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Reduction of intrapartum antibiotic prophylaxis by combining risk factor assessment with a rapid bedside intrapartum polymerase chain reaction testing for group B streptococci

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Neonatal sepsis
Antibiotic Prophylaxis
Infectious Disease Transmission, Vertical
Labor, Obstetric
Polymerase Chain Reaction
Antimicrobial Stewardship
ABSTRACT

Objective: To investigate the impact of administering Intrapartum Antibiotic Prophylaxis (IAP) to laboring women with one or more risk factors for Early Onset Group B Streptococcal neonatal infection (EOGBS) based on the result of a rapid bedside test for Group B Streptococci (GBS).

Study design: Quality assessment study.

Methods: Three-hundred-sixty-six laboring women admitted to our maternity ward, with one or more risk factors for EOGBS, were prospectively included. Rectovaginal swab-samples were examined bedside by the GenomEra® GBS Polymerase Chain Reaction (PCR) assay upon admission. Time from administration of IAP to delivery was registered. According to national guidelines, one-hundred-two women mandatorily received IAP independent of the PCR test result fulfilling one of the following three risk factors: prior infant with EOGBS, preterm labor before 35 gestational week, temperature $\geq 38^\circ$C during labor. Women with GBS bacteriuria during current pregnancy, rupture of membranes $\geq 18$ hours IAP, and preterm labor between 35-37 gestational week, received IAP solely if the PCR test was positive. Predictive values were calculated for each risk factor.

Results: Previous GBS bacteriuria was strongly associated (PPV=71%) with a positive GBS PCR test, whilst the corresponding positive percent of ROM$\geq 18$ hours and of GA 35-37 was only PPV=16% and 22%, respectively. Seventy-four women, 74/251 (31%), received IAP because they were GBS PCR positive. IAP was thus reduced by about two-thirds compared to the risk-based strategy of offering IAP to all women with one or more risk factors for EOGBS. Two women, 2/254 (0.8%), received inferior care, as they did not receive IAP within the recommended 4 hours prior to delivery due to the extra time spend on the test procedure.

Conclusion: Bedside intrapartum PCR testing of women with risk factors for EOGBS effectively diminishes use of IAP during labor compared to the present risk factor-based strategy alone. In this project, the extra time spend on the PCR test procedure did not lead to noticeable delay in IAP.

ABBREVIATIONS
GBS = Group B Streptococci
PCR = Polymerase Chain Reaction
IAP = Intrapartum Prophylaxis
EOGBS = Early Onset Group B Streptococci
GA = Gestational Age
ROM = Rupture of Membranes
1. INTRODUCTION
Early Onset Group B Streptococcal neonatal infection (EOGBS) affects 0.23-3.0 per 1,000 live births and accounts for an estimated 410,000 disease cases and 147,000 preventable stillbirths and infant deaths globally each year [1]. The recto-vaginal colonization rate of group B streptococci (GBS) in pregnant women varies from 10-35%, and without intervention, approximately 50% of the children born by colonized mothers will become colonized. One percent of the colonized children will develop EOGBS, with a mortality rate of 4-10% [2-7]. There are two well-known strategies for identifying pregnant women with infants at increased risk of EOGBS: 1) antepartum culture-based GBS rectovaginal screening at 35-37 weeks’ gestation, and 2) a risk-based approach depending on the presence of one or more of the five risk factors for EOGBS: GBS bacteriuria during current pregnancy, preterm labor < 37 gestational weeks (GA), and rupture of membranes ≥18 hours (ROM), prior infant with EOGBS, temperature ≥38.0°C during labor [2, 8, 9].

Intrapartum antibiotic prophylaxis (IAP) effectively diminishes the perinatal vertical transmission of GBS to the child and is shown to reduce the incidence of EOGBS [2].

The correlation between antibiotic treatment in early life and disturbances in the microbiota of the intestine of the infants is receiving increased attention and concern as it may affect several aspects of child health [10, 11].

According to national guidelines, IAP administration must be conducted 4 hours before delivery to ensure an adequate bactericide concentration in the fetus [2, 12].

The GenomEra® GBS Polymerase Chain Reaction (PCR) assay had been implemented in our department as a standard regime for intrapartum testing about one year prior to the initialization of the study. The turnaround time for the analyses was 50 min [13].

The aim of this study was to investigate the impact on administering IAP to laboring women based on combining the risk-based strategy with the result of a rapid intrapartum GenomEra® GBS PCR assay performed bedside on a rectovaginal sample from women having risk factors for EOGBS neonatal infection.

2. MATERIALS AND METHODS
2.1 Study settings and population
This study is a quality assessment study in the maternity ward after implementation of a new treatment modality. During the period from November 28th 2018 to July 1st 2019, all laboring women at the maternity ward at Lillebaelt University Hospital, Kolding, Denmark were
consecutively included if they fulfilled the criteria. The cohort consists of 366 women with one or more risk factors for EOGBS is described in Fig 1.

