EUROX 22 (2024) 100305

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology: X

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

Risk factors of early spontaneous preterm birth despite carrying a cervical pessary in singleton pregnancies with a short cervix: Development of a risk prediction model

Carme Merced [a], Laia Pratcorona [b], Teresa Higueras [c], Mireia Vargas [d], Esther Del Barco [c], Judit Solà [e], Elena Carreras [c], Maria Goya [c,*]

[a] Department of Obstetrics, Hospital Universitari de Vic, Consorci Hospitalari de Vic. Barcelona, Spain
[b] Department of Obstetrics, Hospital Germans Trias I Pujol. Universitat Autònoma de Barcelona, Barcelona, Spain
[c] Maternal Fetal Medicine Unit, Department of Obstetrics, Hospital Universitari Vall d'Hebron. Universitat Autònoma de Barcelona, Barcelona, Spain
[d] Department of Obstetrics, Althaia Xarxa Assistencial Universitària de Manresa, Barcelona, Spain
[e] Data Analysis and Modeling Research Group, Universitat de Vic-Universitat Central de Catalunya, Vic, Barcelona, Spain

ARTICLE INFO

Keywords:
Cervical pessary
Short cervical length
Risk factors
Premature birth
Spontaneous preterm birth
Preterm birth prevention
Pregnancy high-risk
Probability learning

ABSTRACT

Introduction: We aimed to identify the incidence and risk factors of spontaneous preterm birth in pessary carriers with singleton pregnancies and a short cervix in the mid-trimester of pregnancy.

Material and Methods: Patient data were obtained from the PECEP Trial. We analyzed singleton pregnancies in pessary carriers with a short cervix (≤25 mm) between 18 and 22 gestational weeks. Demographics and obstetric history were compared to identify risk factors for spontaneous preterm birth < 34 gestational weeks. Each demographic and obstetric variable was compared between spontaneous preterm birth < 34 and ≥ 34 weeks of gestation.

Regression analysis was used to identify risk factors. A risk score model was generated using the odds ratio for significant factors. The risk score model and spontaneous preterm birth risk were assessed using the receiver operating characteristic curve. Perinatal outcomes were compared by risk score.

Results: Among 190 pregnant individuals, 12 (6.3%) had spontaneous preterm birth < 34 gestational weeks. In the bivariate analysis, statistically significant differences between those with and without spontaneous preterm birth were only observed for mean cervical length at diagnosis and mean cervical length after pessary placement. By multiple logistic regression analysis, maternal age (OR 0.818; 95% CI 0.69–0.97; *P* 0.020), cervical length at diagnosis (OR 0.560; 95% CI 0.43–0.73; *P* < 0.001) and smoking status (OR 7.276; 95% CI 1.02–51.80; *P* 0.048) remained significantly associated with spontaneous preterm birth.

The ROC curve from the multiple logistic regression analysis, including cervical length, maternal age and smoking status, had an area under the curve (AUC) of 0.952 (*P* < 0.001). The ROC curve for the risk score model incorporating all three variables had an AUC of 0.864 (95% CI 0.77–0.96; *P* < 0.001). A high-risk score was predictive of spontaneous preterm birth with a sensitivity of 75%, specificity of 84%, positive predictive value of 24%, and negative predictive value of 98%.

Women with a high-risk score had a significantly reduced latency to delivery and poorer neonatal outcomes than those with a low-risk score.

Conclusions: Patients at a high risk for spontaneous preterm birth despite pessary therapy may be identified using cervical length at diagnosis added to maternal age and smoking status.

Abbreviations: sPTB, spontaneous preterm birth; CL, cervical length; OR, odds ratio; AUC, the area under the curve.

* Correspondence to: Maternal Foetal Medicine Unit, Department of Obstetrics, Hospital Universitari Vall d'Hebron. Universitat Autònoma de Barcelona, Passeig de la Vall d'Hebron, 119–129, 08036 Barcelona.

https://doi.org/10.1016/j.eurox.2024.100305
Received 12 January 2024; Accepted 25 March 2024
Available online 27 March 2024

Key message

Our trial found that pregnant women at a high risk for sPTB despite pessary intervention might be identified using cervical length at the time of diagnosing a short cervix.

