Kliiniline küsimus nr 1

Kas ähvardava enneaegse sünnituse antenataalse diagnostika meetodid võimaldavad võrreldes diagnostika mitte kasutamisega, prognoosida enneaegset sünnitust ja rakendada interventsiooni raseduse prolongeerimiseks?
- *digitaalne palpatsioon võrreldes ultraheliuuringul emakakaela pikkuse määramine*
- *digitaalne palpatsioon võrreldes kompleksne uuring*
- *ultraheliuuringul emakakaela pikkuse määramine võrreldes kompleksne uuring (fibronektiintest, profülaktilised külvid, digitaalne palpatsioon, ultraheliga emakakaela pikkus)*

Kriitilised tulemusnäitajad: interventsiooni edukus, sünnituse edasilükkumine, lapse peamised tulemusnäitajad

Ravijuhendid

Kokkuvõte: Kasutatud **neli ravijuhendit**, mis antud küsimust käsitlevad.

Hea kvaliteediga **NICE 2015 ravijuhend** soovitab ähvardava enneaegse sünnituse sümptomitega patsiendi puhul emakakaela vaatlust tupepeegliga; kui emakakaela avatust ei saa sedasi hinnata, siis teostada ka digitaalne palpatsioon. Kui läbivaatuse alusel jääb kahtlus ähvardavale enneaegsele sünnitusele ja raseduse kestus on väiksem kui 30+0, siis on soovitatav ravi (kortikosteroidid, tokolüüs). Kui raseduse kestus on 30+0 või suurem, siis kaaluda lisaks diagnostilise testina UH teostamist emakakaela pikkuse hindamiseks, et hinnata sünnituse tõenäolisust järgmise 48 h jooksul. Kui emakakaela pikkus on üle 15 mm, siis selgitada naisele, et enneaegne sünnitus on ebatõenäoline; soovitatakse kaaluda alternatiivseid diagnoose; nõustada naist koju mineku/haiglasse jäämise kasude/kahjude osas ning kui naine otsustab koju minna, siis soovitada tal pöörduda tagasi, kui enneaegse sünnituse sümptomid jäävad püsima/uuesti tekivad. Kui emakakaela pikkus on 15 mm või vähem, siis on soovitatav ravi (kortikosteroidid, tokolüüs).

Emakakaela pikkuse piir (treshold) 15 mm tuleneb GRADE-i järgi hinnatud tõendusmaterjalist, mille põhjal on selle pikkuse juures UH diagnostiline täpsus parim (mõõdukas ja väga kasulik positive ja negative likelihood ratio) ennustamaks enneaegset sünnitust järgneva 48 h jooksul. Gestatsioonivanuse piir 30+0 tuleneb põhimõtteliselt majanduslikust analüüsist, mille põhjal on kulutõhusam ravida madalama gestatsiooniea korral pigem kõiki ähvardava enneaegse sünnituse kliinilise pildiga patsiente, vanemate gestatsioonivanuste puhul võiks enam lisaks UH-ga emakakaela pikkust mõõta/fibronektiini osas testida, see välistaks paljud patsiendid, kes tõenäoliselt ei hakka nädala jooksul enneaegselt sünnitama ja keda ei pea asjatult hospitaliseerima/ravima.

Fibronektiini määramist soovitatakse kaaluda gestatsiooniajas 30 nädalat või enam, kui UH teostamine pole võimalik või pole aktsepteeritav. Fibronektiini osas olid uuringute tulemused väga varieeruvad, järeldati, et fibronektiini määramine on ilmselt rohkem kasulik enneaegset sünnitust välistava testina.

UH ja fibronektiini määramise kombineerimist ähvardava enneaegse sünnituse diagnoosimiseks ei soovitata, kuna uuringud ei näidanud et selline kombinatsioon võimaldaks paremini diagnoosi panna.

Kui naine pöördub PPROMi sümptomitega, siis teostada läbivaatus tupepeegliga. Kui lootevett ei visualiseeru, siis kaaluda tupevooluse insulin-like growth factor binding protein-1 testi või placental alpha-microglobulin-1 testi. Kui test on positiivne, siis võttes arvesse ka kliinilist pilti, anamneesi ja raseduse kestust (st mitte otsustada vaid testi tulemuse põhjal), soovitatakse pakkuda PPROMi puhust ravikäsitlust (profülaktiline antibiootikum, vereanalüüsid, KTG, kortikosteroidid).

Hea kvaliteediga **Queenslandi ravijuhendi** järgi tuleks ähvardava enneaegse sünnituse korral teostada kõigepealt emakakaela vaatlus tupepeeglite abil. Tuleks võtta analüüs fibronektiinile, kui emakakael on alla 3 cm avatud ning looteveepõis on terve (analüüsi peab võtma enne digitaalset palpatsiooni vm manipulatsiooni). Kõrgenenud fibronektiini tase (üle 50 ng/mL) on seotud suurema riskiga enneaegseks sünnituseks, samas madala väärtuse korral on risk enneaegseks sünnituseks järgneva 1-2 nädala jooksul väike. Juhend soovitab emakakaela avatuse hindamiseks emakakaela digitaalselt palpeerida. Soovitatakse mõõta sonograafiliselt emakakaela pikkuse, kuna see võib aidata enneaegse sünnituse riski paremini hinnata. Terapeutilist sekkumist tuleks kaaluda, kui emakakael on alla 25 mm pikk.

Mõõduka kvaliteediga **ICSI juhend** soovitab ähvardava enneaegse sünnitusega patsiendil emakakaela vaadelda tupepeegliga. Kui emakakael on alla 3 cm avatud, siis tuleks võtta analüüs fibronektiinile. Negatiivse fibronektiini testi korral on risk enneaegseks sünnituseks järgneva 7 päeva jooksul väike. Kui lootevesi on puhkemata ja ei esine vaginaalset veritsust, siis teostada emakakaela digitaalne palpatsioon. Ähvardava enneaegse sünnitusega patsiendi jälgimiseks teha TV UH, emakakaela pikkuse korral alla 3,0 cm on enneaegse sünnituse risk suurenenud.

Madala kvaliteediga **SOGC juhendi** soovitusel võiks eelistada UH uuringul emakakaela pikkuse mõõtmist, kuna digitaalne palpatsioon alahindab emakakaela anatoomilist pikkust. Eelistama peaks transvaginaalset UH uuringut. Ähvardava enneaegse sünnituse puhul võiks emakakaela pikkuse määramine UH-ga aidata kindlaks teha patsiente, kel on kõrge risk enneaegseks sünnituseks, samas saaks madala riskiga naistel vältida ebavajalikke sekkumisi. Pole selge, kas emakakaela pikkuse määramine UH-ga aitab enneaegse sünnituse riski vähendada. Transvaginaalset UH peetakse PPROM korral ohutuks. Ultraheliuuringul emakakaela pikkuse määramine ja loote fibronektiini hindamine on enneaegse sünnituse prognoosimise osas võrreldavad ning mõlema meetodi kombineerimine võib tuua kasu kõrge riskiga patsiendide seas.

Analüüsitud ravijuhendites soovitatakse võtta analüüs fibronektiinile, kui emakakael on alla 3 cm avatud ning looteveepõis on terve. Süstemaatiliste ülevaadete tulemuste põhjal on fibronektiini määramisel limiteeritud kuni mõõdukas prognostiline täpsus enneaegse sünnituse riski hindamise osas ning kõige täpsemini võimaldab see hinnata testile järgneva nädala jooksul esinevat riski enneaegseks sünnituseks. Fibronektiini määramine saab probleemiks, sest Eesti seda ei määrata, aparaate ei ole.

