane PCG Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from (1) monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); (2) weekly searches of MEDLINE (Ovid); (3) weekly searches of EMBASE (Ovid); (4) monthly searches of CINAHL (EBSCO); (5) hand-searching of 30 journals and the proceedings of major conferences; and (6) weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts. The search was conducted from the inception of each database to May 2016. Search results were screened by two people and the full text of all relevant trial reports identified through the searching activities described above was reviewed. Based on the intervention described, each trial report was assigned a number that corresponded to a specific PCG review topic (or topics), and was then added to the Register. The Trials Search Co-ordinator searched the Register for each review using this topic number rather than keywords. This resulted in a more specific search set that was fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).

In addition, we contacted the Cochrane Complementary Medicine Field to search their Trials Register and checked again via The Cochrane Register of Studies (CRSO).

Study selection

Selection criteria included RCTs of singleton gestations with threatened PTL randomized to management based on TVS CL screening results (intervention group) or not (control group). Participants included women with singleton gestation at $23+0$ to $36+6$ weeks with threatened PTL. For this review, TVS CL screening modalities on which interventions were based were either (1) knowledge *vs* no knowledge of CL, i.e. CL was measured in all women, but they were randomized so that the results were available to the managing obstetrician only in the intervention group (known CL group), and the managing obstetrician was blinded to the CL results in the control group (no knowledge of CL); or (2) TVS CL *vs* no TVS CL measurement, i.e. women were randomized to TVS CL screening or no TVS CL screening.

Studies that included management based only on fetal fibronectin (FFN) were excluded. Quasirandomized trials (i.e. trials in which allocation was done on the basis of a pseudorandom sequence, e.g. odd/even hospital number or date of birth, alternation), studies on multiple pregnancies and studies on PPROM were also excluded.

Data extraction and risk of bias assessment

The risk of bias in each included study was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions[5]. Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. Review authors' judgments were categorized as 'low risk', 'high risk' or 'unclear risk' of bias[5].

For this review, the quality of the evidence was assessed using the GRADE approach in order to assess the quality of the body of evidence relating to the primary and the main seven secondary outcomes in the overall analysis. The GRADEpro Guideline Development Tool was used

to import data from Review Manager 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark, 2014) in order to create a 'Summary of findings' table. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. This uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias[5].

All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were allocated randomly in the original trials. Primary and secondary outcomes were planned *a priori*. The primary outcome was the incidence of PTB < 37 weeks. Secondary outcomes were PTB < 36, < 34, < 32, < 30 and < 28 weeks, gestational age at delivery, latency (time from randomization to delivery), time from evaluation to discharge, low birth weight (< 2500 g), composite perinatal outcome (defined as at least one of the following: perinatal death, RDS, IVH and sepsis), fetal death (fetal death after 20 weeks), neonatal death (death of a live-born baby within the first 28 days of delivery), perinatal death (fetal death and neonatal death), RDS, IVH, NEC, sepsis, admission to the neonatal intensive care unit (NICU), days in NICU, maternal hospitalization for more than 24 h, maternal wellbeing (stress level), economic analysis (cost-effectiveness, cost-utility), tocolysis, cervical cerclage, steroids for fetal maturity, chorioamnionitis and endometritis. We contacted corresponding authors of all included trials to request access to the data and perform a meta-analysis of individual participant data (IPD). Authors were asked to supply anonymized data (without identifiers) about patient baseline characteristics, experimental intervention, control intervention, co-interventions, and prespecified outcome measures for every randomly assigned subject and were invited to become part of the collaborative group with joint authorship of the final publication. Data provided by the investigators were merged into a master database constructed specifically for the review. Data were checked for missing information, errors and inconsistencies by cross-referencing the publications of the original trials. Quality and integrity of the randomization processes were assessed by reviewing the chronological randomization sequence and pattern of assignment, as well as the balance of baseline characteristics across treatment groups. Inconsistencies or missing data were discussed with the authors and corrections were made when deemed necessary.

Statistical analysis

Data analysis was completed independently by two authors (V.B., G.S.) using Review Manager 5.3[5]. The completed analyses were then compared and any difference was resolved with review of the entire data and independent analysis. IPD were analyzed using the so-called two-stage approach[5]. In this, the IPD are first analyzed separately in each study to produce study-specific estimates of relative treatment effect. A combined estimate is then obtained in the second step by calculating a weighted average (inverse error variance based) of the individual estimates using methods analogous to meta-analyses of aggregate data. Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. Meta-analysis was performed using the random-effects model of DerSimonian and Laird, to produce summary treatment effects in terms of either a RR or a mean difference (MD) with 95% CI.