2.2 Inclusion criteria

Laboring women were included if they presented with one or more of the following risk factors for EOGBS: GBS bacteriuria during current pregnancy, preterm labor < 37 gestational weeks (GA), and rupture of membranes ≥18h (ROM), prior infant with EOGBS, temperature ≥38.0°C during labor.

2.3 Exclusion criteria

Women younger than 18 years, women with a communication barrier, *fetus mors*, and pregnant women who had cesarean section.

**Fig 1.** Flowchart of the cohort

2.4 Methods

Time of arrival to the labor ward, risk factors, time of administration and time of delivery were recorded. Trained midwives performed and handled the rectovaginal samplings prior to administration of IAP. After inserting the swab in the lower one-third of the vagina and subsequently in the rectum 2 cm beyond the anal sphincter, it was rotated to ensure sampling of material from crypts. The samples were analyzed by the GenomEra® GBS PCR assay that detects all known clinically relevant GBS isolates. The assay takes approximately 50 minutes including the final reporting of results. Use of GenomEra® has been thoroughly described previously by S.Y. Nielsen et al [14].

2.5 Ethical clearance

This study describes a routine use of GBS PCR and IAP in a Danish group of laboring women. According to Danish legislation, quality assessment studies do not require approval from an ethics committee. The Science Ethics Committees for the Region of Southern Denmark decided that the project is not subject to notification to the scientific ethics committee system, cf. section 14, subsection 1 of the Act on the ethical treatment of health-science research projects and has confirmed no need for approval. Case number 20202000-50. After thorough information by a doctor, informed consent was expressed verbally by all participants in the presence of the doctor and a midwife and was in all cases documented in the electronic medical record of the women.

2.6 Statistics and calculations

Sample size and power calculation were not performed before study initiation. Positive and negative predictive values were calculated for each risk factor.
3. RESULTS

The mean age of women was 29.9 years (range 19-43 years). PCR results and predictive values for the three risk factor groups are listed in table 1 and illustrated in figure 2.

Table 1

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>PCR results</th>
<th>Predictive values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>GBS bacteriuria</td>
<td>41/58</td>
<td>17/58</td>
</tr>
<tr>
<td>ROM&gt;18 hours</td>
<td>26/161</td>
<td>135/161</td>
</tr>
<tr>
<td>GA 35-37</td>
<td>7/32</td>
<td>25/32</td>
</tr>
<tr>
<td>Total</td>
<td>74/251</td>
<td>177/251</td>
</tr>
</tbody>
</table>

Fig 2 Distribution of positive and negative PCR test results in the three risk factor groups.

Table 2 shows the proportion of the 74 PCR positive women receiving IAP > 4 hours versus < 4 hours before delivery.

Table 2 Administration of IAP in relation to time of delivery

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Received IAP before delivery</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 4 hours</td>
<td>&lt; 4 hours</td>
</tr>
<tr>
<td>Number of women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GBS bacteriuria</td>
<td>12 (29%)</td>
<td>29 (71%)</td>
</tr>
<tr>
<td>ROM&gt;18 hours</td>
<td>14 (54%)</td>
<td>12 (46%)</td>
</tr>
<tr>
<td>GA 35-37</td>
<td>3 (43%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>Total</td>
<td>29 (39%)</td>
<td>45 (61%)</td>
</tr>
</tbody>
</table>

ROM= rupture of membranes, GA = gestational age

Among the 45 women that received IAP less than four hours before delivery (see Table 2), 21 spent more than four hours at the labor ward of which 7 did not receive IAP due to the extra time spend on the test.
The electronic medical records of the seven women who arrived at the labor ward in time (> 4 hours before giving birth) but did not receive IAP > 4 hours before delivery, were thoroughly investigated. We observed the following reasons:

- Two women, 2/251 (0.8%), because of extra time spent on the PCR testing procedure (one with risk factor GA 36+2 and rapid birth, and the other with GBS bacteriuria and induction of labor at GA 41+5 by amniotomy).
- Three patients, 3/251 (1.2%), because IAP was administered too late after a positive PCR result was available, presumably due to bustle at the ward.
- Two patients, 2/251 (0.8%), would not have received IAP > 4 hours before delivery regardless of the PCR test procedure. One woman with ROM>18 hours gave birth less than four hours after fulfilling this risk factor, and one woman with GBS bacteriuria and rapid birth three hours and 50 minutes after induction of labor at GA 41+5 by amniotomy.

4. DISCUSSION

We found that GBS bacteriuria was the risk factor with the strongest positive predictive value for actual rectovaginal GBS colonization with a positive percent of 71, and ROM>18 hours to be the weakest with a positive percent of 16. Overall, a reduction in the use of IAP by 70.5 % was achieved by use of the intrapartum PCR test for GBS among laboring women with risk factors for EOGBS. According to national guidelines, 102 women mandatorily received IAP independent of the PCR test result fulfilling one of the following three risk factors: prior infant with EOGBS, preterm labor before 35 gestational weeks, temperature ≥38°C during labor. Women with a negative intrapartum GBS PCR test who developed fever during labor were treated with antibiotics with broader coverage than penicillin (ampicillin plus gentamicin) according to national guidelines.

