

Original Article

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Risk-based screening and intrapartum group B streptococcus polymerase chain reaction results reduce use of antibiotics during labour

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ABSTRACT

INTRODUCTION: This study investigated the feasibility of a risk-based screening approach combined with testing of Group B streptococcus (GBS) by polymerase chain reaction (PCR), the effect on use of intrapartum antibiotic prophylaxis (IAP) and the impact on the incidence of early-onset GBS infection (EOGBS).

METHODS: During one year, 551 women giving birth at Lillebaelt Hospital, Denmark, having one or more risk factors for EOGBS (previous birth of infant with EOGBS, GBS bacteriuria during current pregnancy, gestational age < 37 weeks, rupture of membranes > 18 hours, and temperature $\geq 38^\circ\text{C}$) were tested by a GBS PCR assay intrapartum. IAP was administered when the woman tested positive.

RESULTS: Among 2,889 women in labour, 19.1% (n = 551) had one or more risk factors for EOGBS, and 5.1% (n = 146) had both risk factors for EOGBS and a positive intrapartum GBS PCR test. In total, 185 women with risk factors for EOGBS received IAP. If the former *risk-based approach* had been applied, 551 women giving birth would have received IAP. Implementing IAP based on the GBS PCR results produced a two-thirds reduction of IAP. No children were diagnosed with EOGBS.

CONCLUSIONS: The GBS PCR assay was easy to perform and provided test results within 50 minutes. Implementation of risk-based screening combined with intrapartum GBS PCR testing reduces the use of IAP by two thirds compared with risk-based screening alone, thus minimising antibiotic resistance. The study material was too small to evaluate the effect on the incidence of EOGBS. Since EOGBS is a rare disease, more studies are required.

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TRIAL REGISTRATION: not relevant.

Streptococcus agalactiae or Group B streptococcus (GBS) is the cause of early-onset infection (EOGBS), which is associated with significant morbidity and mortality in infants [1]. GBS is commonly found in the gastrointestinal and genital tract of pregnant women, where the rate of colonisation varies from 10% to 30% [2]. Without any

intervention, approximately 50% of babies born by colonised mothers become colonised, and about 1% develop invasive disease [3]. Intrapartum antibiotic prophylaxis (IAP) is the most effective available intervention against EOGBS. International guidelines outline two main strategies for identification of women who should be offered IAP; a *risk-based approach* and an *antepartum culture-based screening approach* [2].

The risk-based approach relies on five risk factors: 1) previous infant with EOGBS, 2) GBS bacteriuria during the current pregnancy, 3) temperature > 38 °C during labour, 4) rupture of membranes (ROM) > 18 hours or 5) delivery at < 37 weeks of gestation [2]. However, a substantial fraction of the women in labour who are at risk according to this approach are GBS-negative at delivery [4-6]. The culture-based screening approach recommends screening at 35-37 weeks of gestation for GBS recto-vaginal colonisation. IAP will be offered to positive carriers at labour. Despite the widespread implementation of IAP, 60-80% of cases with EOGBS occur among term infants born to mothers who screened GBS-negative before giving birth [7-9].

Methods with more rapid and accurate identification of GBS carriers at labour may reduce the use of IAP. Prenatal or early use of antibiotics cause growing paediatric concern [10, 11], and reduction of antibiotic use is essential to minimise spread of antibiotic-resistant bacteria. Real-time polymerase chain reaction (PCR) tests for rapid intrapartum detection of GBS have a high sensitivity and specificity. In recent studies, the applied PCR assay has been shown to have a sensitivity of 79.1-92.2% and a specificity of 99.6% [12, 13]. GBS detection based on PCR testing overcomes some of the limitations associated with either risk-based or antepartum culture-based screening and offers point-of-care tests for intrapartum screening at the labour ward.

Recently in a labour ward in Denmark, intrapartum PCR-testing for GBS in women with pre-labour rupture of membranes for > 14 hours, rupture of membranes during delivery for > 14 hours or preterm delivery week 35 + 0 – 36 + 6 was introduced to offer IAP to GBS-positive women only. The new procedure was well accepted, reduced antibiotic use and did not lead to an increase in infection rates in mothers or babies [14].