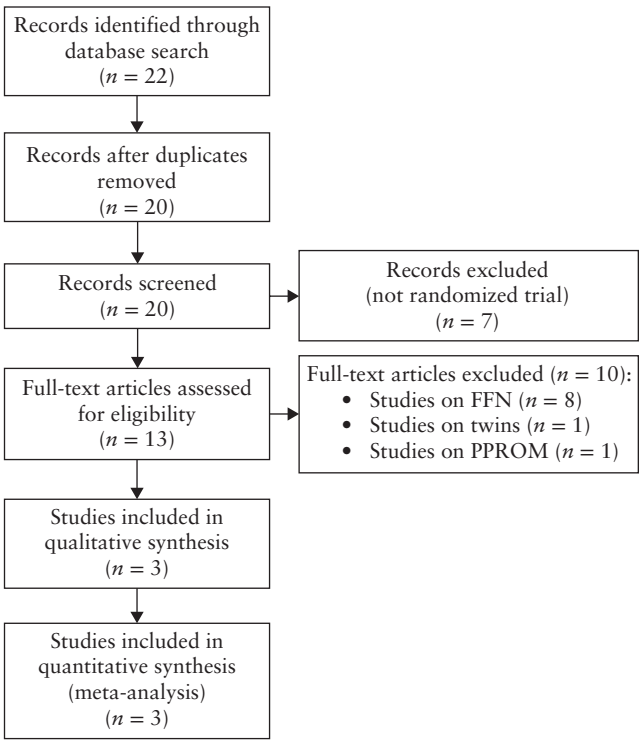

Figure 1 Flowchart of randomized controlled trials identified for systematic review. FFN, fetal fibronectin; PPROM, preterm prelabor rupture of membranes.

We planned to assess the primary outcomes in subsets of women with prior spontaneous PTB and according to the gestational age at randomization.

Potential publication biases were assessed statistically using Begg's and Egger's tests. $P < 0.1$ was considered statistically significant.

Characteristics of the included women obtained in the merged database were analyzed using SPSS Statistics v. 19.0 (IBM Inc., Armonk, NY, USA). Data are shown as mean ± SD or as *n* (%). Univariate comparisons of dichotomous data were performed by the chi-square or Fisher's exact test. Comparisons between groups were performed with the use of Student's *t*-test to test group means with SD. Two-sided *P*-values < 0.05 were considered statistically significant.

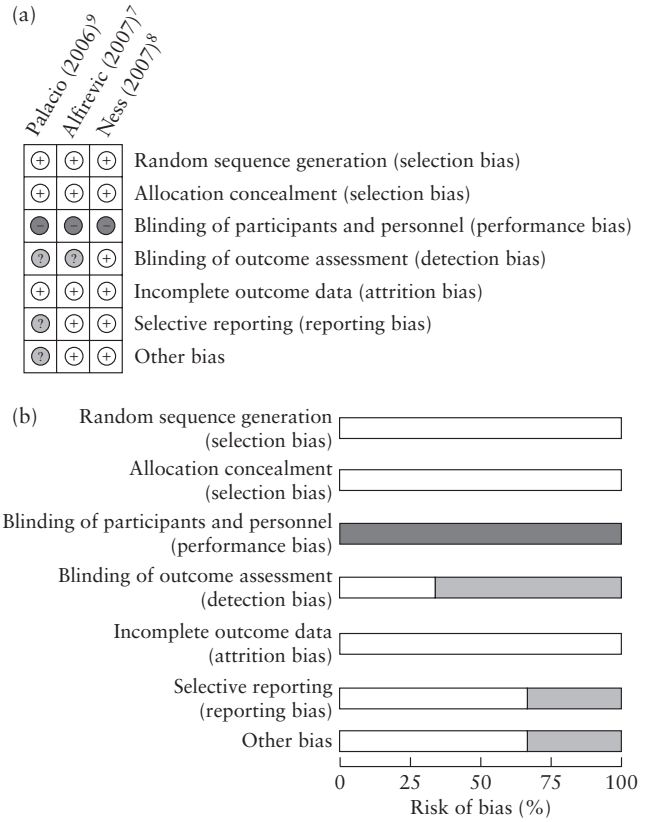

Figure 2 Risk of bias following *The Cochrane Handbook*[5] in individual randomized controlled trials (RCTs) (a) and across RCTs (b) included in meta-analysis. Only first author of each study is given. Risk of bias: □, +, low; ▨, ?, unclear ; ■, −, high.

All review stages were conducted independently by two reviewers (V.B., G.S.). The two authors assessed independently the electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction and data analysis. Disagreements were resolved by discussion.

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) IPD statement[6]. Before data extraction, the review was registered with the Cochrane Database of Systematic Reviews (review no. 0133) and with the PROSPERO International Prospective Register of Systematic Reviews (registration no. CRD42016042023).

