Kliiniline küsimus nr 4. *Kas kõikide ähvardavate enneaegsete sünnituste korral tuleb vastsündinu parema ravitulemi saavutamiseks kasutada antenataalset kopsude ettevalmistust glükokortikoididega võrreldes antenataalse kopsude mitte ettevalmistamisega?*
- beetametasoon võrreldes deksametasoon
- beetametasooni raviskeem: ühekordne (24 mg × 1) võrreldes kahekordne (12 mg × 2) võrreldes neljakordne doos (6 mg × 4)
- beetametasooni korduv ravikuur (kui sünnitus toimub > 7 päeva pärast esimese kuuri lõppu) võrreldes ühekordne kuur ähvardava enneaegse sünnituse korral alla 26 +0 rasedusnädalat

Kriitilised tulemusnäitajad: ema tervisetulem, lapse peamised tulemusnäitajad, hingamistoetuse vajadus ja kestus, surfaktantravi vajadus

Süstemaatilised ülevaated

Kokkuvõte süstemaatilistest ülevaadetest: Leidsime 8 meie otsingukriteeriumitele vastavat süstemaatilist ülevaadet. Kolm ülevaadet olid väga hea kvaliteediga (Cochrane) ning ülejäänud neli, millest kolm hõlmasid endas ka meta-analüüsi, olid mõnevõrra madalama (rahuldava-keskmise) kvaliteediga.
Süstemaatiliste ülevaadete põhjal võiks teha järgnevad soovitused:

- Ähvardava enneaegse sünnituse korral on tõenduspõhine kasutada antenataalselt kortikosteroide loote kopsude ettevalmistamiseks.
- Erinevaid tervisetulemeid hinnates leiti, et kõige efektiivsema tulemuse annab glükokortikosteroidide kasutamine gestatsiooniajas 26+0 kuni 34+6 rasedusnädalat. Hetkel pole piisavalt tõendusmaterjali toetamaks/ümberlükkamaks soovitust antenataalsete kortikosteroidide kasutamise kohta ähvardava enneaegse sünnituse korral enne 26. rasedusnädalat.
- Antenataalsete glükokortikoidide kasutamine on efektiivne ka enneaegselt puhkenud lootevee korral (ei suurenda koorioamnioniidi ega sepsise riski).
- Beetametasooni ja deksametasooni võrdlevate uuringute põhjal ei ole veenvaid argumente eelistamaks ühte teisele. Ühe ülevaate (Roberts et al., 2006) põhjal andis beetametasoon parema ravitulemuse RDS-i osas, deksametasooni seostati sünnitusjärgse sepsise esinemissageduse tõusuga, teises ülevaates (Brownfoot et al., 2013) leiti deksametasoonil olevat parem efekt IVH riski vähendamises, RDS-i esinemise osas olulist erinevust ei leitud.
- Süstemaatiliste ülevaadete põhjal ei saa teha järeldust optimaalse esmase glükokortikoidravi skeemi osas.
- Korduvad glükokortikoidravi kuurid (nädalase või kahenädalase intervalliga) vähendavad üldist neonataalset haigestumust, samas seostatakse korduvaid ravikuure madalama sünnikaaluga. Antud teemat käsitlevatest ülevaadetest 2 korduvaid ravikuure pigem ei soovita (Bevilacqua et al., 2010; Peltoniemi et al., 2011) ning ühe põhjal võiks seda kaaluda (Crowther et al., 2011). Pole teada korduvate ravikuuride ohutus kaugtulemite osas.
- Ühe uuringu (Crowther et al., 2011) põhjal vähendas ühekordne beetametasooni lisakuur kombineeritud raskete tervisetulemite riski ning antud teemat käsitlev teine uuring (Peltoniemi et al., 2011) leidis, et ühekordne beetametasooni lisakuur võib olla efektiivne RDS-i preventsioonis, kui ajastus on õige (24 h enne sünnitust). Ühekordse beetametasooni lisakuuri osas ei leitud seost madalama sünnikaaluga.
- Üks meta-analüüs (Amiya et al, 2016), mis uuris glükokortikoidravi intrauteriinse kasvupeetusega lastel, ei leidnud ravi saanute grupis olulist haigestumuse ja suremuse langust. Analüüs toob välja, et sellises alagrupis glükokortikoidide manustamine ja nende ohutus vajab lisauuringuid.

Viited

Kokkuvõtte ülevaatest (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Antenataalsete kortikosteroidide (ACS) üldisest kasutamisest: **-** Ülevaade hõlmas 21 RCT (3885 naist ja 4269	Roberts D, Dalziel SR. **Antenatal corticosteroids for accelerating fetal lung maturation for women**

vastsündinut). Leiti, et jätkuvalt on tõenduspõhine ühekordse kuurina kortikoidide manustamine ähvardava enneaegse sünnitusega patsientidel kiirendamaks loote kopsude küpsemist. Antenataalselt kortikoidide kasutamine vähendab üldist loote suremust (RR 0,69, CI 0,58-0,81, 18 uuringut, 3956 vastsündinut), respiratoorse distressi sündoomi esinemist (RR 0,66, CI 0,59-0,73, 21 uuringut, 4038 vastsündinut), tserebroventrikulaarse hemorraagia esinemist (RR 0,54, CI 0,43-0,69, 13 uuringut 2872 vastsündinut), nekrotiseeriva enterokoliidi esinemist (RR 0,46, CI 0,29-0,71, 8 uuringut,1675 vastsündinut), respiratoorse toetuse vajadust ja hospitaliseerimist intensiivraviosakonda (RR 0,80, CI 0,65-0,99, 2 uuringut, 277 vastsündinut) ning süsteemse infektsiooni esinemist esimese 48 elutunni jooksul (RR 0,56, CI 0,38-0,85, 5 uuringut, 1319 vastsündinut). Lisaks väheneb vajadus surfaktantravi järele (RR 0,72, CI 0,51-1,03, 3 uuringut, 456 vastsündinut). - ACS vähendavad neonataalset suremust isegi kui loode sünnib vähem kui 24h peale esimese doosi manustamist. RDS väheneb loodetel, kes sünnivad kuni 7 päeva peale esimest doosi. Antud ülevaade ei leidnud erinevust esmastes ravitulemustes, kui loode sündis peale 7 päeva möödumist esimesest ravidoosist. - Ei leitud statistiliselt olulist seost loote kroonilise kopsuhaiguse, sünnikaalu, lapseea suremuse ja neuroloogilise arengu mahajäämuse osas võrreldes nendega, kes ei olnud ekponeeritud ACS-le. - Mõned uuringud väidavad, et ACS-st ei ole kasu manustatuna enne 28 rasedusnädalat, Antud uuring leidis, ACS vähendavad tserebroventrikulaarse hemorraagia esinemissagedust isegi väiksemas gestatsioonivanuses kui 28. Uurides edasisi ACS manustamise tulemusi lähtudes gestatsiooniajast, leiti, et RDS väheneb, kui ACS manustatakse 26 kuni 29.9 nädalas, 30 kuni 32.9 nädalas ja 33 kuni 34.9 nädalas. Lisaks väheneb nii tserebroventrikulaarse hemorraagia esinemissagedus ja neonataalne suremus ACS manustamisel gestatsiooniajas 26 kuni 29.9 nädalat. Esmaste ravitulemite osas ei leitud erinevusi võrreldes kontrollgrupiga, kui ACS manustati enne 26 rasedusnädalat (Samas analüüs vaid 1 uuringu põhjal, 49 vastsündinut). - Antenataalsete glükokortikoidide kasutamine on efektiivne ka naistel, kel on enneagselt puhkenud lootevesi või tegemist rasedusaegse hüpertensiooniga. Ravi ACS-ga ei suurenda emade suremust, koorioamnioniidi esinemist ega sünnitusjärgse sepsise, palaviku ja hüpertensiooni esinemissagedust. - 1 uuring (Amorim 1999) leidis, et kortikosteroide saanud naistel võib kergemini tekkida glükoosi intolerantsus (RR 2,71, CI 1,14-6,46, 1 uuring, 123 naist), (Uuringusse oli võetud patsiendid raske preeklampsiaga ja GTT teostati rohkem kui 72h peale glükokortikoidravi juhul kui nad ei olnud veel sünnitanud. Samas ei pruugi olla õige kohandada seda tulemust naistele ilma preeklampsiata. Lisaks ei ole teada, kas tulemit mõjutas ka see, et antud uuringus kasutati beetametasooni korduvat (nädalase intervalliga) ravikuuri. - Nii deksametasooni kui beetametasooni kasutamine vähendasid oluliselt üldist neonataalset suremust, RDS esinemist ja tserebroventrikulaarse hemorraagia esinemist. Beetametasoonravi (RR 0.56, CI 0.48-0.65, 14 uuringut, 2563 vastsündinut) andis parema ravitulemuse RDS osas	**at risk of preterm birth.** Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD004454. DOI: 10.1002/14651858.CD004454.pub2. Edited (no change to conclusions), comment added to review, published in Issue 3, 2013. (Ülevaateartikkel on publitseeritud küll 2006 aastal, mis ei mahu etteantud 5 aasta otsingupiiridesse, kuid kuna see on üks põhjapanevamaid ülevaateartikleid glükokortikoidide üldisest kasutamisest enneaegse sünnituse korral ning artikkel on uuendatud 2010 aastal, siis otsustasime selle ikkagi meie valimisse kaasata).

