Kliiniline küsimus nr 6

Kas ema urogenitaaltrakti mikrobioloogiliste uuringute teostamine võrreldes mitteteostamisega ähvardava enneaegse sünnituse korral mõjutab ema ja lapse tervisetulemist?

Kriitilised tulemusnäitajad: ema ja lapse peamised tervisetulemid

Tõendusmaterjali antud küsimuse kohta, mis käsitleks mikrobioloogilisi uuringuid just konkreetselt ähvardava enneaegse sünnitusega naistel, mitte skriiningsut varasema raseduse ajal, on väh.

Ravijuhendid

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| • Sterile speculum examination to:  
  - Collect **high vaginal swab** for microscopy culture and sensitivity (MC&S)  
  - Collect combined **low vaginal and anorectal swab** for Group B streptococcus (GBS)  
  - Insert swab 2 cm into vagina and then insert same swab 1 cm into anus  
  - **Midstream specimen of urine** for bacteriology (MC&S)  
  
  • Consider samples for gonorrhea, chlamydia. wet prep for bacterial vaginosis, group B streptococcus (GBS).  
  • Obtain urinalysis, urine culture.  
The following are key components of threatened preterm delivery

**GBS management:**
- Women admitted with signs and symptoms of labor or with rupture of membranes at <37 weeks and 0 days’ gestation should be screened for GBS colonization at hospital admission unless a vaginal-rectal GBS screen was performed within the preceding 5 weeks (AII - Evidence from at least one well-designed clinical trial without randomization, cohort or case-controlled analytic studies (preferably from more than one center), multiple time-series studies, dramatic results from uncontrolled studies, or some evidence from laboratory experiments)
- Swab the lower vagina (vaginal introitus), followed by the rectum (i.e., insert swab through the anal sphincter) using the same swab or two different swabs. Cervical, perianal, perirectal or perineal specimens are not acceptable, and a speculum should not be used for culture collection.

**Euroopa konsensus GBS osas:** In the case of women admitted with signs of threatened preterm delivery or preterm premature rupture of membranes (pPROM), assessing whether preterm labor or rupture of membranes will result in preterm delivery can be difficult; therefore **GBS PCR testing should be performed on a vaginalrectal sample** to evaluate GBS colonization which is then considered valid for 5 weeks. Patient should be regularly assessed for progression to true labor and IAP should be given to patients with a positive GBS screening when entering in true labor. If a woman has not yet delivered 5 weeks after a negative vaginal-rectal GBS NAAT testing, she should be re-screened to re-evaluate GBS colonization.

Administration of IAP in patients in threatened preterm delivery should be weighed against exposing patients in false labor to antibiotics with potential detrimental effects as demonstrated by the ORACLE II study [122]. As the effectiveness of GBS screening strategy depends on timely administration of IAP, the rapid NAAT test should be performed quickly after the specimen collection to avoid delay in results and the start of IAP. Thus, the rapid NAAT test should be implemented at the point of care, in delivery settings except if the premises of laboratory are adjacent.

Physicians, midwives or other qualified caregivers should collect vaginal specimen for rapid GBS testing at the beginning of signs and symptoms of labor.

**For patients entering labor (either term or preterm), only secretions from the lower one-third of the vagina should be swabbed without using a speculum. Sampling the rectum site is not warranted for intrapartum GBS screening.**

Swabbing both the lower vagina and the rectum is warranted only for women with threatened preterm delivery or preterm premature rupture of membranes (pPROM) who

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are not already entering labor