RESULTS

Study selection and characteristics

From a total of 22 records identified through database searching, three trials[7–9] including a total of 287 singleton gestations with threatened PTL, of which 145 were randomized to knowledge of CL and 142 to no knowledge of CL, were included in the meta-analysis (Figure 1). Ness *et al.*[8] used mainly knowledge of TVS CL in the management protocol; however, for women with a CL of 20–29 mm, results of FFN assessment were also used. The overall risk of bias of the included trials was low (Figure 2). All studies had a low risk of bias in

Table 1 Summary of characteristics of randomized controlled trials comparing effectiveness of knowledge of cervical length (CL) with no knowledge of CL (controls) in preventing preterm birth

Study	*Country*	*Sample size** (n)	*Inclusion criteria*	*Definition of PTL*	*GA at randomization (weeks)*	*Exclusion criteria*	*Prior sPTB <37 weeks** (n/N (%))	*Primary outcome*
Palacio (2006)[9]	Spain	149 (*75 vs* 74)	Singleton gestation admitted because of symptoms of PTL	Minimum of two regular painful contractions in 10 min over 30 min, accompanied by change in cervical dilation, effacement or both	24 + 0 to 35 + 6	PPROM, persistent vaginal bleeding, cervical cerclage *in situ*, multiple gestation	10/75 (13.3) *vs* 7/74 (9.5)	Length of hospital stay
Alfirevic (2007)[7]	UK and Spain	41 (*21 vs* 20)	Singleton gestation with symptoms of PTL	Not available	24 + 0 to 34 + 6	PPROM, antenatal steroids given within 7 days of possible randomization, multiple gestation	3/21 (14.3) *vs* 2/20 (10.0)	Incidence of women still pregnant at 7 days
Ness (2007)[8]	USA	97 (*49 vs* 48)	Singleton gestation with symptoms of PTL	More than six contractions per hour by external tocodynometry	24 + 0 to 33 + 6	PPROM, persistent vaginal bleeding, cervical cerclage *in situ*	11/49 (22.4) *vs* 13/48 (27.1)	Time from initial evaluation to discharge

Only first author given for each study. *Intervention group with knowledge of CL *vs* control group with no knowledge of CL. GA, gestational age; PTL, preterm labor; sPTB, spontaneous preterm birth; PPROM, preterm prelabor rupture of membranes.

Table 2 Summary of management protocols in randomized controlled trials comparing effectiveness of knowledge of cervical length (CL) with no knowledge of CL (controls) in preventing preterm birth

Study	*CL cut-off used for management*	*Management of known CL group*	*Incidence of short CL*(n/N (%))*	*Control group*	*Management of controls*
Palacio (2006)[9]	< 25 mm	If positive (short CL), further observation; if negative, early discharge within 12 h	< 25 mm: 22/75 (29.3) *vs* 20/74 (27.0)	CL measured but managing physicians blinded to result	Physician's discretion
Alfirevic (2007)[7]	< 15 mm	If positive (short CL), tocolytics and antenatal corticosteroids; if negative, further observation and early discharge†	< 15 mm: 7/21 (33.3) *vs* not measured in control group	CL not measured	Tocolytics and antenatal corticosteroids
Ness (2007)[8]	< 20 mm‡	If positive (short CL), tocolytics and antenatal corticosteroids; if negative, early discharge	< 20 mm: 11/49 (22.4) *vs* 7/48 (14.6)	CL measured but managing physicians blinded to result	Physician's discretion

Only first author given for each study. *Intervention group with knowledge of CL *vs* control group with no knowledge of CL. †If uterine contractions persisted another transvaginal scan was performed 4 h later. ‡If CL was 20–29 mm, fetal fibronectin (FFN) was assessed; if FFN was negative (< 50 ng/mL) woman was discharged; if FFN was positive woman received tocolytics and antenatal steroids.

Table 3 Characteristics of women with singleton pregnancy and threatened preterm labor (PTL) in randomized controlled trials comparing effectiveness of knowledge of cervical length (CL) with no knowledge of CL (controls) in preventing preterm birth (PTB)

Characteristic	*Known CL group (n = 145)*	*Controls (n = 142)*	P
Race			0.73
African American	37/70 (52.9)	50/68 (73.5)	
Non-Hispanic white	27/70 (38.6)	13/68 (19.1)	
Hispanic	6/70 (8.6)	5/68 (7.4)	
BMI (kg/m^2)	24.7 ± 4.82	25.2 ± 3.77	0.73
Smoker	11/70 (15.7)	9/68 (13.2)	0.68
Prior PTB	24/145 (16.6)	22/142 (15.5)	0.80
Primigravid	44/145 (30.3)	47/142 (33.1)	0.61
GA at presentation with PTL (weeks)	31.4 ± 7.4	31.7 ± 6.4	0.71

Data are given as *n/N* (%) or mean ± SD. Some data are missing as not all variables were registered in every database. BMI, body mass index; GA, gestational age.

random sequence generation and incomplete outcome data. Adequate methods for allocation of women were used in all studies. All randomized women were included in an intention-to-treat analysis. Publication bias, assessed using Begg's and Egger's tests, showed no significant bias ($P = 0.69$ and 0.78, respectively). Authors of all three original trials provided the entire database from their study in order to obtain additional and unpublished data and perform IPD meta-analysis.

