PLOS ONE

Cervical length varies considering different populations and gestational outcomes: Results from a systematic review and meta-analysis

T. G. Bortoletto[1], T. V. Silva[1,2], A. Borovac-Pinheiro[1], C. M. Pereira[1], A. D. Silva[1], M. S. França[3], A. R. Hatanaka[3], J. P. Argenton[1], R. Passini, Jr.[1], B. W. Mol[4], J. G. Cecatti[1], R. C. Pacagnella[1]*

1 School of Medical Sciences, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil, 2 University of Pernambuco (UPE), Recife, Pernambuco, Brazil, 3 Department of Obstetrics and Gynaecology, Federal University of São Paulo (UNIFESP), São Paulo, Brazil, 4 Department of Obstetrics and Gynaecology, Monash University, Clayton, Victoria, Australia

* rodolfop@unicamp.br

Abstract

Background

The uterine cervical length is an important risk factor for preterm birth. The aim of this study was to assess cervical length distribution in women with singleton pregnancies, measured by transvaginal ultrasound between 16 and 24 weeks, and its association with population characteristics.

Materials and methods

We searched electronic databases and other sources for studies published from April 1, 1990 to July 21, 2020. Of the 2019 retrieved publications, full-text versions of 137 articles were considered. We included 77 original articles that reported cervical length measurements of 363,431 women. The main aim of this study was to identify the pattern of cervical length in different populations. We collected demographic and clinical data concerning the population, in addition to information regarding the ultrasound examination and cervical length measurement. Regarding study bias, 56 were at low risk of bias and 21 were at medium risk of bias.

Results

The meta-analysis included 57 articles with data from 158,346 women. The mean cervical length was 37.96. mm (95% CI [36.68, 39.24]). Cervical length was shorter in women from Africa and Asia, in those from low-income countries, with a lower body weight, and in those who delivered before 37 gestational weeks. We found that the cervical length from pooled studies is longer than that usually discussed in the literature. Regarding limitations, we had difficulty assessing our main variable because there was no consistent pattern in the way

authors reported cervical length measurement. Another limitation was the great heterogeneity between studies.

Conclusions

The use of a single cutoff value to define a short cervix diagnosis, an important risk factor for preterm birth, may not be correct and cervical length must be considered according to maternal population characteristics. Future studies should identify different specific curves and cutoff values for cervical length in different populations. This meta-analysis was registered in the PROSPERO database under CRD42017070246 at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=70246.

Introduction

Around 15 million preterm births occur every year worldwide [1]. Prematurity is the primary cause of neonatal death and morbidity around the globe [2], and the earlier the gestational age (GA) at birth, the greater the associated risks [2]. Aside from multiple pregnancy [3] and obstetrical history of a previous preterm birth [4], a short uterine cervix has also been found to be associated with premature delivery, and its presence can be evaluated by transvaginal ultrasound during the second trimester, which allows for risk assessment [5–8].

The transvaginal ultrasound (TVUS) technique is well established [9]. The reference ranges for distribution curve and cervical length percentiles were first defined in the 90s. Since then, several researchers have used these cutoff limits as standards. Iams et al. [10] found the smallest risk of delivering before 35 weeks in women whose cervical length was over 40 mm (75th percentile) and established all comparisons based on this cutoff.

Major trials chose lower limits to propose interventions [5, 11–14], probably also considering the values offered by Iams et al. [10] and other researchers [15–18], in which cutoffs like 15, 20, 25 or 30 mm were suggested, although the most agreed upon value is currently 25 mm. Official guidelines do not recommend transvaginal ultrasound as part of a universal screening program [19–21], especially when women have no history of spontaneous preterm birth. However, they recognize its value as long as clinicians remain aware of the real indications in prescribing (or not) specific interventions [22, 23]. The confidence to do so relies on determining the normality according to the gestational week of screening and maternal characteristics.

In order to understand the distribution of cervical length and its classification as normal or abnormal, this review systematically evaluated original research that reported transvaginal ultrasound imaging of cervical length measurements in women with singleton pregnancies between 16 to 24 gestational weeks. The aim of this study was to identify the cervical length distribution in different populations to guide clinical practice considering population characteristics. We decided to evaluate the cervical length between 16 to 24 gestational weeks because this is the time at which the largest number of interventions to prevent preterm birth are proposed.

Materials and methods

This systematic review and meta-analysis was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [24] (S1 Appendix) and registered under the identification number CRD42017070246 in the PROSPERO database. All

articles were assessed by two independent researchers who retrieved and reviewed studies for eligibility, assessed their risk of bias and extracted data. Divergences were resolved by a senior researcher.

We searched Medline, Embase, Scielo and clinicaltrials.gov, as well as the references of retrieved articles, to identify original papers that performed transvaginal ultrasound with rigorous imaging criteria from 16 to 24 gestational weeks in women with singleton pregnancies to evaluate cervical length in different populations. We only included studies that provided the prevalence of different cervical length measurements with an updated technique; therefore, we searched for randomized controlled trials, cohort and observational studies published between April 1, 1990 to July 21, 2020, with no language restriction. We used a combination of terms related to preterm birth and cervical length for the search strategy (see S2 Appendix for the complete search strategy). Inclusion criteria were as follows: population of women with singleton pregnancies universally evaluated from 16 to 24 gestational weeks; detailed description of TVUS; and published from April 1, 1990 to July 21, 2020. We only included studies that had described the cervical measurement technique adequately and studies that followed Fetal Medicine Foundation cervical assessment orientation.

The exclusion criteria were unclear, absent or outdated TVUS technique description; cervical length measurement after threatened preterm labor; women with symptoms; or those already submitted to cervical cerclage in the current pregnancy.

Once eligible articles had been defined, we extracted information regarding the method (design, TVUS technique, sampling, statistical analysis); country of origin; number of subjects; gestational age at sonography; risk of prematurity (history of preterm birth or cervical procedures, as established by the original authors); cervical length; gestational age at birth; and obstetric, demographic and anthropometric maternal characteristics. In cases where the original article described a gestational age surpassing the scope of the review, we only analyzed these data if the authors made cervical length measurements between 16 and 24 gestational weeks. All included articles collected information concerning the risk of prematurity; however, the classification of women as high or low risk was not homogeneous across the studies (described in S3 Appendix).

After analysis of the full text, excluded articles were arranged in a table according to reason for exclusion, and the included articles were subject to quality assessment using the National Heart, Lung and Blood Institute [25] tool (available in S4 Appendix).

The selected publications that provided cervical length measurements as a continuous variable (mean or median and their standard deviation or interquartile range) were analyzed using meta-analysis to generate a single mean value and its standard deviation. This process was applied to infer mean cervical length measurements for all women (and later, a different meta-analysis excluding those with previous conization), women split according to the economic development status of their continent of origin (low/middle- or high-income country) as defined in the World Development Indicators [26]; and as low or high risk of preterm delivery. It is important to note that the classification criteria used to define low and high risk for preterm birth by the authors were not clear or similar. Some characteristics such as previous preterm birth, cervical procedures or Mullerian malformation were cited for some authors, but overall, there was no complete description of the specific features to classify woman as low or high risk for prematurity. Comparisons estimated the difference in cervical length according to parity, age and birth outcome.

In papers that provided data as categorical variables, we reported the absolute number of individuals who presented in each cervical length stratum for statistical analysis. The Aleatory model was used to estimate the proportion of women in each cervical length stratum. In papers that reported continuous variables, we used meta-analysis to calculate the mean and standard

deviation for cervical length measurement and the proportion of individuals in each cervical length stratum. From publications that reported percentiles, we calculated the mean and standard deviation for each percentile and constructed a descriptive theoretical distribution curve for the entire period from 16 to 24 gestational weeks.

We also analyzed aggregated cervical length breakdown by continents, country income, women's BMI and pregnancy outcome (preterm or term delivery). We used R software, version 3.4, package metaphor 2.0–0 from the R Foundation for Statistical Computing for statistical analysis. The dataset is available as S1 Data.

RCP and BM received funds from the Bill & Melinda Gates Foundation, Seattle, WA [OPP1107597], the Brazilian Ministry of Health and the Brazilian National Council for Scientific and Technological Development (CNPq) [401615/20138] for the study. No author received salary from any funders and the funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Results

We identified 4089 articles through the databases and 23 from other sources, including reference search and experts' suggestions. After removing duplicates, we screened 2825 records, of which 162 were found to be eligible. We then excluded 85 articles due to the following reasons: method (one paper), no description of the screened women (10 papers), ineligible population (18 papers), TVUS technique different from established patterns or not reported (15 papers), cohort already included in another publication (13 papers), and gestational age surpassing the scope of the review (28 papers). Fig 1 shows the PRISMA flow diagram and S1 Table details all excluded articles and the reasons for exclusion.