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<td><strong>Süstemaatiline ülevaade:</strong> The objective of this review was to determine the relationship between maternal colonization with GBS and preterm delivery. Out of more than 60 full-text articles, 16 follow-up studies and four case control studies were included in this review. Follow-up studies were divided into 'cohort studies,' in which cultures were taken early in pregnancy and which reported on pregnancy outcome, and 'cross-sectional studies', in which cultures were collected during delivery. Studies differed widely in methods, validity score, and GBS prevalence. The combined estimate from a random effect meta-analysis of the 11 cohort studies was 1.06 (95% confidence intervals (CI) 0.95-1.19) and for the five cross-sectional studies 1.75 (95% CI 1.43-2.14). For the case control studies, the pooled odds ratio was 1.59 (95% CI 1.03-2.44). This systematic review did not show an association between maternal GBS colonization during pregnancy and preterm delivery. Cross-sectional studies during delivery and case control studies showed positive GBS cultures more frequently in patients with preterm delivery.</td>
<td>Valkenburg-van den Berg, A.W., Sprij, A.J., Dekker, F.W., Dörr, P.J., Kanhai, H.H.H., 2009. Association between colonization with Group B Streptococcus and preterm delivery: a systematic review. Acta Obstet Gynecol Scand 88, 958–967. doi:10.1080/00016340903176800</td>
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<td><strong>Meta-analüüs:</strong> We updated a previously published meta-analysis to evaluate bacterial vaginosis (BV) and intermediate vaginal flora as risk factors for adverse pregnancy outcome. Selection criteria were original, published, English-language reports of cohort studies or control groups of clinical trials including women &lt;37 weeks' gestation with intact amniotic membranes.</td>
<td>Leitich, H., Kiss, H., 2007. Asymptomatic bacterial vaginosis and intermediate flora as risk factors for adverse pregnancy outcome.</td>
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women had to be screened for BV, diagnosed either by clinical criteria or by criteria based on Gram-stain findings. Outcomes were preterm delivery, late miscarriages, maternal or neonatal infections, and perinatal mortality. Fourteen new studies with results for 10,286 patients were included, so that results for 30,518 patients in 32 studies were available for this meta-analysis. BV more than doubled the risk of preterm delivery in asymptomatic patients (OR: 2.16, 95% CI: 1.56-3.00) and in patients with symptoms of preterm labor (OR: 2.38, 95% CI: 1.02-5.58). BV also significantly increased the risk of late miscarriages (OR: 6.32, 95% CI: 3.65-10.94) and maternal infection (OR: 2.53, 95% CI 1.26-5.08) in asymptomatic patients. No significant results were calculated for the outcomes of neonatal infection or perinatal mortality. Also, intermediate vaginal flora was not significantly associated with any outcome included.

In this analysis BV was significantly associated with preterm delivery in symptomatic patients admitted with a diagnosis of preterm labor, and the test of heterogeneity was not significant. Thus, BV as a marker of intrauterine infection may help to identify patients with ‘true’ preterm labor, who subsequently deliver preterm.

The results of this meta-analysis confirm that BV is a risk factor for preterm delivery and maternal infectious morbidity and a strong risk factor for late miscarriage.

doi:10.1016/j.bpobgyn.2006.12.005

Bakteriaalse vaginoosi ravi: Objectives: To assess the effects of antibiotic treatment of bacterial vaginosis in pregnancy. Selection criteria: Randomised trials comparing antibiotic treatment with placebo or no treatment, or comparing two or more antibiotic regimens in pregnant women with bacterial vaginosis or intermediate vaginal flora whether symptomatic or asymptomatic and detected through screening.

Main results: We included 21 trials of good quality, involving 7847 women diagnosed with bacterial vaginosis or intermediate vaginal flora. Treatment did not reduce the risk of PTB before 37 weeks (average RR 0.88; 95% CI 0.71 to 1.09; 13 trials, 6491 women; random-effects, T² = 0.06, P = 48%), or the risk of preterm prelabour rupture of membranes (RR 0.74; 95% CI 0.30 to 1.84; two trials, 493 women). It did increase the risk of side-effects sufficient to stop or change treatment (RR 1.66; 95% CI 1.02 to 2.68; four trials, 2323 women, fixed-effect, P = 0%). In this updated review, treatment before 20 weeks’ gestation did not reduce the risk of PTB less than 37 weeks (average RR 0.85; 95% CI 0.62 to 1.17; five trials, 4088 women; random-effects, T² = 0.06, P = 49%). In women with a previous PTB, treatment did not affect the risk of subsequent PTB (average RR 0.78; 95% CI 0.42 to 1.48; three trials, 421 women; random-effects, T² = 0.19, P = 72%). In women with abnormal vaginal flora (intermediate flora or bacterial vaginosis), treatment may