Ravijuhend	**Viide**
NICE ravijuhend (NICE_preterm_2015). AGREE meetodiga on ravijuhendi kvaliteet hinnatud väga heaks. Juhendis põhineb antud teema materjal 38 madala kuni mõõduka kvaliteediga prospektiivsel kohortuuringul, mis käsitlevad ähvardava enneaegse sünnituse diagnoosimist intaktse looteveepõie puhul,	**NICE Guideline 25. Preterm Labour and Birth. 2015.**

ning 2 väga madala kvaliteedilisel prospektiivsel kohortuuringul, mis käsitlesid diagnoosimist puhkenud lootevee korral. - Explain to women reporting symptoms of preterm labour who have intact membranes (and their family members or carers as appropriate): • about the clinical assessment and diagnostic tests that are available • how the clinical assessment and diagnostic tests are carried out • what the benefits, risks and possible consequences of the clinical assessment and diagnostic tests are, including the consequences of false positive and false negative test results taking into account gestational age. - Offer a clinical assessment to women reporting symptoms of preterm labour who have intact membranes. This should include: • clinical history taking • the observations described for the initial assessment of a woman in labour in the NICE guideline on intrapartum care • **a speculum examination (followed by a digital vaginal examination if the extent of cervical dilatation cannot be assessed).** **- If the clinical assessment suggests that the woman is in suspected preterm labour** and she is **29+6 weeks pregnant or less, advise treatment for preterm labour** (tokolüüs ja kortikosteroidid). **- If the clinical assessment suggests that the woman is in suspected preterm labour** and she is **30+0 weeks pregnant or more**, **consider transvaginal ultrasound measurement of cervical length** as a diagnostic test to determine likelihood of birth within 48 hours. Act on the results as follows: • **if cervical length is more than 15 mm**, explain to the woman that it is unlikely that she is in preterm labour and: o think about alternative diagnoses o discuss with her the benefits and risks of going home compared with continued monitoring and treatment in hospital o advise her that if she does decide to go home, she should return if symptoms suggestive of preterm labour persist or recur • **if cervical length is 15 mm or less, view the woman as being in diagnosed preterm labour and offer treatment** (tokolüüs ja kortikosteroidid). **- Consider fetal fibronectin testing** as a diagnostic test to determine likelihood of birth within 48 hours **for women who are 30+0 weeks pregnant or more if transvaginal ultrasound measurement of cervical length is indicated but is not available or not acceptable.** Act on the results as follows: • if fetal fibronectin testing is negative (concentration 50 ng/ml or less), explain to the woman that it is unlikely that she is in preterm labour and: o think about alternative diagnoses o discuss with her the benefits and risks of going home compared with continued monitoring and treatment in hospital	

o advise her that if she does decide to go home, she should return if symptoms suggestive of preterm labour persist or recur □ if fetal fibronectin testing is positive (concentration more than 50 ng/ml), view the woman as being in diagnosed preterm labour and offer treatment. - If a woman in suspected preterm labour who is 30+0 weeks pregnant or more does not have transvaginal ultrasound measurement of cervical length or fetal fibronectin testing to exclude preterm labour, offer treatment consistent with her being in diagnosed preterm labour. - **Do not use transvaginal ultrasound measurement of cervical length and fetal fibronectin testing in combination** to diagnose preterm labour. - Ultrasound scans should be performed by healthcare professionals with training in, and experience of, transvaginal ultrasound measurement of cervical length. VT GRADE TABELID NICE JUHEND lk 152. -In a woman reporting **symptoms suggestive of P-PROM**, offer a **speculum examination** to look for pooling of amniotic fluid and: □ if pooling of amniotic fluid is observed, do not perform any diagnostic test but offer care consistent with the woman having P-PROM. □ **if pooling of amniotic fluid is not observed, consider performing an insulin-like growth factor binding protein-1 test or placental alpha-microglobulin-1 test of vaginal fluid.** - If the results of the insulin-like growth factor binding protein-1 or placental alpha-microglobulin-1 test are positive, do not use the test results alone to decide what care to offer the woman, but also take into account her clinical condition, her medical and pregnancy history and gestational age, and either: □ offer care consistent with the woman having P-PROM or □ re-evaluate the woman's diagnostic status at a later time point. - - If the results of the insulin-like growth factor binding protein-1 or placental alpha-microglobulin-1 test are negative and no amniotic fluid is observed: □ do not offer antenatal prophylactic antibiotics □ explain to the woman that it is unlikely that she has P-PROM, but that she should return if she has any further symptoms suggestive of P-PROM or preterm labour. - Do not use nitrazine to diagnose P-PROM. - Do not perform diagnostic tests for P-PROM if labour becomes established in a woman reporting symptoms suggestive of P-PROM.	
SOGC ravijuhend (UCLA 2011). **<u>Digitaalne palpatsioon vs UH:</u>** Digital assessment of cervical length is subjective, varies between examiners, and underestimates true anatomic length. In one study, digital examinations before hysterectomy underestimated cervical length	SOGC Clinical Practice Guideline. **Ultrasonographic Cervical Length Assessment in**

by approximately 14 mm, whereas ultrasonography measured length accurately. (Jackson et al., 1992). Investigations using transvaginal ultrasound measurement as the standard confirmed that digital examination underestimates cervical length. (Andersen et al., 1990; Berghella et al., 2009). This underestimation may result from an inability to assess the cervix length digitally beyond the vaginal fornices unless there is 2 cm or more of dilatation and the entire intracervical canal is examined. The majority of studies have found that ultrasound assessment of cervical length is superior to clinical examination for the prediction of preterm birth. (Berghella et al., 1997; Gomez et al., 1994; Onderoglu,1997; Volumenie et al., 2004). Therefore, ultrasound assessment of cervical length is more reliable and more clinically predictive of preterm birth than manual examination of the cervix. **Transvaginal ultrasonography is the preferred route for cervical assessment to identify women at increased risk of spontaneous preterm birth and may be offered to women at increased risk of preterm birth. (II-2B)** **UH:** Spontaneous preterm birth is unlikely if the cervical length is ≥ 30 mm. (Venditteli et al, 2000; Crane et al.,1997; Tsoi et al, 2003; Tsoi et al, 2005). Fuchs et al. showed that a cervical length of < 15 mm in a population presenting with painful contractions (< 32 weeks) had a 5.5-fold increased risk (44%) of delivery within a week, and those with a cervical length of ≥ 15 mm had a 2% risk. In other studies, delivery occurred within 7 days of presentation in 37% of 43 women with cervical length < 15 mm (Tsoi et al, 2003), and a cervical length of < 20 mm had a 93.7% and 87.5% positive predictive value for preterm birth in primiparous and multiparous women respectively.(Daskalakis et al., 2005) In all these studies, the cervical length was an independent predictor of preterm delivery. In **2010, Sotiriadis et al**. published a meta-analysis on the use of cervical length measurements in patients presenting with symptoms of preterm labour. The cumulative data suggest that the cervical length measurement in symptomatic women can be used to discriminate between those at higher and those at lower risk of preterm delivery, which may help to rationalize their management; however, there was considerable heterogeneity across the studies. In a prospective cohort study among several hospitals using different protocols for threatened preterm labour, the use of ultrasound assessment of cervical length appeared to shorten hospital stay without compromising patient care. (**Sanin-Blair et al., 2004**) In a small (N = 41) trial (**Alfirevic et al., 2007**), women with threatened preterm labour were randomized to a control group, who received tocolytics and steroids in keeping with the hospital's protocol, or to an assessment group who had cervical length measured by transvaginal ultrasound. Women in the assessment group who were found to have a cervical length of < 15 mm were	**Predicting Preterm Birth in Singleton Pregnancies.** J Obstet Gynaecol Can 2011;33(5):486–499