This prediction may be enhanced by adding maternal age and tobacco use.

Introduction

Spontaneous preterm birth (sPTB) is the most common cause worldwide of perinatal morbidity and mortality, accounting for 70% of perinatal mortality and 50% of long-term neurodevelopmental disabilities. [1].

Spontaneous preterm birth is a syndrome caused by multiple pathological processes, such as intraamniotic infection, vascular disorders, decidual senescence, uterine over-distension, cervical disease, decline in progesterone action, maternal stress. [2,3] Known risk factors for sPTB include demographics (maternal age, body mass index, ethnicity, smoking status) [4], history of preterm birth [5], previous late miscarriage, previous cervical excisional surgery, [6] genetic factors, [7] and a transvaginal ultrasonographic short cervix. [8] An cervical length (CL) below 25 mm is the most accurate predictor of sPTB. [9].

The pessary modifies uterocervical angulation and increases CL and cervical consistency. [10] In some studies, the pessary has been a valuable intervention for preventing preterm birth in high-risk populations. [11–14] However, this evidence has not been proven in other studies due to [15–18] heterogeneity in the inclusion criteria, such as gestational weeks at diagnosis. Additionally, some of these studies report a high withdrawal rate during follow-up. Furthermore, some of the studies specified whether there was prior training for pessary placement. [19].

The aim of this study was to identify the risk factors of sPTB (<34 gestational weeks) in pessary carriers with singleton pregnancies and asymptomatic short CL (<25 mm) at the second trimester so as to identify prognostic factors of pessary use.

Materials and methods

Patient data was obtained from the PECEP trial, a prospective, open-label, randomized trial which included singleton pregnancies undergoing the routine second-trimester ultrasonography at 18–22 gestational weeks, with a cervical length $\leq$ 25 mm and carrying a pessary.

Demographics, obstetric history and ultrasound characteristics were compared to identify risk factors for sPTB < 34 gestational weeks. Each demographic, obstetric or ultrasonographic variable was compared between sPTB < 34 and $\geq$ 34 gestational weeks.

Continuous variables were compared using the t-Student's test, and categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. Multiple logistic regression analysis was used to identify predictive factors for sPTB with $p < 0.05$. A weighted risk score model was developed using the odds ratio (OR) from the multiple logistic regression. The discrimination ability of the risk model and the constructed scale was assessed using the ROC curves and their areas under the curve (AUC).

An optimal cut-off point for sensitivity, specificity and predictive values was proposed. Kaplan Meier analysis was used to assess latency to delivery, and log-rank test was used to compare the curves. Perinatal outcomes were compared using the risk score model. A value of $p < 0.05$ was considered statistically significant. The SPSS v26 software was used for statistical analysis.

Ethics statement

This sub-analysis was approved by Hospital Vall d'Hebron's Ethical Committee (PR AMI 2014/077). All pregnant women gave their written consent.

Results

In the analysis, we included 190 pregnant individuals with a short CL from the pessary group; of those, 12 (6.3%) had sPTB < 34 gestational weeks and 178 (93.7%) had a delivery $\geq$ 34 gestational weeks.

Upon comparing demographic, obstetric and ultrasonographic characteristics in the bivariate analysis (Table 1), only statistically significant differences were observed for CL at the time of the ultrasound scan and after pessary placement. No differences were observed for funnelling or sludge presence as potential biomarkers for predicting sPTB. In the sPTB group < 34 gestational weeks, 75% (9 of 12) of individuals were nulliparous as compared to 49.4% (88 of 178) of individuals who gave birth $\geq$ 34 gestational weeks, but with a non-significant difference ($P = 0.086$). In the sPTB group < 34 gestational weeks, 41.7% (5 of 12) of individuals smoked during pregnancy vs 18% (32 of 178) of individuals who gave birth $\geq$ 34 gestational weeks ($P = 0.059$).

