

Kliiniline küsimus nr 7

Kas ähvardava enneaegse sünnituse korral tuleb raseduse prolungeerimiseks ja vastsündinu haigestumise sageduse vähendamiseks rakendada antibakteriaalset ravi võrreldes mitterakendamisega:

- enneaegse lootevee puhkemisega (PPROM-iga)/ilma enneaegse lootevee puhkemiseta (PPROM-ita)

Tulemusnäitajad: ema tervisetulem, lapse peamised tulemusnäitajad

Süsteematilised ülevaated

Kokkuvõtte süsteemalistest ülevaadetest

Kokkuvõttes on esitatud tõendus põhine materjal antibakteriaalse ravi kasutamise kohta ähvardava enneaegse sünnituse puhul haarates järgmise aspekte:

Ähvardav enneaegne sünnitus ja PPRM;

Ähvardav enneaegne sünnitus intaktsete membraanidega ilma PPRM-ita;

Ähvardav enneaegne sünnitus ja GBS kandlus;

Ähvardav enneaegne sünnitus ja koorionamnioniit.

Tõendus põhised andmed antibakteriaalse ravi kohta enneaegse sünnituse korral (PPROM-iga ja PPRM-ita) pärinevad kahest Cochrane ülevaatest.

Need metaanalüüsid on täiendatud 2013 aastal.

Ähvardav enneaegne sünnitus ja PPRM:

Kenyon et al., 2013 viisid läbi metaanalüüsi 22 randomiseeritud kontroll-uuringu põhjal, kuhu oli kaasatud 6872 naist PPRM-iga enne 37 rasedusnädalat.

Eesmärgiks oli uurida ab ravi lühi- ja kaugtoimet naistele PPRM-iga enne 37 nädalat: mõju ema haigestumusele, neonataalsele haigestumisele, suremusele ja kaugmõju laste arengule.

Võrreldi antibakteriaalset ravi vs placebo.

Uuritud ravimite režiimid:

ORACLE uuringus erythromycin 250 mg x4 vs placebo, co-amoxiclav 325 mg x 4 vs placebo, eryth + co- amoxiclav vs placebo. 10 päeva jooksul või sünnituseni.

Teistes uuringutes lisaks veel: ampicillin, penicillin, gentamycin, clindamycin, piperacilin, ampi-sulbaktam, mezlocillin vs. placebo.

Metaanalüüsi tulemusi domineerivad andmed ORACLE I RCT uuringust (4826 naist) (Kenyon et al., 2001).

ORACLE I ja II uuringud on väga kõrge kvaliteediga randomiseeritud kontroll-uuringud, kus uuriti antibakteriaalset ravi mõju emadele ja lastele enneaegse sünnituse korral PPRM-iga ja intaktsete membraanidega. Samuti oli uuringute põhjal läbi viidud laste kaugtulemuste analüüs 7 aasta möödudes.

Metaanalüüsi tulemusena leiti, et antibakteriaalse ravi alustamine PROM korral vähendab koorionamnioniidi esinemissagedust RR 0.66 (CI 95%0.46 - 0.96); oluliselt vähenes laste arv, kes sündisid 48 tunni jooksul RR 0.71(CI 95%0.58 - 0.87) ja 7 päeva jooksu vastavalt randomiseerimisele RR 0.79(CI 95% 0.71- 0.89).

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Vähenes neonataalse infektsiooni esinemine (RR 0.67, 95% CI 0.52 to 0.85), surfaktandi vajadus (RR 0.83, 95% CI 0.72 to 0.96), hapnikuravi vajadus (RR 0.88, 95% CI 0.81 to 0.96), laste arv, kellel oli patoloogiline aju ultraheli leid väljakirjutamise hetkel (RR 0.81, 95% CI 0.68 to 0.98).

Co-amoxiclav (Augmentin) oli seotud neonataalse nekrotiseeriva enterekoliidi suurema riskiga (RR 4.72, 95% CI 1.57 to 14.23).

Perinataalses suremuses erinevust ei esinenud (RR 0.93, 95% CI 0.76–1.14).

Sellest võib järeldada, et rutiinne antibakteriaalse ravi kasutamine PPRM-ga ähvardava enneaegse sünnituse korral on seotud raseduse prolungeerimisega ja neonataalse haigestumise parandamisega lühiperspektiivis, kuid olulist perinataalsuremuse vähendamist ei esine. Vaatamata vähestele andmetele kaugtulemustest, head lühitulemused toetavad rutiinset antibakteriaalse ravi alustamist antud juhul. Preparaadi valik ei ole lõplikult selge, kuid co-amoxiclavi kasutamine ei ole soovitatav, kuna see suurendab nekrotiseeriva enterokoliidi esinemist vastsündinul.

Long term outcome ORACLE I 7 yr f/u:

Kaugtulemusi 7 aasta möödudes oli hinnatud 3298 lapsel (75%): ei olnud erinevust funktsionaalsete häirete vahel ravirühmas vs platsebo sõltumata antibakteriaalse ravi kombinatsioonidest.

Ähvardav enneaegne sünnitus intaktsete membraanidega ilma PPRM-ta:

Flenady et al., 2013 viisid läbi metaanalüüsi 14 randomiseeritud kontroll-uuringu põhjal, kuhu oli kaasatud 7837 naist ähvardava enneaegse sünnitusega ilma PPRM-ta 20- kuni 36-rasedusnädalas.

Eesmärgiks oli uurida antibakteriaalset ravi vs placebo mõju emadele ja lastele antud olukorras.

Uuritud ravimite režiimid:

ORACLE II uuringus erythromycin 250 mg x4 vs placebo, co-amoxiclav 325 mg x 4 vs placebo, eryth + co- amoxiclav vs placebo. 10 päeva jooksu või sünnituseni.

Teistes uuringutes: clindamycin, ampicillin, ampicillin-sulbaktam, mezlocillin vs. placebo. Tulemusi samuti domineerivad andmed ORACLE II uuringust (6295naist) (Kenyon et al., 2001).

Metaanalüüsi tulemused näitasid maternaalse infektsiooni langust antibakteriaalse ravi kasutajate rühmas (RR 0.74, 95% CI 0.64–0.87 NNTB 34, 95% CI 24 to 63), aga ei demonstreerinud ühtegi neonataalset kasu.

Lisaks oli pakutud välja hoopiski võimalikku neonataalset kahju antibakteriaalses rühmas, kus oli täheldatud neonataalse suremuse tõusu antibakteriaalse ravi rühmas (RR 1.57, 95% CI 1.03 to 2.40; NNTH 149, 95% CI 2500 to 61).

Ei õnnestunud näidata enneaegse sünnituse arvu langust ravirühmas, ei õnnestunud näidata short-term kasu vastsündinutele ravirühmas võrreldes platseboga.

Long term outcome ORACLE II 7 yr f/u:

Kaugtulemusi 7 aasta möödudes oli hinnatud 3196 lapsel (71%).

Alagrupi analüüsis oli aga täheldatud tserebraalparalüüsi esinemise tõus.

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Lastel, kelle emad said erütromütsiini (monoteraapiana või koos co-amoxiclaviga) esines tserebraalparalüüsi tõus 1.7% -lt 3.3%-le (OR 1.93, 95% CI 1.21–3.09) seotud erütromütsiiniga ja tõus 1.9%-lt to 3.2%.lt (OR 1.69, 95% CI 1.07–2.67) seotud co-amoxiclav. Sellega oli tehtud järeldus, et emade lastel, kes said AB ravi intaktsete membraanidega, areneb rohkem tserebraalparalüüsi.

Järeldus: erütromütsiini määramine enneagse sünnituse korral intaktsete membraanidega on seotud suurenenud riskiga funktsionaalseteks häireteks lastel 7 aasta vanuselt. Samuti ab rühmas oli tõusnud tserebraalparalüüsi esinemissagedus, kuid üldine tserebraalparalüüsi risk oli ikkagi madal.