given tocolytics and steroids. Those with cervical length of ≥15 mm were not given tocolytics and steroids. No babies in the group considered to be at low risk of preterm birth were born prematurely without a full course of antenatal corticosteroid therapy, and babies in this group had significantly lower rates of exposure to steroids and tocolytics.The results suggest that it may be safe to use ultrasonographic cervical length assessment to prevent unnecessary use of tocolytics and steroids. However, the small sample size of this study does not provide adequate power to assess uncommon outcomes such as preterm birth at < 34 weeks and to determine whether this approach could cause harm.
A **meta-analysis by Berghella et al. (2009)** evaluated the efficacy of cervical length measurements to prevent preterm birth by asking whether the knowledge of ultrasonographic cervical length affected the rate of preterm birth. The authors concluded that there was insufficient evidence to recommend routine screening of asymptomatic or symptomatic pregnant women with transvaginal ultrasound. However, it should be noted that the total number of women in the study was small (total N = 290 in preterm labour, n = 92 in premature preterm rupture of membranes). Also, the study did not determine whether progesterone or cerclage was used, and it included clinical presentations in which neither of those interventions would likely be used.
In women presenting with suspected preterm labour, transvaginal sonographic assessment of cervical length may be used to help in determining who is at high risk of preterm delivery and may be helpful in preventing unnecessary intervention. It is unclear whether this information results in a reduced risk of preterm birth. (II-2B)
UH PPROM korral: Several cohort studies have shown that the cervical length measured by TV predicts latency to delivery in preterm premature rupture of membranes. (Rizzo et al.,1998; Tsoi et al., 2004) Transvaginal cervical length measurement in a randomized trial was not found to increase the risk of infection in patients with PPROM. This study did not find that cervical length had predictive value for latency. This is not consistent with the findings of another study. (Carlan et al.,1997)
Transvaginal ultrasound appears to be safe in preterm premature rupture of membranes, but its clinical predictive value is uncertain in this context. (II-2)
UH vs fibronektiin: Direct comparison of these tests can be difficult. Depending on the threshold of cervical length or fetal fibronectin concentration used, the sensitivities and specificities will vary. The definitions of preterm birth and/or the outcome of interest (delivery within a certain interval of time) differ from study to study. These tests have a low sensitivity in a low-risk population and should be used in women at high risk rather than for general screening. Study findings vary, so it is unclear whether one is more predictive than the other. The combination of both (sequentially or in tandem) may be more effective than using one

alone, but again conflicting results have been found. Whether these screening strategies result in reduced interventions and use of resources remains uncertain. **Ultrasonographic cervical length assessment and fetal fibronectin appear to be similar in predictive ability, and the combination of both in a high-risk population may be of value. However, further research is needed in this area. (II-2)**	
Queenslandi ravijuhend (PL Australia 2014) • **Sterile speculum examination** to: o Confirm/exclude rupture of membranes o Assess cervix (dilatation, length, visualisation of membranes) o Assess liquor (e.g. clear, meconium stained, bloody) o Collect high vaginal swab for microscopy culture and sensitivity (MC&S) o **Perform test for the presence of fetal fibronectin** (if not contraindicated) o Collect combined low vaginal and anorectal swab for Group B streptococcus (GBS) • Assess cervical dilatation by sterile **digital vaginal examination** unless contraindicated by ruptured membranes/suspected placenta praevia. • Recommend **TVCL measurement** to women with identified or suspected preterm labour (where available) • Consider therapeutic interventions when the TVCL is measured at less than 25 mm (ACOG 2012). **Fibronektiin:** Indications: symptomatic preterm labour between **22+0 and 36+0** weeks gestation and intact membranes and cervical dilatation less than or equal to 3 cm. • Elevated levels of fFN (typically greater than 50 ng/mL) in cervicovaginal secretions after 22 weeks gestation are associated with an increased risk of PTB (Berghella et al., 2008). • A negative fetal fibronectin (fFN) is associated with a 99.5% negative predictive value for PTB within 7 days and 99.2% in the next 14 days (Abbott et al., 2013; Peaceman, 1997). • Quantitative fetal fibronectin testing may improve assessment of overall risk (Abbott et al., 2013), reduce unnecessary transfer and ultimately reduce longer term costs.	Queensland Clinical Guidelines. **Preterm labour and birth.** 2014.
ICSI juhend (MOL 2011) • Perform a **sterile speculum exam** to visualize the cervix to: - identify any source of bleeding or cervical or vaginal pathology or trauma; - estimate dilation and effacement of the cervix and look for pooling of amniotic fluid as a sign of ruptured membranes; * Perform **fetal fibronectin testing (fFN)** if patient is between **24 and 33 weeks gestation** and cervix is less than 3 cm dilated. A negative fFN result was associated with a 97.4% likelihood of the pregnancy continuing more than seven days after testing (Skoll,	Creedon D, Akkerman D, Atwood L, Bates L, Harper C, Levin A, McCall C, Peterson D, Rose C, Setterlund L, Walkes B, Wingeier R. Institute for Clinical Systems Improvement. **Management of Labor.** Updated March 2013.

2006 [Low Quality Evidence]). • Perform **digital cervical exam** if membranes are intact and there is no vaginal bleeding. If ruptured, digital exams increase the risk of infection. • Obtain **transvaginal sonogram (TVS) for cervical length** for monitoring of patients with sign/symptoms of preterm labor and early cervical change. Cervical length of less than 3.0 cm or a rapidly thinning cervix correlate with increased preterm birth rates (Rose, 2010 [Low Quality Evidence]; Iams, 2003 [Low Quality Evidence]; Vendittelli, 2000 [Low Quality Evidence]).	