We investigated the proportion of women with a risk factor for EOGBS potentially receiving inferior IAP due to extra time spend on the testing procedure. Two pregnant women with risk factors received inferior care as they did not receive IAP > 4 hours in accordance with guidelines even though they were present at the labor ward for > 4 hours. One of these two women received IAP > 2 hours. None of the children from this study developed EOGBS.

Twenty-one of the GBS PCR positive women were present at the ward for more than four hours and did not receive IAP > 4 hours before delivery; however, 13 of them received IAP more than 2 hours before delivery. The timing of administration of IAP and rationale behind IAP > 4 hours before delivery have received only limited attention. Conflicting results seem to exist in the literature. Some
studies find that administration of IAP closer to delivery than four hours seems to have some beneficial effect after all. Boyer KM et al showed that ampicillin >1 hour prior to delivery eliminated vertical transmission [15]. De Cueto M et al concluded that when the time between the start of ampicillin prophylaxis and delivery is at least 2 hours, vertical transmission of GBS is minimized [16]. Lin F. et al found that the overall effectiveness of IAP was 86% (95% CI: 66%-94%), and that the effectiveness of IAP increased to 89% (95% CI: 70%-96%) if IAP was administered > 2hours before delivery [17]. Berardi A et al. concluded that timely inadequate prophylaxis significantly interrupted vertical colonization, and the effect was evident even if prophylaxis was started <2 hours before delivery [18]

The relatively modest size of the cohort might be considered a limitation of the study. However, our findings are in accordance with resent findings of Rosenberg et al [13] conducted at the same hospital the year before. Larger studies are necessary to conclude on prevention of rare outcomes as delay of IAP as for the risk of newborns developing EOGBS.

It is a strength of our study that trained midwives collected the samples and performed the GBS PCR tests themselves. This makes the testing setup applicable in the clinical practice, as it can be performed immediately upon admittance to the ward, regardless of the presence of a doctor. Therefore, it does not interrupt the workflow and the delay of IAP initiation is minimal.

An important issue in the dilemma regarding the choice of approach is that many cases of EOGBS occur in infants of mothers with no previous risk factors. With this bedside technique, it might be possible to perform PCR GBS test on all laboring women in high-risk countries or areas where perhaps antibiotics are accessible but intensive care unit of an infant with EOGBS is not.

5. CONCLUSIONS
The intrapartum GBS PCR test procedure led to a reduction in the use of IAP by 70.5%, however, two women received inferior care, as they did not receive IAP within the recommended 4 hours. Our data may indicate that the extra time spend on the PCR test procedure does not lead to noticeable undertreatment.
6. AUTHOR CONTRIBUTIONS

Conceptualization: C. M. Hartvigsen

Data curation and formal analysis: C. M. Hartvigsen, M. R. Khalil

Methodology: C. M. Hartvigsen, M. R. Khalil, J. K. Møller, S. Y. Nielsen

Project administration: C. M. Hartvigsen, M. R. Khalil

Resources: C. M. Hartvigsen, M. R. Khalil

Software: C. M. Hartvigsen, M. R. Khalil

Supervision: M. R. Khalil, J. K. Møller, S. Y. Nielsen

Writing original draft: C. M. Hartvigsen

Writing – review and editing: C. M. Hartvigsen, M. R. Khalil, J. K. Møller, S. Y. Nielsen

7. ACKNOWLEDGMENTS

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8. CONFLICT OF INTEREST

C. M. Hartvigsen: Declare no conflicts of interests.

S. Y. Nielsen: Declare no conflicts of interests.

J. K. Møller: Declare no conflicts of interests.

M. R. Khalil: Declare no conflicts of interests.

9. REFERENCES

[Dataset] Authors; M.R. Khalil and C.M. Hartvigsen, 2018-2019. Dataset title; PCR in advance of IAP administration. Data repository at shelve 1, office 22nd, Department of Gynecology and Obstetrics, Kolding Sygehus, University Hospital of Southern Denmark, Kolding, Denmark.


**Fig 2.** Flowchart of the cohort

![Flowchart of the cohort](image)

**Fig 2 Distribution of positive and negative PCR test results in the three risk factor groups.**
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J. K. Møller: Declare no conflicts of interests.
M. R. Khalil: Declare no conflicts of interests.

HIGHLIGHTS
- GBS bacteriuria was strongly associated with a positive PCR test, PPV 71%
- ROM>18 hours was weakly associated with a positive PCR test, PPV 16%
- IAP was reduced by two-thirds compared to the risk-based strategy
- Extra time spend on the PCR test did not lead to noticeable undertreatment