Tõendus antibakteriaalse ravi kohta intaktsete membraanide korral on üllatav. Subkliinilise infektsiooni sagedus selles rühmas on pigem madal 13-22%, kuid kasu puudumine on ikkagi ebaselge. Põhjuste osas spekulēriti. Kõige loogilisem tundus olevat otsene ab ravi kahjustav efekt, kuid selle vastu räägivad tulemused PROM grupist, kus kahju ei ole täheldatav.

Aga ravi pikkus intaktsete membraanide grupis oli pikem: ainult 15-20% sünnitasid 7 päeva jooksul. Sellest tuleneb hüpotees, et AB ravi antud situatsioonis ravis subkliinilist infektsioon ja pikendas rasedust/lükkas edasi enneagset sünnitust, mis ei tähenda, et intrauteriinne loote põletik oleks olnud lahendatud. Samas püsiv intrauteriinne põletik võib põhjustada aju kahjustust ja tserebraalparalüüsi.

Lõpuks on ka võimalik, et enneagne sünnitus ei olnud vallandatud infektsioonist, aga on seotud 'preterm parturition sündroomiga'.

Võib järeldada, et metaanalüüs ei demonstreerinud neonataalse tulemuste parandamist, kui ab ravi kasutatakse enneagse sünnituse puhul ilma PPRM-ita, kuna ainuke positiivne tulemus oli maternaalse infektsiooni vähendamine.

Muret aga tekitab short ja long term tervisekahju lastele, kelle emad said AB ravi. Need andmed toetavad AB rutiinset mittekasutamist emadel, kellel esineb enneagne sünnitus intaktsete membraanidega ja puuduvad infektsiooni tunnused.

Oluline on rakkendada AB ravi ähvardava enneagse sünnituse puhul, kui esinevad kliinilise infektsiooni tunnused, kuna koorionamnioniit on jätkuvalt oluline ema, loote ja vastsündinu surma põhjus. Kuid ähvardava enneagse sünnituse korral, kui membraanid on inktaksted ja puuduvad infektsiooni tunnused, rutiinne AB ravi ei ole soovitatav, kuna on tõendeid, et antibiootikumid nendes tingimustes suurendavad riski laste funktsionaalsete häiretele ja tserebraalparalüüsile.

Antibakteriaalse ravi määramine PPRM korral parandab aga neonataalseid lühiajalisi tulemusi: raseduse prolongeerimine, surfaktandi vajaduse vähendamine, hapnikravi vajaduse vähendamine, patoloogilise peaju ultraheli leiu vähendamine.

Kaugtulemustes erinevust rühmade vahel ei ole, perinataalne suremus ei muutu.

Alagrupide analüüs ei näidanud erinevust preparaatide vahel ja ei ole välja toodud kõige efektiivsemat preparaati.

Erytromycin on soovitatud valikraviks, kuna ta on kõige rohkem testitud ORACLE uuringus.

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Co-amoxiclav on seotud aga neonataalse nekrotiseeriva enterokoliidi esinemissagede tõusuga ja seda preparaati võiks vältida raseduse ajal.

Antibakteriaalset ravi ei soovitata alustada, kui PROM diagnoos ei ole kindel, kuna intaktsete membraanidega ravi saanud emade lastel suurem risk tserebraalparalüüsi tekkeks.

Ähvardav enneaegne sünnitus ja GBS kandlus:

Teine keeruline aspekt, mis puudutab antibakteriaalse ravi kasutamist ja valikut enneaegse sünnituse ajal on GBS profülaktika.

Seisukohad profülaktika osas on erinevad üle maailma. Puuduvad head randomiseeritud uuringud antud teema kohta ja erinevad ravijuhised erinevates riikides on koostatud pigem konsensuse baasil.

Seega ka meie oma soovitudest peame lähtuma nendest rekomendatsioonidest, mille aluseks ei ole väga head tõendus põhised.

On tehtud üks Cochrane süstemaatiline ülevaade antibakteriaalse ravi kasutamise kohta sünnituse ajal naistel, kes on koloniseeritud GBS-ga. (Ohlsson and Shah, 2014). See ülevaade ei olnud suunatud ainult enneaegsele sünnitusele ja hõlmas nii enneaegseid kui ka ajalisi sünnitusi.

Metaanalüüs olid tehtud 4 randomiseeritud kontrolluuringu põhjal, kuhu kuulus 852 naist. Kolmes nendest (500 naist) vaadati intranataalse profülaktika mõju ema ja lapse tervisele vs no profülaktika.

Üks uuring (352 naist) võrdles intapartum ampicillin vs penicillin kasutamist.

Kõik kaasatud uuringud olid 20 aastat vanad.

Süstemaatilise analüüsi autorid leidsid palju probleeme uuringu metodoloogias ja läbiviimises, ka osalejate arv oli väga väike.

Uuringute kvaliteet oli hinnatud madalaks. Need asjaolud seavad kahtluse alla ka uuringu tulemused.

Analüüsist selgus, et profülaktika kasutamine oluliselt ei vähendanud neonataalset suremust ega haigestumust GBS infektsiooni või infektsiooni, mis ei ole GBSga seotud.

Varajase GBS infektsiooni haigestumus oli langenud võrreldes no profülaktika rühmaga (risk ratio (RR) 0.17, 95% confidence interval (CI) 0.04 to 0.74, three trials, 488 infants; risk difference -0.04, 95% CI -0.07 to -0.01; number needed to treat to benefit 25, 95% CI 14 to 100, I2 0%).

Hilise GBS infektsiooni haigestumist või sepsist teistest mikroorganismidest (mitte GBS) profülaktika ei vähendanud ja esinemissagedus oli võrdne mõlemas rühmas.

Üks uuring (352 naist) võrdles intapartum ampicillin vs penicillin ja tulemuseks ei olnud erinevust vastsündinute või emade tulemustes.

Ideaalselt ab profülaktika efektiivsus GBS neonataalse infektsiooni preventisioonis peab olema uuritud piisavalt suure arvuga topeltpimedates randomiseeritud uuringutes. Kuid see ilmset ei ole kaasajal enam võimalik, kuna erinevate riikide poolt on presenteeritud juhendid, mis ei põhine heal tõendus põhisel materjalil.

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GBS kolonisatsioon Euroopas oli uuritud süstemaatilises ülevaates (Barcaite et al., 2008). Uuringusse olid kaasatud 21 uuringut, 24093 naist 13 riigist.

Esinemissagedus oli väga varieeruv: 6.5% kuni 36%, üks kolmandik uuringutest raporteerisid esinemissagedust 20%.

Ida-Euroopa 19.7-29.3%, Lääne-Euroopa 11-21%, Skandinaavia 24.3-36% ja Lõuna-Euroopa 6.5-32%.

On teada, et emadel, kes on koloniseeritud GBS-ga, on suurem risk, et vastsündinul areneb varajane GBS nakkus (EOD) või hiline GBS nakkus (LOD), mis tõstab neontaalset suremust.

Varajase GBS infektsiooni esinemissagedus on profülaktika abil aastatega langenud: 1990s oli 1.8 juhtu/1000 ja 2010 0.26 juhtu/1000 (Schrag 2013). Samas hilis-GBS-infektsiooni esinemissagedus ei ole langenud (Schrag 2013).

Probleemiks on, et samad andmed on interpreteeritud erinevalt erinevate eriala organisatsioonide poolt. Selge on see, et kõiki varajase GBS infektsiooni juhtusid ei ole võimalik profülaktikaga ennetada.

Hetkel on väga erinevad GBS profülaktika lähenemised üle maailma: riskil baseeruv lähenemine, skriiningul baseeruv lähenemine (GBS külvid/ GBS PCR), kombineeritud strateegia.

Eestis puudub skriining GBS suhtes, vaid kasutatakse riskil lähenemist.