Brocklehurst P, Gordon A, Heatley E, Milan SJ.
reduce the risk of PTB before 37 weeks (RR 0.53; 95% CI 0.34 to 0.84; two trials, 894 women). Oral antibiotics versus vaginal antibiotics did not reduce the risk of PTB (RR 1.09; 95% CI 0.78 to 1.52; two trials, 264 women). Oral antibiotics had some advantage over vaginal antibiotics (whether metronidazole or clindamycin) with respect to admission to neonatal unit (RR 0.63; 95% CI 0.42 to 0.92, one trial, 156 women), prolongation of gestational age (days) (MD 9.00; 95% CI 8.20 to 9.80; one trial, 156 women) and birthweight (grams) (MD 342.13; 95% CI 293.04 to 391.22; one trial, 156 women). Different frequency of dosing of antibiotics was assessed in one small trial and showed no significant difference for any outcome assessed.

**Authors’ conclusions:** Antibiotic treatment can eradicate bacterial vaginosis in pregnancy. The overall risk of PTB was not significantly reduced. This review provides little evidence that screening and treating all pregnant women with bacterial vaginosis will prevent PTB and its consequences. When screening criteria were broadened to include women with abnormal flora there was a 47% reduction in preterm birth, however this is limited to two included studies.

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<td>Asymptomatic bacteriuria occurs in 2% to 10% of pregnancies and, if not treated, up to 30% of mothers will develop acute pyelonephritis. Asymptomatic bacteriuria has been associated with low birthweight and preterm delivery. <strong>OBJECTIVES:</strong> To assess the effect of antibiotic treatment for asymptomatic bacteriuria on persistent bacteriuria during pregnancy, the development of pyelonephritis and the risk of low birthweight and preterm delivery. Randomized trials comparing antibiotic treatment with placebo or no treatment in pregnant women with asymptomatic bacteriuria found on antenatal screening. <strong>MAIN RESULTS:</strong> Fourteen studies were included. Overall the study quality was poor. <strong>Antibiotic treatment compared to placebo or no treatment was effective in clearing asymptomatic bacteriuria</strong> (risk ratio (RR) 0.25, 95% confidence interval (CI) 0.14 to 0.48). <strong>The incidence of pyelonephritis was reduced</strong> (RR 0.23, 95% CI 0.13 to 0.41). <strong>Antibiotic treatment was also associated with a reduction in the incidence of low birthweight babies</strong> (RR 0.66, 95% CI 0.49 to 0.89) but <strong>a difference in preterm delivery was not seen.</strong> <strong>AUTHORS’ CONCLUSIONS:</strong> Antibiotic treatment is effective in reducing the risk of pyelonephritis in pregnancy. A reduction in low birthweight is consistent with current theories about the role of infection in adverse pregnancy outcomes, but this association should be interpreted with caution given the poor quality of the included studies.</td>
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Üksikuuringud

Kokkuvõte:
Retrospektiivne kohortuuring (Chalermchockchareonkit et al., 2013) leidis, et ähvardava enneaegse sünnitusega naistest 24%-l esines positiivne tupe või urini külv, kuid statistiliselt olulist erinevust enneaegsete sünnituste osas ei esinenud, mistõttu järeldati, et seesugune skriinimine on kaheldav.


Prospektiivne kohortuuring (Laxmi et al., 2012) käitles ähvardava enneaegse sünnitusega rasedate skriinimist bakteriaalse vaginoosi osas. Bakteriaalse vaginoosiga patiendid vastsündinutel esines oluliselt rohkem respiratoorset distressi, vajadust IPPV-ks, intensiivraini osakonda hospitaliseerimisi. Olulist erinevust ei leitud keskmise sünnikaalu, Apgari skoori, neonataalse sepsise, perinataalse suremuse ja sünnitusjärgse palaviku osas.

Kahe randomiseeritud kontrolluuringu sekundaarne analüüs (Tajik et al., 2014) vaatles naisi 34.-37. rasedusnädalas PPROM-iga. Leiti, et kohesest sünnitusest oleks kasu neile naistele, kel on GBS kandlus. GBS positiivsetel naistel esines jälginistaktika korral kõrge risk varaseks neonataalseks sepsiseks, kuid kui rasedus lõpetati kohe, oli risk oluliselt väiksem. GBS negatiivsetel naistel võiks sünnituse induktsiooniga oodata 37. rasedusnädalani.