In the multiple logistic regression analysis, CL at diagnosis (OR: 0.560; 95% CI: 0.43–0.73; $P < 0.001$), maternal age (OR: 0.818; 95% CI: 0.69–0.97; $P = 0.020$) and smoking status (OR: 7.276; 95% CI: 1.02–51.80; $P = 0.048$) remained significantly associated with sPTB.

The ROC curve from the multiple logistic regression analysis including cervical length, maternal age and smoking status had an AUC of 0.952 (95% CI: 0.87–1.00; $P < 0.001$) (Fig. 1).

The risk score model for sPTB< 34 gestational weeks was developed using the OR from the multiple logistic regression analysis (risk score = (0.560 × CL) + (0.818 × maternal age) – (7.2 × smoking status)). A lower score indicated a higher risk. When evaluating the ROC curve, the risk score incorporating our three variables had an AUC of 0.864 (95% CI: 0.77–0.96; $P < 0.001$) (Fig. 2). We selected a cut-off point of 28, below which we found 37 cases (19.5%). A high-risk score was predictive of sPTB with a sensitivity of 75%, a specificity of 84%, a positive

Table 1
Comparison of baseline characteristics. Comparison of demographic, obstetric, and ultrasound characteristics in pregnant individuals with a short cervix carrying a pessary with spontaneous preterm birth (<34 gestational weeks) vs not.

	Delivery ≥ 34 n = 178 (93.7%)	sPTB< 34 n = 12 (6.3%)	*P* value
Demographics			
Maternal age (years), mean (SD)	29.70 (5.3)	28.42 (6.3)	0.425[a]
Body mass index (kg/m2) mean (SD)	24.98 (4.6)	24.07 (3.9)	0.508[a]
Ethnic origin, n (%)			0.498[b]
Caucasian	101(56.7%)	6 (50%)	
Latin American	52 (29.2%)	6 (50%)	
Asian	15 (8.4%)	0 (0%)	
Maghreb	3 (1.7%)	0 (0%)	
Black	7 (3.9%)	0 (0%)	
Smoking during pregnancy, n (%)	32 (18.0%)	5 (41.7%)	0.059[c]
Obstetrical history			
Previous spontaneous preterm birth n (%)	21 (11.8%)	1 (8.3%)	1.00[c]
Nulliparous, n (%)	88 (49.4%)	9 (75%)	0.086[b]
Gestational age at ultrasound scan (weeks), mean (SD)	22.4 (0.9)	22.5 (0.5)	0.833[a]
Ultrasonographic characteristics			
Cervical length (mm), mean (SD)	19.61 (3.8)	9.58 (4.8)	< 0.001[a]
Cervical length after pessary placement (mm), mean (SD)	21.68 (4.5)	19.83 (2.4)	0.029[a]
Funneling, n (%)	18 (10.1%)	2 (16.7%)	0.367[c]
Sludge, n (%)	2 (1.1%)	0 (0%)	1.0[c]

a: t-Student's test
b: Pearson's chi-square
c: Fisher's test

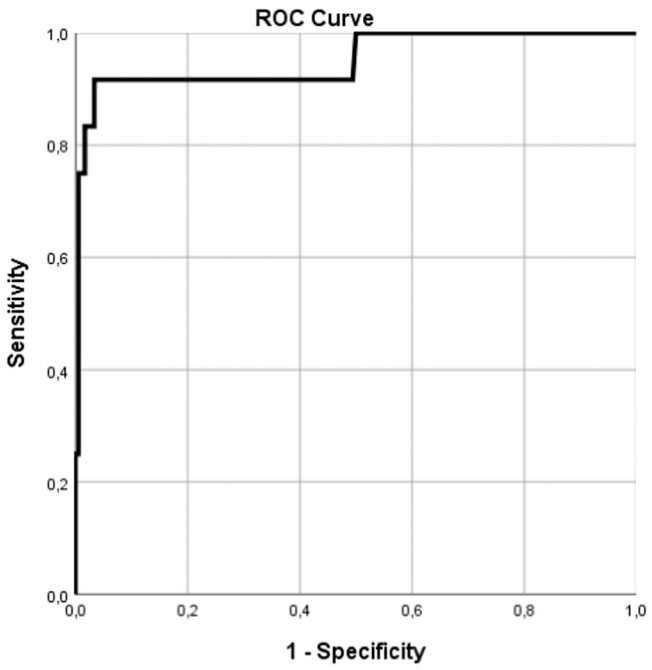

Fig. 1. ROC curve of the model including cervical length, maternal age and pregnant smokers to predict spontaneous preterm birth. AUC 0.952.