Table 1 shows the characteristics of the three included trials. Only singleton gestations with threatened PTL and without PPROM, between 24 + 0 and 35 + 6 weeks, were analyzed. Women in the known CL group were discharged if they had a negative TVS CL screening result (equal to or longer than 15, 20 or 25 mm, dependent on the study) or were treated with hospital admission, tocolytics and antenatal corticosteroids if TVS CL screening was positive (shorter than 15, 20 or 25 mm, dependent on the study) (Table 2). In one study[9], CL was not used to decide on admission but rather to help in the decision of possible early discharge. Women in the control group (no knowledge of CL) were treated at the physician's discretion in two studies[8,9] and were treated with tocolytics and antenatal corticosteroids in one study[7]. Characteristics of the included women are shown in Table 3.

The method of CL ascertainment was defined clearly in all studies. Endocervical canal length was measured as the distance between the internal and external ora using a vaginal probe placed in the anterior fornix of the vagina. Three anatomical landmarks defined the appropriate sagittal view: the internal os, the external os and the endocervical canal. The image was enlarged while visualizing the three landmarks simultaneously. Gentle pressure exerted on the cervix by the transducer was reduced followed by minimal pressure to allow visualization of the three landmarks. In all studies, this procedure was repeated three times and the shortest measurement was recorded. In all trials, the woman had an empty bladder during the ultrasound scan.

Synthesis of results

The pooled results for the primary and secondary outcomes are shown in Table 4. Statistical heterogeneity was low with no inconsistency in the primary outcome and secondary outcomes. The methodological quality of the included studies was mixed. For the primary and seven main secondary outcomes, we graded the quality of the evidence as low according to the GRADE criteria. Compared with the control group, women who were randomized to the known CL group had a significantly lower rate of PTB < 37 weeks (22.1% *vs* 34.5%; RR, 0.64 (95% CI, 0.44–0.94); three trials; 287 participants; Figure 3) and later gestational age at delivery (MD, 0.64 (95% CI, 0.03–1.25) weeks; MD, 4.48 (95% CI, 1.18–8.98) days;

Table 4 Primary and secondary outcomes in randomized controlled trials comparing effectiveness of knowledge of cervical length (CL) with no knowledge of CL (controls) in preventing preterm birth (PTB)

Outcome	*Trials (n[refs])*	*Known CL group*	*Controls*	I^2 *(%)*	*RR or MD*(95% CI)*
All singleton pregnancies with thrPTL ($n=287$)					
PTB < 37 weeks	3[7–9]	32/145 (22.1)	49/142 (34.5)	37	0.64 (0.44 to 0.94)†
PTB < 36 weeks	3[7–9]	28/145 (19.3)	41/142 (28.9)	46	0.67 (0.44 to 1.02)
PTB < 34 weeks	3[7–9]	9/145 (6.2)	16/142 (11.3)	0	0.55 (0.25 to 1.20)
PTB < 32 weeks	3[7–9]	4/145 (2.8)	8/142 (5.6)	0	0.49 (0.15 to 1.59)
PTB < 30 weeks	3[7–9]	1/145 (0.7)	3/142 (2.1)	0	0.49 (0.09 to 2.61)
PTB < 28 weeks	3[7–9]	1/145 (0.7)	0/142 (0)	NA	2.96 (0.12 to 71.52)
GA at delivery (weeks)	3[7–9]	37.9	37.3	0	0.64 (0.03 to 1.25)*†
GA at delivery (days)	3[7–9]	266.5	261.3	0	4.48 (1.18 to 8.98)*†
Latency‡ (days)	3[7–9]	52.1	47.6	0	4.41 (−0.33 to 9.44)*
Delivery within 7 days after randomization	3[7–9]	3/145 (2.1)	6/142 (4.2)	0	0.48 (0.12 to 1.95)
Delivery within 14 days after randomization	3[7–9]	10/145 (6.9)	19/142 (13.4)	0	0.48 (0.21 to 1.07)
Time from evaluation to discharge (h)	1[8]	2.17	2.32	NA	0.16 (−0.44 to 7.42)*
Low birth weight	2[7,8]	8/70 (11.4)	9/68 (13.2)	NA	0.86 (0.36 to 2.08)
Perinatal death	2[7,8]	0/70 (0)	0/68 (0)	NA	NA
Length of stay in NICU (days)	2[7,8]	15.3	17.1	0	−1.80 (−5.18 to 1.58)*
Maternal hospitalization	2[7,8]	25/70 (35.7)	17/68 (25.0)	69	1.57 (0.51 to 4.82)
Tocolysis	2[7,8]	16/70 (22.9)	22/68 (32.4)	91	1.14 (0.08 to 16.80)
Steroids for fetal maturity	2[7,8]	27/70 (38.6)	22/68 (32.4)	92	1.83 (0.13 to 26.36)
Singleton pregnancies with prior sPTB ($n=46$)					
PTB < 37 weeks	3[7–9]	7/24 (29.2)	6/22 (27.3)	0	1.02 (0.43 to 2.41)
Singleton pregnancies with thrPTL < 30 weeks ($n=66$)					
PTB < 37 weeks	3[7–9]	9/35 (25.7)	12/31 (38.7)	0	0.59 (0.21 to 0.98)†
Singleton pregnancies with thrPTL ≥ 30 weeks ($n=221$)					
PTB < 37 weeks	3[7–9]	23/110 (20.9)	37/111 (33.3)	0	0.61 (0.32 to 0.97)†