Retrospektiivne uuring (Anderson 2007) leidis, et ravimata GBS bakteriuuria seostub koorioamnioniidi tekkega.

Üksikuuring

| Tai retrospektiivne kohortuuring: Cultures of genitourinary tract microorganisms have been included in routine evaluation for all pregnant women who present with presumptive preterm labor. However some studies found that this assessment is costly and adds little value. Objective: To determine the proportion of pregnant women with presumptive preterm labor who had positive culture of genitourinary tract microorganisms and to determine the relationship of positive genitourinary infection and pregnancy outcomes. Material and method: This retrospective cohort study was performed at Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital, Mahidol University. Medical records of pregnant women with presumptive preterm labor who were admitted in non-private labor room between January 2003 and December 2008 were reviewed. Characteristics, results of vaginal swab culture and urine culture, and clinical outcomes were analyzed and reported. Results: The prevalence of positive culture of genitourinary tract microorganisms in presumptive preterm labor-women (total n = 704) was 24.3% (95% CI = 21.3-27.6), 22.1% (95% CI = 19.1-25.4) of vaginal swab culture and 5.3% (95% CI = 3.8-7.2) of urine culture. However only 9.8% were pathologic organisms. | Vüide Chalermchockchareonkit, A., Phoethong, S., Ruangvutilert, P., Thamkhantho, M., 2013. Prevalence of positive culture of genitourinary tract microorganisms in pregnant women with presumptive preterm labor. J Med Assoc Thai 96, 1111–1118. |
There were no statistically significant differences in characteristics and rate of preterm labor between women with a positive and a negative culture. Moreover, there were no statistically significant differences in characteristics and preterm birth outcomes between women in both groups. **Conclusion:** There were no clinical significances of positivity of pathologic bacteria from genitourinary tract as a predictor of preterm delivery and its outcomes. Although the prevalence is quite high, the value of these screenings is still questionable.

**USA retrospektiivne juht-kontrolluuring:**
**Objective:** This study was undertaken to determine the association between genitourinary tract infection with *Chlamydia trachomatis* and spontaneous preterm birth.
**Study design:** Genitourinary tract infection with *C trachomatis* was determined with a ligase chain reaction assay of voided urine samples collected at **24 weeks' gestation** (22 weeks' to 24 weeks 6 days' gestation) and **28 weeks' gestation** (27 weeks' to 28 weeks 6 days' gestation). **Case patients** (spontaneous preterm birth at <37 weeks' gestation; n = 190) and control subjects (delivery at >/=37 weeks' gestation, matched for race, parity, and center; n = 190) were selected from 2929 women enrolled in the Preterm Prediction Study of the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network.
**Results:** Genitourinary *C trachomatis* infection (11% overall) was significantly more common among the case patients than among the control subjects at 24 weeks' gestation (15.8% vs 6.3%; P =.003) but not at 28 weeks' gestation (12.6% vs 10.9%; P =.61). Women with chlamydia infection were more likely to have bacterial vaginosis (57.1% vs 32.9%; P =.002) and a short cervical length (<25 mm; 33.0% vs 17.9%; P =.02) but not a body mass index <19.8 kg/m(2) (35.0% vs 23.9%; P =.17) or a positive fetal fibronectin test result (7.1% vs 9.5%; P =.62). After adjustment for risk factors for spontaneous preterm birth, **women with *C trachomatis* infection at 24 weeks' gestation were 2 times as likely as uninfected women to have a spontaneous preterm birth at <37 weeks' gestation** (odds ratio, 2.2; 95% confidence interval, 1.03-4.78) and **3 times as likely to have a spontaneous preterm birth at <35 weeks' gestation** (odds ratio, 3.2; 95% confidence interval, 1.08-9.57).
**Conclusion:** Genitourinary *C trachomatis* infection at 24 weeks' gestation was associated with a 2-fold to 3-fold increased risk of subsequent spontaneous preterm birth.