The remaining 77 articles (64 cohorts, 10 clinical trials and 3 cross-sectional study) included 363,431 women. We included one study from South Africa, Belgium, Botswana, Catalonia, Croatia, Egypt, Finland, Greece, Hong Kong, India, Iran, Italy, Japan, Romania, South Korea, Sweden, Taiwan, two studies from Tukey and UK, three from The Netherlands and Thailand, four from China and Spain, ten from Brazil and 24 from the United States. Also, five studies included women from two or more countries.

The papers were evaluated according to the mode of describing the main variable, the cervical length. The four overlapping categories were: mean cervical length (57 articles), number of women in each stratum of cervical length (52 articles), percentile (15 articles), and mean cervical length according to gestational week (9 articles) (S2 Table).

In the quality assessment, 56 papers were determined to have a low risk of bias, 21 had medium risk, and none were considered to have a high risk of bias (S5 Appendix). Nine categories presented homogeneous performance, with over 62 studies complying with high quality criteria. Inferior performance was presented in two categories based on the description of statistical analysis (item 5 with 29 papers complying, and item 14 with 39 papers complying): multiple assessment of exposure (item 10 with 22 papers complying) and considerations about blinding of assessors (item 12 with 12 papers complying). Considering the variable of exposure (item 8), 39 articles provided both categorical and continuous variables, 19 articles presented continuous variables and 19 provided categorical variables.

The meta-analysis included 57 publications, accounting for 158,346 women. Considering the Q test of heterogeneity, studies were considered heterogeneous ($p < 0.0001$), with an I^2 of 100%. The mean cervical length was 37.96. mm (95% CI [36.68, 39.24]); Fig 2). Year of publication did not influence cervical length.

In a second different meta-analysis, we included only studies that studied a population without previous cervical conization (S1 Fig). This second meta-analysis included 40 publications
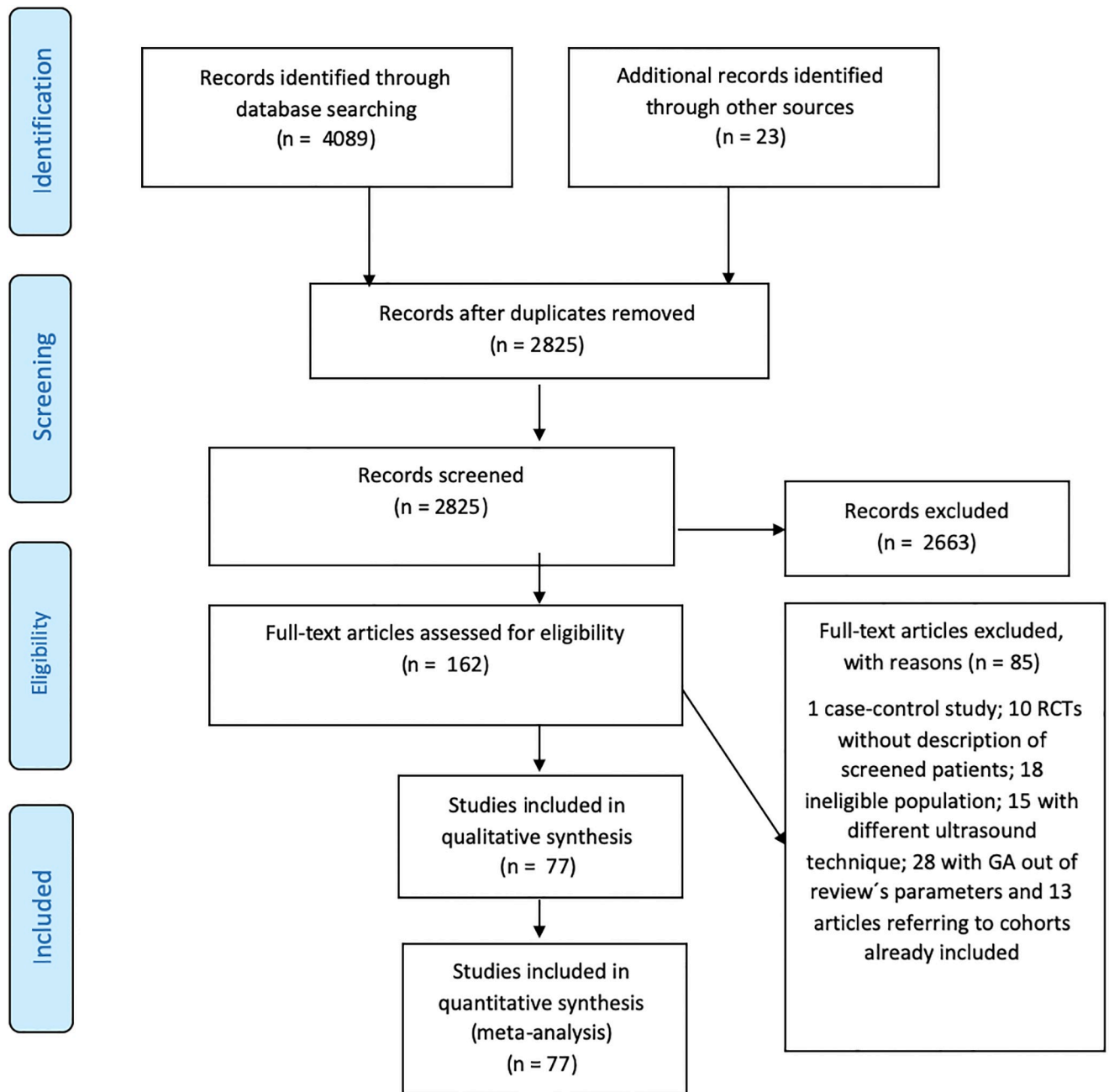
Fig 1. PRISMA diagram. Flow diagram of included articles according to PRISMA 2009 guidelines.

and a total of 91,408 women. The mean cervical length was 38.21 mm with a 95% CI of 36.70 to 39.71 mm.

When cervical length was evaluated according to the continent of origin, the mean cervical length was 32.77mm for Africa (95% CI [31.76, 33.78]), 36.59mm (95% CI [35.33, 37.84]) for South American, 39.37 mm (95% CI [35.34, 43.40]) for North American, 35.98mm (95% CI [34.21, 37.76]) for Asian and 39.81 mm (95% CI [38.23, 41.40]) for European populations (Fig 3).