The aim of this study was 1) to investigate the reduction of IAP based on positive test results of an intrapartum GBS PCR assay on rectovaginal swabs obtained from women with EOGBS risk factors, and 2) to observe if this new screening strategy affected the incidence of EOGBS during the study period.

METHODS

This descriptive observational study was conducted at Lillebaelt Hospital, Kolding, Denmark. Unselected women giving birth in the study period from April 2017 to March 2018 were included if one or more risk factors for EOGBS were found. Women delivering by planned Caesarean section were not considered for inclusion. Data on the following characteristics were collected: previous infant with EOGBS disease, GBS bacteriuria during current pregnancy, gestational age at delivery, duration of ROM, temperature ≥ 38 °C and whether newborns received a diagnosis of EOGBS disease.

Women giving labour who presented with one or more risk factors were administered IAP according to the study protocol, as presented in **Table 1**. A second dose was given after four hours and then every two hours until delivery. If the GBS PCR test was inconclusive (neither negative nor positive), a repeat test was performed. In case of inconclusive PCR test results, the women were also treated with IAP. According to the national guideline on risk factors of EOGBS disease, the study intention was to offer IAP when labour occurred before GA 34 weeks or in cases with previous EOGBS.

TABLE 1 / Study protocol for intrapartum antibiotic treatment^a.

GBS PCR test	Temperature		
	< 38 °C	≥ 38 °C	≥ 38.5 °C
<i>GA ≥ 34 + 0</i>			
Positive	IV penicillin	IV penicillin	IV penicillin + IV gentamicin
Negative	No prophylactic GBS treatment	IV ampicillin	IV ampicillin + IV gentamicin
<i>GA < 34 + 0</i>			
Positive	IV penicillin + oral metronidazole	IV penicillin + oral metronidazole	IV penicillin + IV gentamicin + oral metronidazole
Negative	IV ampicillin + oral metronidazole	IV ampicillin + oral metronidazole	IV ampicillin + IV gentamicin + oral metronidazole

EOGBS = early-onset GBS infection; GA = gestational age; GBS = Group B streptococcus; IV = intravenous; PCR = polymerase chain reaction.

a) Women with a previous child with EOGBS should be treated with IV penicillin.

A recto-vaginal specimen was obtained from women in labour with one or more risk factors for EOGBS. In case of ROM, the swab was performed after 17 hours to have the test result ready after 18 hours. The midwife inserted and rotated an E-Swab 1.5-2 cm inside the vagina and then in the rectum 1.5-2 cm beyond the anal sphincter. Midwives were trained to uniformly collect samples and perform the PCR assay on an instrument installed in the labour ward. The subsequent implementation of the technique was carefully monitored, and potential handling problems were noted.

The GBS assay is an in vitro diagnostic nucleic acid test for qualitative detection of GBS. The assay takes about 50 minutes to complete and was performed using specimens collected in Copan eSwab transport medium without prior broth enrichment. In case of inconclusive results, a new recto-vaginal specimen was obtained and re-tested immediately.

Newborns with suspicion of infection were admitted to the neonatal intensive care unit. Following sampling of blood and tracheal secretion for culture, antibiotic treatment was initiated when the neonatologist on duty found it appropriate. Microbiological assessment of spinal fluid was supplied on suspicion of meningitis. All newborns of women with one or more risk factors for EOGBS were observed in hospital for 48 hours. EOGBS was defined by culture of GBS from cerebrospinal liquid and/or blood from the infant.

The present study was performed in the maternity ward as an implementation of a new treatment modality and as a quality assurance measure. The implementation was based on earlier studies approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20130089). The Danish Data Protection Agency approved this prospective, descriptive observational study (2008-58-0035). All women included provided informed consent [4].

Trial registration: not relevant.