Data are presented as *n/N* (%) or mean. Some data are missing as not all variables were registered in every database. *Mean difference (MD). †Statistically significant. ‡Time from randomization to delivery. GA, gestational age; NA, not applicable; NICU, neonatal intensive care unit; PTL, preterm labor; refs, references; RR, relative risk; sPTB, spontaneous preterm birth; thrPTL, threatened preterm labor.

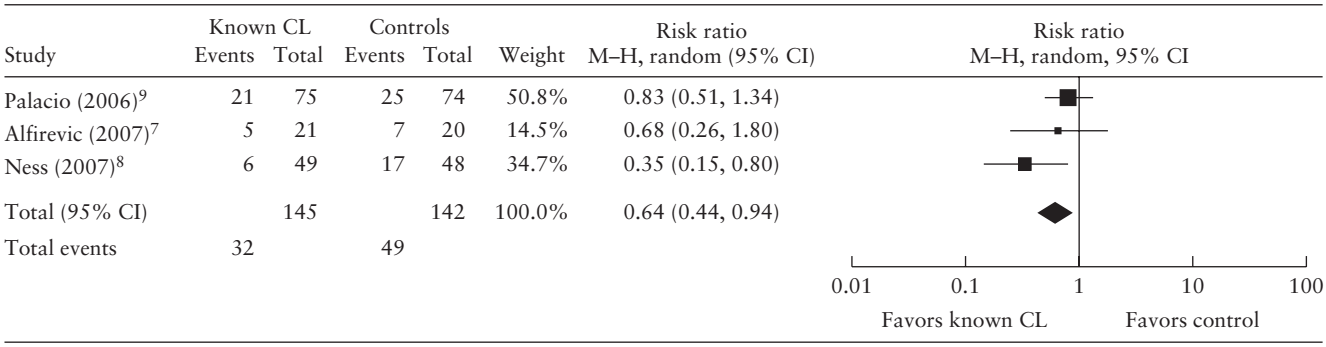

Figure 3 Forest plot for risk of preterm birth < 37 weeks in women with singleton pregnancy and threatened preterm labor randomized to cervical length (CL) screening with knowledge of results (known CL group) or to no knowledge of CL (controls). Only first author is given for each study. M–H, Mantel–Haenszel.

three trials; 287 participants). All other outcomes for which there were available data were similar in the two groups. No data were available regarding the following prespecified outcomes: composite perinatal outcome, fetal death, neonatal death, RDS, IVH, NEC, sepsis, admission to NICU, maternal wellbeing, economic analysis, cervical cerclage, chorioamnionitis and endometritis.

Subgroup analysis showed no difference in the incidence of PTB < 37 weeks with knowledge of CL in women with prior spontaneous PTB (29.2% *vs* 27.3%; RR, 1.02 (95% CI, 0.43–2.41); three trials; 46 participants; Table 4; Figure 4). However, we found significantly lower rates of PTB < 37 weeks in the known CL group in the subgroup of women with threatened PTL < 30 weeks (25.7% *vs* 38.7%; RR, 0.59 (95% CI, 0.21–0.98); three trials; 66 participants; Table 4) and ≥ 30 weeks (20.9% *vs* 33.3%; RR, 0.61 (95% CI, 0.32–0.97); three trials; 221 participants; Table 4).

Quality of evidence

For the comparison of intervention group *vs* control group, the quality of evidence was downgraded because of serious imprecision. Outcomes were imprecise because studies included relatively few patients and few events and thus had wide CIs around the estimate of the effect and because the optimal information size was not reached.