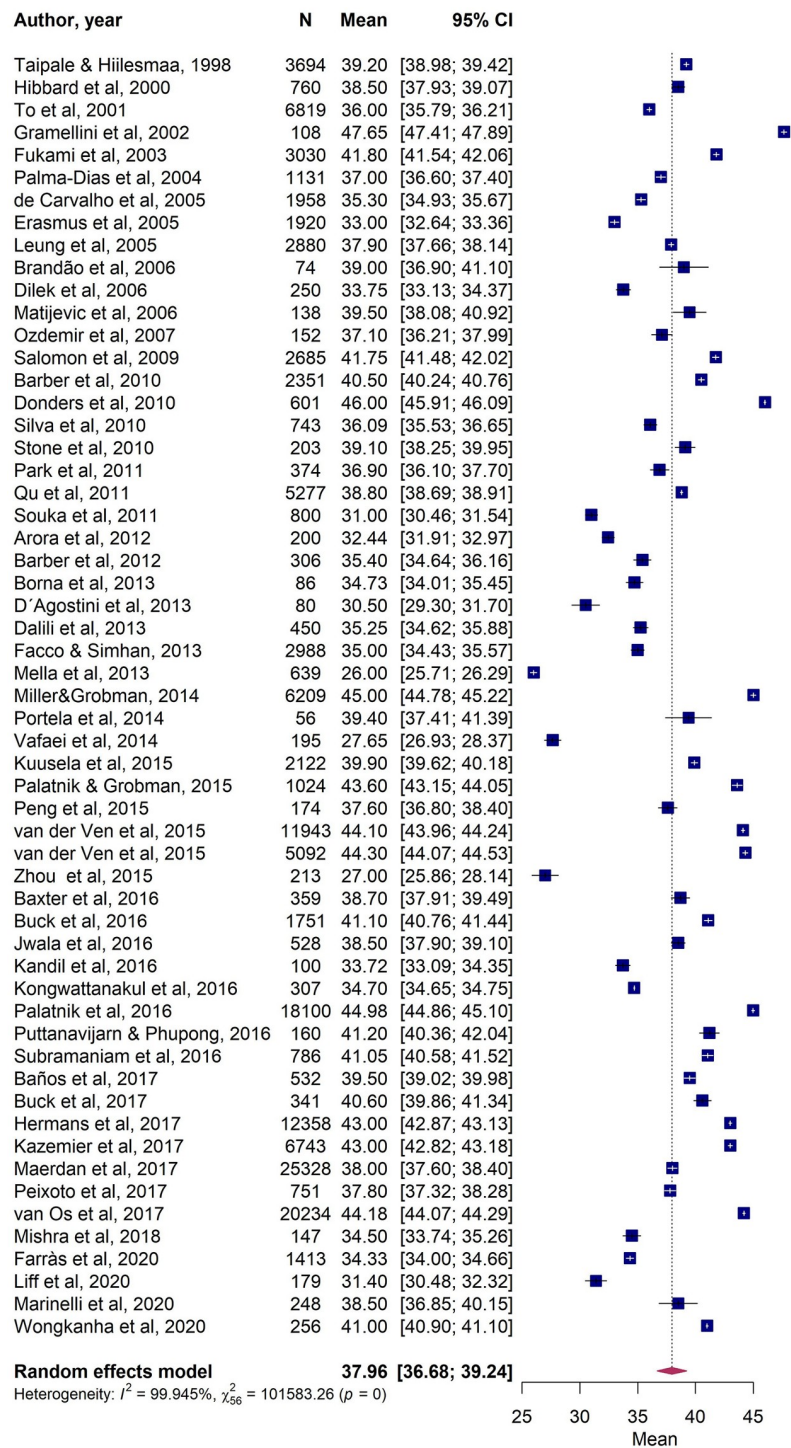| Author, year	N	Mean	95% CI
Taipale & Hiilesmaa, 1998	3694	39.20	[38.98; 39.42]
Hibbard et al, 2000	760	38.50	[37.93; 39.07]
To et al, 2001	6819	36.00	[35.79; 36.21]
Gramellini et al, 2002	108	47.65	[47.41; 47.89]
Fukami et al, 2003	3030	41.80	[41.54; 42.06]
Palma-Dias et al, 2004	1131	37.00	[36.60; 37.40]
de Carvalho et al, 2005	1958	35.30	[34.93; 35.67]
Erasmus et al, 2005	1920	33.00	[32.64; 33.36]
Leung et al, 2005	2880	37.90	[37.66; 38.14]
Brandão et al, 2006	74	39.00	[36.90; 41.10]
Dilek et al, 2006	250	33.75	[33.13; 34.37]
Matijevic et al, 2006	138	39.50	[38.08; 40.92]
Ozdemir et al, 2007	152	37.10	[36.21; 37.99]
Salomon et al, 2009	2685	41.75	[41.48; 42.02]
Barber et al, 2010	2351	40.50	[40.24; 40.76]
Donders et al, 2010	601	46.00	[45.91; 46.09]
Silva et al, 2010	743	36.09	[35.53; 36.65]
Stone et al, 2010	203	39.10	[38.25; 39.95]
Park et al, 2011	374	36.90	[36.10; 37.70]
Qu et al, 2011	5277	38.80	[38.69; 38.91]
Souka et al, 2011	800	31.00	[30.46; 31.54]
Arora et al, 2012	200	32.44	[31.91; 32.97]
Barber et al, 2012	306	35.40	[34.64; 36.16]
Borna et al, 2013	86	34.73	[34.01; 35.45]
D´Agostini et al, 2013	80	30.50	[29.30; 31.70]
Dalili et al, 2013	450	35.25	[34.62; 35.88]
Facco & Simhan, 2013	2988	35.00	[34.43; 35.57]
Mella et al, 2013	639	26.00	[25.71; 26.29]
Miller&Grobman, 2014	6209	45.00	[44.78; 45.22]
Portela et al, 2014	56	39.40	[37.41; 41.39]
Vafaei et al, 2014	195	27.65	[26.93; 28.37]
Kuusela et al, 2015	2122	39.90	[39.62; 40.18]
Palatnik & Grobman, 2015	1024	43.60	[43.15; 44.05]
Peng et al, 2015	174	37.60	[36.80; 38.40]
van der Ven et al, 2015	11943	44.10	[43.96; 44.24]
van der Ven et al, 2015	5092	44.30	[44.07; 44.53]
Zhou et al, 2015	213	27.00	[25.86; 28.14]
Baxter et al, 2016	359	38.70	[37.91; 39.49]
Buck et al, 2016	1751	41.10	[40.76; 41.44]
Jwala et al, 2016	528	38.50	[37.90; 39.10]
Kandil et al, 2016	100	33.72	[33.09; 34.35]
Kongwattanakul et al, 2016	307	34.70	[34.65; 34.75]
Palatnik et al, 2016	18100	44.98	[44.86; 45.10]
Puttanavijarn & Phupong, 2016	160	41.20	[40.36; 42.04]
Subramaniam et al, 2016	786	41.05	[40.58; 41.52]
Baños et al, 2017	532	39.50	[39.02; 39.98]
Buck et al, 2017	341	40.60	[39.86; 41.34]
Hermans et al, 2017	12358	43.00	[42.87; 43.13]
Kazemier et al, 2017	6743	43.00	[42.82; 43.18]
Maerdan et al, 2017	25328	38.00	[37.60; 38.40]
Peixoto et al, 2017	751	37.80	[37.32; 38.28]
van Os et al, 2017	20234	44.18	[44.07; 44.29]
Mishra et al, 2018	147	34.50	[33.74; 35.26]
Farràs et al, 2020	1413	34.33	[34.00; 34.66]
Liff et al, 2020	179	31.40	[30.48; 32.32]
Marinelli et al, 2020	248	38.50	[36.85; 40.15]
Wongkanha et al, 2020	256	41.00	[40.90; 41.10]
Random effects model		**37.96**	**[36.68; 39.24]**

Heterogeneity: I^2 = 99.945%, χ^2_{56} = 101583.26 (p = 0)

Fig 2. Forest plot of cervical length measurements (in millimeters) of 57 publications included in the meta-analysis.