RESULTS

Between April 2017 and March 2018, 3,152 women gave birth at Lillebaelt Hospital. Within this group, 263 women delivered by planned Caesarean section, whereas the remaining 2,889 were considered for inclusion. Among the latter, 19.1% (n = 551) had one or more risk factors for EOGBS and were finally included in the study.

The distribution of risk factors is shown in Table 2. The PCR test for GBS was positive in 27% (146/551) of all cases with one or more risk factors for EOGBS; however, among women with GBS bacteriuria during their current pregnancy, 70% were positive versus only 13% among women with ROM for more than 18 hours (Table 2). Overall, 5.1% (146/2889) had both risk factors for EOGBS and a positive intrapartum GBS PCR test.

A total of 128 of the 146 women (88%) with a positive GBS PCR test received IAP, primarily intravenous penicillin. However, for 12% of women with a positive GBS PCR test (18/146), the GBS PCR result was not yet available before a rapid labour took place.

TABLE 2 / Intrapartum polymerase chain reaction test results from women with one or more risk factors for Group B streptococcus.

Risk factor	Intrapartum PCR GBS test, n (%)			Total, N (%)
	negative	positive	missed test	
GBS in urine	29 (28)	73 (70)	2 (2)	104 (100)
Preterm delivery < 37 wks	92 (88)	11 (10)	2 (2)	105 (100)
ROM > 18 h	220 (87)	34 (13)	0	254 (100)
Temperature > 38 °C	37 (76)	11 (22)	1 (2)	49 (100)
Previous child with EOGBS	4 (57)	2 (29)	1 (14)	7 (100)
> 1 risk factor	16 (50)	15 (47)	1 (3)	32 (100)
Total	398 (72)	146 (27)	7 ^a (1)	551 (100)

EOGBS = early-onset GBS infection; GA = gestational age; GBS = Group B streptococcus; IV = intravenous; PCR = polymerase chain reaction; ROM = rupture of membranes.

a) In total, 7 tests were missed due to repeated inconclusive results, failure to repeat test, and failure to perform swab.

During labour, 12% (n = 65/551) of all women with risk factors had a temperature of 38.0 °C or higher. Among the 65 women with a temperature of 38 °C, 16 women had more than one risk factor (14 women with ROM > 18 hours, one woman with GBS in urine and one woman with preterm delivery < 37 weeks). All women with a temperature of 38.5 °C or higher who were GBS PCR-negative (n = 5) were treated with a combination of gentamicin and intravenous ampicillin according to the study protocol (Table 1). Only 23.6% of the women with a temperature 38.0-38.4 °C had a positive GBS PCR result compared with 50% of the women with a temperature of 38.5 °C or higher (Table 3).

TABLE 3 / Intrapartum polymerase chain reaction test results among 65 women with fever during labour.

Risk factor	Temperature, n (%)	
	38.0-38.4 °C	≥ 38.5 °C
Positive for GBS	13 (23.6)	5 (50)
Negative for GBS	41 (74.6)	5 (50)
Missed test	1 (1.8)	0
Total	55 (100)	10 (100)

GBS = Group B streptococcus.

Among the seven women with a previous infant with EOGBS disease, four were treated with IAP, whereas three women did not receive IAP. In total, 119 women gave birth before GA 37 + 0. Within this group, 27 women gave birth before GA 34 + 0. Among women giving birth before GA 34 + 0, a positive PCR test was found in four cases, and those four women were treated with IAP. In 23 cases, the PCR test was negative, and 12 of those women were treated with IAP, whereas 11 women did not receive IAP.

In total, 23 of 551 primary PCR tests (4%) were unsuccessful. Three tests were still inconclusive after repeat testing, whereas three tests were not repeated because of rapid labour. In one case, the midwife failed to perform the swab. Thus, seven tests were missed (Table 2). Of the seven women with missed tests, six received IAP.

Among the 551 women in the study population with one or more EOGBS risk factors and supposed targets for IAP according to the *risk-based approach*, only 185 women were treated with IAP. Thus, the use of antibiotics was reduced to about 34% of previous IAP practice. Of note, 57 women with risk factors received IAP despite a negative GBS PCR test.

