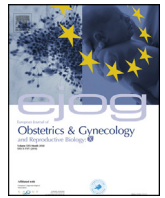




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Intrapartum PCR-assay for detection of Group B Streptococci (GBS)

Rikke B Helmig^{a,*}, Jan B Gertsen^b^a Department of Obstetrics and Gynecology, Aarhus University Hospital, Skejby, Denmark^b Department of Clinical Microbiology, Aarhus University Hospital, Skejby, Denmark

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ABSTRACT

Objective: We have recently introduced intrapartum PCR-testing for group B streptococcus (GBS) in women in labor with prolonged rupture of membranes or preterm delivery to offer intrapartum antibiotic prophylaxis only for GBS positive women.

The goal of the present study is to report our experience and results from the first half year of GBS testing. **Study design:** This is a retrospective study. Rectovaginal swabs from 321 women presenting in the labor ward with pre-labor rupture of membranes for > 14 h/rupture of membranes during delivery for > 14 h, or labor between gestational weeks 35 0/7 and 36 6/7 from February 7, 2017 to August 6, 2017, were tested. We performed a molecular GBS test (Xpert GBS[®], Cepheid Ltd., Sunnyvale, USA).

Data from patient files including mode of delivery, use of antibiotics, infection of mother and child are presented in more detail.

Data on the PCR results from the first year of testing were also collected.

Results: In the first half-year of testing a positive GBS test result was found in 58 (18.1%) and a negative test result in 263 women (81.9%). No invalid test result was achieved.

The indication for performing PCR testing was PROM > 14 h or rupture of membranes during labor for > 14 h in 266 women (82.9%) and labor in gestational weeks 35 0/7–36 6/7 in 44 women (13.7%). In the remaining 11 women, the PCR test was performed for other reasons.

Of the 321 women tested 126 (39%) received antibiotics during labor.

Ten women (3.4%) were treated after delivery on suspicion of infection. 25 newborns (7.8%) were treated with antibiotics. In 11 cases, the treatment was stopped after 2–4 days as there were no signs of infection. **Conclusions:** The introduction of the intrapartum GBS test in selected groups of women who gave birth in our department has been well accepted by the women, the midwives and doctors. The result of the test is available within two hours, and as we only offer intrapartum antibiotic prophylaxis to GBS-positive women, we have reduced the use of antibiotics to approximately 40% in the groups tested, without an increase of infection in mother or child.

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Introduction

Many pregnant women are treated with antibiotics during labor to prevent vertical transmission of Group B Streptococcus (GBS, *Streptococcus agalactiae*) to their babies during their passage through the birth canal.

Incidences of early-onset GBS disease (EOD) in newborns in Denmark is 0.1–0.3/1000 live births [2].

Abbreviations: EOD, Early-onset disease; GBS, Group B Streptococcus; IAP, Intrapartum antibiotic prophylaxis; PCR, Polymerase chain reaction; PROM, Pre-labor rupture of membranes.

* Corresponding author at: Department of Obstetrics and Gynecology, Aarhus University Hospital, Skejby, Palle Juhl-Jensen Boulevard 99, 8200 Århus N, Denmark.

E-mail address: rikke.bek.helmig@dadlnet.dk (R.B. Helmig).

There are two well-known strategies for prevention of GBS disease in newborns [3]. One strategy is based on universal screening of a pregnant woman in gestational weeks 35–37, treatment of all GBS-positive women during labor, and of women with no available test result upon arrival at the labor ward. In addition, women with a previous infant with a GBS infection or GBS bacteriuria during their current pregnancy will be treated.

The other strategy is based on risk assessment of the pregnant woman and has been used in our department until recently and is used in Denmark in general. Intrapartum antibiotics prophylaxis (IAP) is given to women with a previous infant with GBS infection, women with GBS bacteriuria during their current pregnancy, women with a temperature $\geq 38^{\circ}\text{C}$ during labor, women in preterm labor before week 37 0/7 and women with pre-labor rupture of membranes (PROM) ≥ 18 h.