Although the confidence intervals overlap with each other when analyzing data exclusively within a single continent, comparison of five continents using data from all articles included in the meta-analysis demonstrated a statistical difference between countries (p = 0). Fig 4 presents the difference between low/medium- and high-income countries, which presented
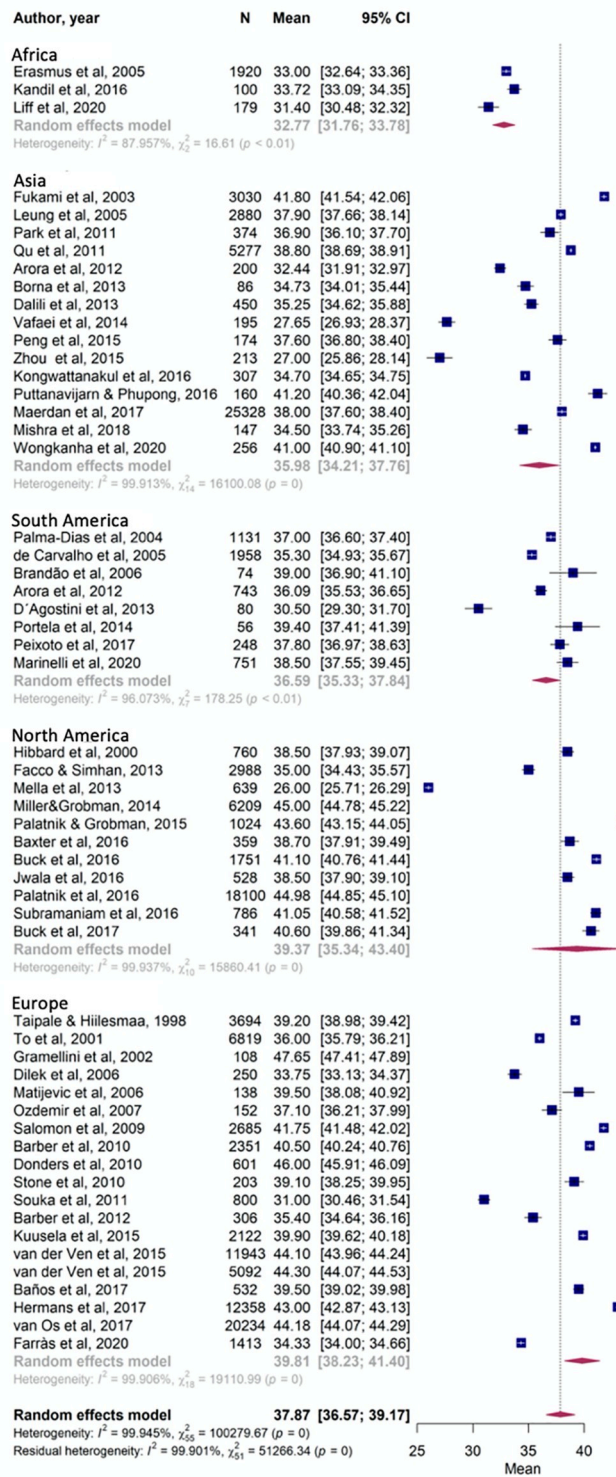
Fig 3. Forest plots for the cervical length of women from each continent (Africa, South America, North America, Asia and Europe).
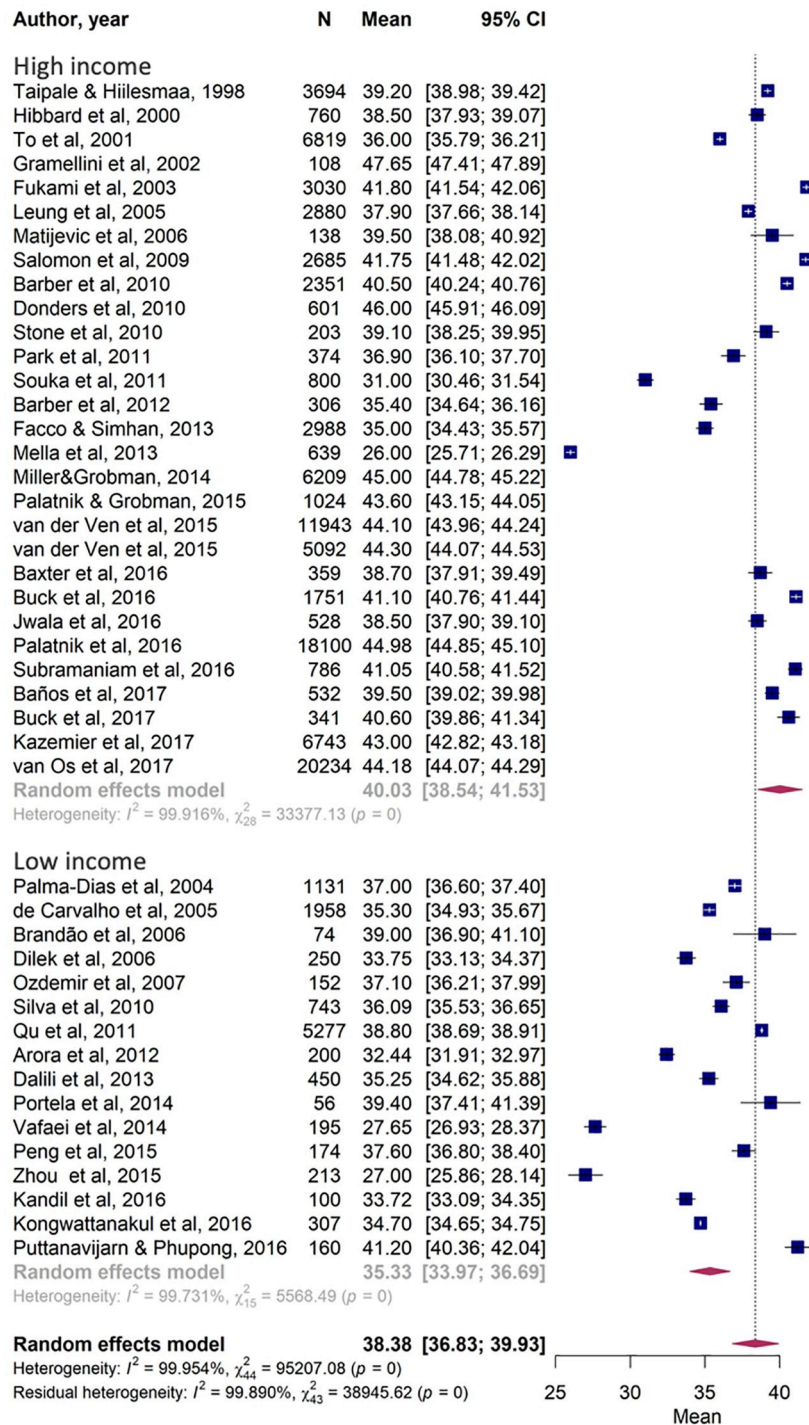
Fig 4. Comparison of cervical length according to low/medium-income versus high-income countries.

https://doi.org/10.1371/journal.pone.0245746.g004

significantly different mean cervical lengths of 35.33 mm (95% CI [33.97, 36.69]) and 40.03 mm (95% CI [38.54, 41.53]), respectively (p = 0).

Cervical length was statistically shorter for nulliparous women; however, this finding was not clinically significant (mean difference 1.02 mm, 95% CI [-1.96, -0.07], S2 Fig). No

differences were found according to age (adolescents vs. adults; S3 Fig) or risk for preterm birth (low risk vs. high risk; S3 Appendix).

When comparing cervical measurements according to anthropometric features, we observed differences between women with the highest and lowest body mass index (BMI), with thinner women presenting cervical lengths 12.58 mm shorter than obese women (Fig 5).

Another comparison was regarding to birth outcomes. Ten publications (19,399 women) reported cervical length according to gestational age at birth. Preterm births (under 37 weeks) presented a mean cervical length -3.80 mm shorter than term births (95% CI [-5.15, -2.44], P<0.01; Fig 6).

Fifteen articles reported cervical length as percentiles, 14 of which used 26.8 mm as the cut-off for percentile 5, and the second most commonly reported one (by 13 articles) was percentile 50, corresponding to 38 mm. Fig 7 shows a descriptive theoretical distribution curve (red line) and compares it to those originally presented by Iams et al. (blue line).

When analyzing data according to cervical length cutoff values, 20 studies considered 20 mm as the cutoff limit, totaling 88,009 women, thus 3% of the study population were considered under the cutoff. For the 25 mm limit, there were 39 studies accounting for 146,500 women, 6,7% of whom were under the cutoff value. The 30 mm limit was used in 19 papers, including 88,380 subjects, with 13,1% of women classified as having a cervical length under the cutoff.

Discussion

The main finding of this study is that cervical length ranges vary across populations when evaluated between 16 to 24 weeks gestation. Also, the cervical length was found to be shorter in women with a low body weight and in those who had a preterm birth.

Our largest meta-analysis of 57 publications included approximately one-third of the total number of women (158,346 out of 363,431) and reported a mean cervical length of 37.96 mm. This measurement was virtually the same (38.21 mm) when evaluating studies whose data did not include women who had undergone a previous cervical excisional procedure, which is consistent with the findings of other authors in publications describing cervical lengths, with no modifications in pregnancies observed after excisional procedures [27, 28].

Our main hypothesis was that cervical length would vary according to population characteristics. We demonstrated associations of cervical length with regional and demographic features when measurements were compared by continent and by income.

Mean measurements between continents presented clinically relevant differences of more than 6 mm when comparing Africa to North American or European women and almost 4 mm when comparing Asia to European women. Moreover, the statistical analysis presented a significant p-value. When countries were grouped according to income, which meant transferring data from Japan, Hong Kong and South Korea from the Asian group to the high-income group and transferring data from Turkey from the European group to the middle/low-income group, we also identified a clinically relevant and statistically significant difference over 4mm. High-income countries presented a mean cervical length of 40.03 mm while middle/low-income countries presented 35.33 mm.