Süstemaatilised ülevaated

Kokkuvõte: Leidus 13 antud küsimust käsitlevat süstemaatilist ülevaadet/metaanalüüsi.
Üks ülevaade **(Reiter et al., 2012)** võrdles **emakakaela digitaalset hindamist ultraheliuuringul emakakaela pikkuse määramisega.** Leiti, et ähvardava enneaegse sünnitusega naistel ei paranda emakakaela pikkuse (UH) teadmine oluliselt tervisetulemit, kuid see võib aidata vähendada hospitaliseerimise kestust. Bishopi skoori järgi valitud naistel võiks transvaginaalne UH vähendada valepositiivsust. Tõdeti, et emakakaela küpsuse hindamise meetodid ei ole üheselt mõistetavad. Järeldati, et emakakaela hindamise meetodeid peaks võtma pigem üksteist täiendavana kui üksteisega konkureerivana.
4 ülevaadet käsitlevad emakakaela pikkuse määramist UH-ga (TV UH). Cochrane'i süstemaatiline ülevaade (**Berghella et al., 2013**) järeldab, et pole piisavalt tõendusmaterjali soovitamaks ähvardava enneaegse sünnituse sümptomitega rasedatele rutiinselt TV UH. Leiti, et nende patsientide seas, kelle emakakaela pikkus oli teada, oli enneaegset sünnitust statistiliselt mitteoluliselt vähem. Ei leitud, et TV UH seostuks ema/neonataalse infektsiooni sageduse tõusuga. Teine meta-analüüs (**Sotiriadis et al., 2010**) leidis, et TV UH emakakaela pikkuse määramisega (CL cutoff <15 mm) saab leida olulise hulga patsientidest, kes sünnitavad 1 nädala jooksul, ning selle alusel saab ravi paremini korraldada, kuid meta-analüüsi kaasatud uuringud olid väga heterogeensed. 2 meta-analüüsi (**Conde-Agudelo et al., 2010, Liem et al., 2013**) käsitlesid TV UH kaksikraseduste korral. Mõlema põhjal on TV UH emakakaela pikkuse määramine madala prognostilise väärtusega. Kokkuvõttes võib öelda, et TV UH on ähvardava enneaegse sünnituse korral limiteeritud prognostilise väärtusega. Pole teada kindlat emakakaela pikkuse piiri (cutoff), mille juures oleks täpsus parim, erinevad uuringud käsitlevad erinevaid piire (15-30 mm). TV UH ja digitaalne palpatsioon võiksid olla üksteist täiendavad uuringud.
6 ülevaadet käsitlevad loote fibronektiini määramist. Cochrane'i ülevaate (**Berghella et al., 2008**) järgi vähendab fibronektiini määramisel põhinev ravikäsitlus enneaegsete sünnituste (alla 37 GN) taset, kuid teiste tulemite osas olulist erinevust ei leitud. Üks süstemaatiline ülevaade, mis hõlmas ka kuluanalüüsi (**Deshpande et al., 2013**), leidis, et fibronektiini määramine on enneaegse sünnituse prognoosimise osas mõõduka täpsusega. Kõige paremat prognostilist täpsust enneaegse sünnituse osas omas test 7-10 päeva jooksul pärast testimist. Sama leidis ka teine varasem süstemaatiline ülevaade (**Honest et al., 2002**). Meta-analüüs (**Leitich et al., 2003**) leidis, et fibronektiini tase on efektiivne lühiajaline enneaegse sünnituse prognoosija, kuid uuringute tulemused olid heterogeensed. Teise meta-analüüsi (**Sanchez-Ramos et al., 2009**) järgi on fibronektiinil limiteeritud täpsus enneaegse sünnituse ennustamise osas 7 päeva jooksul pärast analüüsi võtmist. Üks süstemaastiline ülevaade (**Conde-Agudelo et al., 2010**) käsitles fibronektiini määramist mitmikraseduste puhul. Järeldati, et fibronektiini määramisel on enneaegse sünnituse prognoosimises limiteeritud täpsus ja et see uuring on kõige täpsem ennustamaks

enneaegset sünnitust ette 7 päeva jooksul pärast testimist. Kokkuvõttes on uuringute järgi fibronektiini määramisel limiteeritud kuni mõõdukas prognostiline täpsus enneaegse sünnituse riski hindamise osas ning kõige täpsemini võimaldab see hinnata testile järgneva nädala jooksul esinevat riski enneaegseks sünnituseks.
Üks süstemaatiline ülevaade (**Boots et al., 2014**) võrdles omavahel **TV UH ja fibronektiini** määramist. Ei leitud olulist erinevust sensitiivsuse ja spetsiifilisuse osas ennustamaks sünnitust järgneva 48 h või 7 päeva jooksul.
Üks süstemaatiline ülevaade (**DeFranco et al., 2013**) võrdles omavahel **TV UH ja fibronektiini kombinatsiooni digitaalse palpatsiooniga**. Leiti, et kombineeritud uuringutel on enneaegse sünnituse osas tagasihoidlik positiivne ennustav väärtus, kuid see on kõrgem kui ainult digitaalset palpatsiooni kasutades. Kombinatsiooni parim sensitiivsus on enneaegse sünnituse ennustamise osas 7 päeva jooksul alates testimisest.

Süst. ülevaade/meta-analüüs	**Viide**
Digitaalne palpatsioon vs UH: **OBJECTIVE:** To review the predictive value of **digital examination and transvaginal scan** in low-risk asymptomatic and **symptomatic women** before treatment. **RESULTS:** The studies showed **that methods for the estimation of cervical ripening are not unequivocal nor is the nomenclature for digital examination**. Evidence for routine screening for premature cervical ripening in asymptomatic low-risk women is insufficient. **Knowledge of ultrasonographic cervical length in symptomatic women was not associated with a significantly improved outcome in symptomatic women, but may help to reduce length of hospitalization. In women selected by the Bishop Score, a transvaginal scan may reduce the number of false-positive results.** **CONCLUSIONS:** Clarification on the methods for performing cervical assessment is needed. **The evidence that transvaginal scanning of the cervix improves outcome in symptomatic women is insufficient.** The methods for assessing cervical change **should be regarded as complementary.**	Reiter, E., Nielsen, K.A., Fedder, J., **2012**. **Digital examination and transvaginal scan - competing or complementary for predicting preterm birth?** Acta Obstet Gynecol Scand 91, 428–438. doi:10.1111/j.1600-0412.2011.01341.x
TV UH	
Cochrane'i süstemaatiline ülevaade **UH emakakaela pikkuse mõõtmisest:** Objectives: To assess the effectiveness of antenatal management based on **transvaginal ultrasound of cervical length (TVU CL)** screening for preventing PTB. Kaasati **5 uuringut (507 patsienti).** Three included singleton gestations with **preterm labor (PTL)**; one included singleton gestations with **preterm premature rupture of membranes** (PPROM); and one included **twin gestations with or without PTL.** In the three trials of singleton gestations with PTL, 290 women were randomized; 147 to knowledge and 143 to no	Berghella V, Baxter JK, Hendrix NW. **Cervical assessment by ultrasound for preventing preterm delivery.** Cochrane Database of Systematic Reviews **2013**, Issue 1. Art. No.: CD007235. DOI: 10.1002/14651858.CD00

knowledge of TVU CL. **Knowledge of TVU CL results was associated with a non-significant decrease in PTB at less than 37 weeks** (22.3% versus 34.7%, respectively; average risk ratio 0.59, 95% confidence interval (CI) 0.26 to 1.32; two trials, 242 women) **and at less than 34 weeks** (6.9% verus 12.6%; RR 0.55, 95% CI 0.25 to 1.20; three trials, 256 women). **Delivery occurred at a later gestational age in the knowledge versus no knowledge groups** (mean difference (MD) 0.64 weeks, 95% CI 0.03 to 1.25; three trials, 290 women). **For all other outcomes for which there were available data (PTB at less than 34 or 28 weeks; birthweight less than 2500 grams; perinatal death; maternal hospitalization; tocolysis; and steroids for fetal lung maturity), there was no evidence of a difference between groups.** The trial of singleton gestations with **PPROM (n = 92)** evaluated as its primary outcome safety of TVU CL in this population, and not its effect on management. **There was no evidence of a difference in incidence of maternal and neonatal infections between the TVU CL and no TVU CL groups.** In the trial of **twin gestations with or without PTL (n = 125)**, there was **no evidence of a difference in PTB** at less than 36, 34, or 30 weeks, gestational age at delivery, and other perinatal and maternal outcomes between the TVU CL and the no TVU CL groups. Lifetable analysis revealed significantly less PTB at less than 35 weeks in the TVU CL group compared with the no TVU CL group (P = 0.02). **Authors' conclusions:** Currently, **there is insufficient evidence to recommend routine screening of asymptomatic or symptomatic pregnant women with TVU CL.** Since there is a non-significant association between knowledge of TVU CL results and a lower incidence of PTB at less than 37 weeks in symptomatic women, we encourage further research.	7235.pub3.
Hea kvaliteediga meta-analüüs UH emakakaela pikkuse määramise kohta: Objectives: To integrate data on the performance of **cervical length measurement** for the prediction of preterm birth in **symptomatic women.** **Results: Twenty-eight studies** fulfilled the selection criteria. For **birth within 1 week from presentation**, the pooled sensitivity, specificity, LR+ and LR− of **cervical length <15 mm** were **59.9%** (95% CI, 52.7–66.8%), **90.5%** (95% CI, 89.0–91.9%), **5.71** (95% CI, 3.77–8.65) and **0.51** (95% CI, 0.33–0.80), respectively. The same estimates for studies with **presentation at or before 34+ 0 weeks** were **71.0%** (95% CI, 60.6–79.9%), **89.8%** (95% CI, 87.4–91.9%), **5.19** (95% CI, 2.29–11.74) and **0.38** (95% CI, 0.11–1.34), respectively. For prediction of **birth before 34 weeks**, the pooled sensitivity, specificity, LR+ and LR− of **cervical length <15 mm** were **46.2%** (95% CI, 34.8–57.8%), **93.7%** (95% CI, 90.7–96.0%), **4.31** (95% CI, 2.73–6.82) and **0.63**	Sotiriadis, A., Papatheodorou, S., Kavvadias, A., Makrydimas, G., **2010**. **Transvaginal cervical length measurement for prediction of preterm birth in women with threatened preterm labor: a meta-analysis.** Ultrasound Obstet Gynecol 35, 54–64.doi:10.1002/uog.7457