Enneagne sünnitus on teada olevalt suur riskifaktor varajase ja hilise GBS infektsiooni väljakujunemises vastsündinul (Dillon 1987; Garland 1991; Yagupsky 1991).

Vaatamata sellele nt UK oma juhendites ei käsitle enneaegset sünnitust riskifaktorina ja on soovitatud lähtuda ORACLE II tulemustest, kus intaktsete membraanide korral ja infektsiooni puudumise korral ei ole soovitatav rutiinne ab alustamine, kuna see mõjub negatiivselt neuroloogilisele arengule kaugperspektiivis ja puuduvad andmed positiivsete lähitulemuste kohta vastsündinule.

Pärast tutvumist erinevate riikide juhenditega GBS profülaktika osas, leian, et kõige paremini saaksime adpteerida soovitusi, mis pärinevad Euroopa GBS Konsensuse koosolekult, mis toimus juunis 2013. aastal Firenzes ja kus osales 16 eksperti erinevatest riikidest, esindatud olid kõige suuremad eriala organisatsioonid: the European Association of Perinatal Medicine (EAPM), the European Society for Pediatric Research and the European Society of Neonatology (ESPR-ESN) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID).

Sisuline konsensus oli publitseeritud augustis 2014. aastal ajakirjas Journal of Maternal-Fetal and Neonatal Medicine.

Sellest tuleneb:

Sünnitusaegne profülaktika on vajalik:

1. Neonataalne GBS infektsioon eelmisel lapsel.

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2.GBS bakteruuria käesoleva raseduse käigus.

3.Positiivne GBS analüüs skriiningu käigus 35-37 nädalal järgenvatel juhtudel:

- *Kui riigis on vastu võetud skriiningul baseeruv profülaktika soovitus.*
- *Kui riigis skriininguks kasutatakse PCR analüüsi sünnituse ajal ja on teada, et naine on allergiline penicillinnile, siis 35-37 nädala külv on vajalik dalacini resistentsuse väljaselgitamiseks.*

4.Positiivne GBS PCR sünnituse ajal, kui riigis on võetud vastu vastav skriiningu poliitika.

5.Negatiivne GBS PCR sünnituse ajal, kuid esinevad järgmised probleemid:

- *Pikk veeta periood üle 18 tundi*
- *Palavik üle 38 C (juhul, kui koorionamnioniit on kahtlustatav, siis tuleks valida laia spektriga ab peniciliini asemel, mis kataks samuti GBS).*

6.Teadmata GBS ja järgmised probleemid:

- *Pikk veeta periood üle 18 tundi*
- *Palavik üle 38 C*
- *Enneaegne sünnitus alla 37 nädalat*

Sünnituse profülaktika ei ole vajalik.

1.GBS kolonisatsioon eelmise raseduse ajal

2.GBS bakteruuria eelmise sünnituse ajal

3.Negatiivne GBS külv või PCR

4.Plaaniline keisrilõige vaatamata GBS staatusele.

Juhul, kui rasedal esineb PPI või PPRM, on mõnikord raske aru saada, kas sünnitus läheb käiku; haiglasse saabumisel on oluline võtta GBS külv/ PCR, mille vastus kehtib 5 nädalat. Patsient peab olema üle vaadatud regulaarselt, et hinnata tõelise sünnituse alguse võimalust ja sünnituse ajal GBS profülaktika peab olema pakutud kõigile GBS positiivsetele naistele. Kui naine ei ole 5 nädala jooksul sünnitanud, tuleks uus analüüs võtta, et hinnata kolonisatsiooni.

Antibakteriaalse ravi alustamine ähvardava enneaegse sünnituse puhul peab olema kaalutud, kuna antibakteriaalne ravi ilma sünnituseta ja ilma infektsioonita võib tuua neonataalset kahju, nagu näidatud ORACLE II uuringus.

Ähvardav enneaegne sünnitus ja koorionamnioniit:

Koorionamnioniit on tavaliselt diagnoositud järgmiste kriteeriumite põhjal: palavik, emaka hellus, ema või loote tahhükardia, foul-smelling lootevesi, leukotsütoos ja CRP tõus ning see avaldub 4-10% naistest sünnituse ajal.

Läbi viidud metaanalüüsid näitavad, et koorionamnioniit on seotud suurema riskiga nekrotiseeriva enterokoliidi tekkeks (OR:1.24; 95% CI = 1.01–1.52) (Been et al., 2013), tserebraalparalüüsi tekkeks (OR: 2.42; 95% CI = 1.52–3.84) (Wu and Colford, 2000), samuti ema metroendometriidi ja sepsis tekeks.

On leitud, et laia spektri antibakteriaalne ravi aitab eelkõige vältida ema komplikatsioone, kahjuks sama ravi toime tserebraalparalüüsi ennatamiseks ei ole nii kindel ja vaatamata ravile risk neurokahjustusele jääb kõrgeks.

Kui koorionamnioniit on kahtlustatud, vajalik alustada laia spektri AB raviga, mis toimib ka GBS-le (ravi peab asendama penicillini, mida kasutatakse profülaktikaks) ja sünnituse induktsioon peab olema kaalutud.

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Tulemused randomiseeritud uuringutest demonstreerivad, et laia toimespektiga AB ravi vähendab ema ja loote koorionamnioniidiga seotud tüsitsusi. Neonataalse sepsis esinemissagedes langeb 80% tänu AB ravile sünnituse ajal. Väiksemas randomiseeritud uuringus selgus, et 26 sünnitusest, kus kasutati ab ravi sünnituse ajal, ei tekkinud ühtegi neonataalset sepsist võrreldes 21%-ga 19-st vastsündinutes, kes said ravi postpartum. (Gibbs et al., 1988)

Optimaalne antibakteriaalse ravi režiim ei ole uuringutest selgunud.

Metaanalüüs tehtud Chapman et al., 2014 poolt üritas välja selgitada koorionamnioniidi ravis kasutatavate erinevate ab ravi režiimide efektiivsust ema ja vastsündinu haigestumisele ja suremusele ning mõju infektsiooniga seotud tüsistustele.

See metaanalüüs ei olnud suunatud spetsiifiliselt enneaegsele sünnitusele.

Põhilised uuringu inklusiooni kriteerium oli emal diagnoositud intra-amniotiline infektsioon (koorionamnioniit) vastavalt standardsetele kriteeriumitele. Gestatsiooniaja limit ei olnud määratud, kuigi osad RCT välistasid naised alla 34 nädalat ja alla 36 nädalat, osades uuringutest gestatsiooni vanus ei ole välja toodud.

Metaanalüüs võrdles erinevate režiimide efektiivsust: intapartum, intrapartum ja postpartum, ainult postpartum.

Primaarsed tulemusnäitajad oli ema ja vastsündinu suremus, ema ja vastsündinu tõsine infektsioon, ema ja vastsündinu hospitalisatsiooni pikkus.

Kaasatud oli 11 RCT (1296 naist), mõned uuringud on veel käigus ja andmed ei olnud täielikud. Kahjuks GRADEi järgi hinnates kaasatud RCT uuringud olid pigem madala või väga madala kvaliteediga. Peamised põhjused, mis halvendasid andmete kvaliteeti, olid piirangud uuringu ülesehituses või läbi viimises (risk of bias), ebatäpsus ja vastuolulised tulemused.

Järgmised antibiootikumid olid kaasatud: ampicillin, ampicillin/sulbactam, gentamicin, clindamycin, and cefotetan.

Kahjuks ei tulnud välja erinevust erinevate režiimide vahel.