kui deksametasoonravi (RR 0.80, 95% CI 0.68 - 0.93, 6 uuringut, 1457 vastsündinut). Statistiliselt olulisi erinevusi ei leitud nende kahe ravimi puhul loote suremuse osas, sünnikaalu ega ka koorioamnioniidi esinemissageduse osas. Siiski deksametasoon suurendas sünnitusjärgse sepsise esinemissagedust (RR 1.74, 95%CI1.04 - 2.89, 4 uuringut, 536 naist), samas kui beetametasooni puhul seda ei täheldatud (RR 1.00, 95% CI 0.58 - 1.72, 4 uuringut, 467 naist).	
ACS enne 26. ras. näd: Ülevaade hõlmab 9 keskmise kuni hea kvaliteediga RCT (1118 vastsündinut). Ükski kaasatud uuringutest ei esitanud informatsiooni ACS toimest enne 26. ras. nädalat sündinud vastsündinute puhul, mistõttu otsest võrdlust hindamaks ACS kasu/kahju antud patsientide alagrupis ei saanud teha. Kasutati meta-regressiooni analüüsi ja meta-analüüsi, mis ei näidanud olulist statistilist erinevust neonataalse haigestumuse ja suremuse osas võrreldes ACS manustamist mitte manustamisega antud gestatsioonivanuses. - Autorid järeldasid, et pole piisavalt tõendusmaterjali toetamaks/ümberlükkamaks soovitust antenataalsete kortikosteroidide kasutamise kohta ähvardava enneaegse sünnituse korral enne 26. ras. nädalat.	Onland W1, de Laat MW, Mol BW, Offringa M. **Effects of antenatal corticosteroids given prior to 26 weeks' gestation: a systematic review of randomized controlled trials.** Am J Perinatol. 2011 Jan;28(1):33-44. doi: 10.1055/s-0030-1262509. Epub 2010 Jul 20.
Beetametasoon vs deksametasoon: Kaasatud olid 12 keskmise kvaliteediga RCT (1557 naist ja 1661 imikut). Võrreldi erinevaid kortikosteroide ja manustamisskeeme. - Deksametasooni kasutamist seostati olulise IVH riski vähenemisega (RR 0,44; 95% CI 0,21-0,92; 4 uuringut) beetametasooniga võrreldes, kuid RDS-i (RR 1,06; 95% CI 0,88-1,27; 5 uuringut) ega perinataalsete surmade (RR 1,41; 95% CI 0,54-3,67; 4 uuringut) osas ei leitud olulist statistilist erinevust. - Imikute teiseste tulemusnäitajate (nt Apgari skoor, sünnikaal, -pikkus, vasopressorite vajadus, BPD, NEK, ROP) osas olulisi erinevusi ei leitud. Ei ole andmeid hingamistoetuse vajaduse/kestuse ja surfaktantravi vajaduse osas. Intensiivraviosakonda hospitaliseerimistes üldiselt olulist erinevust ei leitud, kuid esines heterogeensus selle tulemusnäitaja osas. Ühes uuringus selgus, et deksametasoonile eksponeeritud imikute seas oli intensiivravi osakonnas viibimise aeg oluliselt lühem (MD 0,91 päeva; 95% CI -1,77 kuni -0,05; 70 imikut). - Emade tervisetulemite kohta uuringutes andmed puuduvad. Kaugtulemite osas on väga vähe andmeid. - Autorid järeldavad, et jääb ebaselgeks, kas eelistada üht kortikosteroidi teisele, kuigi deksametasoonil võib olla paar eelist beetametasooni ees. Deksametasooni kaugtulemite osas on vähem informatsiooni. Optimaalse raviskeemi osas järelduse tegemise jaoks on tõendusmaterjali vähe.	Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA. **Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth.** Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD006764. DOI: 10.1002/14651858.CD006764.pub3
Beetametasooni korduv ravikuur: Kaasatud oli 10 keskmise kuni kõrge kvaliteediga uuringut (4733 naist ja 5650 imikut). - Leiti, et korduva(te) doosi(de) manustamisel naistele, kel ähvardava enneaegse sünnituse risk püsib pärast 7 või enamat päeva peale esialgset kortikosteroidide manustamist, vähenes nende vastsündinutel RDS-i (RR 0,83; 95% CI 0,75-0,91; 8 uuringut; NNT 17) ja imiku raskete tervisetulemite (uuringutes erinevalt defineeritud; üldiselt kombineerituna neonataalne surm, RDS, 3.-4. astme IVH, periventrikulaarne leukomalaatsia, NEK, BPD)	Crowther CA, McKinlay CJD, Middleton P, Harding JE. **Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes.** Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD003935. DOI: 10.1002/14651858.CD003935.pub3

(RR 0,84; 95% CI 0,75-0,94; 7 uuringut; NNT 30) risk võrreldes korduva doosi manustamiseta. Statistiliselt olulist erinevust uuringugruppide vahel ei leitud raske ega kroonilise kopsuhaiguse, neonataalse suremuse ega IVH osas. Korduva(te) ravikuuri(de) manustamisel vähenes mehhaanilise ventilatsiooni (RR 0,84), lisahapniku (RR 0,92), surfaktandi (RR 0,78) ja inotroopide (RR 0,80) kasutamise vajadus. - Korduv(ad) ravikuur(id) seostusid keskmise sünnikaalu langusega (MD -75,79g; 9 uuringut), kuid gestatsiooniajaga korreleeritud sünnikaalude osas erinevust ei leitud. - Varase lapseea primaarsete tervisetulemite (surmad, elu ilma ühegi/tõsise puudeta, puude esinemine) ja sekundaarsete tervisetulemite (areng, kurtus, pimedus, tserebraalparalüüs, kasvamine) osas statistilisi erinevusi uuringugruppide vahel ei esinenud. - Emadel koorioamnioniidi ja sünnitusjärgse sepsise osas statistilist erinevust ei leitud. - Kaugtulemuste kohta uuringutes informatsiooni ei olnud. - **Vaid 3 uuringut käsitlesid ainult ühe korduva beetametasooni kuuri manustamist (kahes 12mg x 2 ja ühes uuringus 12mg x1). Võrreldes platseeboga esines vähenemine kombineeritud raskete tervisetulemite osas (erinetes uuringutes erinevalt defineeritud; RR 0,75), kuid olulist erinevust ei leitud RDS-i, IVH, suremuse, kroonilise kopsuhaiguse esinemise osas. Sünnikaalu osas ei leitud samuti olulist statistilist erinevust.** - Autorid järeldasid, et arvestades RDS-i ja tõsiste terviseprobleemide vähenemist peaks kaaluma korduvat ACS manustamist naistel, kes on saanud esialgse kortikosteroidide kuuri 7 või enam päeva varem, kuid kel endiselt esineb enneaegse sünnituse risk enne 34. rasedusnädalat. Korduvad ravikuurid seostuvad sünnikaalu vähese langusega. Naisi, kellele plaanitakse teha korduv ravikuur, tuleks nõustada kasu ja riskide osas ning teavitada, et hetkeinformatsioon kaugtulemuste osas on mõnevõrra limiteeritud. Kuniks on olemas selgem informatsioon optimaalse doosi ja manustamissageduse kohta, oleks mõistlik kasutada ühte käsitletud uuringutes kasu toonud raviskeemidest.	
Glükortikoidide korduvast manustamisest: Sissearvatud 11 RCT-s osales kokku 4390 naist ja 5227 vastsündinut. Uuringud võrdlesid beetametasooni korduvaid kuure ühekordse kuuriga. - MC (multiple courses) ravi seostus RDS ja PDA (patent ductus arteriosus) vähenemisega, surfaktantravi kasutamise ja hingamistoetuse vähenemisega, ka emapoolsete kõrvalnähtude vähenemisega, ning leiti trend madalama üldise neonataalse haigestumuse suunas. - Siiski, leiti ka, et MC seostus madalama sünnikaalu ja pea ümbermõõduga ning oli trend suurenenud vajaduse järgi postnataalsete steroidide kasutamise osas ning tõusnud koorioamnioniidi esinemissageduse suunas. - MC ja esmase ACS kuuri kasutamise korral ei leitud statistilist erinevust järgnevate seisundite osas: raske RDS, BPD, IVH, raske IVH, periventrikulaarne leukomalaatsia, neonataalne sepsis, NEC, ROP, perinataalne suremus, üldine neonataalne haigestumine korrigeeritus gestatsioonivanuse järgi, endometriit, gestatsioonivanus sünnitusel. - Kokkuvõtlikult: Korduvad ravikuurid ei anna lisakasu kombineeritud neonataalse haigestumise osas, isegi kui see	E Bevilacqua, R Brunelli, M Anceschi. **Review and meta-analysis: Benefits and risks of multiple courses of antenatal corticosteroids.** 2010. The Journal of Maternal-Fetal and Neonatal Medicine.