(95% CI, 0.38–1.04), respectively. There was **considerable heterogeneity across studies in most estimates**. Conclusions: **Measurement of cervical length in symptomatic women can detect a significant proportion of those who will deliver within 1 week and help to rationalize their management.** The considerable heterogeneity across studies may be indicative of **methodological flaws, which either were not reported at all or were underreported**.	
UH emakakaela pikkuse mõõtmine kaksikraseduse korral: Objective—To assess the **accuracy of transvaginal sonographic cervical length (CL)** in predicting spontaneous preterm birth in women with **twin pregnancies**. Results—**Twenty-one studies** (16 in asymptomatic women and **5 in symptomatic women**) with a total of **3523 women** met the inclusion criteria. Among **asymptomatic** women, a CL ≤20 mm 20-24 weeks' gestation was the most accurate in predicting preterm birth <32 and <34 weeks' gestation (pooled sensitivities, specificities, and positive and negative likelihood ratios of 39% and 29%, 96% and 97%, 10.1 and 9.0, and 0.64 and 0.74, respectively). A CL ≤25 mm 20-24 weeks' gestation had a pooled positive likelihood ratio of 9.6 to predict preterm birth <28 weeks' gestation. **The predictive accuracy of CL for preterm birth was low in symptomatic women.** (Enamikus uuringutes oli cutoff'iks 2,5 cm). **Among women with threatened preterm labor, the measurement of CL had a minimal predictive accuracy for preterm birth <34 and <37 weeks of gestation** (pooled positive and negative likelihood ratios between 1.2 and 1.9, and between 0.65 and 0.69, respectively). Conclusion—Transvaginal sonographic CL 20-24 weeks' gestation is a good predictor of spontaneous preterm birth in asymptomatic women with twin pregnancies.	Conde-Agudelo, A., Romero, R., Hassan, S.S., Yeo, L., **2010**. **Transvaginal sonographic cervical length for the prediction of spontaneous preterm birth in twin pregnancies: a systematic review and metaanalysis.** Am. J. Obstet. Gynecol. 203, 128.e1–12. doi:10.1016/j.ajog.2010.02.064
UH emakakaela pikkuse mõõtmine kaksikraseduse korral: Objective. The aim of this study was to assess whether **cervical length measurement (CL)** could predict preterm birth (PTB) in **symptomatic women** with a **twin pregnancy**. Results. **Five studies (N = 226)** were included. **Variation in definition of PTB and cut-off points for CL was strong**. One study investigated **delivery within seven days**, demonstrating a **sensitivity of 1.0 (95% CI: 0.83–1.0) and a specificity of 0.31 (95% CI 0.2–0.43) for a CL cut off at 25 mm.** Three studies reported on predicting PTB < 37 weeks at a CL cutoff of 30 mm, with sROC point estimates of 0.76 (95% CI: 0.66 to 0.84) and 0.37 (95% CI: 0.21 to 0.56) for sensitivity and specificity, respectively. For preterm birth <34 weeks, no pooled estimates could be estimated since only 2 studies with large heterogeneity were identified. Conclusions.There is **limited evidence on the accuracy of cervical length measurement testing the prediction of preterm**	Liem, S.M.S., van de Mheen, L., Bekedam, D.J., van Pampus, M.G., Opmeer, B.C., Lim, A.C., Mol, B.W.J., **2013**. **Cervical length measurement for the prediction of preterm birth in symptomatic women with a twin pregnancy: a systematic review and meta-analysis.** Obstet Gynecol Int 2013, 125897. doi:10.1155/2013/125897

birth in symptomatic women with a twin pregnancy, especially on the most important outcome, that is, delivery within 7 days.	
FIBRONEKTIIN	
Cochrane'i süstemaatiline ülevaade **fibronektiini** kohta: Objectives: To assess the effectiveness of management based on knowledge of **FFN testing** results for preventing preterm birth. The **five included studies randomized 474 women (kõik ähvardava enneaegse sünnitusega)**, of which 235 were randomized to knowledge and 249 to no knowledge of FFN. **Preterm birth less than 37 weeks was significantly decreased with management based on knowledge of FFN results (15.6%) versus controls without such knowledge (28.6%; risk ratio 0.54; 95% CI 0.34 to 0.87). All other outcomes for which there were available data** (preterm birth at less than 34, 32, or 28 weeks; gestational age at delivery; birthweight less than 2500 grams; perinatal death; **maternal hospitalization; tocolysis; steroids for fetal lung maturity; and time to evaluate**) **were similar in the two groups.** No other maternal or neonatal outcome was available for meaningful analysis. Conclusions: **Knowledge of fetal fibronectin results in the management of women with symptoms of preterm labor is associated with a lower incidence of preterm birth before 37 weeks.** As all our available outcomes were not affected, and no perinatal outcome other than perinatal death was reported, **further research is necessary before fetal fibronectin testing can be recommended in this clinical scenario.** Furthermore, it is still unclear which interventions are most beneficial once fetal fibronectin results are known.	Berghella V, Hayes E, Visintine J, Baxter JK. **Fetal fibronectin testing for reducing the risk of preterm birth.** Cochrane Database of Systematic Reviews **2008**, Issue 4. Art. No.: CD006843. DOI: 10.1002/14651858.CD006843.pub2.
Fibronektiin mitmikraseduse korral: Objective—To investigate the **accuracy of cervicovaginal fetal fibronectin** in predicting preterm birth in women carrying **multiple pregnancies.** Fifteen studies (11 in asymptomatic women and **4 in women with symptoms of preterm labor**) involving **1221 women** with **multiple pregnancies** were included. **Among women with twin pregnancies and threatened preterm labor, the test was most accurate in predicting spontaneous preterm birth within 7 days of testing** (pooled sensitivity, specificity, and positive and negative likelihood ratios of 85%, 78%, 3.9, and 0.20, respectively). Conclusions— In this systematic review, we found evidence that **cervicovaginal fetal fibronectin has limited accuracy in predicting spontaneous preterm birth in both asymptomatic and symptomatic women with multiple pregnancies because the likelihood ratios for positive and negative test results generated only minimal to moderate changes in the pretest**	Conde-Agudelo, A., Romero, R., **2010**. **Cervicovaginal fetal fibronectin for the prediction of spontaneous preterm birth in multiple pregnancies: a systematic review and meta-analysis.** J. Matern. Fetal. Neonatal. Med. 23, 1365–1376. doi:10.3109/14767058.2010.499484