When evaluating a population exclusively from the Netherlands, the ProTWIN Study reported mean cervical length measurements ranging from 43.6 to 44.2 mm, and the 25th percentile was 38 mm in 813 twin pregnancies from 16 to 22 weeks [29]. Although our review refers to single pregnancies only, we consider the ProTWIN Study as representative of high-income countries. This trial corroborates the idea of population differences in cervical length measurements.
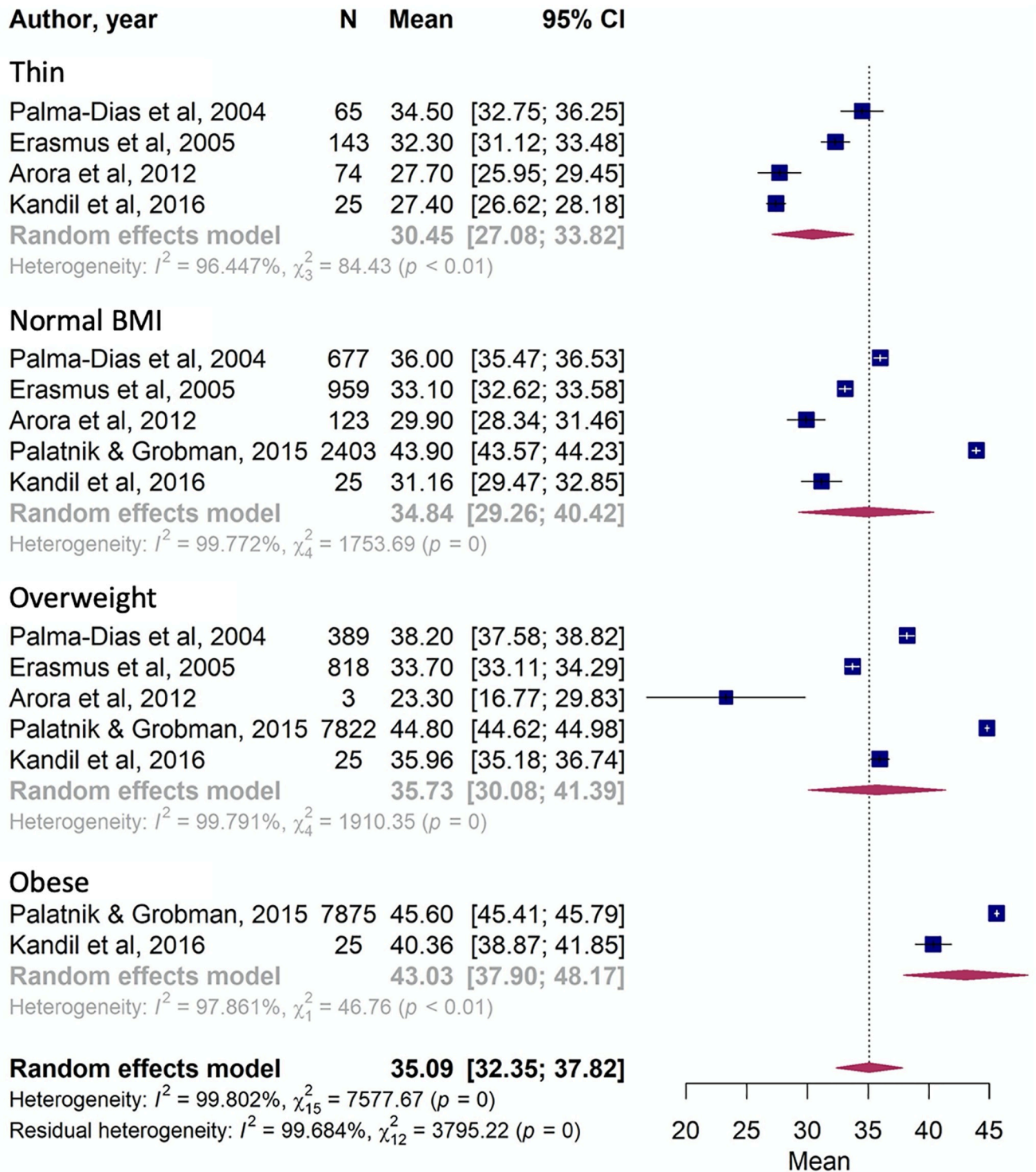
Author, year	N	Mean	95% CI
Thin			
Palma-Dias et al, 2004	65	34.50	[32.75; 36.25]
Erasmus et al, 2005	143	32.30	[31.12; 33.48]
Arora et al, 2012	74	27.70	[25.95; 29.45]
Kandil et al, 2016	25	27.40	[26.62; 28.18]
Random effects model		30.45	[27.08; 33.82]

Heterogeneity: $I^2 = 96.447\%$, $\chi_3^2 = 84.43$ ($p < 0.01$)

Normal BMI			
Palma-Dias et al, 2004	677	36.00	[35.47; 36.53]
Erasmus et al, 2005	959	33.10	[32.62; 33.58]
Arora et al, 2012	123	29.90	[28.34; 31.46]
Palatnik & Grobman, 2015	2403	43.90	[43.57; 44.23]
Kandil et al, 2016	25	31.16	[29.47; 32.85]
Random effects model		34.84	[29.26; 40.42]

Heterogeneity: $I^2 = 99.772\%$, $\chi_4^2 = 1753.69$ ($p = 0$)

Overweight			
Palma-Dias et al, 2004	389	38.20	[37.58; 38.82]
Erasmus et al, 2005	818	33.70	[33.11; 34.29]
Arora et al, 2012	3	23.30	[16.77; 29.83]
Palatnik & Grobman, 2015	7822	44.80	[44.62; 44.98]
Kandil et al, 2016	25	35.96	[35.18; 36.74]
Random effects model		35.73	[30.08; 41.39]

Heterogeneity: $I^2 = 99.791\%$, $\chi_4^2 = 1910.35$ ($p = 0$)

Obese			
Palatnik & Grobman, 2015	7875	45.60	[45.41; 45.79]
Kandil et al, 2016	25	40.36	[38.87; 41.85]
Random effects model		43.03	[37.90; 48.17]

Heterogeneity: $I^2 = 97.861\%$, $\chi_1^2 = 46.76$ ($p < 0.01$)

Random effects model		**35.09**	**[32.35; 37.82]**

Heterogeneity: $I^2 = 99.802\%$, $\chi_{15}^2 = 7577.67$ ($p = 0$)
Residual heterogeneity: $I^2 = 99.684\%$, $\chi_{12}^2 = 3795.22$ ($p = 0$)

Fig 5. Comparison of cervical length according body mass index (BMI).

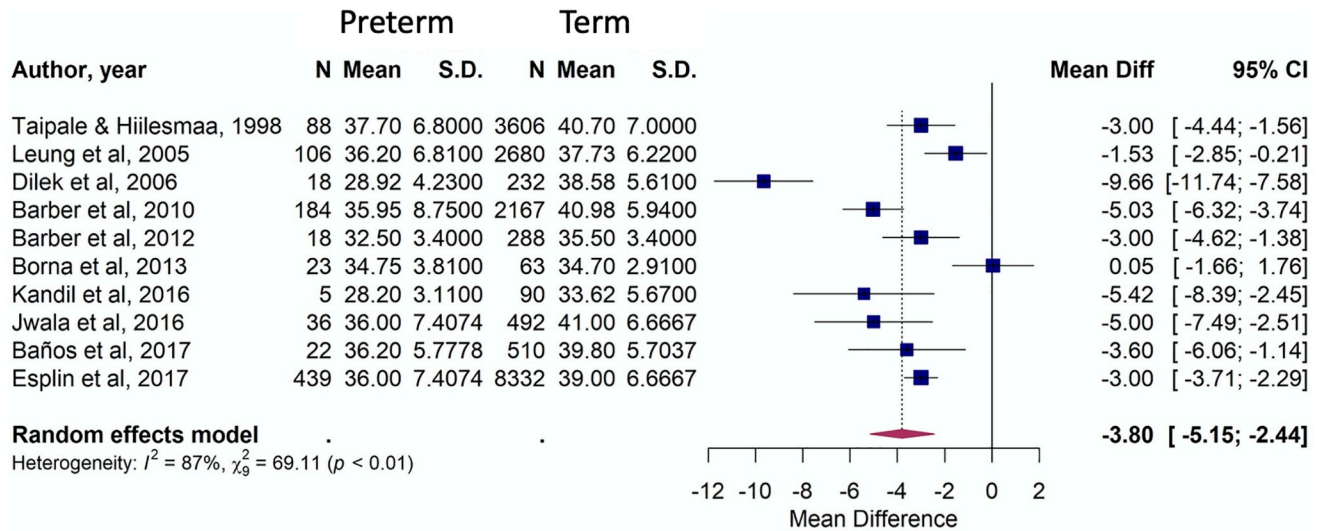https://doi.org/10.1371/journal.pone.0245746.g005

Fig 6. Forest plots of mean cervical length measurements in pregnancies evolving to term and preterm births.

It remains unclear whether the difference in cervical length between populations is due to environmental factors that would interfere in population growth capability, such as nutrition and access to health services, or due to intrinsic characteristics such as ethnicity/race [30] and anthropometric features. It is clear that there is an important association amid socioeconomic status and race in all western world, nevertheless, few included studies described information of short cervix for race/skin color groups and, in our study, it is difficult to analyze this data and infer association between race and short cervix without possible bias. However, it is an ecological approach and it is important to acknowledge that this association does not directly infer that shorter cervical lengths were more common in socially and economically vulnerable women. To clarify this question, future studies on cervical length should consider individual socioeconomic characteristics in the same population.

Socioeconomic characteristics are only starting points to consider when proposing limits of normality in studies and guidelines. A defined cutoff point represents a dichotomous boundary from which clinicians begin to consider different risk levels, and it is yet to be established if the 5 mm cervical shortening in women from low-income countries seen in our review is indeed a determining factor for preterm birth. Considering the same cutoff points for different population characteristics, perhaps doctors are deciding whether or not to intervene based on an incorrect level of association between the risk of preterm birth and the cervical length measurement.