on seotud mõningase lühiajalise kasuga (nt. RDS, PDA vähenemine, surfaktantravi ja hingamistoetuse vajaduse vähenemine). Puuduvad teadmised MC kasutamise kaugtulemuste ohutuse osas.	
Glükortikosteroide korduvast manustamisest: - Süstemaatiline ülevaateartikkel ja meta-analüüs, mis hõlmas 8 platseebo-kontrollitud topelt-pimedat randomiseeritud uuringut, kus teine doos glükokortikosteroidi manustati vähemalt 7 päeva peale I ravikuuri. Kõigis meta-analüüsis kasutatud uuringutes oli glükokortikosteroidiks beetametasoon. - Korduv beetametasooni kuur (nii üks lisaannus kui ka nädalase või kahenädalase intervalliga korratud annused) vähendas RDS esinemissagedust (RR0,85, CI 0,77-0,93). - Intrauteriinne kasvupeetus esines neil enneaegsetel vastsündinutel, kes olid eksponeeritud nädalase või kahenädalase intervalliga beetametasooni ravikuuridele. Lisaks esines sellistel lastel ka peaümbermõõdu ning sünnipikkuse vähenemist võrreldes kontrollgrupiga. - Ühekordne lisakuur ei mõjutanud loote kasvu. Lisadoosi kasulikkust hinnati ühes kohortuuringus, kus leiti, et lisadoos manustatuna 24h enne sünnitust vähendab RDS esinemissagedust vastsündinutel gestatsioonieas 28-34 nädalat. Samas leiti ühes randomiseeritud uuringus, et lisadoos kasuefekti ei anna ja hoopiski võib raske RDS esinemissagedus tõusta, kui ravim on manustatud vähem kui 24h enne sünnitust. Kahe hiljutisemalt (2009 ja 2010) publitseeritud randomiseeritud uuringu põhjal üks täielik korduskuur (BM 12mg x2 24h intervalliga või DM 6mgx4 12h intervalliga) oluliselt vähendas RDS esinemissagedust ja lisahapniku vajadust. - Kokkuvõtlikult: ühekordne BM lisakuur võib olla efektiivne RDS preventsioonis, kui ajastus on õige (24h enne sünnitust). Olemasolevate andmete põhjal nädalase intervalliga korduvaid BM ravikuure ei soovitata.	OUTI M. PELTONIEMI, M. ANNELI KARI, MIKKO HALLMAN, **Repeated antenatal corticosteroid treatment: a systematic review and meta-analysis**, 13 March 2011 DOI: 10.1111/j.1600-0412.2011.01132.x
Glükokortikoidide kõrvaltoimetest: - Eesmärk: uurida sünteetilise glükokortikoidravi seoseid sünnikaalu, pea ümbermõõdu ja sünnipikkusega. Sisse arvati 17 uuringut, mis hõlmasid nii dexametasooni kui betametasooni kasutamist, nii ühekordset kui korduvaid kuure. 17 artiklist kõik uurisid sünnikaalu, 9 pea ümbermõõtu, 4 sünni pikkust, ja 1 ponderaalindeksit (ponderal index). Kogu valim oli 27 760 inimest sünniaastatega 1988-2006. - Sünnikaal – gestatsioonivanust arvesse võttes leidis 10 katset 17st statistiliselt tähendusliku sünnikaalu vähenemise glükokortikoidravi saanud vastsündinutel (vahemikus 12 kuni 332 g). Tulemuste erinevuse potentsiaalseks põhjuseks arvatakse uurimuste vahelised metodoloogilised erinevused (erinevus ravimi doosis, stratifikatsioon gestatsioonivanuses ja mõjutavate faktorite arvstamises). - Pea ümbermõõt – 5 uuringut 9st leidsid seose väiksema pea ümbermõõdu ja ravi vahel (0.023 – 1.02 cm). Pea ümbermõõdu juures ei arvestanud ükski katse sünniviisi (mõjutab pea kuju). - (Kõrvalmärge: antud ülevaate puuduseks peaks seda, et kõrvaltoimete esinemissagedus ei ole välja toodud doosipõhiselt).	AA Khan, A Rodriguez, M Kaakinen et al., **Does in utero exposure to synthetic glucocorticoids influence birthweight, head circumference and birth length?** A systematic review of current evidence in humans. 2010. Paediatric and Perinatal Epidemiology.
Glükokortikoidide kasutamine SGA/IUGR loodete korral.	Amiya RM, Mlunde LB, Ota E, Swa T, Oladapo OT, Mori R. Antenatal

Süstemaatiline ülevaade ja meta-analüüs, mis hõlmas endas 8 madala või väga madala kvaliteediga uuringut, kokku 2846 ema/loodet. From the available studies, administration of ACS to growth-restricted preterm infants did not improve neonatal mortality or morbidity, though some positive effects in terms of childhood health status were observed. In particular, meta-analysis revealed no reduction in RDS incidence or incidence of major brain lesion after ACS therapy in growth-restricted infants. As far as follow-up into childhood, a reduction in handicaps has been reported in steroid-treated growth-restricted infants at two years of age . However, data on such risk into school age is lacking from this cohort, while no differences were observed in behaviour among ACS-treated infants followed into school age and physical growth below the 10th percentile was significantly more frequent in the treatment group. Given the chronic intrauterine stress to which the growth-restricted infant has already been subjected and the prolonged stimulation of the adrenal gland thus stimulated, intrauterine growth restriction itself may effectively lead to enhanced fetal lung maturation as well as accelerated development of the central nervous system. Through such stabilizing mechanisms, growth-restricted infants as a group may have a lower baseline susceptibility to morbidities like RDS and brain lesions, as a result of which exogenous corticosteroid administration in this particular group may have no additional benefit, at least in the short term. In this review, we found an improvement in major brain lesions among SGA infants—a trend not identified in the previous review by Torrance et al. However, overall, the benefit of ACS therapy in SGA infants remains unclear from our review of the current literature, possibly due to heterogeneity in the populations and treatment regimens studied. Namely, as the included studies on SGA infants did not report whether cases were examined for signs of placental insufficiency (as indicated by abnormal umbilical blood flow Doppler studies and/or placental pathology), a heterogeneous SGA/growth-restricted population is likely in this evidence. Moreover, two of the designated SGA studies did not strictly define the type of steroid treatment used or designate completion of ACS therapy as a requirement for inclusion in the treatment group. Overall, there is thus insufficient evidence to conclude on the benefits or harms of ACS therapy in women whose infants were growth-restricted in-utero or who are likely to deliver SGA preterm infants. Routine use of ACS in growth-restricted infants should thus be re-evaluated, as the potential detrimental side effects of steroids on growth are specifically unwarranted in this already growth-restricted group. An RCT is merited to clarify whether treatment brings any added benefit in growth-restricted infants and to address further questions regarding ACS treatment of SGA infants.	Corticosteroids for Reducing Adverse Maternal and Child Outcomes in Special Populations of Women at Risk of Imminent Preterm Birth: A Systematic Review and Meta-Analysis. PloS One. 2016;11(2):e0147604

Ravijuhendid

Kokkuvõte ravijuhendites leiduvast: Viimase 10 aasta ravijuhenditest leidsime 5 antud kliinilist küsimust käsitlevat ravijuhendit. Soovitused ravijuhendite põhjal: • Ühekordset antenataalsete kortikosteroidide (ACS) kuuri tuleks pakkuda naistele

ähvardava enneaegse sünnituse puhul raseduse kestuses 23/24 nädalat kuni 34+6 nädalat (gestatsiooniaeg erinevates ravijuhendites varieerub).

- Tõendusmaterjal ACS kasutamise kohta alla 26 GN ja üle 34 GN on madalam, mistõttu soovitus kasutada ACS nende raseduse kestuste korral on nõrgem.
- Kortikosteroidide manustamine on efektiivne ka juhul, kui sünnitus leiab aset varem kui 24 h peale I doosi kortikosteroidi manustamist.
- Ravimitest sobivad antenataalseks loote kopsude ettevalmistuseks nii beetametasoon kui ka deksametasoon. Raviskeemid: beetametasoon 12 mg i/m 2 doosi 24 h intervalliga või deksametasoon 6 mg i/m 4 doosi 12 h intervalliga.
- Korduvaid ravikuure rutiinselt kasutada ei soovitata, küll aga võiks 2 ravijuhendi põhjal kaaluda ühekordse lisakuuri manustamist, kui enneaegse sünnituse risk püsib 7 või rohkem päeva pärast I kuuri manustamist ja I kuur on manustatud enne 26 rasedusnädalat.
- Korduva ravikuuri kaalumisel tuleb arvesse võtta: gestatsiooniaega, tõenäosust sünnitada järgneva 48 h jooksul, ajaintervalli eelmisest ACS kuurist.

Kokkuvõte ravijuhendist	**Viide kirjandusallikal**
RCOG juhend ACS kohta (ACRNMM_2010): AGREE tööriistaga hindamise põhjal hea kvaliteediga ravijuhend (76 punkti 100-st, hinnatud 3 sekretariaadi liikme poolt). - Antenataalse kortikosteroidide (ACS) manustamine on seotud neonataalsete surmade, RDS-i ja IVH olulise vähenemisega ja on ema jaoks ohutu (hinnatud Grade järgi – Grade A) - ACS kuuri tuleks pakkuda naistele ähvardava enneaegse sünnituse puhul raseduse kestuses 24+0 kuni 34+6 (A). ACS kasutamist raseduse kestuses 23+0 kuni 23+6 võib kaaluda (C), kuid see otsus tuleks sel puhul teha kõrgemal tasemel võttes arvesse kõiki kliinilisi aspekte. - ACS on RDS-i vähendamise suhtes kõige efektiivsemad, kui sünnitus leiab aset 24 h kuni 7 päeva pärast 1. doosi ACS manustamist (A). ACS vähendavad neonataalsete hukkude esinemist ka manustamisele järgneva 24 h sees, mistõttu neid tuleks anda ka sel juhul, kui eeldatakse, et sünnitus toimub selle aja jooksul (A). - Ühekordset ACS kuuri ei seostata ühegi olulise lähituleviku kahjuliku toimega ema ega loote tervisele (A). Tõendusmaterjal ühekordse ACS kuuri kasude ja kahjude kohta pikas ajaperspektiivis ei näita selgeid erinevusi neuroloogiliste ja kognitiivsete kõrvalmõjude kohta (A). Pikemaajaliste efektide kohta on siiani tõendusmaterjali vähe (A). - Loote kopsude ettevalmistuse valikravimiteks ja -skeemideks on 2 doosi BM 12 mg i/m või 4 doosi DM 6 mg i/m (A). - Nädalase intervalliga korratud ACS kuurid vähendavad neonataalsete hingamishäirete esinemist ja raskust, kuid lühiaegsed kasud on seotud sünnikaalu ja pea ümbermõõdu vähenemisega, mistõttu seesugust skeemi ei soovitata (A). Ravijuhendi koostajad arvavad, et ühekordset lisakuuri (kaks doosi 12 mg beetametasooni) peaks kaaluma ettevaatlikkusega kõrgemal tasemel raseduste korral, mil esialgne ACS kuur tehti enne 26+0 gestatsioonivanust, kuid hilisemas raseduse kulus tekib uus näidustus ACS manustamiseks.	**2010 Antenatal corticosteroids to reduce neonatal morbidity and mortality.** Greentop Guideline no 7. London: Royal College of Obstetricians and Gynaecologists. Available at www.rcog.org.uk (Accessed on February 18, 2015)
ICSI juhend sünnituse kohta (MOL_2011): AGREE tööriistaga hindamisel saanud üsna madala punktiskoori - rahuldav kvaliteet (64 100-st; hinnatud 4 sekretariaadi	Creedon D, Akkerman D, Atwood L, Bates L, Harper C, Levin A, McCall C, Peterson D, Rose C, Setterlund