Ainuke statistiliselt oluline tulemus oli see, et intrapartum AB ravi kasutamine võrreldes postpartum kasutamisega vähendab hospitalisatsiooni emal ja vastsündinul. See pärines väga väiksest randomiseeritud kontroll-uuringust (45 naist), kus võrreldi ampicillin/gentamicin intrapartum kasutamine versus kohene postpartum kasutamine ja leiti, et intrapartum kasutamine lühendab hospitalisatsiooni emal ja vastsündinul. (one trial, 45 women; MD -1.00 days, 95% CI -1.94 to - 0.06; very low quality of evidence) and the mean number of neonatal hospital stay days (one trial, 45 neonates; MD -1.90 days, 95% CI -3.91 to -0.49; very low quality of evidence). Neonataalse pneumoonia ja sepsis risk oli samuti väiksem intrapartum ravi rühmas. (one trial, 45 neonates; RR 0.06, 95% CI 0.00 to 0.95; very low quality of evidence). (Gibbs et al., 1988)

Seega hetkel on vähe andmeid, et pakkuda välja kõige sobivam antibakteriaalse ravi režiim koorionamnioniidi puhul.

Viited

<p>Kokkuvõtte (abstract või kokkuvõtlikum info)</p>	<p>Viide kirjandusallikale</p>
<p>Objectives To evaluate the immediate and long-term effects of administering antibiotics to women with PROM before 37 weeks, on maternal infectious morbidity, neonatal morbidity and mortality, and longer-term childhood development.</p> <p>Main results We included 22 trials, involving 6872 women and babies. The use of antibiotics following PROM is associated with statistically significant reductions in chorioamnionitis (average risk ratio (RR) 0.66, 95% confidence interval (CI) 0.46 to 0.96, and a reduction in the numbers of babies born within 48 hours (average RR 0.71, 95% CI 0.58 to 0.87) and seven days of randomisation (average RR 0.79, 95% CI 0.71 to 0.89). The following markers of neonatal morbidity were reduced: neonatal infection (RR 0.67, 95% CI 0.52 to 0.85), use of surfactant (RR 0.83, 95% CI 0.72 to 0.96), oxygen therapy (RR 0.88, 95% CI 0.81 to 0.96), and abnormal cerebral ultrasound scan prior to discharge from hospital (RR 0.81, 95% CI 0.68 to 0.98). Co-amoxiclav was associated with an increased risk of neonatal necrotising enterocolitis (RR 4.72, 95% CI 1.57 to 14.23). One study evaluated the children’s health at seven years of age (ORACLE Children Study) and found antibiotics seemed to have little effect on the health of children.</p> <p>Authors’ conclusions Routine prescription of antibiotics for women with preterm rupture of the membranes is associated with prolongation of pregnancy and improvements in a number of short-term neonatal morbidities, but no significant reduction in perinatal mortality. Despite lack of evidence of longer-term benefit in childhood, the advantages on short-term morbidities are such that we would recommend antibiotics are routinely prescribed. The antibiotic of choice is not clear but co-amoxiclav should be avoided in women due to increased risk of neonatal necrotising enterocolitis.</p>	<p>1. Kenyon, S., Boulvain, M., Neilson, J.P., 2013.</p> <p>Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev 12, CD001058. doi:10.1002/14651858.CD001058.p ub3</p>
<p>Background The ORACLE I trial compared the use of erythromycin and/or amoxicillin–clavulanate (co-amoxiclav) with that of placebo for women with preterm rupture of the membranes without overt signs of clinical infection, by use of a factorial randomised design. The aim of the present study—the ORACLE Children Study was to determine the long-term effects on children of these interventions.</p> <p>Methods We assessed children at age 7 years born to the 4148 women who had completed the ORACLE I trial and who were eligible for follow-up with a structured parental questionnaire to assess the child’s health status. Functional impairment was defined as the presence of any level of functional impairment (severe, moderate, or mild) derived from the mark III Multi-Attribute Health Status classification system. Educational outcomes were assessed with national curriculum test results for children resident in England.</p> <p>Findings Outcome was determined for 3298 (75%) eligible children. There was no difference in the proportion of children with any functional impairment after prescription of erythromycin, with or without co-amoxiclav, compared with those born to mothers who received no erythromycin (594 [38·3%] of 1551 children vs 655 [40·4%] of 1620; odds ratio 0·91, 95% CI 0·79–1·05) or after prescription of co-amoxiclav, with or without erythromycin, compared with those born to mothers who</p>	<p>2. Kenyon, S., Pike, K., Jones, D.R., Brocklehurst, P., Marlow, N., Salt, A., Taylor, D.J., 2008. Childhood outcomes after prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7-year follow-up of the ORACLE I trial. Lancet 372, 1310–1318. doi:10.1016/S0140-6736(08)61202-</p>

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<p>received no co-amoxiclav (645 [40·6%] of 1587 vs 604 [38·1%] of 1584; 1·11, 0·96–1·28). Neither antibiotic had a significant effect on the overall level of behavioural difficulties experienced, on specific medical conditions, or on the proportions of children achieving each level in reading, writing, or mathematics at key stage one.</p> <p>Interpretation The prescription of antibiotics for women with preterm rupture of the membranes seems to have little effect on the health of children at 7 years of age.</p>	7
<p>Objectives To assess the effects of prophylactic antibiotics administered to women in preterm labour with intact membranes, on maternal and neonatal outcomes.</p> <p>Main results In this update (2013), with the addition of three trials (305 women), the large ORACLE II 2001 trial continues to dominate the results of this review. This review now includes a total of 14 studies randomising 7837 women. No significant difference was shown in perinatal or infant mortality for infants of women allocated to any prophylactic antibiotics compared with no antibiotics. However, an increase in neonatal deaths was shown for infants of women receiving any prophylactic antibiotics when compared with placebo (RR 1.57, 95% CI 1.03 to 2.40; NNT_H 149, 95% CI 2500 to 61). No reduction in preterm birth or other clinically important short-term outcomes for the infant were shown.</p> <p>Long-term child outcomes to seven years of age were available for infants in the UK enrolled in the ORACLE II trial. Comparing any antibiotics with placebo, a marginally non-statistically significant increase was shown in any functional impairment (RR 1.10, 95% CI 0.99 to 1.23) and cerebral palsy (CP) (RR 1.82, 95% CI 0.99 to 3.34). In subgroup analysis, CP was statistically significantly increased for infants of women allocated to macrolide and beta-lactam antibiotics combined compared with placebo (RR 2.83, 95% CI 1.02 to 7.88; NNT_H 35, 95% CI 333 to 9).</p> <p>Further, exposure to any macrolide antibiotics (including erythromycin alone or erythromycin plus co-amoxiclav) versus no macrolide antibiotics (including placebo and co-amoxiclav alone) was shown to increase neonatal death (RR 1.52, 95% CI 1.05 to 2.19; NNT_H 139, 95% CI 1429 to 61), any functional impairment (RR 1.11, 95% CI 1.01 to 1.20; NNT_H 24, 95% CI 263 to 13) and CP (RR 1.90, 95% CI 1.20 to 3.01; NNT_H 64, 95% CI 286 to 29). Exposure to any beta-lactam (beta-lactam alone or in combination with macrolide antibiotics) versus no beta-lactam antibiotics resulted in more neonatal deaths (RR 1.51, 95% CI 1.06 to 2.15; NNT_H 143, 95% CI 1250 to 63) and CP (RR 1.67, 95% CI 1.06 to 2.61; NNT_H 79, 95% CI 909 to 33), however no difference was shown in functional impairment.</p> <p>Maternal infection was reduced with the use of any prophylactic antibiotics compared with placebo (RR 0.74, 95% CI 0.63 to 0.86; NNT_B 34, 95% CI 24 to 63) and any beta-lactam compared with no beta-lactam antibiotics (RR 0.80, 95% CI 0.69 to 0.92; NNT_B 47, 95% CI 31 to 119). However, caution should be exercised with this finding due to the possibility of bias shown by funnel plot asymmetry. Any beta-lactam compared with no beta-lactam antibiotics was associated with an increase in maternal adverse drug reaction (RR 1.61, 95% CI 1.02 to 2.54; NNT_H 17, 95% CI 526 to 7).</p> <p>Authors' conclusions This review did not demonstrate any benefit in important</p>	<p>3. Flenady, V., Hawley, G., Stock, O.M., Kenyon, S., Badawi, N., 2013.</p> <p>Prophylactic antibiotics for inhibiting preterm labour with intact membranes.</p> <p>Cochrane Database Syst Rev 12, CD000246. doi:10.1002/14651858.CD000246.pub2</p>