Anthropometric characteristics also presented a significant difference when thin women were compared to women with obesity. The first group had a clinically relevant 12.58 mm shorter cervix. This result is consistent with The Preterm Prediction Study, where non-obese women had mean cervical measurements shorter (34.9 mm) than obese women (36.5 mm) [31]. However, our study identified an even greater difference between these two groups. Women with lower weight gain during pregnancy present a more significant odds ratio of spontaneous preterm birth [3]. In constrast, overweight and grade I obese women have a lower risk of spontaneous preterm delivery, and maternal BMI has a different effect according to different etiological subtypes of preterm birth [32]. This should be explored in further studies and considered in terms of a possible association with confounding factors such as income and maternal age.Another hypothesis of the current review was that the uterine cervix would
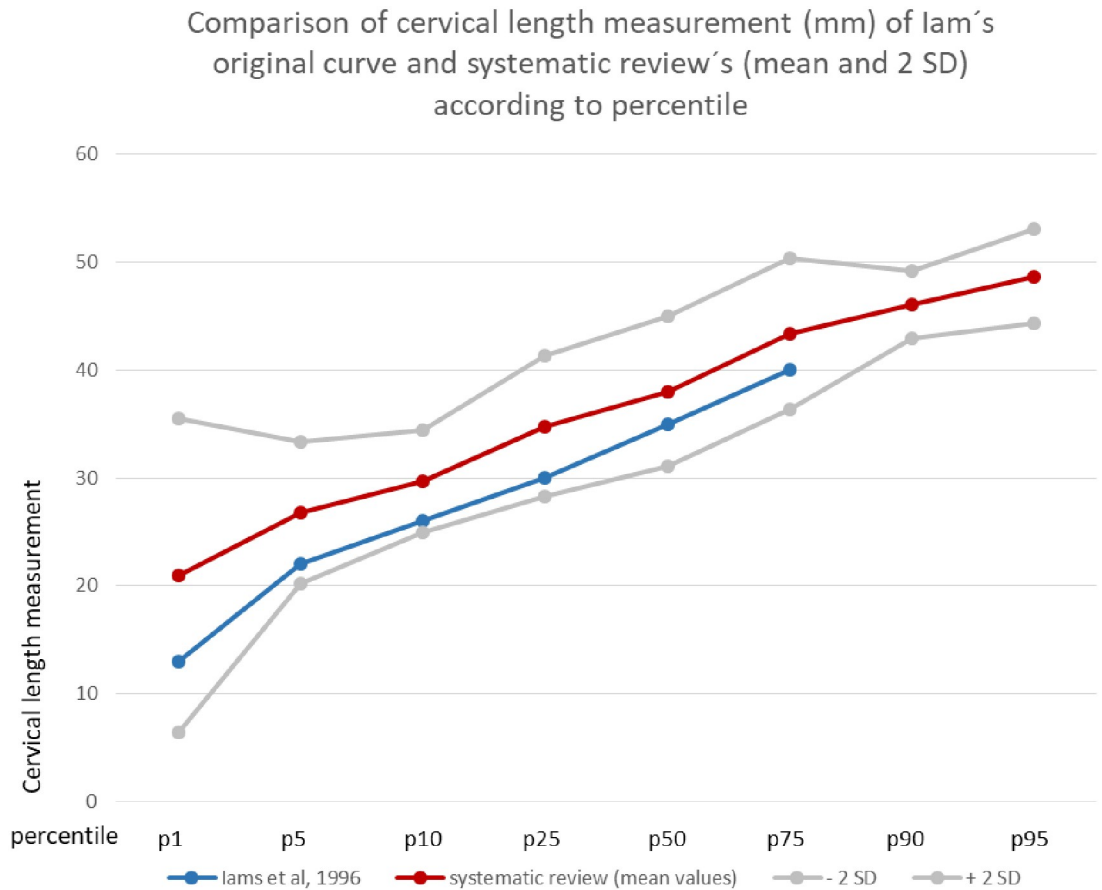
Fig 7. Cervical length measurement according to percentile.

be shorter in women who had a preterm birth. We retrieved 10 articles using the homogeneous reference of birth before 37 gestational weeks, and were able to separate measurements for groups of women who had a term or preterm birth. The results showed statistically significant and clinically relevant differences, with the preterm group found to have a mean cervical length measurement 3.80 mm (-5.15, -2.44) shorter than the term group. A retrospective cohort involving 17,295 women identified a higher rate of preterm birth in asymptomatic women with a short cervix when compared to the general cohort (40.4% versus 8.7%, p < 0.001) [33]. This corroborates the use of cervical length measurement as an important predictor of prematurity and highlights the need to separate specific groups as previous preterm birth and parity in the analysis to establish clear parameters of normality and interventions performing an IPD analysis.

The corresponding cutoff values observed for each percentile in the current study were similar to those defined by Iams et al. [10], with an increase of approximately 3 to 4 millimeters in

each corresponding percentile. Although we cannot present our data as an actual distribution curve, we can argue that these are theoretical values from which we can begin to delineate a population reference range.

Historically, Iams' 10th percentile (rounded to 25 mm) was chosen as a landmark for increased risk; however, it has been proposed that better predictive accuracy is achieved using thresholds of 20 mm or less, depending on the population studied [34]. Considering results from a cohort developed in our hospital, the comparable percentiles from 21 to 24 weeks were even longer, with a 10th percentile of 33.9 mm, 50th percentile of 41.4 mm and 90th percentile of 51.7 mm [35]. A cohort performed with nulliparous women in Switzerland demonstrated similar data, with mean cervical lengths of 40.3 mm at 20 weeks, 38.7 mm at 21 weeks, 39.6 mm at 23 weeks and 41.4 mm at 24 gestational weeks [36]. Furthermore, in a Japanese cohort, the mean cervical length at 16 weeks was 43 mm [37]. These differences could be explained by the population selection of exclusively low-risk women that evolved to term deliveries, but they could also suggest that the cutoff points commonly used in clinical practice may be underestimated.

Considering the limitations of our review, we had difficulty appraising our primary variable because there was no consistent pattern in the way authors reported cervical length measurement. Even if different publications were considered to be in the same category, sometimes the authors diverged concerning the cutoff limits chosen or the reported percentiles. Some authors reported percentiles as median and interquartile range [10, 38–41], while others opted to report only percentiles under the 10th percentile [17, 42, 43]. As acknowledged in other systematic reviews [7, 8, 44], differences in definitions of reference values limit the ability to make comparisons in reviews.

Publications reporting results as categorical variables referred to the number of women with a cervical length measurement under a particular cutoff value. We identified 20 publications that evaluated the cutoff limit of 20 mm for 88,009 women, 39 articles evaluating 25 mm for 146,500 patients, and 19 papers evaluating 30 mm for 88,380 women. The proportion of cervix measurements under each one of these limits were 3%, 6,7% and 13,1%, respectively.

This information is relevant when we consider the relative risk of 3.8 under 30 mm, 6.2 under 26 mm and 9.49 under 22 mm, as proposed in 1996 by Iams et al. [12]. This means that around 13% of the worldwide population have almost four times higher risk of prematurity, approximately 7% can have more than six times greater risk, and 3% of global population may have around 10 times higher risk of having a preterm birth. Therefore, we suggest that if the health system allows the possibility to perform a screening for preterm birth using transvaginal ultrasound to identify short cervix in the same ultrasound appointment as the second trimester morphological ultrasound (between 20–24 weeks gestation) universal screening should be recommended. This opportunity may reduce costs associated to the preterm birth screening implementation.

Another limitation of this systematic review is the significant heterogeneity between the studies in numerous aspects. The first question is regarding the origin of the studies: we had one third of the studies and the study population from the United States. However, when conducting a large-scale systematic review, it is natural to suppose that certain countries with more scientific investment present more studies with the necessary criteria to be included in the systematic review.

Also, It was not possible to assemble all the subjects into one large cohort because the studies did not prioritize the same features to report. We opted to extract as much information as provided by the original paper concerning cervical length and relate it, where possible, to the outcome and to obstetric, demographic and anthropometric variables. Therefore, our greatest difficulty in this review was extracting homogeneous information. Compiling data is a

common problem in the medical literature. If we consider completed studies, one possible method to aggregate data is by individual patient data (IPD) meta-analysis, a method where all raw information is combined and analyzed as if it was all part of one large trial/cohort. This could be the next approach following this review.

Regarding studies that are yet to begin, an interesting proposal comes from the Core Outcomes in Women's and Newborn Health (CROWN) Initiative, a journal consortium that intends to establish sets of outcomes according to specific conditions. Predefining common results before the stage of study design would allow better agreement on interpreting the information altogether [45].