probabilities of preterm birth. The test was most accurate in predicting spontaneous preterm birth before 32 weeks' gestation in asymptomatic women with multiple or twin pregnancies, and spontaneous preterm birth **within 7 days of testing in women with twin pregnancies and threatened preterm labor.**	
Hea kvaliteediga süstem. ülevaade ja kuluanalüüs fibronektiini kohta: Objective: To assess the clinical effectiveness and cost-effectiveness of **rapid fFN testing** in predicting preterm birth (PTB) in **symptomatic women.** Results: Five RCTs and 15 new DTAs (diagnostic test accuracy study) were identified. **No RCT reported significant effects of fFN testing on maternal or neonatal outcomes. One study reported a subgroup analysis of women with negative fFN test observed > 6 hours, which showed a reduction in length of hospital stay where results were known to clinicians**. Combining data from new studies and the previous systematic review, **the pooled estimates of sensitivity and specificity were: 76.7% and 82.7% for delivery within 7–10 days of testing; 69.1% and 84.4% for delivery < 34 weeks' gestation; and 60.8% and 82.3% for delivery < 37 weeks' gestation.** Estimates were similar across all subgroups sensitivity analyses. The **base-case cost analysis** resulted in a **cost saving of £23.87 for fFN testing compared with usual care.** The fFN testing was cost-neutral at an approximate cost of £45. Probabilistic sensitivity analysis gave an incremental cost (saving) of –£25.59 (97.5% confidence interval –£304.96 to £240.06), indicating substantial uncertainty. **Sensitivity analyses indicated that admission rate had the largest impact on results.** Conclusions: **Fetal fibronectin testing has moderate accuracy for predicting PTB.** The main potential role is likely to be reducing health-care resource usage by identifying women not requiring intervention. Evidence from RCTs suggests that fFN does not increase adverse outcomes and may reduce resource use. **The base-case analysis showed a modest cost difference in favour of fFN testing, which is largely dependent on whether or not fFN testing reduces hospital admission.** Currently, there are no high-quality studies and the existing trials were generally underpowered. Hence, there is a need for high-quality adequately powered trials using appropriate study designs to confirm the findings presented.	Deshpande, S.N., van Asselt, A.D.I., Tomini, F., Armstrong, N., Allen, A., Noake, C., Khan, K., Severens, J.L., Kleijnen, J., Westwood, M.E., **2013**. **Rapid fetal fibronectin testing to predict preterm birth in women with symptoms of premature labour: a systematic review and cost analysis.** Health Technol Assess 17, 1–138. doi:10.3310/hta17400
Hea kvaliteediga süstemaatiline ülevaade fibronektiini kohta: Objective: To determine the accuracy with which a **cervicovaginal fetal fibronectin test** predicts spontaneous preterm birth in **women with or without symptoms** of preterm labour. Data synthesis: **64 primary articles** were identified, consisting of **28 studies in asymptomatic women** and **40 in symptomatic**	Honest, H., Bachmann, L.M., Gupta, J.K., Kleijnen, J., Khan, K.S., **2002**. **Accuracy of cervicovaginal fetal fibronectin test in predicting risk of**

women, with a total of **26 876 women**. Among asymptomatic women the best summary likelihood ratio for positive results was 4.01 (95% confidence interval 2.93 to 5.49) for predicting birth before 34 weeks'gestation, with corresponding summary likelihood ratio for negative results of 0.78 (0.72 to 0.84). **Among symptomatic women the best summary likelihood ratio for positive results was 5.42 (4.36 to 6.74) for predicting birth within 7-10 days of testing, with corresponding ratio for negative results of 0.25 (0.20 to 0.31).** Conclusion: **Cervicovaginal fetal fibronectin test is <u>most accurate in predicting spontaneous preterm birth within 7-10 days of testing</u> among women with symptoms of threatened preterm birth before advanced cervical dilatation.**	**spontaneous preterm birth: systematic review.** BMJ 325, 301.
Meta-analüüs fibronektiini kohta: Objective: **To determine the value of cervicovaginal fetal fibronectin as a marker for preterm delivery, a previously published meta-analysis was updated**. Results: A total of **40 studies** were included. **Statistical heterogeneity** was seen in the majority of calculations of combined results and a random-effects model was used in these cases. **For the subgroup of women with symptoms of preterm labour, sensitivity rates for delivery <37 and <34 weeks' gestation or delivery within 7, 14, and 21 days of 54%, 63%, 77%, 74%, and 70% and specificity rates of 85%, 86%, 87%, 87%, and 90% were calculated.** Conclusion: **Cervicovaginal fetal fibronectin is an <u>effective short-term marker of preterm delivery</u>, especially in women with symptoms of preterm labour**. Because **results appear to be heterogeneous in different studies**, caution should be taken when they are applied to a specific population.	Leitich, H., Kaider, A., **2003**. **Fetal fibronectin--how useful is it in the prediction of preterm birth?** BJOG 110 Suppl 20, 66–70.
Hea kvaliteediga meta-analüüs fibronektiini kohta: OBJECTIVE: To appraise critically the diagnostic accuracy of cervicovaginal **fetal fibronectin** as a short-term predictor as a short-term predictor of preterm birth in patients with **signs and symptoms of preterm labor.** METHODS OF STUDY SELECTION: We targeted cohort studies reporting data on the diagnostic accuracy of fetal fibronectin for the prediction of preterm birth within 7 days in symptomatic patients before 37 weeks of gestation. Case–control studies were excluded. The total analysis included **32 trials with 5,355 overall participants.** RESULTS: **The overall pooled estimates for sensitivity and specificity were 76.1%** (95% confidence interval [CI] 69.1–81.9) **and 81.9%** (95% CI 78.9–84.5), respectively. **Likelihood ratios for a positive and negative fetal fibronectin test were 4.20** (95% CI 3.53–4.99) **and 0.29** (95% CI 0.22–0.38), respectively. Meta-regression analyses found that test accuracy was affected by prevalence, publication year, and blinding of studies. When	Sanchez-Ramos, L., Delke, I., Zamora, J., Kaunitz, A.M., **2009**. **Fetal fibronectin as a short-term predictor of preterm birth in symptomatic patients: a meta-analysis.** Obstet Gynecol 114, 631–640. doi:10.1097/AOG.0b013e3181b47217