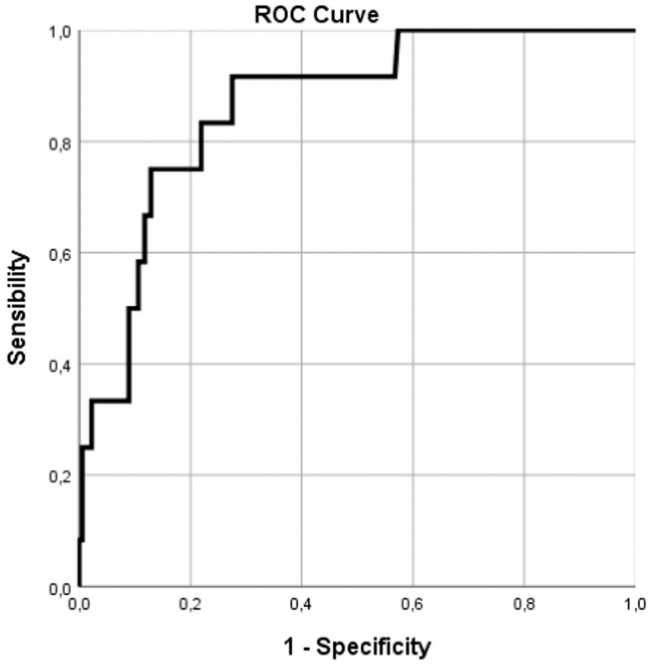

Fig. 2. ROC curve: risk score model incorporating cervical length, maternal age and smoking status. AUC 0.864.

predictive value of 24%, and a negative predictive value of 98%.

Individuals with a high-risk score had a significantly reduced latency to delivery as compared to individuals with a low-risk score (Log rank; $P < 0.001$) (Fig. 3).

Moreover, individuals with a high-risk score had babies with significantly lower birth weights and experienced more adverse composite outcomes, which although were not statistically significant, displayed a discernible trend (Table 2).

Discussion

Based on our results, pregnant individuals at a high risk for sPTB despite pessary intervention might be identified using CL at the time of diagnosing a short cervix, added to maternal age and smoking status.

Our findings agree with previous analyses, where CL is the most accurate preterm birth predictor. Indeed, a randomized trial on pessary intervention in asymptomatic singleton pregnancies concluded that a CL $\leq$ 11 mm can identify pregnant individuals at a high risk of asymptomatic cervical dilation. Similar results were obtained with other interventions, such as the cerclage. [20] Cervical dilation in the second trimester is associated with poor neonatal outcomes, and these cases may potentially benefit from a cerclage. [21] A recent study with pregnant individuals having cervical dilation and exposed membranes concluded that the pessary does not decrease preterm birth risk. [22] Therefore, in our study, we conducted vaginal examinations (visual examination with a speculum, without touching the cervix) to identify cervical dilation or visible membranes, and pessary placement was avoided if membrane exposure or cervical dilation were detected. Therefore, based on the unfavorable gestational prognosis, we believe it is important to adequately assess cervical dilation in pregnant individuals with a CL < 10–11 mm.

In our study, 10/12 individuals with sPTB < 34 gestational weeks had a CL< 11 mm at the time of diagnosis without cervical dilation. Our findings of a higher rate of preterm birth in pessary carriers with a short cervical length (<11 mm) highlight the importance of identifying and monitoring this group of pregnant individuals to allow for adjunctive therapies contributing to improved outcomes.

On the other hand, smoking is associated with sPTB, with an OR of 1.4 (95% CI: 1.3–1.4). [23] In our study, smokers had an OR of 7.276 (95% CI: 1.02–51.80; $P = 0.048$). Furthermore, 41.7% of pregnant individuals who had sPTB were smokers versus only 18% of those who gave birth after 34 gestational weeks.