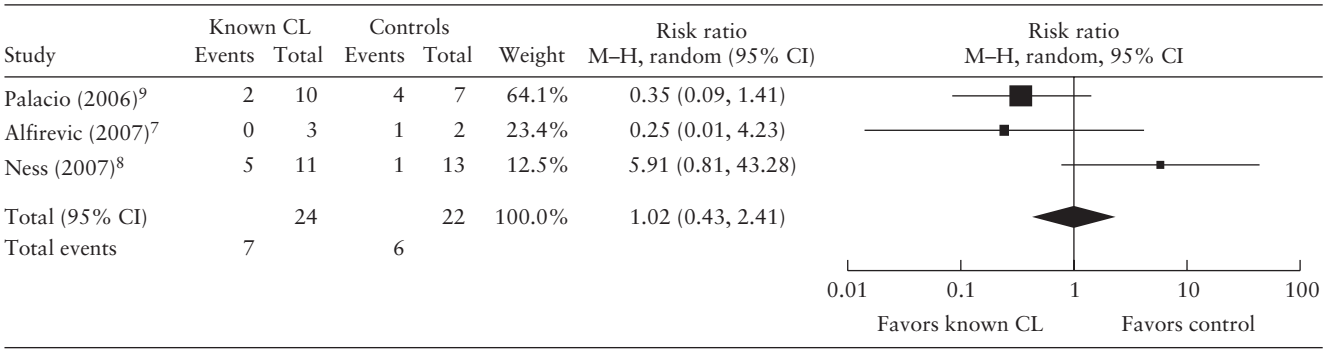

Figure 4 Forest plot for risk of preterm birth < 37 weeks in women with singleton pregnancy, threatened preterm labor and prior spontaneous preterm birth randomized to cervical length (CL) screening with knowledge of results (known CL group) or to no knowledge of CL (controls). Only first author is given for each study. M–H, Mantel–Haenszel.

The quality of the evidence was also downgraded another level because of serious indirectness due to the different interventions (Table S1).

DISCUSSION

Main findings

This IPD meta-analysis of three RCTs at low risk of bias, including 287 women, showed that TVS CL screening in singleton gestations with threatened PTL between 24 and 35 weeks reduced the rate of PTB and resulted in a later gestational age at delivery. No other outcomes were different. However, the quality level of summary estimates was low, as assessed by GRADE, indicating that the true effect may, or is even likely to, be substantially different from the estimate of the effect.

Comparison with previous studies

Our data, which included Level-1 data from well-designed trials, did not support earlier findings of a Cochrane review of five trials[4]. That review, which included also women with PPROM and multiple gestations, concluded that there was insufficient evidence to recommend routine screening of TVS CL in asymptomatic or symptomatic pregnant women[4]. Recently, a meta-analysis of six RCTs, including 546 singleton gestations with symptoms of PTL, showed that FFN testing alone in women with threatened PTL was not associated with prevention of spontaneous PTB or improvement in perinatal outcome but was associated with higher costs[10]. As four of the six RCTs included did not use a standardized management protocol based on the FFN results, more research may be needed in the use of FFN alone if TVS CL is unavailable.

Strengths and limitations

An IPD has several distinct advantages over aggregate data meta-analysis (ADMA). IPD involves the synthesis of individual-level data from the individual trials, and therefore allows for the verification of published results. As IPD are available, an IPD meta-analysis allows for more flexibility regarding the inclusion and exclusion of individuals, and the choice of endpoints and subgroups, compared with ADMA. Furthermore, IPD from unpublished studies can be included in the analysis. Other strengths of the study are that this is the largest meta-analysis so far conducted on the topic and it includes all currently published RCTs. Moreover, our study is strengthened by the low influence of publication bias. Notably, given the low number of included studies, we were not able to construct reliably funnel plots and the Begg's and Egger's tests have low power. Instead, studies were identified through trial registries, from which we were able to identify continuing, as well as terminated and unpublished, studies.

Many of the limitations of our study are those inherent to the RCTs included. Only three trials were included in the meta-analysis. One trial has been published only as an abstract[9]. The small number of studies and the small number of included women did not permit meaningful stratified meta-analyses to explore the test performance in subgroups of patients that may be less or more susceptible to bias. The TVS CL cut-off for intervention was different among the three trials, < 15 mm[7], < 20 mm[8] and < 25 mm[9]. As management of the included women was based on the TVS CL cut-offs used in the original trials, analyses to explore the effect of using different CL cut-offs in the different datasets are not feasible even with an IPD. Importantly, in one study, TVS CL was not used to decide on whether to admit the patient, but rather to help in the decision of possible early discharge[9]. The lack of neonatal outcome data limits the conclusions that can be drawn from this meta-analysis. The only data available were the duration of stay in NICU, which did not differ between the groups. The small number of included trials, different primary outcomes of the original trials and different definitions for PTL represent the major limitations of this systematic review. The lack of definition for threatened PTL in one trial[7] and the lack of uniformity in the definition for PTL among the trials was the major shortcoming of the meta-analysis. Defined criteria for NICU admission were lacking. Our meta-analysis was probably underpowered to detect significant decreases in PTB at cut-offs other than 37 weeks, but trends at 36 weeks (RR, 0.67), 34 weeks (RR, 0.55),

32 weeks (RR, 0.49) and 30 weeks (RR, 0.49) all showed about a 50% decrease in PTB (Table 4). Finally, the study was also underpowered to detect differences in the number and duration of maternal admissions and costs.