One strength of our review is the overall good quality of included papers, especially considering that the texts were evaluated based on all aspects of the original research, not only focusing on our main variable. One other important strength is that the gestational age of 16 to 24 weeks, chosen to perform this review, is aligned with experts' recommendations [19] and relies on the fact that before 16 weeks there is no significant modification in cervical length associated with preterm birth [46], and after 24 weeks, due to threshold limits of fetal viability, there are many other confounding factors associated with corticotherapy and tocolysis treatment [47]. Clinical practice supports studies during this period as this gestational age range is crucial for the implementation of different approaches for preventing preterm birth if a risk factor is identified.

Even with the vast number of publications and data we were able to put together in the current review, including a total of 363,431 women, significant losses in the revision process were seen in the group of articles excluded because they exceeded the gestational age. Moreover, another expressive loss was the unquantifiable number of women undergoing universal screening in large clinical trials. Both difficulties could probably also be resolved by using an IPD meta-analysis.

Conclusions

Cervical length ranges vary across populations and different income countries. This should be considered and interventions should be offered cautiously, especially in borderline cases. It is possible that one only cutoff to define the short cervix diagnosis cannot identify correctly this risk factor for preterm birth in different populations. New studies must be considered to identify different specific curves and cutoffs for cervical length measurement in different populations.

Supporting information

S1 Appendix. Prisma checklist.
(DOCX)

S2 Appendix. Database research: Search syntaxes.
(DOCX)

S3 Appendix. Women classification in high or low-risk for preterm birth.
(DOCX)

S4 Appendix. Quality assessment tool for observational cohort and cross-sectional studies —National Heart, Lung and Blood Institute.
(DOCX)

S5 Appendix. Risk of bias in included articles.
(DOCX)

S1 Fig. Meta-analysis without previous conization. Forest plot for cervical length measurement in patients without previous conization.
(DOCX)

S2 Fig. Nulliparous versus multiparous. Difference of mean of cervical length between nulliparous versus parous women.
(DOCX)

S3 Fig. Adolescents versus adults. Comparison of cervical length measurements in adolescents and adults.
(DOCX)

S1 Table. Excluded articles classified according to exclusion reasons.
(DOCX)

S2 Table. Main characteristics of included articles.
(DOCX)

S1 Data. Complete dataset.
(XLSX)

Author Contributions

Conceptualization: A. Borovac-Pinheiro, M. S. França, R. Passini, Jr., B. W. Mol, J. G. Cecatti, R. C. Pacagnella.

Data curation: R. C. Pacagnella.

Formal analysis: T. G. Bortoletto, T. V. Silva, A. Borovac-Pinheiro, A. R. Hatanaka, J. P. Argenton, R. C. Pacagnella.

Funding acquisition: R. C. Pacagnella.

Investigation: T. G. Bortoletto, T. V. Silva, A. Borovac-Pinheiro, C. M. Pereira, A. D. Silva, M. S. França, A. R. Hatanaka.

Methodology: T. G. Bortoletto, T. V. Silva, A. Borovac-Pinheiro, C. M. Pereira, A. D. Silva, M. S. França, A. R. Hatanaka, J. P. Argenton, R. Passini, Jr., B. W. Mol, J. G. Cecatti, R. C. Pacagnella.

Project administration: T. V. Silva.

Supervision: R. C. Pacagnella.

Validation: B. W. Mol, J. G. Cecatti.

Writing – original draft: T. G. Bortoletto, T. V. Silva, A. Borovac-Pinheiro, C. M. Pereira, M. S. França, R. Passini, Jr., B. W. Mol, R. C. Pacagnella.

Writing – review & editing: T. G. Bortoletto, T. V. Silva, A. Borovac-Pinheiro, C. M. Pereira, A. D. Silva, M. S. França, A. R. Hatanaka, J. P. Argenton, R. Passini, Jr., B. W. Mol, J. G. Cecatti, R. C. Pacagnella.

References

1. WHO World Health Organization. Fact Sheet No. 363 [Internet]. 2015 [cited 2016 Apr 8]. http://www.who.int/mediacentre/factsheets/fs363/en/

2. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller A-B, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health [Internet]. 2013; 10 Suppl 1(Suppl 1):S2.

Available from: /pmc/articles/PMC3828585/?report=abstract https://doi.org/10.1186/1742-4755-10-S1-S2 PMID: 24625129

3. Passini R, Cecatti JG, Lajos GJ, Tedesco RP, Nomura ML, Dias TZ, et al. Brazilian multicentre study on preterm birth (EMIP): Prevalence and factors associated with spontaneous preterm birth. PLoS One. 2014; 9(10). https://doi.org/10.1371/journal.pone.0109069 PMID: 25299699

4. Varner MW, Esplin MS. Current understanding of genetic factors in preterm birth. BJOG An Int J Obstet Gynaecol. 2005; 112(March):28–31.

5. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. 2007; 357(5):462–9. https://doi.org/10.1056/NEJMoa067815 PMID: 17671254

6. Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien JM, Cetingoz E, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: A systematic review and metaanalysis of individual patient data. Am J Obstet Gynecol [Internet]. 2012; 206(2):124.e1–124.e19. Available from: 10.1016/j.ajog.2011.12.003 PMID: 22284156

7. Conde-Agudelo A, Romero R. Predictive accuracy of changes in transvaginal sonographic cervical length over time for preterm birth: A systematic review and metaanalysis. Am J Obstet Gynecol [Internet]. 2015; 213(6):789–801. Available from: http://dx.doi.org/10.1016/j.ajog.2015.06.015 PMID: 26070703

8. Li Q, Reeves M, Owen J, Keith LG. Precocious cervical ripening as a screening target to predict spontaneous preterm delivery among asymptomatic singleton pregnancies: A systematic review. Am J Obstet Gynecol [Internet]. 2015; 212(2):145–56. Available from: http://dx.doi.org/10.1016/j.ajog.2014.07.003 PMID: 25017411

9. Kagan KO, Sonek J. How to measure cervical length. Ultrasound Obstet Gynecol. 2015; 45(3):358–62. https://doi.org/10.1002/uog.14742 PMID: 25632014

10. Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A, et al. The Length of the Cervix and the Risk of Spontaneous Premature Delivery. N Engl J Med [Internet]. 1996; 334(9):567–73. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM199602293340904 PMID: 8569824

11. Norman JE, Marlow N, Messow C, Shennan A, Bennett PR, Thornton S, et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. Lancet [Internet]. 2016; 387(10033):2106–16. Available from: http://dx.doi.org/10.1016/S0140-6736(16)00350-0 PMID: 26921136

12. Hassan SS, Romero R, Vidyadhari D, Fusey S, Baxter JK, Khandelwal M, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: A multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2011; 38(1):18–31. https://doi.org/10.1002/uog.9017 PMID: 21472815

13. Nicolaides KH, Syngelaki A, Poon LC, Picciarelli G, Tul N, Zamprakou A, et al. A Randomized Trial of a Cervical Pessary to Prevent Preterm Singleton Birth. N Engl J Med [Internet]. 2016; 374(11):1044–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26981934 https://doi.org/10.1056/NEJMoa1511014

14. Goya M, De La Calle M, Pratcorona L, Merced C, Rodó C, Muñoz B, et al. Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: A multicenter randomized controlled trial (PECEP-Twins). Am J Obstet Gynecol. 2016; 214(2):145–52. https://doi.org/10.1016/j.ajog.2015.11.012 PMID: 26627728

15. Owen J, Yost N, Thom E, Swain M, Iii G a D. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. 2001; 286(11):1340–8.