Currently, no studies explain this effect in pessary carriers. Smoking cessation has been shown to reduce sPTB risk, with a relative risk of 0.86 (95% CI: 0.74 - 0.98). [24] Despite the influence of the pessary, tobacco use appears to be a significant risk factor for sPTB. Therefore, pregnant individuals with a short cervix who are undergoing secondary prevention with a cervical pessary should cease smoking.

Preterm birth risk varies according to maternal age. In cohort studies, Lawlor et al. and Fuchs et al. found a U-shaped relationship between maternal age and preterm birth risk, with the highest risk at both age extremes. [25],[26] However, preterm birth was mainly spontaneous in younger individuals (aged 20 to 24 years), whereas it was more frequently of iatrogenic origin in individuals over 40.[26] In a large cohort study, Khalil et al. concluded that advanced age (>40 years) was not associated with an increased sPTB risk. [27] Our data shows that younger individuals have a higher rate of sPTB despite prophylactic pessary intervention, which seems to agree with previous findings. However, in our cohort, only a small number of cases aged > 40 were included, so our risk calculation does not apply to individuals older than 40.

This study has several strengths. It is the first article evaluating a wide range of sPTB risk factors and establishing a risk score model incorporating CL, maternal age, and smoking status during pregnancy to identify a subgroup of individuals with a high sPTB risk carrying a cervical pessary.

Furthermore, other interventions for preventing preterm birth, such as progesterone or cerclage, which are potential confounding factors, were not used. Another strength of this trial is the fact that participants were managed by obstetricians trained in pessary management, with the lower rate of early removal pessary rate published. This may have helped to determine the actual effect of the pessary.

This study has some limitations. The sample size was limited, which may have impacted the ability to detect weaker, yet statistically significant sPTB predictors in individuals with a short CL carrying a cervical

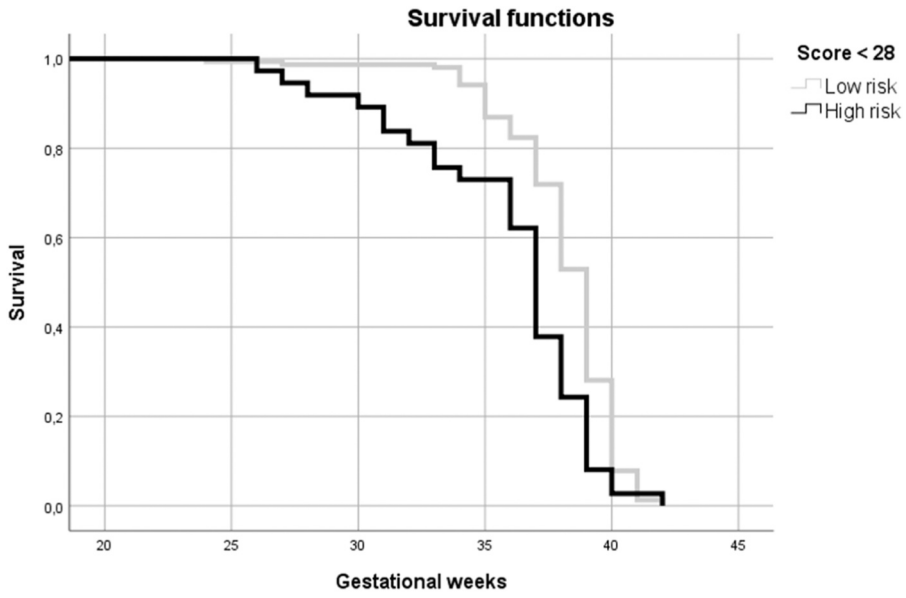

Fig. 3. Kaplan–Meier survival curve for latency to delivery by risk score stratification of latency to delivery (high (black) vs low (gray)) in pregnant women with a short cervix treated with a pessary, log-rank $p < 0.001$.

Table 2
Risk score and neonatal outcomes.