Within the study period (one year), no children were diagnosed with EOGBS. During the previous five years, six children had EOGBS (one child in 2012, three children in 2015 and two children in 2016).

Upon completing proper training, the midwives were able to implement the intrapartum GBS PCR screening without any observed handling problems.

DISCUSSION

In an unselected group of Danish women in labour, the proportion of women with known risk factors for having a child with EOGBS and who were thus targets for IAP was reduced to one third by implementing intrapartum GBS PCR screening. No cases of EOGBS, defined as newborns with GBS detected by culture of blood or cerebrospinal fluids, were found during the study period. This indicates substantial overtreatment with antibiotics if everyone with EOGBS risk factors is offered IAP in accordance with the risk-based approach.

The prospective cohort design and the relatively high number of participants are the strengths of our study. These strengths allow us to draw conclusions about the feasibility of implementing IAP based on the results of the intrapartum GBS assay on women with EOGBS risk factors. Furthermore, our prospective GBS screening study has been performed bedside in a busy labour ward, which contributes to a realistic insight into implementation of a simple and rapid intrapartum point-of-care GBS PCR assay. The weaknesses of our study are the observational design and the size of the material, which is too small to evaluate the effect on EOGBS.

In the present study, the majority of women with one or more risk factors who had a positive GBS PCR test received IAP. However, 12% did not receive IAP regardless of a positive PCR test for GBS. In many cases, this was due to birth taking place before a PCR result was available and, in few cases, it was due to a busy ward.

Women giving birth rapidly are a challenge, which underscores the importance of a fast PCR assay and focused attention to risk factors on arrival to the labour ward. This goal was obtained for 88% of the women with one or more risk factors for EOGBS. We suggest that women with one or more risk factors who are at an advanced stage of labour on arrival at the labour ward are offered IAP immediately and do not await the result of the PCR test. This is one of the reasons why 57 women received IAP despite a negative PCR test. Another reason was that IAP was offered to women with GBS risk factors, a temperature of 38.5 °C or higher and a negative PCR test.

Fever during labour occurred in 2.3% of the labouring women in the present study, which is in accordance with the 3.3% seen in earlier studies [2]. Romero et al found GBS in cultures from amniotic fluid in 19% of women with clinical chorioamnionitis at term (defined as a maternal temperature of 37.8 °C or higher and at least two of the following criteria: uterine tenderness, malodorous vaginal discharge, foetal or maternal tachycardia or maternal leukocytosis) [15]. Our findings suggest an almost similar prevalence of chorioamnionitis with GBS (22%) defined by a high maternal temperature and the positive results of a GBS PCR assay on rectovaginal swabs.

In our study, trained midwives performed the PCR test in the labour ward. Only 23 of 551 primary PCR tests (4%) were unsuccessful. In the study by Helmig et al, samples were analysed by experienced laboratory staff and only 0.4% had an invalid PCR test result [14]. However, Håkonsson et al and Mueller et al, who also ran the PCR tests in the labour ward, had about 15% invalid test results [16, 17]. These results stress the importance of sufficient training of midwives. However, running the GBS PCR assays as point-of-care tests in the labour ward may save critical time spent on sample transportation to a laboratory and awaiting the test result.

Remarkably, this study ended up testing a regime more vigorous than intended. The study design included IAP to all preterm births before GA 34 weeks/births with previous EOGBS, but the majority received IAP guided by intrapartum GBS results. A total of 14 women with negative GBS PCR did not receive IAP. Luckily, the unintended under-treatment did not result in any cases of EOGBS, but the data are far too small to conclude that this is a safe approach.

CONCLUSIONS

Implementation of GBS PCR tests among women giving birth who have risk factors for EOGBS would reduce the use of IAP by two thirds compared with the risk-based approach alone. The material was too small to evaluate an effect on the incidence of EOGBS. Since EOGBS is a rare disease, more studies with larger populations are required to evaluate the effect on EOGBS. Furthermore, it is also important to evaluate the incidence of other birth-related infections when reducing the use of IAP.

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