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<p>neonatal outcomes with the use of prophylactic antibiotics for women in preterm labour with intact membranes, although maternal infection may be reduced. Of concern, is the finding of short- and longer- term harm for children of mothers exposed to antibiotics. The evidence supports not giving antibiotics routinely to women in preterm labour with intact membranes in the absence of overt signs of infection.</p> <p>Further research is required to develop sensitive markers of subclinical infection for women in preterm labour with intact membranes, as this is a group that might benefit from future novel interventions, including new modalities of antibiotic therapy. The results of this review demonstrate the need for future trials in the area of preterm birth to include assessment of long-term neurodevelopmental outcome.</p>	
<p>Background The ORACLE II trial compared the use of erythromycin and/or amoxicillin–clavulanate (co-amoxiclav) with that of placebo for women in spontaneous preterm labour and intact membranes, without overt signs of clinical infection, by use of a factorial randomised design. The aim of the present study—the ORACLE Children Study II—was to determine the long-term effects on children after exposure to antibiotics in this clinical situation.</p> <p>Methods We assessed children at age 7 years born to the 4221 women who had completed the ORACLE II study and who were eligible for follow-up with a structured parental questionnaire to assess the child’s health status. Functional impairment was defined as the presence of any level of functional impairment (severe, moderate, or mild) derived from the mark III Multi-Attribute Health Status classification system. Educational outcomes were assessed with national curriculum test results for children resident in England.</p> <p>Findings Outcome was determined for 3196 (71%) eligible children. Overall, a greater proportion of children whose mothers had been prescribed erythromycin, with or without co-amoxiclav, had any functional impairment than did those whose mothers had received no erythromycin (658 [42·3%] of 1554 children vs 574 [38·3%] of 1498; odds ratio 1·18, 95% CI 1·02–1·37). Co-amoxiclav (with or without erythromycin) had no effect on the proportion of children with any functional impairment, compared with receipt of no co-amoxiclav (624 [40·7%] of 1523 vs 608 [40·0%] of 1520; 1·03, 0·89–1·19). No effects were seen with either antibiotic on the number of deaths, other medical conditions, behavioural patterns, or educational attainment. However, more children whose mothers had received erythromycin or co-amoxiclav developed cerebral palsy than did those born to mothers who received no erythromycin or no co-amoxiclav, respectively (erythromycin: 53 [3·3%] of 1611 vs 27 [1·7%] of 1562, 1·93, 1·21–3·09; co-amoxiclav: 50 [3·2%] of 1587 vs 30 [1·9%] of 1586, 1·69, 1·07–2·67). The number needed to harm with erythromycin was 64 (95% CI 37–209) and with co-amoxiclav 79 (42–591).</p> <p>Interpretation The prescription of erythromycin for women in spontaneous preterm labour with intact membranes was associated with an increase in functional impairment among their children at 7 years of age. The risk of cerebral palsy was increased by either antibiotic, although the overall risk of this condition was low.</p>	<p>4. Kenyon, S., Pike, K., Jones, D.R., Brocklehurst, P., Marlow, N., Salt, A., Taylor, D.J., 2008.</p> <p>Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. <i>Lancet</i> 372, 1319–1327. doi:10.1016/S0140-6736(08)61203-9</p>

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Objectives

To assess the effects of administering antibiotic regimens for intra-amniotic infection on maternal and perinatal morbidity and mortality and on infection-related complications.

Main results

Our prespecified primary outcomes were maternal and neonatal mortality, maternal and neonatal severe infection, and duration of maternal and neonatal hospital stay.

We included 11 studies (involving 1296 women) and assessed them as having low to moderate risk of bias - mainly because allocation concealment methods were not adequately reported, most studies were open, and outcome reporting was incomplete. The quality of the evidence was low to very low for most outcomes, as per the GRADE approach. The following antibiotics were assessed in the included trials: ampicillin, ampicillin/sulbactam, gentamicin, clindamycin, and cefotetan.

During labor: meta-analysis of two studies found no clear differences in rates of neonatal sepsis (163 neonates; risk ratio (RR) 1.07, 95% confidence interval (CI) 0.40 to 2.86; I² = 9%; low quality of evidence), treatment failure (endometritis) (163 participants; RR 0.86, 95% CI 0.27 to 2.70; I² = 0%; low quality of evidence), and postpartum hemorrhage (RR 1.39, 95% CI 0.76 to 2.56; I² = 0%; low quality of evidence) when two different dosages/regimens of gentamicin were assessed. No clear differences between groups were found for any reported maternal or neonatal outcomes. The review did not identify data for a comparison of antibiotics versus no treatment/placebo.

Postpartum: meta-analysis of two studies that evaluated use of antibiotics versus placebo after vaginal delivery showed no significant differences between groups in rates of treatment failure or postpartum endometritis. No significant differences were found in rates of neonatal death and postpartum endometritis when use of antibiotics was compared with no treatment. Four trials assessing two different dosages/regimens of gentamicin or dual-agent therapy versus triple-agent therapy, or comparing antibiotics, found no significant differences in most reported neonatal or maternal outcomes; the duration of hospital stay showed a difference in favor of the group of women who received short-duration antibiotics (one study, 292 women; mean difference (MD) -0.90 days, 95% CI -1.64 to -0.16; moderate quality of evidence).

Intrapartum versus postpartum: one small study (45 women) evaluating use of ampicillin/gentamicin during intrapartum versus immediate postpartum treatment found significant differences favoring the intrapartum group in the mean number of days of maternal postpartum hospital stay (one trial, 45 women; MD -1.00 days, 95% CI -1.94 to -0.06; very low quality of evidence) and the mean number of neonatal hospital stay days (one trial, 45 neonates; MD -1.90 days, 95% CI -3.91 to -0.49; very low quality of evidence). Although no significant differences were found in the rate of maternal bacteremia or early neonatal sepsis, for the outcome of neonatal pneumonia or sepsis we observed a significant difference favoring intrapartum treatment (one trial, 45 neonates; RR 0.06, 95% CI 0.00 to 0.95; very low quality of evidence).

5. Chapman, E., Reveiz, L., Illanes, E., Bonfill Cosp, X., 2014.

Antibiotic regimens for management of intra-amniotic infection.