	Low-risk score (n = 153)	High-risk score (n = 37)	*P* value
Gestational age (mean wk (SD))	38.05 (2.50)	35.89 (3.80)	0.002[a]
Birthweight (g), mean (SD)	3296.34 (581.13)	2698.11 (862.94)	< 0.001[a]
Neonatal death	0	0	
Necrotising enterocolitis	0	0	
Intraventricular haemorrhage	0	0	
Respiratory distress syndrome	2 (1.3%)	3 (8.1%)	0.052[c]
Retinopathy	0	0	
Treatment for sepsis	1 (0.7%)	2 (5.4%)	0.097[c]
Composite adverse outcomes	2 (1.3%)	3 (8.1%)	0.052[c]

a: t-Student's test
b: Pearson's chi-square
c: Fisher's test

pessary. This was a prospective study; however, pregnant individuals with active vaginal bleeding, ruptured membranes, placenta praevia, diagnoses before pessary insertion and a history of cone biopsy were excluded. As a result, these risk factors were not evaluated.

We are currently conducting an external validation of the risk score model developed in this trial for use in the routine clinical practice.

Given the multifactorial nature of sPTB, this intervention may not benefit equally all pregnant individuals with a short cervix. Therefore, it is necessary to emphasize the importance of tailoring medical therapy.

Conclusions

In our population, pregnant individuals at high risk for spontaneous preterm birth despite pessary intervention may be identified using cervical length at the time of diagnosing a short cervix, added to age and smoking status, using a risk score model. External validation of this risk score model may improve the indication of pessary intervention in pregnant individuals with preterm birth risk.

Funding

This study received no funding; however, Vall d'Hebron Hospital provided research support.

CRediT authorship contribution statement

Laia Pratcorona: Investigation. **Maria Goya:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing. **Carme Merced:** Investigation, Methodology, Conceptualization, Data curation, Formal analysis, Funding acquisition, Writing – original draft, Writing – review & editing. **Ester del Barco:** Methodology. **Judit Sola:** Methodology. **Elena Carreras:** Methodology. **Teresa Higueras:** Investigation. **Mireia Vargas:** Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

References

[1] Goldenberg RL, Culhane JF, Iams JD, Romero R, et al. Epidemiology and i causes of preterm birth. Lancet 2008;371(9606):75–84.
[2] Romero R, Espinoza J, Kusanovic JP, et al. The preterm parturition syndrome. BJOG 2006 Dec;113 Suppl 3(Suppl 3):17-42 Errat– : BJOG 2008;115(5):674–5.
[3] Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. Science 2014;345(6198):760–5.
[4] Cobo T, Kacerovsky M, Jacobsson B. Risk factors for spontaneous preterm delivery. Int J Gynaecol Obstet 2020;150(1):17–23.
[5] Kazemier BM, Buijs PE, Mignini L, Limpens J, de Groot CJ, Mol BW. EBM CONNECT. Impact of obstetric history on the risk of spontaneous preterm birth in singleton and multiple pregnancies: a systematic review. BJOG 2014;121(10): 1197–208. discussion 1209. d.
[6] Kyrgiou M, Athanasiou A, Paraskevaidi M, et al. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. BMJ 2016;354:i3633.
[7] Couceiro J, Matos I, Mendes JJ, Baptista PV, Fernandes AR, Quintas A. Inflammatory factors, genetic variants, and predisposition for preterm birth. Clin Genet 2021;100(4):357–67.
[8] Grimes-Dennis J, Berghella V. Cervical length and prediction of preterm delivery. Curr Opin Obstet Gynecol 2007;19(2):191–5.
[9] (National Institute of Child Health and Human Development Maternal-Fetal Medicine Unit Network.) Iams JD, Goldenberg RL, Meis PJ. The length of the cervix