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The reason for treatment during labor before week 37 0/7 is that babies born preterm are more susceptible to infection than babies born at term [3]. Treatment in cases of prolonged rupture of membranes is because of an increased risk of infection in both mother and child the longer the interval from PROM to active labor and delivery [4].

The introduction of the two preventive strategies have reduced, but not eliminated, the incidences of early-onset GBS disease in neonates.

To further reduce the incidences of EOD, it has been advised in a recent publication from a European consensus conference, to implement intrapartum antimicrobial prophylaxis based on universal intrapartum GBS screening using a rapid real-time PCR-testing method [5].

At term, approximately 10–36% of pregnant Danish women are colonized with GBS in the vagina or the rectum [6]. Perinatal transmission of GBS to the child is found in approximately 50% of colonized mothers, and one percent of exposed children contracts early-onset neonatal infection.

In an earlier publication, we evaluated the accuracy of the polymerase chain reaction (PCR) assay (Xpert GBS®, Cepheid Ltd., Sunnyvale, USA) compared to an optimized-culture method for GBS. We found that the PCR test performed very well, with a sensitivity of 100% (86.28–100%) and a specificity of 97.5% (91.26–99.70%) [7]. Consequently, we changed strategy from February 2017, and the PCR test is now performed in all women in labor with prolonged rupture of membranes at term and in women in labor in gestational weeks 35 0/7–36 6/7.

By intrapartum testing of these two risk groups and treating only those with positive tests, a reduction in antibiotic treatment is expected without an increased risk of GBS infection in the newborn. There is a strong desire to restrict the use of antibiotics for many reasons, but one of the most important being the increasing problem worldwide of antibiotic-resistant bacteria resulting in difficulties in treating even simple infections.

The goal of the present study is to report the results of the test and our procedures from the first half-year of use of the GBS test.

Materials and methods

The molecular GBS test (Xpert GBS®, Cepheid Ltd., Sunnyvale, USA) was introduced as a standard in the Department of Obstetrics and Gynecology, Aarhus University Hospital, Skejby, Denmark from February 7, 2017. The test is performed in all women in the labor ward with pre-labor rupture of membranes (PROM) for >14 h/rupture of membranes during delivery for >14 h or in labor between gestational weeks 35 0/7 and 36 6/7. The department undergoes approximately 4800 deliveries per year.

The sampling of the vaginal swabs and PCR analysis was done prospectively.

After the first half year of using the PCR test routinely in the department we retrospectively identified the women tested for GBS colonization during labor using the laboratory information system at the Department of Clinical Microbiology, Aarhus University Hospital. The overall data from the first half-year of testing from February 7, 2017 to August 6, 2017, are presented. Data from the women's files including mode of delivery, use of antibiotics, infection of mother and child and admission to the postnatal ward and neonatal intensive care unit, were extracted.

In addition, we present data on the PCR results from the first year of testing from February 7, 2017 to February 6, 2018.

Rectovaginal sampling was, in all cases, performed by midwives using the Cepheid sample collection device (Cepheid #900-0370). The double transport swab was carefully inserted into the lower third of the vagina and rotated to ensure uniform samples on both swabs before being carefully withdrawn. The same swab was then

carefully inserted 2 cm beyond the anal sphincter and gently rotated to sample anal crypts. After sampling, the swab for PCR was placed in the plastic transport tube of the Cepheid sample collection device and transported to the Department of Clinical Microbiology for immediate processing.

At the Department of Clinical Microbiology, the PCR assay (Xpert GBS®, Cepheid Ltd., Sunnyvale, USA) was performed by experienced, biomedical laboratory scientists in accordance with the manufacturer's standard operating procedures. In situations in which the processing of the first swab gave an invalid result, the second swab was processed. The result of the test was in the patient's file within 2 h of collection in all cases, and thus available to the midwife.