Conclusions

In summary, based on these Level-1 data, at least as used so far in these trials, there is a significant association between the knowledge of CL and a lower incidence of PTB < 37 weeks and later gestational age at delivery in symptomatic singleton gestations with threatened PTL. Of the three included trials, the one that was, by itself, associated with a significant decrease in PTB < 37 weeks used a management protocol that recommended intervention (admission, tocolysis and steroids) for women with TVS CL < 20 mm and for those with a CL of 20–29 mm and a positive FFN test, and recommended discharge for those with a TVS CL ≥ 30 mm[8]. Therefore, we suggest the use of this management protocol for women with threatened PTL between 23 + 7 and 33 + 6 weeks[8–11].

Our meta-analysis also included women randomized between 34 + 0 and 35 + 6 weeks. A recent meta-analysis of six trials, including 5698 singleton pregnancies, showed that antenatal steroids at ≥ 34 weeks reduce neonatal respiratory morbidity, and that a single course of corticosteroids can be considered for women at risk of imminent late PTB[12].

The biological plausibility of our findings is not completely clear. The benefit may come from better use of interventions (e.g. admission, tocolysis, steroids) aimed at women with true PTL, i.e. those with a CL < 20 mm or 20–29 mm with positive FFN. The other possible benefit is to avoid unnecessary intervention in women with threatened PTL who have a reassuring TVS CL. For example, in the RCT by Ness *et al.*[8], more than 50% of women had a TVS CL ≥ 30 mm, and were therefore discharged, as their risk of delivery within 7 days was < 2%[11]. Some tocolytics have been shown in some RCTs and meta-analyses[13] to be associated with significant decreases in PTB at different cut-offs. It is unknown but possible that these tocolytics may be shown to be more effective in prevention of PTB in women with not only preterm contractions, but also short TVS CL, i.e. women truly at high risk for PTB. Moreover, TVS CL assessment may also be associated with a reduction in PTB by reducing the need for serial digital vaginal examinations. Indeed, serial digital examination has been associated in several studies with an increased risk for PTB[14,15], possibly because these examinations have also been associated with introduction of vaginal organisms into the cervical canal[16].

Given that we found a significant 36% reduction in the primary outcome, but other outcomes, including clinically challenging outcomes, were mostly statistically similar, further study needs to be undertaken to understand better whether and under what circumstances the predictive characteristics of TVS CL screening can be translated into better clinical management, and therefore better outcomes. Future studies should report on all pertinent maternal and perinatal outcomes, and include analyses on cost-effectiveness. Most importantly, future studies should include a clear protocol (e.g. tocolysis or no tocolysis) for management of women based on TVS CL results, so that it can be evaluated and replicated easily.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Summary of findings and quality of evidence of randomized controlled trials (RCTs) included in meta-analysis

This article has been selected for Journal Club.

A slide presentation, prepared by Dr Shireen Meher, one of UOG's Editors for Trainees, is available online.

Chinese translation by Dr Yang Fang.
Spanish translation by Dr Ruben Dario Fernandez.

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Cribado mediante la longitud cervical para la prevención del parto pretérmino en embarazos con feto único y riesgo de parto prematuro: revisión sistemática y metaanálisis de ensayos controlados aleatorizados haciendo uso de los datos individuales de las pacientes

RESUMEN

Objetivo El cribado mediante la longitud cervical obtenida con ecografía transvaginal (ETV) ha demostrado ser una buena prueba para la predicción del parto pretérmino espontáneo (PPTE) en embarazos con feto único sintomáticos debido a la amenaza de parto pretérmino (PPT). El objetivo de esta revisión y metaanálisis de los datos de participantes individuales fue evaluar el efecto de medir la longitud cervical (LC) mediante ETV con el fin de prevenir el parto prematuro en embarazos únicos con amenaza de PPT.

Métodos Se realizaron búsquedas en los ficheros de ensayos de Cochrane *Pregnancy and Childbirth Group* y *Complementary Medicine Field* (mayo de 2016), y en las listas de referencias de los estudios encontrados. Los criterios de selección incluyeron ensayos controlados aleatorizados de embarazos con feto único y riesgo de PPT con aleatorización de la paciente basada principalmente en el cribado mediante la LC (grupo de intervención), el cribado mediante la LC sin conocimiento de los resultados, o sin cribado de LC (grupo de control). Las participantes fueron mujeres embarazadas con feto único desde las 23 + 0 hasta las 36 + 6 semanas y con riesgo de PPT. Se estableció contacto con los autores de los ensayos incluidos para solicitar el acceso a los datos y llevar a cabo un metaanálisis de los datos de las participantes individualmente. Los datos proporcionados por los investigadores se agregaron a una base de datos maestra creada específicamente para esta revisión. El resultado primario fue el PPTE < 37 semanas. Las medidas resumen se reportaron como riesgo relativo (RR) o como diferencia de medias (DM) con IC del 95%.