and the risk of spontaneous premature delivery. N Engl J Med 1996;334(09): 567–72.
[10] Mendoza Cobaleda M, Ribera I, Maiz N, et al. Cervical modifications after pessary placement in singleton pregnancies with maternal short cervical length: 2D and 3D ultrasound evaluation. Acta Obstet Gynecol Scand 2019.
[11] Goya M, Pratcorona L, Merced C, Rodó C, et al. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. Lancet 2012;379(9828):1800–6.
[12] Saccone G, Maruotti GM, Giudicepietro A, Martinelli P. Italian Preterm Birth Prevention (IPP) Working Group. Effect of cervical pessary on spontaneous preterm birth in women with singleton pregnancies and short cervical length: a randomized clinical trial. JAMA 2017;318:2317–24. Erratum in: JAMA 2018;319:1824.
[13] Alfirevic Z, Owen J, Carreras Moratonas E, Sharp AN, Szychowski JM, Goya M. 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. Ultrasound Obstet Gynecol, 41; 2013. p. 146–51.
[14] Cruz-Melguizo S, San-Frutos L, Martínez-Payo C, et al. Cervical pessary compared with vaginal progesterone for preventing early preterm birth: a randomized controlled trial. Obstet Gynecol 2018 Oct;132(4):907-915 Errat– : Obstet Gynecol 2018;132(6):1507.
[15] Nicolaides KH, Syngelaki A, Poon LC, et al. Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial. Am J Obstet Gyne- Col 2016;214. 3.e1e9.
[16] Dugoff L, Berghella V, Sehdev H, Mackeen AD, Goetzl L, Ludmir J. Prevention of preterm birth with pessary in singletons (PoPPS): randomized controlled trial. Ultrasound Obstet Gynecol 2018;51(5):573–9.
[17] Hui SY, Chor CM, Lau TK, Lao TT, Leung TY. Cerclage pessary for preventing preterm birth in women with a singleton pregnancy and a short cervix at 20 to 24 weeks: a randomized controlled trial. Am J Perinatol 2013;30(4):283–8.
[18] Karbasian N, Sheikh M, Pirjani R, Hazrati S, Tara F, Hantoushzadeh S. Combined treatment with cervical pessary and vaginal progesterone for the prevention of preterm birth: a randomized clinical trial. J Obstet Gynaecol Res 2016;42(12): 1673–9.
[19] Vargas M, Mendoza M, García I, et al. Implications of training for pessary placement and accuracy of cervical length measurements after pessary placement: a prospective, double-blind, randomized clinical trial. Eur J Obstet Gynecol Reprod Biol 2022;279:12–8.
[20] Berghella V, Ciardulli A, Rust OA, et al. Cerclage for sonographic short cervix in singleton gestations without prior spontaneous preterm birth: systematic review and meta-analysis of randomized controlled trials using individual patient-level data. Ultrasound Obstet Gynecol 2017;50(5):569–77.
[21] Ehsanipoor RM, Seligman NS, Saccone G, et al. Physical examination-indicated cerclage: a systematic review and meta-analysis. Obstet Gynecol 2015;126(1): 125–35.
[22] Hoffman MK, Clifton RG, Biggio JR, et al. Cervical Pessary for Prevention of Preterm Birth in Individuals With a Short Cervix: the TOPS Randomized Clinical Trial. JAMA 2023;330(4):340–8.
[23] Ferrero DM, Larson J, Jacobsson B, et al. Cross-country individual participant analysis of 4.1 million singleton births in 5 countries with very high human development index confirms known associations but provides no biologic explanation for 2/3 of all preterm births. PLoS One 2016;11(9):e0162506. https://doi.org/10.1371/journal.pone.0162506. PMID: 27622562; PMCID: PMC5021369.
[24] Lumley J, Chamberlain C, Dowswell T, Oliver S, Oakley L, Watson L. Interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst Rev 2009;(3). CD001055. Update in: Cochrane Database Syst Rev. 2013;10:CD001055.
[25] Lawlor DA, Mortensen L, Andersen AM. Mechanisms underlying the associations of maternal age with adverse perinatal outcomes: a sibling study of 264 695 Danish women and their firstborn offspring. Int J Epidemiol 2011;40(5). 1205±14.
[26] Fuchs F, Monet B, Ducruet T, Chaillet N, Audibert F. Effect of maternal age on the risk of preterm birth: a large cohort study. PLoS One 2018;13(1):e0191002.
[27] Khalil A, Syngelaki A, Maiz N, Zinevich Y, Nicolaides KH. Maternal age and adverse pregnancy outcome: a cohort study. Ultrasound Obstet Gynecol 2013;42 (6):634–43.