Cochrane Database Syst Rev 12, CD010976. doi:10.1002/14651858.CD010976.pub2

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<p>Authors' conclusions</p> <p>This review included 11 studies (having low to moderate risk of bias). The quality of the evidence was low to very low for most outcomes, as per the GRADE approach. Only one outcome (duration of hospital stay) was considered to provide moderate quality of evidence when antibiotics (short duration) were compared with antibiotics (long duration) during postpartum management of intra- amniotic infection. Our main reasons for downgrading the quality of evidence were limitations in study design or execution (risk of bias), imprecision, and inconsistency of results.</p> <p>Currently, limited evidence is available to reveal the most appropriate antimicrobial regimen for the treatment of patients with intra- amniotic infection; whether antibiotics should be continued during the postpartum period; and which antibiotic regimen or what treatment duration should be used. Also, no evidence was found on adverse effects of the intervention (not reported in any of the included studies). One small RCT showed that use of antibiotics during the intrapartum period is superior to their use during the postpartum period in reducing the number of days of maternal and neonatal hospital stay.</p>	
<p>Objectives To assess the effect of intrapartum antibiotics for maternal Group B haemolytic <i>streptococci</i> (GBS) colonization on mortality from any cause, from GBS infection and from organisms other than GBS.</p> <p>Main results We did not identify any new trials from the updated search so the results remain unchanged as follows. We included four trials involving 852 women.</p> <p>Three trials (involving 500 women) evaluating the effects of IAP versus no treatment were included. The use of IAP did not significantly reduce the incidence of all cause mortality, mortality from GBS infection or from infections caused by bacteria other than GBS. The incidence of early GBS infection was reduced with IAP compared to no treatment (risk ratio (RR) 0.17, 95% confidence interval (CI) 0.04 to 0.74, three trials, 488 infants; risk difference -0.04, 95% CI -0.07 to -0.01; number needed to treat to benefit 25, 95% CI 14 to 100, I2 0%). The incidence of LOD or sepsis from organisms other than GBS and puerperal infection was not significantly different between groups.</p> <p>One trial (involving 352 women) compared intrapartum ampicillin versus penicillin and reported no significant difference in neonatal or maternal outcomes.</p> <p>We found a high risk of bias for one or more key domains in the study methodology and execution.</p> <p>Authors' conclusions Intrapartum antibiotic prophylaxis appeared to reduce EOGBSD, but this result may well be due to bias as we found a high risk of bias for one or more key domains in the study methodology and execution. There is lack of evidence from well designed and conducted trials to recommend IAP to reduce neonatal EOGBSD. Ideally the effectiveness of IAP to reduce neonatal GBS infections should be studied in adequately sized double-blind controlled trials. The opportunity to conduct such trials has likely been lost, as practice guidelines (albeit without good evidence) have been introduced in many jurisdictions.</p>	<p>6. Ohlsson, A., Shah, V.S., 2014.</p> <p>Intrapartum antibiotics for known maternal Group B streptococcal colonization.</p> <p>Cochrane Database Syst Rev 6, CD007467. doi:10.1002/14651858.CD007467.pub4</p>

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<p>Objective To accumulate available evidence regarding the association between antenatal inflammation and necrotizing enterocolitis (NEC).</p> <p>Study design A systematic literature search was performed using Medline, Embase, Cochrane Library, ISI Web of Knowledge, and reference hand searches. Human studies published in English that reported associations between chorioamnionitis or other indicators of antenatal inflammation and NEC were eligible. Relevant associations were extracted and reported. Studies reporting associations between histological chorioamnionitis (HC) and NEC, HC with fetal involvement and NEC, and clinical chorioamnionitis and NEC were pooled in separate meta-analyses.</p> <p>Results A total of 33 relevant studies were identified. Clinical chorioamnionitis was significantly associated with NEC (12 studies; n = 22 601; OR, 1.24; 95% CI, 1.01-1.52; $P = .04$; $I^2 = 12\%$), but the association between HC and NEC was not statistically significant (13 studies; n = 5889; OR, 1.39; 95% CI, 0.95-2.04; $P = .09$; $I^2 = 49\%$). However, HC with fetal involvement was highly associated with NEC (3 studies; n = 1640; OR, 3.29; 95% CI, 1.87-5.78; $P = .0001$; $I^2 = 10\%$). Selection based on study quality did not affect the results. No indications of publication bias were apparent. Multivariate analyses in single studies generally attenuated the reported associations. Several associations between other markers of antenatal inflammation and NEC are reported.</p> <p>Conclusion Currently available evidence supports a role for antenatal inflammation in NEC pathophysiology. This finding emphasizes the need to further study the underlying mechanisms and evaluate potential interventions to improve postnatal intestinal outcomes. (<i>J Pediatr</i> 2013;162:236-42).</p>	<p>7. Been, J.V., Lievens, S., Zimmermann, L.J.I., Kramer, B.W., Wolfs, T.G.A.M., 2013.</p> <p>Chorioamnionitis as a risk factor for necrotizing enterocolitis: a systematic review and meta-analysis. <i>J. Pediatr.</i> 162, 236–242.e2. doi:10.1016/j.jpeds.2012.07.012</p>
<p>Context Chorioamnionitis has been implicated in the pathogenesis of cerebral palsy, but most studies have not reported a significant association. Cystic periventricular leukomalacia (cPVL) is believed to be a precursor of cerebral palsy in preterm infants.</p> <p>Objectives To determine whether chorioamnionitis is associated with cerebral palsy or cPVL and to examine factors that may explain differences in study results.</p> <p>Study Selection Of 229 initially identified publications, meta-analyses were performed on studies that addressed the association between clinical (n=19) or histologic (n = 7) chorioamnionitis and cerebral palsy or cPVL in both preterm and full-term infants. Inclusion criteria were: presence of appropriate exposure and outcome measures, case-control or cohort study design, and provision of sufficient data to calculate relative risks (RRs) or odds ratios with 95% confidence intervals (CIs). Studies evaluating risk of cerebral palsy following maternal fever, urinary tract infection, or other maternal infection were collected, but not included in the meta-analysis.</p> <p>Data Synthesis</p> <p>Using a random effects model, clinical chorioamnionitis was significantly associated with both cerebral palsy (RR, 1.9; 95% CI, 1.4-2.5) and cPVL (RR, 3.0; 95% CI, 2.2-4.0) in preterm infants. The RR of histologic chorioamnionitis and cerebral palsy was 1.6 (95% CI, 0.9-2.7) in preterm infants, and histologic chorioamnionitis was</p>	<p>8. Wu, Y.W., Colford, J.M., 2000.</p> <p>Chorioamnionitis as a risk factor for cerebral palsy: A meta-analysis. <i>JAMA</i> 284, 1417–1424.</p>

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significantly associated with cPVL (RR, 2.1; 95% CI, 1.5-2.9). Among full-term infants, a positive association was found between clinical chorioamnionitis and cerebral palsy (RR, 4.7; 95% CI, 1.3-16.2). Factors explaining differences in study results included varying definitions of clinical chorioamnionitis, extent of blinding in determining exposure status, and whether individual studies adjusted for potential confounders.

Conclusion Our meta-analysis indicates that chorioamnionitis is a risk factor for both cerebral palsy and cPVL.

Table 3. Indications and non-indications for intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal (GBS) disease for term deliveries and preterm labor <37 weeks gestation. *Adapted from revised guidelines from CDC 2010 [4].*

Intrapartum GBS prophylaxis indicated	Intrapartum GBS prophylaxis non indicated
<ul style="list-style-type: none"> ● Previous infant with GBS invasive disease ● GBS bacteriuria during any trimester of the current pregnancy¹ ● Positive late antenatal GBS vaginal-rectal screening culture² performed during the current pregnancy in the following cases: <ul style="list-style-type: none"> – If intrapartum PCR screening strategy³ is adopted and the patient is allergic to penicillin⁴ – If late antenatal vaginal-rectal GBS culture screening² strategy is used for GBS EOD prevention. ● Positive intrapartum GBS vaginal screening with rapid real time PCR³ ● Negative intrapartum GBS vaginal screening with rapid real time PCR³ and any of the following: <ul style="list-style-type: none"> – Amniotic membrane rupture ≥18 hours following the PCR testing – Intrapartum temperature ≥38 °C⁵ ● Unknown GBS status at the onset of labor (results indeterminate for intrapartum PCR or missed PCR testing⁴, missed antenatal culture screening or antenatal culture screening results not available³) and any of the following: <ul style="list-style-type: none"> – Amniotic membrane rupture ≥18 hours – Intrapartum temperature ≥38 °C⁵ – Preterm labor <37 weeks 	<ul style="list-style-type: none"> ● GBS colonization during a previous pregnancy (unless an indication for GBS prophylaxis is present during the current pregnancy) ● GBS bacteriuria during a previous pregnancy (unless an indication for GBS prophylaxis is present during the current pregnancy) ● Negative intrapartum GBS vaginal screening with rapid real time PCR³ unless the duration of amniotic membrane rupture is ≥18 hours following PCR testing or if intrapartum temperature is ≥38 °C⁵ ● Cesarean delivery performed before onset of labor on a woman with intact amniotic membranes, regardless of GBS colonization status or gestational age.

¹Intrapartum antibiotic prophylaxis is not indicated in this circumstance if a cesarean delivery is performed before onset of labor on women with intact amniotic membranes.