Resultados En el metaanálisis se incluyeron tres ensayos con un total de 287 embarazos con feto único y riesgo de PPT entre 24 + 0 y 35 + 6 semanas, de los cuales 145 fueron asignados al azar a un cribado mediante la LC con conocimiento de los resultados y 142 a aquellos para los que se desconocía la LC. En comparación con el grupo control, las mujeres que fueron asignadas aleatoriamente al grupo en el que se conocía la LC tuvieron una tasa de parto prematuro a < 37 semanas significativamente menor (22,1% vs. 34,5%; RR 0,64 (IC 95%, 0,44–0,94); 3 ensayos; 287 participantes) y una edad gestacional al momento del parto más tardía (DM 0,64 (IC 95%, 0.03–1.25) semanas; DM 4,48 (IC 95%, 1,18–8,98) días; 3 ensayos; 287 participantes). El resto de los resultados para los cuales había datos disponibles fueron similares en ambos grupos.

Conclusiones Existe una asociación significativa entre el conocimiento de la LC obtenida mediante ETV y una menor incidencia de PPTE y edad gestacional más tardía en el momento del parto en embarazos con feto único sintomáticos debido al riesgo de parto pretérmino (PPT). Teniendo en cuenta que en el metaanálisis se encontró una reducción significativa del 36% en el resultado primario, pero que los otros resultados fueron estadísticamente similares en su mayoría, serán necesarios más estudios para entender mejor si las propiedades predictivas del cribado mediante la LC obtenida con ETV se pueden traducir en una mejor atención clínica y por lo tanto mejores resultados dependiendo de las circunstancias.

出现先兆早产的单胎妊娠中筛查宫颈长度预防早产的发生：采用单个病例数据进行随机对照试验的系统综述和 meta 分析

目的：已有研究显示，在出现先兆早产（preterm labor，PTL）的有症状的单胎妊娠中，采用经阴道超声检查（transvaginal sonography，TVS）进行宫颈长度筛查是一种很好的预测自发性早产（spontaneous preterm birth，PTB）发生的方法。本篇对单个病例数据的综述和 meta 分析的目的是评估在出现先兆 PTL 的单胎妊娠中，知晓 TVS 宫颈长度（cervical length，CL）对预防 PTB 的作用。

方法：检索 Cochrane 妊娠和分娩组试验注册资料库和 Cochrane 辅助医学试验注册资料库（2016 年 5 月）以及检索到的研究的参考文献列表。纳入标准为出现先兆 PTL 的单胎妊娠的随机对照试验，随机分为主要根据 CL 筛查结果进行处理（干预组）或者进行 CL 筛查但不知晓结果或未进行 CL 筛查（对照组）。研究对象为孕 23+0 周至孕 36+6 周出现先兆 PTL 的单胎妊娠孕妇。我们与纳入试验的通信作者取得联系，获准使用数据，并进行单个病例数据的 meta 分析。将研究人员提供的数据合并到特别建立的主数据库中以进行评价。主要结局为孕 37 周前发生 PTB。综合检测结果以相对危险度（relative risk，RR）或平均差和 95%CI（mean difference，MD）表示。

结果：meta 分析纳入 3 项试验，共包括 287 例在孕 24+0 周至孕 35+6 周间出现先兆 PTL 的单胎妊娠，其中 145 例随机分至知晓结果的 CL 筛查组，142 例分至不知晓 CL 组。与对照组相比，随机分至知晓 CL 组的孕妇孕 37 周前 PTB 发生率明显较低[22.1%和 34.5%；RR，0.64（95% CI，0.44~0.94）；3 项试验；287 名研究对象]，分娩孕周延长[MD，0.64（95% CI，0.03~1.25）周；MD，4.48（95% CI，1.18~8.98）天；3 项试验；287 研究对象]。2 组相比，现有数据的所有其他结局相似。

结论：出现先兆 PTL 的有症状的单胎妊娠中，知晓 TVS CL 与 PTB 发病率较低和分娩孕周延长呈显著相关。鉴于在 meta 分析中我们发现主要结局发生率显著降低 36%，而其他结局大多统计学相似，因此需要进行进一步研究，以更深入了解采用 TVS 进行 CL 筛查的预测特点能否以及在何种情况下可以用于进行更好的临床管理，从而得到更好的结局。