In order to further elucidate the safety of this procedure, an additional search was performed at the department of Clinical Microbiology, Aarhus University Hospital. Women, from 0 to 7 days with blood cultures or cerebrospinal fluid positive for GBS from February 7, 2017 to February 6, 2018 from all hospitals in the Central Denmark Region, were identified using the laboratory information system.

Ethical approval

The study was approved by the Danish Data Protection Agency (j. number 1-16-02-76-17). According to Danish legislation, quality assessment studies do not require approval from an ethics committee.

Results

In the first half-year period from February 7, 2017 to August 6, 2017, 321 women were tested, 58 (18.1%) had a positive test, and a negative test was found in 263 (81.9%). No invalid test results were found.

The indication for performing PCR testing was PROM > 14 h or rupture of membranes during labor for >14 h in 266 women (82.9%) and labor in gestational weeks 35 0/7–36 0/6 in 44 women (13.7%). In the remaining 11 women, the PCR test was performed for other reasons – most often due to suspicion of PROM for days.

266 women (82.9%) were nulliparous and 259 (80.7%) delivered vaginally.

Of the 321 women tested in the first half-year period, 126 (39%) received antibiotics during labor (Table 1). 295 (91.9%) of the women were admitted to the postnatal ward or patient hotel after delivery. 144 (48.9%) were admitted for two days and the mean admittance time for all admitted was 3.29 days. 26 (8.1%) women went home within 4–6 h after delivery. 5 women were readmitted to the maternity ward within the first week after delivery.

Ten women (3.4%) were treated after delivery on suspicion of mastitis, cystitis and endometritis.

There were four twin deliveries among the women in the study, thus data on 325 children was retrieved.

Eleven children (3.4%) were treated with antibiotics on suspicion of infection, but the treatment was stopped after 2–4

Table 1
Indication for antibiotic therapy.

	N (%)
GBS prophylaxis (positive GBS PCR test)	33 (26.2)
Fever >38 °C (negative GBS PCR test)	19 (15.1)
Prophylaxis due to Cesarean section (negative PCR test)	38 (30.2)
>1 of the above	27 (21.4)
Various (previous child with GBS disease, positive GBS culture from urine or vaginal swab in current pregnancy)	9 (7.1)
Total	126

days. Five of these mothers had positive PCR tests for GBS during delivery. 14 (4.3%) of the children were treated with antibiotics for 7 days on suspicion of infection or sepsis. In one case, coagulase negative staphylococcus was found in the blood sample. Half of these mothers [7] had positive PCR tests during delivery. One child was admitted at 23-days old due to suspicion of late-onset GBS disease. GBS was found in the blood and the child was treated for meningitis.

During the first year, PCR testing for GBS was performed in 744 women. A positive test result was found in 131 women (17.61%) and a negative test result in 610 women (81.99%). In three cases (0.4%), an invalid result was achieved.

Comment

In a recent European consensus conference, it was advised to implement intrapartum antimicrobial prophylaxis based on universal intrapartum GBS screening using a rapid, real-time, PCR-testing method [5].

In Denmark, a country with 62,000 deliveries in 2017, the strategy so far for prevention of GBS disease in newborns has been risk based. In our department, a tertiary hospital for the Central Region in Denmark, a region with approximately 25% of the deliveries in Denmark, we have chosen another strategy based on PCR testing, when certain risk factors in labor are present.

In the first half year period we tested 321 women with the PCR test. We have described details on mother and child for these. To evaluate the expected use of the PCR test in a department with approximately 4800 deliveries, we also included data on the test result from the whole first year of testing. In the first year of use of the intrapartum PCR GBS tests, we performed 744 tests. Thus approximately 15% of the women in labor are tested, which is what we expected when taking the risk factor into account.

The rectovaginal swab was positive for GBS in 18% of the women tested. This is in accordance with earlier studies on the colonization rate with GBS in pregnant Danish women between 10–36% [6,7].

It is a strength of our study, that we had extremely few instances of PCR test with invalid answers compared to others. In our setting, the PCR test is performed by experienced laboratory scientists and during the first year we had less than 0.5% with an invalid answer.