liikme poolt) tingituna puudustest koostamise täpsuses ja rakendatavuses. -Soovitatakse kasutada ACS gestatsiooniajas 23-34. -Tavaskeem: BM 12 mg i/m 2 doosi 24 h intervalliga. Alternatiivina tuuakse välja DM 24 mg (tavaliselt 6 mg i/m 4 doosi 12 h intervalliga). -ACS lisakuure ei soovitata. -ACS efekt on suurim, kui ravi algusest on möödas vähemalt 24 h. Samas tuleks ACS manustada ka siis, kui võib eeldada, et sünnitus leiab aset lähema 24 h jooksul 1. doosi manustamisest, kuna ACS võivad siiski tervisetulemit parandada.	L, Walkes B, Wingeier R. **Institute for Clinical Systems Improvement. Management of Labor.** Updated March 2013.
Queensland'i juhend enneaegse sünnituse kohta (PL_Aus_2014): AGREE tööriistaga hinnates sai see 74 punkti 100-st (hinnatud 3 sekretariaadi liikme poolt)- hea kvaliteet. Soovitused: • Soovitus rutiinselt kasutada antenataalselt kortikosteroide enneaegse sünnituse riski korral gestatsiooniajas **alla 35+0 nädala.(Soovitus põhineb RCOG-i ACRNMM_2010 juhendil)** • Tee kindlaks korduva kuuri vajadus lähtudes enneaegse sünnituse jätkuvast riskist. Kui enneaegse sünnituse risk püsib 7 või rohkem päeva peale I kuuri manustamist, siis on soovitav teostada korduskuur. • Kui emal on diabeet, siis monitoorida glükoosi taset veres. Manustamine: • Kortikosteroidide algne kuur: (2 doosi, 24h intervalliga) o I doos: Beetametasoon 11.4 mg IM o II doos: Beetametasoon 11.4 mg IM, 24 tundi peale I doosi. (Kui kahtus enneaegsele sünnitusele järgneva 24h jooksul, siis II doos manustada 12h möödudes). • Antenataalse kortikosteroidi korduskuur (1 doos): Beetametasoon 11.4 mg IM.	**Queensland Clinical Guidelines, Preterm labour and birth**, December 2014 MN14.6-V5.R19
Euroopa RDS juhend: AGREE tööriistaga hinnates saanud 82 punkti 100-st - hea kvaliteediga ravijuhend. -Clinicians should offer a single course of prenatal corticosteroids to all women at risk of preterm delivery from **about 23 weeks up to 34 completed weeks' gestation (A).** *Ei selgu, millel põhineb soovitus gestatsiooniaja alumise piiri kohta.* -A second course of antenatal steroids may be appropriate if the first course was administered **more than 2–3 weeks earlier and the baby is <33 weeks' gestation when another obstetric indication arises (A).** *Soovitus lähtub ilmselt uuringul, mille põhjal 2 nädalat pärast ACS manustamist soodne efekt väheneb/kaob, kuid ei selgu täpselt, millel põhineb lisamanustamine kuni 33. GN.* Prenatal steroids given to women with anticipated preterm delivery reduce the risk of neonatal death (RR 0.55; 95% CI 0.43–0.72; NNT= 9), and the use of a single course of prenatal corticosteroids does not appear to be associated with any significant maternal or short-term fetal adverse effects (Roberts et al). Prenatal steroids decrease the risk of RDS and additionally decrease the risk of intraventricular haemorrhage and NEC (Roberts et al). Prenatal corticosteroid	Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, Saugstad OD, Simeoni U, Speer CP, Vento M, Halliday HL; European Association of Perinatal Medicine. **European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants**--2013 update. Neonatology. 2013;103(4):353-68. doi: 10.1159/000349928. Epub 2013 May 31.

therapy is recommended in all pregnancies with threatened preterm labour below 34 weeks' gestation. In pregnancies delivering between 34 and 36 weeks prenatal steroids do not appear to improve outcome (Porto et al). The optimal treatment to delivery interval is more than 24 h and less than 7 days after the start of steroid treatment (Roberts et al). Beyond 14 days after administration the benefits of antenatal steroids are diminished (Gyamfi-Bannerman et al). **A single repeat course** of antenatal betamethasone given a week after the first course to women with threatened preterm labour reduces RDS and other short-term health problems, although birth weight is reduced (Crowther et al). Effects of multiple courses of steroids on fetal growth have raised concerns about recommending more than a single additional rescue course until further long-term studies are completed (Peltoniemi et al). *Jääb arusaamatuks, kuidas tehakse A taseme soovitus ühekordse lisaannustamise kohta, kui tõendusmaterjal, millel see baseerub, ei anna ühest kindlat vastust ainult ühe lisadoosi manustamise kohta.*	
RCOG-i ravijuhend (PPROM 2010) - hea kvaliteediga ravijuhend (AGREE 78 punkti 100-st, hinnatud 3 inimese poolt). • Enneaegse lootevee puhkemise (PPROM) korral tuleks manustada antenataalseid kortikosteroide. (A)	**2010 Preterm Prelabour Rupture of Membranes.** Greentop Guideline no 44. London: Royal College of Obstetricians and Gynaecologists. Available at www.rcog.org.uk (Accessed on February 18, 2015)
NICE ravijuhend (2015) – väga hea kvaliteediga (AGREE 98 punkti, 3 hindajat): - For women between **23+0 and 23+6** weeks of pregnancy who are in suspected or established preterm labour, are having a planned preterm birth or have P-PROM, **discuss with the woman** (and her family members or carers as appropriate) the use of maternal corticosteroids in the context of her individual circumstances. - **Consider** maternal corticosteroids for women between **24+0 and 25+6** weeks of pregnancy who are in suspected or established preterm labour, are having a planned preterm birth or have P-PROM. - **Offer** maternal corticosteroids to women between **26+0 and 33+6** weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have P-PROM. - **Consider** maternal corticosteroids for women between **34+0 and 35+6** weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have P-PROM. - When offering or considering maternal corticosteroids, discuss with the woman (and her family members or carers as appropriate): how corticosteroids may help; the potential risks associated with them. Soovitused põhinevad: a Cochrane review (SR) and meta-analysis (Roberts 2013) and 1 RCT (Porto 2011) from Brazil. **Korduv manustamine:** There was sufficient evidence of benefit without concomitant harm to justify a strong recommendation for the use of corticosteroids in women who are thought to be in spontaneous preterm labour, having planned a preterm birth or have preterm prelabour rupture	

of membranes **between 26 and 34 weeks' gestation.** The Guideline Development Committee concluded that **some of these benefits would be seen in babies born at lower and higher gestational ages, but that the evidence was less robust at these gestations**. The extrapolation of findings to groups outside the gestational age range of 26–34 weeks was more complex in terms of clinical effectiveness, which warranted **less strong recommendations at gestations below 26 weeks and above 34 weeks.** **Korduv manustamine:** - **Do not routinely offer repeat courses** of maternal corticosteroids, **but take into account:** ▪ the interval since the end of last course ▪ gestational age ▪ the likelihood of birth within 48 hours. Korduva manustamise soovitus põhineb: an SR of 10 RCTs (Crowther 2013), an RCT (Atarod 2014) and a 5-year follow-up study (Asztalos 2013) of an RCT (Murphy 2008) already included in the SR (Crowther 2013). Based on the evidence reviewed, the committee concluded that **there was insufficient evidence of benefit to support a recommendation that courses of steroids should be repeated routinely**, but that this should not rule out the judicious use of repeat courses of corticosteroids in circumstances where clinical judgement suggested that it might be beneficial given the lack of clear evidence that such practice would cause harm. Decisions should be based upon gestation, likelihood of imminent birth and time period since the last course of steroids.	

Randomiseeritud kontrollitud uuringud

Otsisime lisaks viimase 5 aasta RCT, mis võrdleksid beetametasooni erinevaid manustamisskeeme (*ühekordne (24 mg × 1) võrreldes kahekordne (12 mg × 2) võrreldes neljakordne doos (6 mg × 4))*, kuid Pubmed-ist selliseid uuringuid ei leidnud.

Viimase 5 aasta RCT, mis ei ole hõlmatud ülevaadetesse:

Kokkuvõte RCT-st	**Viide kirjandusallikale**
OBJECTIVE: **To determine the effects of single vs multiple courses of antenatal corticosteroid therapy on death or neurodevelopmental disability (neuromotor, neurosensory, or neurocognitive/neurobehavioral function) at 5 years of age in children** whose mothers participated in MACS. Our secondary aims were to determine the effect on height, weight, head circumference, blood pressure, intelligence, and specific cognitive (visual, spatial, and language) skills. DESIGN, SETTING, AND PARTICIPANTS: Cohort follow-up study of children seen between June 2006 and May 2012 at 55 centers. In total, 1724 women (2141 children) were eligible for the study, of whom 1728 children (80.7% of the 2141 eligible children) participated and 1719 children contributed to the primary outcome. INTERVENTION: Single and multiple courses of antenatal corticosteroid therapy. MAIN OUTCOMES AND MEASURES: The primary outcome was death or survival with a neurodevelopmental disability in 1 of the following domains: neuromotor (nonambulatory cerebral palsy), neurosensory (blindness, deafness, or need for visual/hearing aids), or	Asztalos EV1, Murphy KE, Willan AR, Matthews SG, Ohlsson A, Saigal S, Armson BA, Kelly EN, Delisle MF, Gafni A, Lee SK, Sananes R, Rovet J, Guselle P,Amankwah K, Saleem M, Sanchez J; MACS-5 Collaborative Group. **Multiple courses of antenatal corticosteroids for preterm birth study: outcomes in children at 5 years of age (MACS-5).** JAMA Pediatr. 2013 Dec;167(12):1102-10. doi:

neurocognitive/neurobehavioral function (abnormal attention, memory, or behavior). RESULTS: There was no significant difference between the groups in the risk of death or neurodevelopmental disability: 217 of 871 children (24.9%) in the multiple-courses group vs 210 of 848 children (24.8%) in the single-course group (odds ratio, 1.02 [95% CI, 0.81 to 1.29]; P = .84). CONCLUSIONS AND RELEVANCE: **Multiple courses, compared with a single course, of antenatal corticosteroid therapy did not increase or decrease the risk of death or disability at 5 years of age.** Because of a lack of strong conclusive evidence of short-term or long-term benefits, it remains our opinion that multiple courses not be recommended in women with ongoing risk of preterm birth.	10.1001/jamapediatrics.2013.2764.
OBJECTIVE: To estimate the effect of multiple courses of antenatal corticosteroids on neonatal size, controlling for gestational age at birth and other confounders, and to determine whether there was a dose-response relationship between number of courses of antenatal corticosteroids and neonatal size. **METHODS:** This is a secondary analysis of the Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study, a double-blind randomized controlled trial of single compared with multiple courses of antenatal corticosteroids in women at risk for preterm birth and in which fetuses administered multiple courses of antenatal corticosteroids weighed less, were shorter, and had smaller head circumferences at birth. All women (n=1,858) and children (n=2,304) enrolled in the Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study were included in the current analysis. Multiple linear regression analyses were undertaken. **RESULTS:** Compared with placebo, neonates in the antenatal corticosteroids group were born earlier (estimated difference and confidence interval [CI]: -0.428 weeks, CI -0.10264 to -0.75336; P=.01). Controlling for gestational age at birth and confounding factors, multiple courses of antenatal corticosteroids were associated with a decrease in birth weight (-33.50 g, CI -66.27120 to -0.72880; P=.045), length (-0.339 cm, CI -0.6212 to -0.05676]; P=.019), and head circumference (-0.296 cm, -0.45672 to -0.13528; P<.001). For each additional course of antenatal corticosteroids, there was a trend toward an incremental decrease in birth weight, length, and head circumference. **CONCLUSION: Fetuses exposed to multiple courses of antenatal corticosteroids were smaller at birth. The reduction in size was partially attributed to being born at an earlier gestational age but also was attributed to decreased fetal growth. Finally, a dose-response relationship exists between the number of corticosteroid courses and a decrease in fetal growth. The long-term effect of these findings is unknown.**	Murphy KE1, Willan AR, Hannah ME, Ohlsson A, Kelly EN, Matthews SG, Saigal S, Asztalos E, Ross S, Delisle MF, Amankwah K, Guselle P, Gafni A, Lee SK,Armson BA; Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study Collaborative Group. **Effect of antenatal corticosteroids on fetal growth and gestational age at birth.** Obstet Gynecol. 2012 May;119(5):917-23. doi: 10.1097/AOG.0b013e31825189dc.
OBJECTIVE: A single course of antenatal corticosteroids (ACS) is associated with a reduction in respiratory distress syndrome and neonatal death. Multiple Courses of Antenatal Corticosteroids Study (MACS), a study involving 1858 women, was a multicentre randomized placebo-controlled trial of multiple courses of ACS, given every 14 days until 33+6 weeks or birth, whichever came first. The primary outcome of the study, a composite of neonatal mortality and morbidity, was similar for the multiple ACS and placebo groups (12.9% vs. 12.5%), but infants exposed to multiple courses of ACS weighed less, were shorter, and had smaller head circumferences. Thus for women who remain at increased risk of preterm birth, multiple courses of ACS (every 14 days) are not recommended. Chronic use of corticosteroids is associated with numerous side effects including weight gain and depression. **The aim of this postpartum assessment was to ascertain if multiple courses of ACS were associated with maternal side effects.** **METHODS:** Three months postpartum, women who participated in MACS were asked to complete a structured questionnaire that asked about maternal side effects of corticosteroid use during MACS and included the Edinburgh Postnatal Depression Scale. Women were also asked to evaluate their study participation. **RESULTS:**Of the 1858 women randomized, 1712 (92.1%) completed the postpartum questionnaire. There were no significant differences in the risk of maternal side effects between the two groups. Large numbers of	Murphy KE1, Hannah ME, Willan AR, Ohlsson A, Kelly EN, Matthews SG, Saigal S, Asztalos E, Ross S, Delisle MF, Tomat L, Amankwah K, Guselle P, Gafni A,Lee SK, Armson BA; MACS Collaborative Group. **Maternal side-effects after multiple courses of antenatal corticosteroids (MACS): the three-month follow-up of women in the randomized controlled trial of MACS for preterm birth study.** J Obstet Gynaecol Can. 2011 Sep;33(9):909-21.

women met the criteria for postpartum depression (14.1% in the ACS vs. 16.0% in the placebo group). Most women (94.1%) responded that they would participate in the trial again. **CONCLUSION:** In pregnancy, corticosteroids are given to women for fetal lung maturation and for the treatment of various maternal diseases. In this international multicentre randomized controlled trial, **multiple courses of ACS (every 14 days) were not associated with maternal side effects,** and the majority of women responded that they would participate in such a study again.	
OBJECTIVE: To determine the effect of repeated antenatal corticosteroids on postnatal changes in weight, linear growth and head circumference. **METHODS:** Mothers who entered the repeated dose of antenatal steroids (ACTORDS) trial were randomised to additional weekly steroid or placebo. Infant occipital-frontal head circumference, weight and crown-heel length were measured at birth and weekly for 4 weeks or until discharge, whichever was later. Lower leg length was measured using a knemometer daily for the first week, then thrice weekly. **RESULTS:** Of 145 babies studied (77.5% of the ACTORDS study infants from this centre), 70 were exposed to repeated antenatal steroids and 75 to placebo. There were no significant differences in prerandomisation demographic and pregnancy data. The mean gestational age at ACTORDS entry was 28.7 weeks and at birth was 31.4 weeks. The mean birth weight was 1618 g. There were no significant differences in postmenstrual age, weight, length or head circumference, nor in z-scores for these measurements, at birth, 4 weeks or discharge. **In the first 2 weeks after birth, babies in both groups showed a decrease in z-scores for weight and length. After week 2, growth improved in both groups but babies exposed to repeat antenatal corticosteroids grew more rapidly,** as measured by weight gain, increasing head circumference and increasing lower leg length knemometry. This rapid growth was most apparent around weeks 3-5 after birth. **CONCLUSION: Babies exposed to weekly doses of repeat antenatal corticosteroids demonstrate postnatal growth acceleration 3-5 weeks after birth.**	**Battin M1, Bevan C, Harding J.** **Growth in the neonatal period after repeat courses of antenatal corticosteroids: data from the ACTORDS randomised trial.** Arch Dis Child Fetal Neonatal Ed. 2012 Mar;97(2):F99-105. doi: 10.1136/adc.2011.211318. Epub 2011 Jul 27.
OBJECTIVES: To determine the effectiveness of corticosteroids in reducing respiratory disorders in infants born at 34-36 weeks' gestation. Design Randomised triple blind clinical trial. Setting A large tertiary teaching hospital in northeast of Brazil. Participants Women at 34-36 weeks of pregnancy at risk of imminent premature delivery. Interventions Betamethasone 12 mg or placebo intramuscularly for two consecutive days. Main outcomes measures Primary outcome was the incidence of respiratory disorders (respiratory distress syndrome and transient tachypnoea of the newborn). Secondary outcomes included the need for ventilatory support, neonatal morbidity, and duration of stay in hospital. **RESULTS:** 320 women were randomised, 163 of whom were assigned to the treatment group and 157 to the controls. Final analysis included 143 and 130 infants, respectively. **The rate of respiratory distress syndrome was low (two (1.4%) in the corticosteroid group; one (0.8%) in the placebo group; P = 0.54), while the rate of transient tachypnoea was high in both groups (34 (24%) v 29 (22%); P = 0.77). There was no reduction in the risk of respiratory morbidity with corticosteroid use even after adjustment for subgroups of gestational age (34-34(+6) weeks, 35-35(+6) weeks, and ≥ 36 weeks).** The adjusted risk of respiratory morbidity was 1.12 (95% confidence interval 0.74 to 1.70). The need for ventilatory support was around 20% in both groups. There was no difference in neonatal morbidity (88 (62%) v 93 (72%); P = 0.08) or in the duration of stay in hospital between the two groups (5.12 v 5.22 days; P = 0.87). Phototherapy for jaundice was required less often in babies whose mothers received corticosteroids (risk ratio 0.63, 0.44 to 0.91). **CONCLUSIONS: Antenatal treatment with corticosteroids at 34-36 weeks of pregnancy does not reduce the incidence of respiratory disorders in newborn infants.**	Porto AM1, Coutinho IC, Correia JB, Amorim MM. **Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial.** BMJ. 2011 Apr 12;342:d1696. doi: 10.1136/bmj.d1696.

LISAMATERJAL/ EELNEVAST MATERJALIST VÄLJA TOODUD INFORMATSIOON KONKREETSE TEEMA KOHTA:

ACS manustamine raseduse kestuses 22.-26. GN:

Cochrane süstemaatiline ülevaade: RDS is reduced when corticosteroids are first given at **26** to 29.9 weeks, 30 to 32.9 weeks and 33 to 34.9 weeks. Furthermore, both cerebroventricular haemorrhage and neonatal death are reduced at **26** to 29.9 weeks. **No difference is shown for primary outcomes at gestational ages of less than 26 weeks.** While eight trials included in this review recruited pregnancies from less than 26 weeks' gestation, and a further three did not specify the lower gestational age for entry, **only one trial (n = 49 infants) contributed data to this review at this extreme gestation.** Autorite järeldus: There is evidence to suggest benefit across a wide range of gestational ages from **26 to 34+6** weeks.	Roberts D, Dalziel SR. **Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth.** Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD004454. DOI: 10.1002/14651858.CD004454.pub2. Edited (no change to conclusions), comment added to review, published in Issue 3, 2013.
Süstem. ülevaade: There is **no evidence** from randomized controlled trials showing beneficial effects of corticosteroid-treatment to women with threatened preterm labour **prior to 26 weeks** gestation. All recent practice guidelines that we found, distinctly recommend the administration of antenatal corticosteroids to mothers with threatened preterm delivery from 24 weeks gestational age onwards. However, none of these guidelines provide sufficient supporting evidence for this recommendation.	Onland W1, de Laat MW, Mol BW, Offringa M. **Effects of antenatal corticosteroids given prior to 26 weeks' gestation: a systematic review of randomized controlled trials.** Am J Perinatol. 2011 Jan;28(1):33-44. doi: 10.1055/s-0030-1262509. Epub 2010 Jul 20.
RCOG juhend: The data are strongest for gestations between 26+0 and 34+6 weeks. The data for pregnancies between 24+0 and 26+0 weeks of gestation are scarce, with only one trial (49 infants) contributing data to the Cochrane review. **(Roberts et al. 2006. Evidence level 1++)** The conclusion of the authors of the Cochrane review and the ACOG Committee opinion (2008) is that, despite the paucity of data at earlier gestations, the reduction in outcomes other than RDS at 26+0 weeks of gestation would **suggest that there is some benefit in corticosteroid prophylaxis at earlier gestations between 24+0 and 26+0 weeks. (Evidence level 4)** In a **prospective cohort** of 4446 infants between **22+0 and 25+0** weeks of gestation, multivariable analyses showed that those who received intensive care, were exposed to antenatal corticosteroids, were of female sex, were from singleton pregnancies, and of higher birth weight (per each 100g increment) had a **reduced risk of death**. Among survivors, the risk of death, or profound or any neurodevelopmental impairment at 18–22 months corrected age, was reduced. These reductions were similar to those associated with a 1-week increase in gestational age. **(Tyson et al., 2008. Evidence level 2+)** A **retrospective cohort study** on 181 infants born at **23 weeks** of gestation revealed that those exposed to antenatal corticosteroids had **decreased odds of death** (OR 0.32, 95% CI 0.12–0.84), with no significant differences in the occurrence of necrotising enterocolitis among survivors (15.4% compared with 28.6%, P=0.59) or severe intraventricular hemorrhage (23.1% compared with 57.1%, P=0.17). Only a complete course of corticosteroids was associated with a decreased odds of death (OR 0.18, 95% CI 0.06–0.54). The study	2010 **Antenatal corticosteroids to reduce neonatal morbidity and mortality.** Greentop Guideline no 7. London: Royal College of Obstetricians and Gynaecologists. Available at www.rcog.org.uk (Accessed on February 18, 2015)

concluded that neonates at 23 weeks of gestation whose mothers completed a course of antenatal corticosteroids had an associated 82% reduction in odds of death. **(Hayes et al., 2008. Evidence level 2-)** Evidence from the EPICure study, a **prospective cohort study**, showed that of 283 babies born at **less than 26+0 weeks** of gestation assessed at 2.5 years and 241 assessed at 6 years, antenatal corticosteroids was associated with an **increased mental development index. (Costeloe et al., 2006. Evidence level 2+)** **Trial data are scanty for pregnancies at the extreme of prematurity. Obstetricians currently have the discretion to administer steroids before the 24th week of pregnancy, but the whole clinical picture needs to be taken into account with respect to intact survival data as well as the chance of any survival based on antenatal assessment of viability at these extremes (e.g. by estimation of fetal weight). In this context, we have advised caution and discussion at senior level prior to considering antenatal corticosteroid administration at 23+0 to 23+6 weeks of gestation.**	
Queenslandi ravijuhend eluvõimelisuse piiri kohta: Recommend corticosteroids to women who are at risk of preterm birth **where life sustaining interventions are planned or may be a possibility** **•Not indicated if birth is imminent at < 23+0 weeks** • If life sustaining interventions are to be initiated only if a specific gestational age achieved, (e.g. only if gestation reaches 24 weeks) then administer corticosteroids prior to the specified gestation (i.e. don't wait until 24 weeks+0 days) • Inform the family that administration does not oblige or necessarily equate to a final decision for life sustaining interventions	Queensland Clinical Guideline: **Perinatal care at the threshold of viability; 2014**
Šveitsi ravijuhend eluvõimelisuse piiri kohta: In the presence of threatened preterm delivery, foetal lung maturation should be accelerated **as early as 24 0/7 weeks of gestation** with a single course of 2 doses of betamethasone 12 mg i.m. 24 hours apart. **In certain situations, acceleration of foetal lung maturation can be started a few days earlier, but not before 23 0/7 weeks.** As an exception, a second course can be administered if the first two doses of betamethasone have been given very early and the risk of preterm delivery has again increased.	Berger TM1, Bernet V, El Alama S, Fauchère JC, Hösli I, Irion O, Kind C, Latal B, Nelle M, Pfister RE, Surbek D, Truttmann AC, Wisser J, Zimmermann R. **Perinatal care at the limit of viability between 22 and 26 completed weeks of gestation in Switzerland. 2011 revision of the Swiss recommendations.** Swiss Med Wkly. 2011 Oct 18;141:w13280. doi: 10.4414/smw.2011.13280.
Prospektiivne kohortuuring: OBJECTIVE: To determine if use of antenatal corticosteroids is associated with improvement in major outcomes for **infants born at 22 and 23 weeks' gestation. DESIGN, SETTING, AND PARTICIPANTS: Cohort study of data collected prospectively** on inborn infants with a **birth weight between 401 g and 1000 g** (N = 10,541) **born at 22 to 25 weeks'** gestation between January 1, 1993, and December 31, 2009, at 23 academic perinatal centers in the United States. Certified examiners unaware of exposure to antenatal corticosteroids performed follow-up examinations on 4924 (86.5%) of the infants born between 1993 and 2008 who survived to 18 to 22 months. Logistic regression models generated adjusted odds ratios (AORs), controlling for maternal and neonatal variables. **MAIN OUTCOME MEASURES:** Mortality and neurodevelopmental impairment at 18 to 22 months' corrected age. **RESULTS:** Death or neurodevelopmental impairment at 18 to 22 months was significantly lower for infants who had been exposed to antenatal	Carlo WA, McDonald SA, Fanaroff AA, et al. **Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation.** JAMA 2011; 306:2348.

corticosteroids and were born at 23 weeks' gestation (83.4% with exposure to antenatal corticosteroids vs 90.5% without exposure; AOR, 0.58 [95% CI, 0.42-0.80]), at 24 weeks' gestation (68.4% with exposure to antenatal corticosteroids vs 80.3% without exposure; AOR, 0.62 [95% CI, 0.49-0.78]), and at 25 weeks' gestation (52.7% with exposure to antenatal corticosteroids vs 67.9% without exposure; AOR, 0.61 [95% CI, 0.50-0.74]) but not in those infants born at 22 weeks' gestation (90.2% with exposure to antenatal corticosteroids vs 93.1% without exposure; AOR, 0.80 [95% CI, 0.29-2.21]). If the mothers had received antenatal corticosteroids, the following events occurred significantly less in infants born at 23, 24, and 25 weeks' gestation: death by 18 to 22 months; hospital death; death, intraventricular hemorrhage, or periventricular leukomalacia; and death or necrotizing enterocolitis. **For infants born at 22 weeks' gestation, the only outcome that occurred significantly less was death or necrotizing enterocolitis** (73.5% with exposure to antenatal corticosteroids vs 84.5% without exposure; AOR, 0.54 [95% CI, 0.30-0.97]). **CONCLUSION: Among infants born at 23 to 25 weeks' gestation, antenatal exposure to corticosteroids compared with nonexposure was associated with a lower rate of death or neurodevelopmental impairment at 18 to 22 months.**	
Retrospektiivne uuring: OBJECTIVE: To evaluate the effectiveness of antenatal corticosteroid (ACS) to improve neonatal outcomes for infants **born at <24 weeks of gestation**. **STUDY DESIGN:** We performed a **retrospective analysis** of 11,607 infants born at 22 to 33 weeks of gestation between 2003 and 2007 from the Neonatal Research Network of Japan. We evaluated the gestational age effects of ACS administered to mothers with threatened preterm birth on several factors related to neonatal morbidity and mortality. **RESULTS:** By logistic regression analysis, ACS exposure decreased respiratory distress syndrome and severe intraventricular hemorrhage in infants born between 24 and 29 weeks of gestation. Cox regression analysis revealed that **ACS exposure was associated with a significant decrease in mortality of preterm infants born at 22 or 23 weeks of gestation** (adjusted hazard ratio, 0.72; 95% CI, 0.53 to 0.97; P=.03). This effect was also observed at 24 to 25 and 26 to 27 weeks of gestation and in the overall study population. **CONCLUSIONS:** ACS exposure improved survival of extremely preterm infants. ACS treatment should be considered for threatened preterm birth at 22 to 23 weeks of gestation.	Mori R1, Kusuda S, Fujimura M; Neonatal Research Network Japan. **Antenatal corticosteroids promote survival of extremely preterm infants born at 22 to 23 weeks of gestation.** J Pediatr. 2011 Jul;159(1):110-114.e1. doi: 10.1016/j.jpeds.2010.12.039. Epub 2011 Feb 22.

Table 2

Summary of Cohort of Periviable Birth Studies Reporting Neonatal Outcomes of Steroid Treated vs. Non-Treated Pregnancies

Study PI[I]	Year Published	Country of Origin	Time of Delivery	OR[II] Deaths	OI
Costelo[11]	2000	U.K	<26 weeks	0.6	0.1
Tyson[5]	2008.	U.S.	<26 weeks	0.6	-
Hayes[12]	2008.	U.S.	<23 weeks	0.3	-
Mori[4]	2011	Japan	<26 weeks	0.7	0.(
Bader[13]	2010	Israel	<26 weeks	0.6	-
Carlo[1]	2011	U.S.	<26 weeks	0.6	0.1

[I]Principal Investigator

[II]Odds Ratio

[III]Intraventricular Hemorrhage

Wapner RJ. Antenatal Corticosteroids for Periviable Birth. *Seminars in perinatology*. 2013;37(6):10.1053/j.semperi.2013.06.024. doi:10.1053/j.semperi.2013.06.024.