²The optimal timing for antenatal vaginal-rectal GBS culture screening is at 35–37 weeks gestation.

³Intrapartum rapid real time PCR testing for GBS, or other NAAT showing high analytical performances, might not be available in all maternities, then these settings should adopt the antenatal 35–37 weeks GBS culture screening strategy with strict adherence to either timing of screening or recommended protocols of specimen collection and processing for GBS screening.

⁴When the intrapartum rapid real time GBS PCR screening strategy is used and the patient is allergic to penicillin, a vaginal-rectal GBS culture should be done at 35–37 weeks in order to test clindamycin susceptibility (Table 1).

⁵If chorioamnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS antibiotic prophylaxis.

9. Di Renzo, G.C., Melin, P., Berardi, A., Blennow, M., Carbonell-Estrany, X., Donzelli, G.P., Hakansson, S., Hod, M., Hughes, R., Kurtzer, M., Poyart, C., Shinwell, E., Stray-Pedersen, B., Wielgos, M., El Helali, N., 2014.

Intrapartum GBS screening and antibiotic prophylaxis: a European consensus conference. J.

Matern. Fetal. Neonatal. Med. 1–17.

doi:10.3109/14767058.2014.934804

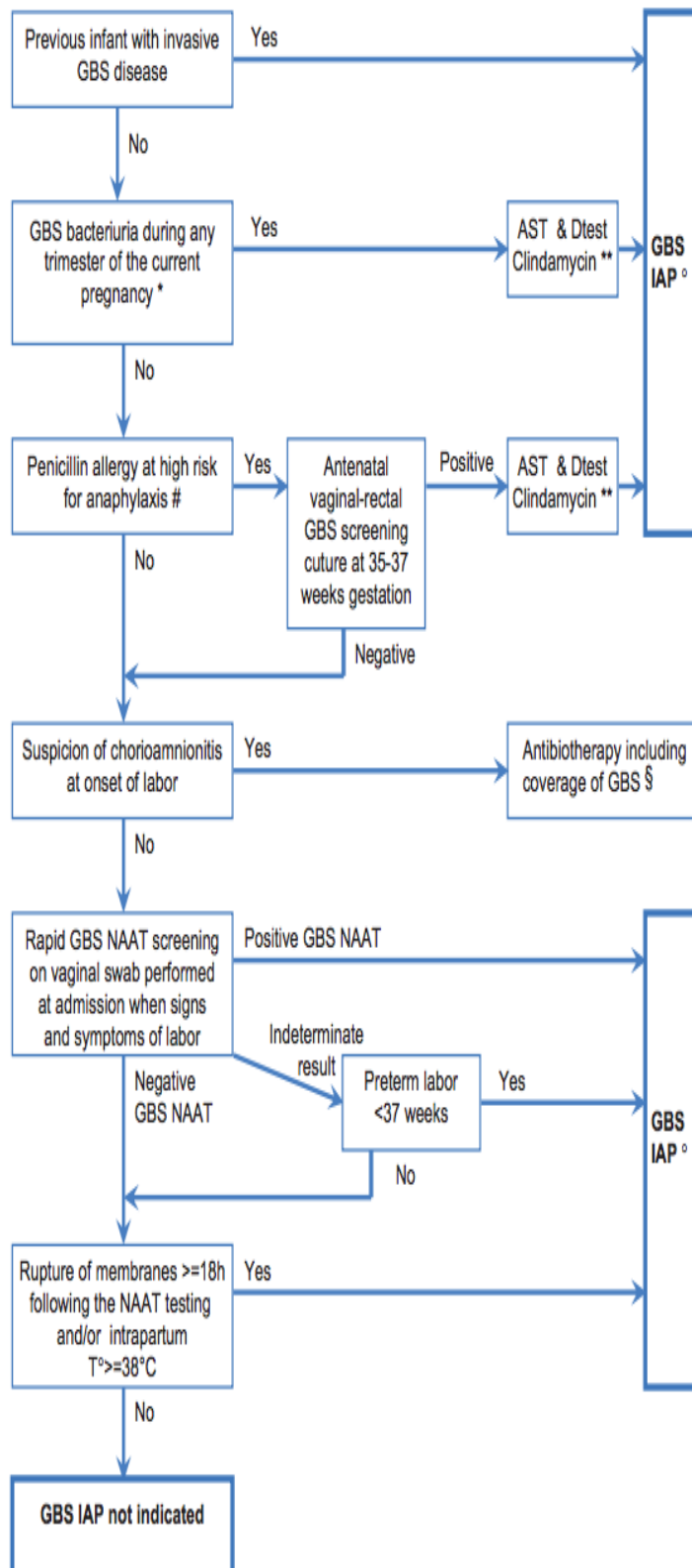
Figure 1. Algorithm for screening for GBS colonization and use of IAP for women with term labor or preterm labor <37 weeks. °IAP is started either at the onset of true labor or rupture of membranes, except in the instance of cesarean delivery performed before onset of labor on a woman with intact amniotic membranes. In penicillin allergic women at high risk for anaphylaxis, clindamycin is given for susceptible isolate and vancomycin for resistant isolate to clindamycin. Penicillin allergic women entering in spontaneous labor before either vaginal-rectal 35-37 weeks screening or susceptibility testing were done should receive vancomycin.

*Routine screening for asymptomatic bacteriuria is recommended in pregnant women. Laboratories should screen urine culture specimen for the presence of GBS in concentration $\geq 10^4$ cfu/ml either in pure culture or mixed with a second microorganism. Women with symptomatic or asymptomatic GBS urinary tract infection detected during pregnancy should be treated according to current standards of care for urinary tract infection during pregnancy and they should also receive IAP at the onset of labor.

**Antimicrobial susceptibility testing should be performed on antenatal GBS isolates and include detection of clindamycin resistance either constitutive or inducible.

#Before 35 weeks gestation, the pregnant women's potential allergic status should have been established by an anesthetist or other specialist.

§In case of suspicion of chorioamnionitis, antibiotics given for therapy usually include antibiotics effective on GBS. If other regimens are used IAP for GBS prevention should be added.