16. Guzman ER, Walters C, Ananth C V., O'Reilly-Green C, Benito CW, Palermo A, et al. A comparison of sonographic cervical parameters in predicting spontaneous preterm birth in high-risk singleton gestations. Ultrasound Obstet Gynecol. 2001; 18(3):204–10. https://doi.org/10.1046/j.0960-7692.2001.00526.x PMID: 11555447

17. Taipale P, Hiilesmaa V. Sonographic measurement of uterine cervix at 18–22 weeks' gestation and the risk of preterm delivery. Obstet Gynecol. 1998; 92(6):902–7. https://doi.org/10.1016/s0029-7844(98)00346-9 PMID: 9840546

18. Hassan SS, Romero R, Berry SM, Dang K, Blackwell SC, Treadwell MC, et al. Patients with an ultrasonographic cervical length ≤15 mm have nearly a 50% risk of early spontaneous preterm delivery. Am J Obstet Gynecol. 2000; 182(6):1458–67. https://doi.org/10.1067/mob.2000.106851 PMID: 10871466

19. Berghella V. Progesterone and preterm birth prevention: Translating clinical trials data into clinical practice. Am J Obstet Gynecol [Internet]. 2012; 206(5):376–86. Available from: http://dx.doi.org/10.1016/j.ajog.2012.03.010 PMID: 22542113

20. Sentilhes L, Sénat MV, Ancel PY, Azria E, Benoist G, Blanc J, et al. Prevention of spontaneous preterm birth: Guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol. 2017; 210:217–24. https://doi.org/10.1016/j.ejogrb.2016.12.035 PMID: 28068594

21. American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 130: Prediction and Prevetion of Preterm Birth. Obstet Gynecol [Internet]. 2012; 120(4):964–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22617615 https://doi.org/10.1097/AOG.0b013e3182723b1b PMID: 22996126

22. Parry S, Elovitz MA. Pros and cons of maternal cervical length screening to identify women at risk of spontaneous preterm delivery. Clin Obstet Gynecol. 2014; 57(3):537–46. https://doi.org/10.1097/GRF.0000000000000051 PMID: 24979358

23. Parry S, Simhan H, Elovitz M, Iams J. Universal maternal cervical length screening during the second trimester: Pros and cons of a strategy to identify women at risk of spontaneous preterm delivery. Am J Obstet Gynecol [Internet]. 2012; 207(2):101–6. Available from: http://dx.doi.org/10.1016/j.ajog.2012.04.021 PMID: 22633270

24. Moher D, Liberati A, Tetzlaff J, Altman DG, Grp P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj-British Med J. 2009; 339(2):1–13.

25. Institute National Heart Lung and Blood. Study Quality Assessment Tools [Internet]. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

26. World Bank. World Development Indicators [Internet]. 2016. http://datatopics.worldbank.org/world-development-indicators/stories/the-classification-of-countries-by-income.html

27. Althuisius SM, Schornagel IJ, Dekker GA, Van Geijn HP, Hummel P. Loop electrosurgical excision procedure of the cervix and time of delivery in subsequent pregnancy. Int J Gynecol Obstet. 2001; 72 (1):31–4. https://doi.org/10.1016/s0020-7292(00)00326-x PMID: 11146074

28. Acharya G, Kjeldberg I, Hansen SM, Sørheim N, Jacobsen BK, Maltau JM. Pregnancy outcome after loop electrosurgical excision procedure for the management of cervical intraepithelial neoplasia. Arch Gynecol Obstet. 2005; 272(2):109–12. https://doi.org/10.1007/s00404-005-0727-1 PMID: 15912414

29. Liem S, Schuit E, Hegeman M, Bais J, De Boer K, Bloemenkamp K, et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): A multicentre, open-label randomised controlled trial. Lancet. 2013; 382(9901):1341–9. https://doi.org/10.1016/S0140-6736(13)61408-7 PMID: 23924878

30. de Oliveira KA, de Araújo EM, de Oliveira KA, Casotti CA, da Silva CAL, Dos Santos DB. Association between race/skin color and premature birth: a systematic review with meta-analysis. Rev Saude Publica [Internet]. 2018; 52:26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29641651%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5893270 https://doi.org/10.11606/S1518-8787.2018052000406 PMID: 29641651

31. Hendler I, Goldenberg RL, Mercer BM, Iams JD, Meis PJ, Moawad AH, et al. The Preterm Prediction study: Association between maternal body mass index and spontaneous and indicated preterm birth. Am J Obstet Gynecol. 2005; 192(3):882–6. https://doi.org/10.1016/j.ajog.2004.09.021 PMID: 15746686

32. Torloni MR, Betrán AP, Daher S, Widmer M, Dolan SM, Menon R, et al. Maternal BMI and preterm birth: A systematic review of the literature with meta-analysis. J Matern Neonatal Med. 2009; 22 (11):957–70. https://doi.org/10.3109/14767050903042561 PMID: 19900068

33. Liu CZ, Nguyen AD, Lehner C, Sekar R, Amoako AA. The risk of preterm delivery and pregnancy outcomes in women with asymptomatic short cervix: a retrospective cohort study. J Matern Fetal Neonatal Med 2019; 6:1–7 https://doi.org/10.1080/14767058.2019.1647163 PMID: 31327275

34. Domin CM, Smith EJ, Terplan M. Transvaginal ultrasonographic measurement of cervical length as a predictor of preterm birth: a systematic review with meta-analysis. Ultrasound Q [Internet]. 2010; 26 (4):241–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21084959 https://doi.org/10.1097/RUQ.0b013e3181fe0e05

35. Andrade K, Bortoletto TG, Almeida C, Daniel R, Avo H, Pacagnella R, et al. Reference Ranges for Ultrasonographic Measurements of the Uterine Cervix in Low-Risk Pregnant Women. Rev Bras Ginecol e Obs / RBGO Gynecol Obstet. 2017; 39(09):443–52. https://doi.org/10.1055/s-0037-1605556 PMID: 28778109

36. Hoesli IM, Strutas D, Tercanli S, Holzgreve W. Charts for cervical length in singleton pregnancy. Int J Gynaecol Obstet. 2003; 82:161–5. https://doi.org/10.1016/s0020-7292(02)00443-5 PMID: 12873776

37. Okitsu O, Mimura T, Nakayama T, Aono T. Early prediction of preterm delivery by transvaginal ultrasonography. [Internet]. Vol. 2, Ultrasound in obstetrics & gynecology: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 1992. p. 402–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12796914 https://doi.org/10.1046/j.1469-0705.1992.02060402.x

38. Peng CR, Chen CP, Wang KG, Wang LK, Chen CY, Chen YY. The reliability of transabdominal cervical length measurement in a low-risk obstetric population: Comparison with transvaginal measurement. Taiwan J Obstet Gynecol [Internet]. 2015; 54(2):167–71. Available from: http://dx.doi.org/10.1016/j. tjog.2014.03.007 PMID: 25951722

39. Van Der Ven J, Kazemier BM, VO M., K E., K P., D J., et al. Is cervical length associated with maternal characteristics? Am J Obstet Gynecol [Internet]. 2013; 208(1):S288. Available from: http://www. embase.com/search/results?subaction=viewrecord&from=export&id=L70967698

40. Kuusela P, Jacobsson B, Söderlund M, Bejlum C, Almström E, Ladfors L, et al. Transvaginal sonographic evaluation of cervical length in the second trimester of asymptomatic singleton pregnancies, and the risk of preterm delivery. Acta Obstet Gynecol Scand. 2015; 94(6):598–607. https://doi.org/10. 1111/aogs.12622 PMID: 25732204

41. Stone PR, Chan EHY, McCowan LME, Taylor RS, Mitchell JM. Transabdominal scanning of the cervix at the 20-week morphology scan: Comparison with transvaginal cervical measurements in a healthy nulliparous population. Aust New Zeal J Obstet Gynaecol. 2010; 50(6):523–7.

42. Leung TN, Pang MW, Leung TY, Poon CF, Wong SM, Lau TK. Cervical length at 18–22 weeks of gestation for prediction of spontaneous preterm delivery in Hong Kong Chinese women. Ultrasound Obstet Gynecol. 2005; 26(7):713–7. https://doi.org/10.1002/uog.2617 PMID: 16308894

43. Matijevic R, Grgic O, Vasilj O. Is sonographic assessment of cervical length better than digital examination in screening for preterm delivery in a low-risk population? Acta Obstet Gynecol Scand [Internet]. 2006; 85(11):1342–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17091415 https://doi.org/ 10.1080/00016340600935722

44. Phillips C, Velji Z, Hanly C, Metcalfe A. Risk of recurrent spontaneous preterm birth: A systematic review and meta-analysis. BMJ Open. 2017; 7(6):1–6. https://doi.org/10.1136/bmjopen-2016-015402 PMID: 28679674

45. van 't Hooft J, Alfirevic Z, Asztalos E V., Biggio JR, Dugoff L, Hoffman M, et al. CROWN initiative and preterm birth prevention: researchers and editors commit to implement core outcome sets. BJOG An Int J Obstet Gynaecol. 2018; 125(1):8–11. https://doi.org/10.1111/1471-0528.14987 PMID: 29055092

46. Carvalho MHB, Bittar RE, Brizot ML, Maganha PPS, Borges Da Fonseca ES V, Zugaib M. Cervical length at 11–14 weeks' and 22–24 weeks' gestation evaluated by transvaginal sonography, and gestational age at delivery. Ultrasound Obstet Gynecol. 2003; 21(2):135–9. https://doi.org/10.1002/uog.32 PMID: 12601833

47. El-Sayed YY, Borders AEB, Gyamfi-Bannerman C. Antenatal Corticosteroid Therapy for Fetal Maturation. Obstet Gynecol. 2017; 130(2):102–9. https://doi.org/10.1097/AOG.0000000000002237 PMID: 28742678