subgroup analyses were performed for studies using the same assay, the results were similar. CONCLUSION: The cervicovaginal fetal fibronectin assay has **limited accuracy in predicting preterm birth within 7 days of sampling in symptomatic pregnant women.**	
Fibronektiin vs emakakaela pikkuse mõõtmine UH-ga: OBJECTIVE: To assess the diagnostic accuracy of **fetal fibronectin (fFN), fetal breathing movements (FBM), and cervical length (CL)** for the short-term prediction of preterm birth **in symptomatic patients.** RESULTS: Full-text review left 72 studies for inclusion: 38 fFN, 10 FBM, and 24 TVS. **For the prediction of delivery within 48 hours, pooled sensitivity was higher for TVS, but pooled specificity was higher for FBM**. Both the likelihood ratio for a positive test and the diagnostic odds ratio were higher for FBM than for TVS. However, the likelihood ratios for a negative test were similar for the 2 tests. **For the prediction of delivery within 7 days, pooled sensitivity for fFN was highest and pooled sensitivity was again higher for TVS than for FBM, however, pooled specificity was higher for FBM.** Both the likelihood ratio for a positive test and the diagnostic odds ratio were higher for FBM than for fFN or TVS. Yet, the likelihood ratio for a negative test was lowest for TVS and similar for fFN and FBM. Increasing CL cutoff was positively correlated with sensitivity and negatively correlated with specificity. **The comparisons of sensitivity and specificity among the 3 tests showed no statistically significant differences in predicting delivery within 48 hours or within 7 days. However, FBM at 48 hours and 7 days showed statistically significant higher specificity than fFN and TVS**. CONCLUSION: **In symptomatic patients, for fFN, absence of FBM, and CL have diagnostic use as predictors of delivery within 48 hours and within 7 days of testing. Absence of FBM appears to be the best test for predicting preterm birth.**	Boots AB, Sanchez-Ramos L, Bowers DM, et al. **The short-term prediction of preterm birth: a systematic review and diagnostic metaanalysis.** Am J Obstet Gynecol **2014**;210:54.e1-10
Fibronektiin + UH vs digitaalne palpatsioon: Our objective was to systematically review the current medical literature to assess the **accuracy of the combination of fetal fibronectin (fFN) plus ultrasound assessment of cervical length (CL)** as screening tools for preterm labor and prediction of preterm birth (PTB), and **to compare this to the traditional clinical method of digital cervical examination.** RESULTS: Nine studies reported the association between fFN positivity plus CL measurement with PTB in women presenting with symptomatic uterine contractions. **The studies reporting screening efficacy for the prediction of PTB at later gestational ages (<37 weeks) demonstrated lower sensitivity and positive likelihood ratio compared to those aimed to predict PTB at earlier gestational ages (34 and 35 weeks). The highest sensitivities were demonstrated by studies**	DeFranco, E.A., Lewis, D.F., Odibo, A.O., 2013. **Improving the screening accuracy for preterm labor: is the combination of fetal fibronectin and cervical length in symptomatic patients a useful predictor of preterm birth? A systematic review.** Am. J. Obstet. Gynecol. 208, 233.e1–6. doi:10.1016/j.ajog.2012.12.015

reporting PTB prediction in prescribed time intervals of <7 or <28 days when compared to those utilizing gestational age cutoffs of 34, 35, and 37 weeks. The pooled specificities were high for all included studies, regardless of outcome definition (specificity range, 83–97%). CONCLUSION: We conclude that **this approach has a modest PPV for PTB at <37 weeks of 49.4%, but higher than that of clinical diagnostic criteria alone. The sensitivity and positive likelihood for this combined screening approach is higher for predicting PTB risk within short periods of time (<7 days) and at earlier gestational ages (<28 weeks),** when neonatal risks related to prematurity are highest. We found that the **sensitivity of predicting PTB in short intervals of time, <7 days from onset of diagnosis, is>70%.** Likewise, the **NPV for delivery within this short time period is also very high, >98%.** Therefore, this combined screening approach not only yields useful information regarding short-term risks that can be used to guide acute management, but also effectively identifies a population at low risk in whom expensive and potentially dangerous interventions could be avoided. **We conclude that this combined screening approach yields useful information regarding short-term risks that can be used to guide acute management, and effectively identifies a population at low risk in whom expensive and potentially dangerous interventions could be avoided.**	

Üksikuuringud

Kokkuvõte: Leitud üksikuuringud olid kaasatud eelnevalt välja toodud süstemaatilistesse ülevaadetesse/meta-analüüsidesse. Tegin mitmeid otsinguid üksikuuringute leidmiseks, mis käsitleksid kompleksset uuringut ning mis võrdleks seda erinevate diagnostika meetoditega, kuid selliseid uuringuid ei leidnud. Leidsin retrospektiivse kohortuuringu (**Alexander et al., 2000**), mis käsitleb PPROM-i ja digitaalset palpatsiooni. Ei leitud olulist erinevust infektsioonide (koorioamnioniit, endometriit, haavainfektsioon) ega vastsündinu erinevate tervisetulemite osas. Leiti, et digitaalse palpatsiooni korral on aeg lootevee puhkemisest sünnituseni lühem kui neil, kel bimanuaalset läbivaatust ei tehtud.

Üksikuuring	**Viide**
Retrospektiivne kohortuuring. PPROM ja digitaalne palpatsioon: OBJECTIVE: The purpose of this study was to examine the effects of **digital cervical examination** on maternal and neonatal outcomes among women with **preterm rupture of membranes.** STUDY DESIGN: This analysis includes data from a previously reported trial of antibiotic treatment during expectant management of rupture of membranes at 24 to 32 weeks' gestation in singleton and twin gestations. Patients from both the randomized trial (n =	Alexander, J.M., Mercer, B.M., Miodovnik, M., Thurnau, G.R., Goldenberg, R.L., Das, A.F., Meis, P.J., Moawad, A.H., Iams, J.D., Vandorsten, J.P., Paul, R.H.,

299 in the antibiotic group and n = 312 in the placebo group) and the observational component (n = 183) are included in this analysis. **The groups were divided into those with one (n = 161) or two digital cervical examinations (n = 27) and those with no digital cervical examinations (n = 606).** RESULTS: The gestational ages at enrollment were similar in the two groups (29 +/- 2 weeks' gestation for one or two examinations vs 29 +/- 2 weeks' gestation for no examinations; P =.85). There were **no differences in chorioamnionitis** (27% vs 29%; P =.69), **endometritis** (13% vs 11%; P =.5), **or wound infection** (0.5% vs 1%; P >.999) between the group with one or two examinations and the no-examination group. **Infant outcomes were also similar in the two groups, including early sepsis** (6% vs 5%; P =.68), **respiratory distress syndrome** (51% vs 45%; P =.18), **intraventricular hemorrhage** (7% vs 7%; P =.67), **necrotizing enterocolitis** (5% vs 3%; P =.19), **and perinatal death** (7% vs 5%; P =.45). **A composite outcome made up of these neonatal outcomes was not different** (56% vs 48%; P =.10) between the group with one or two examinations and the no-examination group. **The time from rupture to delivery was shorter in the digital examination group (median value, 3 vs 5 days; P <. 009).** Multivariable analysis to adjust for antibiotic study group, group B streptococcal culture status, race, and maternal transfer did not modify these results. CONCLUSION: **Performance of one or two digital cervical examinations during the course of expectant management of rupture of membranes between 24 and 32 weeks' gestation was associated with shorter latency but did not appear to worsen either maternal or neonatal outcome.**	Dombrowski, M.P., Roberts, J.M., McNellis, D., **2000**. **The impact of digital cervical examination on expectantly managed preterm rupture of membranes.** Am. J. Obstet. Gynecol. 183, 1003–1007. doi:10.1067/mob.2000.106765

Majanduslik analüüs:

Objective: The objective of the study was to evaluate the cost-effectiveness of risk stratification with cervical length (CL) measurement and/or fetal fibronectin (fFN) tests in women with threatened preterm labor between 24 and 34 weeks' gestation. Study Design: We performed a model-based cost-effectiveness analysis to evaluate 7 test-treatment strategies in women with threatened preterm labor from a health care system perspective. Estimates on disease prevalence, costs, and test accuracy were based on medical literature. Results: **We found that additional fFN testing in the case of a CL between 10 and 30 mm is cost saving without compromising neonatal health outcomes, compared with a treat-all strategy or single CL testing**. Implementing this strategy could lead to an annual cost saving between €2.8 million and €14.4 **million in The Netherlands**, a country with about 180,000 deliveries annually. Conclusion: In women with threatened preterm labor between 24	Baaren, G.-J., Vis, J.Y., Grobman, W.A., Bossuyt, P.M., Opmeer, B.C., Mol, B.W., **2013. Cost-effectiveness analysis of cervical length measurement and fibronectin testing in women with threatened preterm labor.** Am. J. Obstet. Gynecol. 209, 436.e1–8. doi:10.1016/j.ajog.2013.06.029

and 34 weeks of gestation, **the most cost-effective test strategy uses a combination of CL and fFN testing.**	
NICE ravijuhend: Cost utility analysis. The analysis undertaken for this question utilised the output of the health economic model produced for the tocolytic review, as that is a treatment that could be offered as the result of a diagnostic assessment for women with suspected preterm labour and intact membranes. Due to the limitations of the diagnostic accuracy review studies included in the clinical review, the evaluation took a 'what-if' approach to diagnostic accuracy. In this 'what-if' model, the treatment benefit is only obtained by 'true positives' (which in this case means those in actual preterm labour who are treated). The absolute risk of adverse outcomes for 'true positives' was modelled using the relative treatment effect of calcium channel blockers, which were assessed in as being the most cost-effective tocolytic, applied to the baseline risk of these outcomes in the absence of treatment. 'False negatives' are assumed to have the baseline risk of adverse outcomes. 'False positives' do not receive any benefit from treatment but do incur the relevant treatment costs. The baseline data used in this guideline suggested that the baseline risk of adverse outcomes varied with gestational age with, as expected, declining risk with increasing gestational age. It was assumed in the tocolytic model that the relative treatment effect would be constant across the different gestational ages. However, the difference in baseline risk means that the absolute treatment benefit, a key component of cost effectiveness, declines with increasing gestational age. Although the model supports recommendations which use a 'treat all' strategy at lower gestational age and the use of a diagnostic test to determine treatment at higher gestational ages, the limitations of the diagnostic accuracy evidence means that the model does not give a definitive gestational age at which the strategy should change. Both studies of transvaginal ultrasound using a cervical length of 15 mm or less have diagnostic accuracy figures that are sufficient to make treatment based on a diagnostic test cost effective relative to 'treat all' at 30 weeks. Using transvaginal ultrasound and cervical length of 10 mm or less also has diagnostic accuracy figures that would support a recommendation when compared with 'treat all', but this is only based on a single study and an element of clinical judgement and pragmatism was used to inform the recommendations to 'treat all' below a gestational age of 30 weeks and to use transvaginal ultrasound and cervical length of 15 mm or less as a diagnostic test to determine treatment where gestational age is 30 weeks and above. The model does not show that 'treat all' is a cheap strategy but rather that the additional costs are worth the reduction in adverse outcomes at lower gestational ages. Sensitivity analysis suggested that the cost of the diagnostic test (within plausible ranges) was not an important driver of cost-effective thresholds for 'treat all', 'treat based on diagnostic test'	**NICE Guideline 25. Preterm Labour and Birth. 2015.**

and 'no diagnosis and no treatment'. The inclusion of a cost for false negatives was also found to have little impact on model results. However, the analysis did suggest that model conclusions about cost-effective combinations of sensitivity and specificity could be sensitive to relatively small changes in prevalence. There is also a concern that the implications of a 'treat all' strategy might require some units to transfer women out of their hospital and therefore a sensitivity analysis was undertaken where the treatment cost was increased by £300 per woman to allow for the costs of such transfers. As expected this change lowers the threshold for diagnostic accuracy to be considered cost effective relative to 'treat all' and increases the threshold for diagnostic accuracy to be considered cost effective relative to 'no diagnosis and no treat'. At the lowest gestational ages the higher treatment cost has a relatively small impact on the diagnostic threshold but this increases with increasing gestational age.	

Otsingustrateegiad:

02.08.2015 Search: ((((premature) OR preterm)) AND ((((birth) OR labour) OR labor) OR rupture of membranes)) AND (((((((((ultrasound) OR cervix) OR incompetent cervix) OR transvaginal) OR transperineal) OR cervical length) OR fibronectin) OR digital assessment) OR digital examination) Filters: Meta-Analysis, Systematic Reviews, Guideline, Practice Guideline n=215 (Neist teemakohaseid 22)

03.08.2015 Search: ((((premature) OR preterm)) AND ((((birth) OR labour) OR labor) OR rupture of membranes)) AND (((((((((ultrasound) OR cervix) OR incompetent cervix) OR transvaginal) OR transperineal) OR cervical length) OR fibronectin) OR digital assessment) OR digital examination) Filters: Clinical Trial, Controlled Clinical Trial, Full text, 10 years, Humans n=301

Digitaalne palpatsioon: 11.08.2015 Search: (((((preterm) OR premature)) AND ((((birth*) OR labor*) OR labour*) OR rupture of membranes))) AND ((((((((((cervical exam*) OR cervical examination*) OR digital evaluation) OR digital examination*) OR digital assessment**) OR manual examination*) OR pelvic examination*) OR manual cervical exam*) OR digital cervical examination*) OR pelvic exam*) Filters: Humans, English n=158 (neist teemakohaseid 6)

Digitaalne palpatsioon ja UH: 11.08.2015 Search: ((((((preterm) OR premature)) AND ((((birth*) OR labor*) OR labour*) OR rupture of membranes))) AND ((((((preterm) OR premature)) AND ((((birth*) OR labor*) OR labour*) OR rupture of membranes))) AND (((((((cervical) OR cervix) OR sonography) OR ultrasound) OR ultrasonography) OR transvaginal) OR length))) AND (((((bimanual examination*) OR pelvic examination*) OR digital assessment) OR digital examination*) OR digital evaluation) Filters: Humans, English n=74 (neist mitte ühtegi uut sobilikku vastet)

Fibronektiin ja UH: 11.08.2015 Search: (((((preterm) OR premature)) AND ((((birth*) OR labor*) OR labour*) OR rupture of membranes))) AND (((fibronectin) AND ultrasonograph*) AND cervical length) Filters: Humans, English n=54 (neist teemakohaseid 8)

UH ja digitaalne palpatsioon 14.08.2015 Search ((((((preterm) OR premature)) AND ((((birth) OR labor) OR labour) OR rupture of membranes))) AND ((((sonography) OR ultrasound) OR cervical length) OR cervical measurement)) AND (((((digital examination) OR digital evaluation) OR digital exam) OR pelvic exam) OR bimanual examination)Filters: Meta-Analysis; Systematic Reviews

Kombineeritud uuring 14.08.2015 Search (((((((sonography) OR ultrasound) OR cervical length) OR cervical measurement)) AND (((((digital examination) OR digital evaluation) OR digital exam) OR pelvic exam) OR bimanual examination)) AND (((vaginal swab*) OR cervical swab*) OR microscopy)) AND fibronectin - n=0
UH + digitaalne palpatsioon + fibronektiin 14.08.15 Search (((((((preterm) OR premature)) AND ((((birth) OR labor) OR labour) OR rupture of membranes))) AND ((((sonography) OR ultrasound) OR cervical length) OR cervical measurement)) AND (((((digital examination) OR digital evaluation) OR digital exam) OR pelvic exam) OR bimanual examination)) AND fetal fibronectin n=9 (neist mitte ühtegi uut)
Kokku leidsin 4 teemakohast ravijuhendit, 13 süstemaatilist ülevaadet/meta-analüüsi, 1 retrospektiivse kohortuuringu, 1 majandusliku analüüsi.