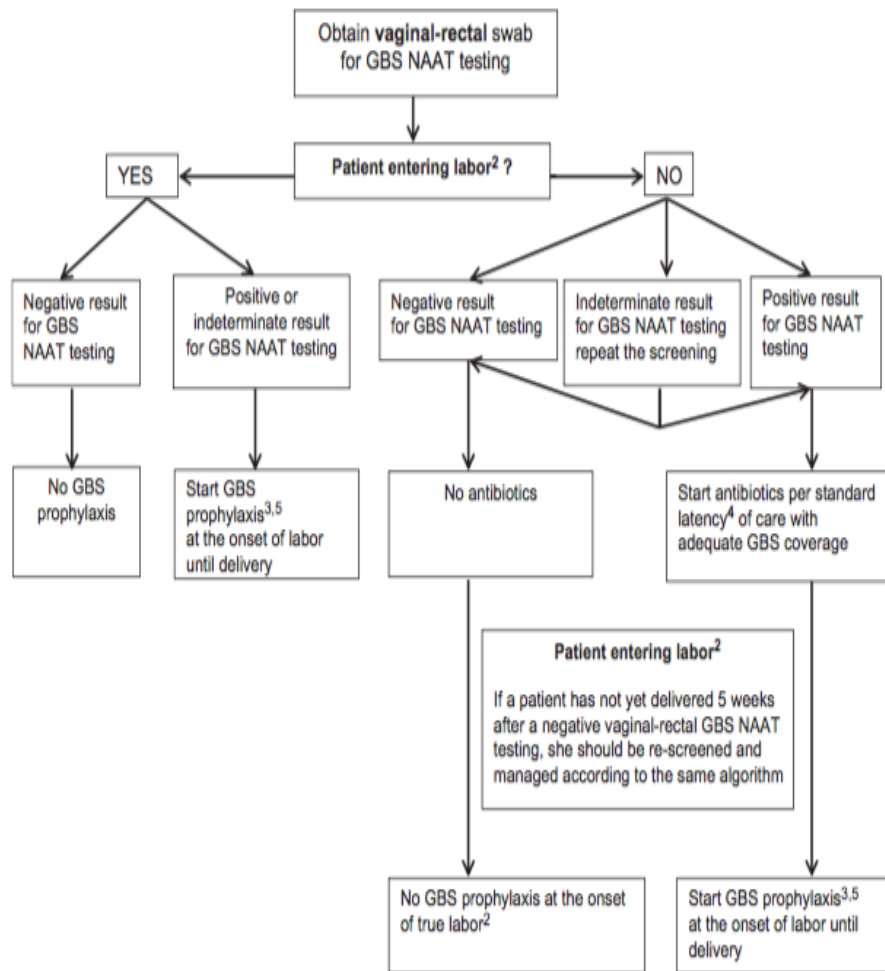


Figure 2. Algorithm for screening for group B streptococcal colonization and use of intrapartum prophylaxis for women with threatened preterm delivery and preterm premature rupture of membranes (pPROM) in the settings where NAAT GBS test is available (Adapted from revised guidelines from CDC 2010 [4].

¹At <37 weeks gestation.

²Patient should be regularly assessed for progression to true labor.

³See Table 4 for the recommended regimen. The potential allergic status of pregnant women should have been established by an anesthesiologist or other specialist before 35 weeks gestation. In penicillin allergic women a vaginal-rectal GBS culture screening at 35–37 weeks and susceptibility testing should be done. For women at high risk for anaphylaxis, clindamycin is given for susceptible isolate and vancomycin for resistant isolate to clindamycin. Women at high risk for anaphylaxis entering in labor before vaginal-rectal 35–37 weeks GBS screening and susceptibility testing were done, should receive vancomycin.

⁴Antibiotics given for latency in case of pPROM that include ampicillin 2 g intravenously (IV) once, followed by 1 g every 6 hours for at least 48 hours are adequate for GBS prophylaxis if delivery occurs while the patient is receiving that antibiotic regimen (oral antibiotics alone are not adequate for GBS prophylaxis). If broad spectrum antibiotics are used to cover other suspected pathogens, they should be also effective on GBS. If not, GBS prophylaxis should be initiated in addition.

⁵In case of suspicion of chorioamnionitis antibiotics given for therapy usually include antibiotics effective on GBS; if other regimens are used IAP for GBS should be added.

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Preterm labour and birth 2015 NICE guideline

Preterm Prelabour Rupture of Membranes 2010 RCOG

The Prevention of Early-onset Neonatal Group B Streptococcal Disease 2012 RCOG

Preterm labour and birth 2014 Queensland Clinical Guideline

Early onset Group B streptococcal disease 2010 Queensland Clinical Guideline

The Prevention of Early-Onset Neonatal Group B Streptococcal Disease SOGC 2013

Prevention of Perinatal Group B Streptococcal Disease US 2010

Oleme hinnanud AGREE tööriistaga neli ravijuhendit:

Preterm labour and birth 2015 NICE guideline, Preterm Prelabour Rupture of Membranes 2010 RCOG, The Prevention of Early-onset Neonatal Group B Streptococcal Disease 2012 RCOG, Preterm labour and birth 2014 Queensland Clinical Guideline.

NICE, PPROM UK ja Austraalia enneaegse sünnituse juhendid on hea kvaliteediga ja põhinevad samal teadusmaterjalil, mis on eelnevalt kokkuvõttes esitatud.

Soovitused AB ravi osas pärinevad ORACLE I ja II uuringutest. Seega PPROM korral soovitatakse alustada Tab. Erytromycini 250 mg x 4 10 päeva jooskul ja koorionamnioniidi korral alustada laia spektriga ja vältida raseduse prolongeerimist (A). Kui membraanid on intaktsed ja puuduvad infektsiooni tunnused, siis soovitatakse AB ravi mitte kasutada. (A)

NICE Guideline komitee soovitav eütromütsiini PPROMi korral esmavalikuna ja toob eraldi välja erütromütsiini eeliseid.

1. Erütromütsiin ei ole seotud nekrotiseeriva enterokoliidi riski tõusga.
2. Preparaati saab suukauselt manustada
3. Erütromütsiinil on lai toimespekter ja ta sobib GBS, teiste streptokokk ja stafülokokk infektsioonide raviks.
4. Erütromütsiinil on teoreetiline eelis mõjuda ka mükoplasma infektsioonile, mida seostatakse koorionaminoniidiga (see toime penicilliinil puudub).
5. Erütromütsiin läbib halvasti platsentat, mille tõttu toime lootele on minimaalne.
6. Ei ole kirjeldatud erütromütsiini kahjustavat toimet lootele.

GBS puudutavad juhendid ja soovitused on madala tõenduspõhise kvaliteediga ja põhinevad eririikide ekspertide konsensusel.

UK ja Austraalia GBS strateegia põhineb riskifaktorite tuvastamisel, kus riskifaktoriteks on PROM pikem kui 18 tundi, ema palavik sünnituse ajal, GBS kolonisatsioon antud raseduse ajal, eelmine laps EOGBD, GBS bakteruuria raseduse ajal. Austraalias riskifaktoriks peetakse ka enneaegset sünnitust, UK-s enneaegset sünnitust ei loeta riskifaktoriks ja PPI intakstete membraanidega ja ilma infektsioonita ei vaja GBS profülaktikat. Nad lähtuvad ORACLE II uuringust.

[Type text]

<p>Ameerika ja Kanada GBS strateegia põhinevad skriiningul. Enneaegset sünnitust loetakse riskifaktoriks. GBS profülaktika enneaegse sünnituse ajal ei ole näidustatud ainult juhul, kui on tõestatud GBS negatiivne tulemus hospitaliseerimisel. Teistel juhtudel enneaegse sünnituse ajal tuleks profülaktikat teha, kuni saabub negatiivne tulemus.</p>	
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Otsingu strateegia.

Andmebaas	Medline (PUBMED)
Otsingustrateegia	<p>Key words:antibiotics, premature birth, premature labor,pretermrupture of membranes,chorionamnionitis, GBS.</p> <p>MESH:("Anti-Bacterial Agents"[Mesh]) AND "Premature Birth"[Mesh]</p>
Tulemustearv	MA: 6SR: 13, RCT: 11(MESHterminitega)
Filtrid	Meta-Analysis, Systematic Review, Randomised Controlled Trial .
Ajalinepiirang	5 years
Muudpiirangud	English language

Andmebaas	Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE)
Otsingustrateegia	Key words:antibiotictreatment(1), preterm birth(2),Chorioamnionitis(3), preterm rupture of membranes(4), GBS(5).
Tulemustearv	<p>(1)AND(2)-> 13</p> <p>(1)AND(2) AND (3)-> 7</p> <p>(1)AND(2) AND (4)-> 3</p> <p>(1)AND(2) AND (5)-> 4</p>
Filtrid	Systematic review
Ajalinepiirand	5 years
Muudpiirangud	English language

Andmebaas	Trip Database
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[Type text]

Otsingustrateegia	“antibiotic treatment for preterm labor”
Tulemustearv	16
Filtrid	Systematicreview ,Randomisedcontrolled trial.
Ajalinepiirand	5 years
Muudpiirangud	English language

Andmebaas	Sum Search
Otsingustrateegia	“antibiotic treatment for preterm labor”
Tulemustearv	30
Filtrid	Systematicreview .
Ajalinepiirand	5 years
Muudpiirangud	English language

Andmebaas	CochraneCentral Register of Controlled Trials
Otsingustrateegia	Key words:antibiotic treatment, premature birth
Tulemustearv	12
Filtrid	Randomisedcontrolled trial.
Ajalinepiirand	5 years
Muudpiirangud	English language