Other studies have shown that the rate of invalid test results was high when the test was performed at the labor ward and could be reduced when performed in a laboratory. In phase 2 in the study by Håkonsson [8] they had 15% of invalid answers, most due to the handling of specimens. In the study by Mueller [9] with testing at the labor ward, they reduced the number of invalid answers from 23.5% to 13.4%. In a recent publication, in which performances of Xpert® GBS polymerase chain reaction (PCR), in labor wards were compared to standard cultures for intrapartum GBS detection, the conclusion stressed that laboratory training of non-specialized staff is mandatory to meet the performances required for point-of-care tests [10].

As another strength of our study, the results of the PCR test were available in the patient files within two hours of testing.

In most cases, the indication for performing the PCR GBS test was PROM > 14 h or rupture of membranes during labor for > 14 h. We chose to test after 14 h, because we expected to have the result of the PCR test within a few hours. If the result was positive, we could treat the woman with IAP within 18 h according to the Danish national guideline.

It is a drawback, that the study retrieved the information from the patient's files retrospectively, but a strength, that data was available for all 321 mothers and 325 children concerned in the first half year of using the PCR test. We thoroughly reviewed the

patient files for both mother and child to ensure we did no harm in altering our strategy for prevention of EOD.

Before the test was introduced, all women with risk factors for GBS infection were treated with antibiotics during labor and, where admitted, for at least 48 h at the postnatal ward for observation of the child.

After introduction of the intrapartum GBS test, we are able to document a 60% reduction in the use of antibiotics in the two groups of women tested. As seen in Table 1 it is not only GBS positive women who were treated with antibiotics. Nearly half of the women treated were GBS negative but treated according to guidelines because of fever during labor or with prophylaxis before Cesarean section. Eight percent of the women, mostly multipara, went home within 4–6 hours after delivery. All nulliparous women are offered two or more days in the postnatal ward in our department. As 83% of the women tested fell into this category, we did not expect them to go home after delivery. The introduction of the test, however, makes it possible for GBS negative women to give birth in the hospital and go home within a few hours after delivery, whether they are nulliparous or multiparous.

We had few cases of infection in the mother after delivery. None of these infections were serious and in no case was GBS isolated.

In the first half-year period, 25 children were treated with antibiotics after delivery. In nearly half of the cases, the treatment was stopped within 2–4 days as there were no signs of infection. GBS was not isolated in any of the blood cultures or cerebrospinal fluids taken from these children. Only in one case was bacteria found in the blood, and most likely this was due to contamination.

When searching the database in the first year of testing, there were no cases of blood cultures positive for GBS in the first week after delivery and thus no cases of EOD in our hospital. Before the introduction of the intrapartum GBS test, children of mothers with risk factors, in accordance with international guidelines [3], had blood samples taken 12 h after birth if the mothers had not received antibiotics more than 4 h before delivery. After introduction of the intrapartum GBS test, fewer children had blood samples taken in the postnatal ward after delivery as the mothers were found to be GBS negative. This is considered as an improvement by both parents and nursing staff.

We believe that the results presented here support the introduction and use of the intrapartum GBS test in selected groups of women giving birth in our department. We believe that the strategy is safe. We do not think that universal intrapartum GBS testing is warranted in Denmark as the incidence of early-onset GBS disease is very low, and universal screening would increase the number of women in labor receiving antibiotics. The latter is highly controversial as an increased use of antibiotics may increase the risk of resistant bacteria and cause harm to the neonate. The introduction of universal intrapartum screening for GBS may also increase costs [10,11]. Introduction of the test has made it possible for us to reduce the number of women unnecessarily receiving IAP without increasing the risk of infection with GBS in newborns. In addition, significantly fewer infants have been exposed to antibiotics during their birth, which may result in less disturbance of their microbiome.

We find the logistics with the midwife performing the rectovaginal swab in the labor ward, the experienced biomedical laboratory scientists performing the test in the Department of Clinical Microbiology around the clock, and the results being available in the patient file within two hours, are ideal results.

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Declarations of interest

None.

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