Diabeediga rase - kas ACS peaks manustama pärast 34. GN:

Infants of diabetic mothers delivered early might have pulmonary immaturity at a more advanced gestation than infants of nondiabetic mothers. Elective and spontaneous preterm delivery is more likely to occur in women with pregestational diabetes than in healthy controls, with preeclampsia, polyhydramnios and infections being common complications. Close maternal glycemic control before and during pregnancy is essential, and has been demonstrated to reduce the incidence of hyaline membrane disease (RDS) in this group of infants. Administration of a course of betamethasone at the usual dose and interval is recommended in diabetic pregnant women although there is little evidence of efficacy and safety of this practice. Women with gestational or pregestational diabetes were excluded from the majority of early randomized trials. Caution is advised during ACS administration with close glycemic control during three days after the first dose. The steroid effect begins approximately 12 h after the first dose and lasts for five days. Obstetricians should consider the use of ACS in diabetic pregnant women above 34 weeks' gestation if there is evidence of pulmonary immaturity by amniotic fluid analysis. The fluorescence polarization test is the most common test used for assessing fetal lung maturation.	**J. Perinat. Med. 36 (2008) 191–196** **Guideline for the use of antenatal corticosteroids for fetal maturation***
Women with either insulin-dependent diabetes or gestational diabetes were not entered into randomised controlled trials of antenatal corticosteroid therapy. There is therefore no evidence from randomised controlled trials that antenatal corticosteroid therapy is either safe or effective in these circumstances. Maternal hyperglycaemia can adversely affect fetal lung maturity. It is possible that any benefit of corticosteroids could be offset by corticosteroid-induced	2010 **Antenatal corticosteroids to reduce neonatal morbidity and mortality.** Greentop Guideline no 7. London: Royal College of

hyperglycaemia. However, the National Institute of Health and Clinical Excellence (NICE) has published a clinical guideline for diabetes in pregnancy that states that 'diabetes should not be considered a contraindication to antenatal corticosteroids'. The NICE guideline recommends that diabetic women receiving steroids should have additional insulin according to an agreed protocol.	Obstetricians and Gynaecologists. Available at www.rcog.org.uk (Accessed on February 18, 2015)

Beetametasooni ja deksametasooni võrdlus:

Süstemaatiline ülevaade: Both dexamethasone and betamethasone significantly reduced combined fetal and neonatal death, neonatal death, RDS and cerebroventricular haemorrhage. **Betamethasone treatment** (RR 0.56, 95% CI 0.48 to 0.65,14 studies, 2563 infants) **resulted in a greater reduction in RDS than dexamethasone treatment** (RR 0.80, 95% CI 0.68 to 0.93, six studies, 1457 infants). No statistically significant differences between groups treated with antenatal corticosteroids and controls in fetal death, birthweight or chorioamnionitis were seen in subgroups treated with dexamethasone or betamethasone separately . However, **dexamethasone significantly increased the incidence of puerperal sepsis** (RR 1.74, 95% CI 1.04 to 2.89, four studies, 536 women) while betamethasone did not (RR 1.00, 95% CI 0.58 to 1.72, four studies, 467 women).	Roberts et al., 2006
Süstemaatiline ülevaade: No statistically significant differences between those exposed to dexamethasone or betamethasone were seen for neonatal death (risk ratio (RR) 1.41, 95% confidence interval (CI) 0.54 to 3.67; four trials, 596 infants) or respiratory distress syndrome (RDS) (RR 1.06, 95% CI 0.88 to 1.27; five trials; 753 infants). **Dexamethasone significantly decreased the risk of intraventricular haemorrhage (IVH)** compared with betamethasone (RR 0.44, 95% CI 0.21 to 0.92; four trials, 549 infants). **Kaugtulem:** Out of a small subgroup assessed at 18 months in the Subtil 2003 trial, one child in the dexamethasone group was recorded as having a neurosensory disability (RR 1.67, 95% CI 0.08 to 33.75; one trial, 12 infants - Subtil 2003).	Brownfoot et al., 2013
OBJECTIVE: We compared the development of **adverse neurodevelopmental outcomes at corrected ages of 18 to 22 months for extremely low birth weight infants** exposed prenatally to dexamethasone, betamethasone, or no steroid. METHODS: Study infants were **extremely low birth weight (401-1000 g) infants** who were in the care of National Institute of Child Health and Human Development Neonatal Research Network centers between January 1, 2002, and April 30, 2003; they were assessed neurodevelopmentally at corrected ages of 18 to 22 months. Outcomes were defined as Bayley Scales of Infant Development-II Mental Development Index of < 70, Bayley Scales of Infant Development-II Psychomotor Development Index of < 70, bilateral blindness, bilateral hearing aid use, cerebral palsy, and neurodevelopmental impairment. Neurodevelopmental impairment was defined as > or = 1 of the aforementioned outcomes. RESULTS: A total of 1124 infants met entry criteria. There were no statistically significant associations between prenatal dexamethasone exposure and any follow-up outcome, compared with no prenatal steroid exposure. **Prenatal betamethasone exposure was associated with reduced risks of hearing impairment and neurodevelopmental impairment and with increased likelihood of unimpaired status, compared with no prenatal steroid exposure.** Compared with betamethasone, **dexamethasone was associated with a trend for increased risk of Psychomotor Development Index of < 70, increased risk of hearing impairment, and decreased likelihood of unimpaired status.**	Lee BH[1], Stoll BJ, McDonald SA, Higgins RD; National Institute of Child Health and Human Development Neonatal Research Network. **Neurodevelopmental outcomes of extremely low birth weight infants exposed prenatally to dexamethasone versus betamethasone.** Pediatrics. 2008 Feb;121(2):289-96. doi: 10.1542/peds.2007-1103.

CONCLUSIONS: Prenatal betamethasone exposure was associated with increased likelihood of unimpaired neurodevelopmental status and reduced risk of hearing impairment at corrected ages of 18 to 22 months among extremely low birth weight infants, compared with prenatal dexamethasone exposure or no prenatal steroid exposure. Pending a randomized, clinical trial, **it may be in the best interests of infants to receive betamethasone, rather than dexamethasone, when possible.**	
Retrospektiivne kohortuuring: OBJECTIVE: The purpose of this study was to investigate the influence of prenatal exposure to one or two dosages of **dexamethasone on neonatal physical and cognitive development of children at 1, 3 and 6 years** of age. METHODS: This was a **retrospective cohort study.** The body length, head circumference and body weight were measured in every infant and child to evaluate physical development. The mental development index (MDI) and a psychomotor development index (PDI) were used to evaluate mental and cognitive development in children of ages **1 year and 3 years** while verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ) scores were used to evaluate mental and cognitive development in children of age of **6 years.** There were 1554 infants at 1 year, 1328 children at 3 years and 1297 preschool children at 6 years followed. RESULTS: **There were no significant differences between antenatal dexamethasone exposure groups and antenatal dexamethasone non-exposure groups on physical development index and MDI, PDI, VIQ and PIQ.** CONCLUSIONS: The results of this investigation suggested that one or two dosages of antenatal dexamethasone is safe for the use of inevitable preterm birth.	Liu J1, Feng ZC, Li J, Wang Q. **Antenatal dexamethasone has no adverse effects on child physical and cognitive development: a long-term cohort follow-up investigation.** J Matern Fetal Neonatal Med. 2012 Nov;25(11):2369-71. doi: 10.3109/14767058.2012.696162. Epub 2012 Jun 14.
Retrospektiivne kohortuuring 1999 a: BACKGROUND: Antenatal glucocorticoid therapy decreases the incidence of several complications among very premature infants. However, its effect on the occurrence of cystic periventricular leukomalacia, a major cause of cerebral palsy, remains unknown. METHODS: We **retrospectively analyzed a cohort of 883 live-born infants**, with gestational ages ranging from 24 to 31 weeks, who were born between January 1993 and December 1996 at three perinatal centers in the Paris area. The mothers of 361 infants had received betamethasone before delivery, the mothers of 165 infants had received dexamethasone before delivery, and the mothers of 357 infants did not receive glucocorticoids. We compared the rates of cystic periventricular leukomalacia among the three groups of infants in bivariate and multivariate analyses after adjustment for confounding factors. RESULTS: The rate of cystic periventricular leukomalacia was 4.4 percent among the infants whose mothers had received betamethasone, 11.0 percent among the infants whose mothers had received dexamethasone, and 8.4 percent among the infants whose mothers had not received a glucocorticoid. After adjustment for gestational age, the mode of delivery, and the presence or absence of chorioamnionitis, prolonged interval between the rupture of membranes and delivery (>24 hours), preeclampsia, and the use of tocolytic drugs, **antenatal exposure to betamethasone was associated with a lower risk of cystic periventricular leukomalacia** than was either the absence of glucocorticoid therapy (adjusted odds ratio, 0.5; 95 percent confidence interval, 0.2 to 0.9) or exposure to dexamethasone (adjusted odds ratio, 0.3; 95 percent confidence interval, 0.1 to 0.7). The adjusted odds ratio for the group of infants whose mothers had received dexamethasone as compared with the group of infants whose mothers had not received a glucocorticoid was 1.5 (95 percent confidence interval, 0.8 to 2.9). CONCLUSIONS: **Antenatal exposure to betamethasone but not dexamethasone is associated with a decreased risk of cystic periventricular leukomalacia among very premature infants.**	Baud O[1], Foix-L'Helias L, Kaminski M, Audibert F, Jarreau PH, Papiernik E, Huon C, Lepercq J, Dehan M, Lacaze-Masmonteil T. **Antenatal glucocorticoid treatment and cystic periventricular leukomalacia in very premature infants.** N Engl J Med. **1999** Oct 14;341(16):1190-6.
Praegu on käimas beetametasooni ja deksametasooni võrdlev randomiseeritud uuring, mille tulemusi on oodata 2016.a: A*STEROID: Australian Antenatal Study To Evaluate the Role Of Intramuscular Desamethasone prior to preterm birth to increase survival free of childhood neurosensory disability.	https://www.adelaide.edu.au/arch/research/clinical_trials/asteroid.html

Lisakuuri manustamise GN ülemine piir. Lisakuuri doos:

One single repeat course (variously defined) was planned for three trials (Garite 2009; McEvoy 2010; Peltoniemi 2007). **Two trials used a single course consisting of two doses of 12 mg betamethasone** (Garite 2009; McEvoy 2010) and **for one trial the course of repeat corticosteroids was a single dose of 12 mg betamethasone** (Peltoniemi 2007). Women were eligible for inclusion seven or more days after a pre-trial course in Peltoniemi 2007, and 14 or more days after a pre-trial course in Garite 2009 and McEvoy 2010.The eligible gestational age at trial entry was similar between these three trials: being 25 to **less than 33 weeks *(kuni 32+6)*** in Garite 2009, 26 **to 33 weeks *(kuni 33+6 ?)*** McEvoy 2010, and **up to 34 weeks (kuni 33+6)** in Peltoniemi 2007. Repeat pre- natal corticosteroids should be considered for women who have received a course of prenatal corticosteroids seven or more days previously, and who remain at risk of preterm birth before 34 weeks' gestation. Women eligible for repeat prenatal corticosteroid treatment should be informed of the known benefits and risks and counselled about the available but limited information about childhood health outcomes. **Until clearer information is available on optimal dose of treatment, and frequency of administration it would seem prudent to use a treatment regimen of one of the trials reporting neonatal benefit.**	Crowther CA, McKinlay CJD, Middleton P, Harding JE. **Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes.** Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD003935. DOI: 10.1002/14651858.CD003935.pub3
Antenataalse kortikosteroidi korduskuur (1 doos): Beetametasoon 11.4 mg IM. GN ülemine piir 34+6	**Queensland Clinical Guidelines, Preterm labour and birth**, December 2014 MN14.6-V5.R19
Kahe hiljutisemalt (2009 ja 2010) publitseeritud randomiseeritud uuringu põhjal üks täielik korduskuur (BM 12mg x2 24h intervalliga või DM 6mgx4 12h intervalliga) oluliselt vähendas RDS esinemissagedust ja lisahapniku vajadust.	OUTI M. PELTONIEMI, M. ANNELI KARI, MIKKO HALLMAN, **Repeated antenatal corticosteroid treatment: a systematic review and meta-analysis**, 13 March 2011 DOI: 10.1111/j.1600-0412.2011.01132.x
Korduskuuriks kaks doosi 12 mg beetametasooni GN ülemine piir 34+6	**2010 Antenatal corticosteroids to reduce neonatal morbidity and mortality.** Greentop Guideline no 7. London: Royal College of Obstetricians and Gynaecologists. Available at www.rcog.org.uk (Accessed on February 18, 2015)

Glükokortikoidi manustamine IUGR loodete korral.

Ülevaateartikkel kirjandusest, mis käsitleb loomade peal tehtud uuringuid IUGR loodetel. Evidence from our group and suggests that antenatal glucocorticoids may not have the same effects in IUGR preterm fetuses, as they do in normally grown preterm fetuses. The	Viide: Morrison JL, et al. Antenatal Steroids and the IUGR Fetus: Are Exposure and Physiological Effects on the Lung and Cardiovascular

different responses of the IUGR fetus are likely related to its altered neurohormonal status and the adaptations that the fetus must undergo in the face of reduced substrate supply. Therefore, the effects of antenatal glucocorticoids on the fetus may be dependent on the timing, degree, and duration of hypoxemia, hypercortisolemia, and hypoglycaemia. Furthermore, it is not clear if the benefits of antenatal glucocorticoids outweigh the costs for all fetuses. Of particular concern is the controversy about the effects of antenatal glucocorticoids on lung and cardiovascular function in the IUGR fetus, as the physiological adaptations that this group experiences in response to nutrient and oxygen restriction appear to alter the fetus' ability to regulate endogenous glucocorticoid availability. As a result, these fetuses may be exposed to higher antenatal glucocorticoid concentrations for longer, which may result in an exacerbation of the potentially negative neurological and cardiovascular side effects of antenatal glucocorticoid treatment, possibly without the full capacity to benefit from the lung maturational effects.	System the Same as in Normally Grown Fetuses? 2012. Journal of Pregnancy.
Ülevaateartikkel kirjandusest: ACS tõhusus IUGR loodete puhul on ebaselge. Puuduvad randomiseeritud uuringud sellel patsientide alagrupil ja IUGR looteid pole sageli uuringutesse kaasatud. On uuringuid (large population-based study – Bernstein et al, 2000; case control study – Schaap et al, 2001), mis on leidnud, et ACS kasutamise korral IUGR loodete puhul on tõhusus sama hea kui normotroofikutel. Samas on uuringuid (systematic review – Torrance et al, 2009), mis on leidnud, et ACS ei oma IUGR loodete puhul toimet neonataalsele haigestumusele ega suremusele. Samuti ei saa olla päris kindel ACS kasutamise ohutuse osas IUGR loodete puhul: Intrauterine growth restriction is associated with alterations in cardiovascular function to maintain adequate blood flow to vital organs. Glucocorticoids are powerful regulators of vascular tone, and it is possible that this has a particularly detrimental effect on brain development and long-term function. In a compelling study by Miller and colleagues using a sheep model, these investigators demonstrated that IUGR fetuses display significant carotid blood flow reperfusion in response to maternal betamethasone administration, which may lead to lipid peroxidation in the fetal brain, thereby contributing to an increased incidence of cell death. There may also be adverse effects of corticosteroid administration on placental function and fetoplacental dynamics, which place these fetuses at risk for adverse neurological outcomes.	Viide: Bonanno C, et al. Antenatal Corticosteroids in the Management of Preterm Birth: Are we back where we started? Obstet Gynecol Clin North Am. 2012 March ; 39(1): 47–63. doi:10.1016/j.ogc.2011.12.006 .

Otsingusõnad:

preterm, premature, prematurity, birth, delivery, infant, fetus, neonate, labor, labour, corticosteroid, glucocorticosteroid, glucocorticoid, betamethasone, dexamethasone

Mesh terminid: obstetric labor, premature; infant, premature; betamethasone; dexamethasone

Otsingustrateegiad:

Piirangud: Inglise keel, ilmunud 5 aasta jooksul (v.a. üks süstemaatiline ülevaade, mis ilmunud 2006.a.), süstemaatilised ülevaated, meta-analüüsid.

Süstemaatilised ülevaated/meta-analüüsid:

07.02.15 Pubmed: Search: (((((((preterm) OR premature)) AND ((((((birth*) OR deliver*) OR infant*) OR fetus) OR labor) OR labour))) OR (("Obstetric Labor, Premature"[Mesh]) OR

"Infant, Premature"[Mesh]))) AND ((((((glucocorticoid*) OR cortiocosteroid*) OR betamethasone) OR dexamethasone)) OR (("Betamethasone"[Mesh]) OR "Dexamethasone"[Mesh])) Filters: Systematic Reviews, Meta-Analysis, 5 years, English. Vasteid: 35 – neist sobilikke 5.
Sama otsingut korrates ilma ajalise piiranguta leidsime lisaks 1 Cochrane süstemaatiline ülevaate ilmumisaastaga 2006. Samas on 2010.a. korraldatud uus tõendusmaterjali otsing ja 2013.a. on seda ülevaadet selle põhjal täiendatud, mistõttu antud süstemaatiline ülevaade hõlmatud siiski ravijuhendi koostamisse.
07.02.15 Pubmed: Search: (((((((glucocorticosteroid*) OR glucocorticoid*) OR corticosteroid*) OR betamethasone) OR dexamethasone)) OR ((betamethasone[MeSH Terms]) OR dexamethasone[MeSH Terms]))) AND (((((preterm) OR premature) OR prematurity)) AND (((((((((birth*) OR deliver*) OR infant*) OR fetus) OR neonate*) OR labor) OR labour)) OR ((obstetric labor, premature[MeSH Terms]) OR infant, premature[MeSH Terms]))) Filters: Meta-Analysis, Systematic Reviews, 5 years, English. Vasteid 72 - neist lisaks eelmistele sobilikke 1.
RCT:
Beetametasooni erinevad manustamisskeemid: 19.02.15 Pubmed: Search: ((((antenatal) OR prenatal)) AND ((betamethasone) OR betamethasone[MeSH Terms])) AND (((regimen) OR dosage) OR dose) Filters: Clinical Trial, Controlled Clinical Trial, 10 years, Humans, English. Vasteid 32 - asjakohaseid 1 (lähemal vaatlusel selgub, et võrreldud on skeeme beetametasoon 12 mg 2 doosi 24 h intervalliga ja beetametasoon 4 mg 6 doosi 8 h intervalliga - selline skeem ei ole meie ravijuhendis küsimuse all)
10.03.15 Pubmed Search: (((((((glucocorticosteroid*) OR glucocorticoid*) OR corticosteroid*) OR betamethasone) OR dexamethasone)) OR ((betamethasone[MeSH Terms]) OR dexamethasone[MeSH Terms]))) AND (((((preterm) OR premature) OR prematurity)) AND (((((((((birth*) OR deliver*) OR infant*) OR fetus) OR neonate*) OR labor) OR labour)) OR ((obstetric labor, premature[MeSH Terms]) OR infant, premature[MeSH Terms]))) Filters: Randomized Controlled Trial, 5 years, Humans, English. n=34 - neist asjakohaseid 5
26.03.15 Pubmed search: ((((antenatal) OR prenatal)) AND (((periviability) OR viability) OR extremely premature infant)) AND (((((corticosteroid*) OR glucocorticosteroid*) OR betamethasone) OR dexamethasone) OR glucocorticoid*) Filters: Humans, English. n=81, neist asjakohaseid 4.
26.03.15 Pubmed search: (((((antenatal) OR prenatal)) AND ((betamethasone) AND dexamethasone))) AND (((preterm birth) OR preterm labor) OR preterm labour) Filters: Humans, English. n=77
31.03.15 Pubmed search: (antenatal[All Fields] AND (("betamethasone"[MeSH Terms] OR "betamethasone"[All Fields]) OR ("dexamethasone"[MeSH Terms] OR "dexamethasone"[All Fields]))) AND (((18 month[All Fields] OR 18 month's[All Fields] OR 18 monthers[All Fields] OR 18
monthly[All Fields] OR 18 months[All Fields]) OR (neurodevelopmental[All Fields] AND disability[All Fields])) OR follow-up[All Fields]) AND "humans"[MeSH Terms] n=66
Cost-effectiveness otsing:
22.02 Pubmed: Search: (((cost-effectiveness) OR economic)) AND (((((((corticosteroid*) OR glucocorticosteroid*) OR glucocorticoid*) OR betamethasone) OR dexamethasone)) AND (((preterm birth) OR preterm labour) OR preterm labor)) Filters: 10 years. n=15 (ei ole teemakohased).