**India prospektiivne kohortuuring:**
**Objective:** To compare the fetomaternal outcome in women with spontaneous preterm labor, with or without bacterial vaginosis (BV).
**Methods.** One hundred and fifty-two (152 – väike valim) pregnant patients presenting with **spontaneous preterm labor between 28 and 35 weeks of gestation** were

screened for BV using Amsel’s criteria and Nugent score, and were divided into two groups of 30 patients each, based on the BV positive or negative screen. Both the groups were followed till puerperium, and the fetal–maternal outcome was studied. The data was analyzed using Chi-square test and Man–Whitney test.

**Results.** BV was detected in 37 out of 152 women with preterm labor (24.34%). There was a significant increase in the incidence of respiratory distress (14% vs. 6%), requirement of intermittent positive pressure ventilation (IPPV) (14% vs. 5%), admission in neonatal intensive care unit (NICU) (15% vs. 6%), and duration of NICU stay 42 days (15% vs. 6%) in patients with BV. No significant difference was found in the mean birth weight, Apgar score, incidence of neonatal sepsis, perinatal mortality, and postpartum fever between the two groups.

**Conclusions.** BV is a risk factor for increased neonatal morbidity. More research is needed for designing appropriate screening and treatment guidelines for prevention of adverse outcomes associated with BV.

**Hollandi 2 RCT-i sekundaarne analüüs:**

Objective: To investigate whether vaginal Group B Streptococcus (GBS) colonisation or other baseline characteristics of women with preterm premature rupture of membranes (PPROM) can help in identifying subgroups of women who would benefit from immediate delivery.

Design: Secondary analysis of the PPROMEXIL trials.

Setting Sixty hospitals in the Netherlands.

Population: Women with PPROM between 34 and 37 weeks of gestation.

Methods: Random assignment of 723 women to immediate delivery or expectant management.

Main outcome measures: Early onset neonatal sepsis.

Results: Vaginal GBS colonisation status was the only marker which was significantly associated with the benefit of immediate delivery (P for interaction: 0.04). GBS colonisation was observed in 14% of women. The risk of early onset neonatal sepsis in GBS-positive women was high (15.2%) when they were managed expectantly but this risk was reduced to 1.8% with immediate delivery. The early onset neonatal sepsis risk was much lower in neonates of GBS-negative women: 2.6% after expectant management and 2.9% with immediate delivery. We estimated that by inducing labour only in GBS-positive women, there would be a 10.4% increase in term delivery rate, while keeping neonatal sepsis and caesarean delivery rates comparable to a strategy of labour induction for all.

Conclusions: Our post hoc findings suggest that women with PROM between 34 and 37 weeks might benefit from immediate delivery if they have GBS vaginal colonisation, while in GBS-negative women labour induction could be delayed until 37 weeks.
OBJECTIVE: The objective of the study was to determine the frequency of adverse pregnancy outcomes in women with untreated asymptomatic group B beta-hemolytic streptococcal (GBS) bacteriuria during pregnancy. RESULTS: One hundred twenty-two women with bacteriuria (study group) and 183 women with negative antepartum cultures (controls) were included. Thirty-one women (10.2%) had chorioamnionitis. Untreated GBS bacteriuria was associated with chorioamnionitis after controlling for confounding variables, adjusted odds ratio 7.2 (95% confidence interval 2.4 to 21.2). There was also a significant positive rank correlation between increasing colony count of GBS bacteriuria and increasing grade of chorioamnionitis (P = .02). CONCLUSION: Untreated antepartum GBS bacteriuria is associated with chorioamnionitis.


Otsingustateegia kliinilisele küsimusele nr 6:
Otsingud Pubmedist ja lisaks oluliste viidete läbivaatamine

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<td>22.04.15 Search: ((((((pretermbirth*) OR preterm labor*) OR preterm labour*) OR preterm deliver*) OR premature birth*) OR premature labor*) OR premature labour*) OR premature deliver*) OR preterm premature rupture of membranes) OR PPROM)) AND ((((((microscopy) OR microbiology) OR (microscopy, Culture and Sensitivities)) OR MC AND S) OR swab*) OR gonorrhea) OR chlamydia) OR GBS) OR urinalysis) OR urogenital infection*) OR bacterial vaginosis)</td>
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Leidsin 3 ravijuhendit, 4 süstemaatilist ülevaadet/meta-analüüsi, 2 retrospektiivset uuringut, 1 prospektiivse uuringu