Chapter 3

Preterm labor and/or prolonged rupture of membranes is not associated with antenatal carriage of Group B Streptococcus (GBS)

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ABSTRACT

Background Up to 36% of pregnant women is colonized with GBS. Labor before 37 weeks of gestation, rupture of membranes for more than 18-24 hours, intrapartum temperature of > 38°C, maternal GBS bacteriuria during pregnancy and a history of a previous child with invasive neonatal GBS disease are established risk factors for early onset neonatal GBS disease (GBS-EOD). Dutch guidelines do not recommend general screening, but in case of preterm labor and prolonged rupture of membranes, they advise to start intrapartum antibiotic prophylaxis if GBS cultures are positive. However, childbirth frequently occurs before culture results are available and therefore opportunities for prevention of GBS-EOD can be missed.

Objective The objective of this study was to evaluate whether the occurance of labor before 37 weeks of gestation or prolonged rupture of membranes can predict maternal GBS carriage.

Study Design From 1702 pregnant women rectovaginal swabs were collected at 35-37 weeks' gestation, with the assumption that GBS status at 35-37 weeks is a good indicator for GBS status during labor.

Risk factors for GBS-EOD were registered during labor. To assess whether the occurrence of preterm labor or prolonged rupture of membranes was associated with GBS carriership, four-fold prognostic tables were constructed.

Results Prevalence of GBS colonization in our population was 21.4%. At least one of the five established risk factors for GBS-EOD was present in 12.2% of women. For preterm labor and for prolonged rupture of membranes odds ratios for GBS colonization were RR 1.35 (95% CI 0.77-2.37) and RR 0.82 (95% CI 0.55-1.21) respectively. Women with one of these risk factors alone or in combination do not show a higher risk on GBS colonization.

Conclusions Prevalence of GBS colonization in pregnant women in our population is 21.4%. The risk factors preterm labor between 35 and 37 weeks of pregnancy and prolonged rupture of membranes after 35 weeks separately or combined do not show association with GBS carriage at 35-37 weeks. Occurrence of one of these risk factors during labor does not predict GBS carriage and is therefore not helpful in identifying mothers at higher risk for a baby with GBS-EOD.

INTRODUCTION

Despite decline in incidence of neonatal group B streptococcal disease (GBS-EOD) over the past 10 years, GBS continues to be an important cause of neonatal infections and early neonatal mortality within the first seven days of life.(1-4) The gastrointestinal tract of the mother is the source of vaginal GBS colonization. Tansmission from mother to child occurs during labor. Prevalence of GBS colonization in women of reproductive age ranges from 10% to 36%.(5;6) GBS colonization can be transient, intermittent or persistent.(7-9) GBS cultures at gestational age of 35-37 weeks are predictive for GBS carriage during labor. (10;11) Established risk factors for GBS-EOD are preterm birth (before 37 weeks of gestation) (12-18), prolonged rupture of the membranes(17-22), intrapartum temperature > 38°C(16-18;21;23;24), maternal GBS bacteriuria during pregnancy(25;26) and a history of a previous child with GBS-EOD.(27-29)

Intrapartum antibiotic prophylaxis (IAP) given to women at risk of transmitting GBS to their baby can prevent GBS-EOD.(30;31) Identifying these mothers at risk may be performed by screening (taking a culture during pregnancy to detect maternal colonization) and/ or by identifying women during pregnancy with one of the established risk factors for GBS-EOD. The Centres for Disease Control and Prevention (CDC) have recommended screening of all pregnant women in the United States at 35-37 weeks' gestation and IAP during labor for all carriers.(32) In the Netherlands, the Dutch Society of Obstetrics and Gynaecology (NVOG) and the Dutch Society of Pediatrics (NVK) approved a modified risk factor based guideline for prevention of GBS-EOD in 1998. This guideline advises IAP for women with intrapartum fever (>38°C), GBS bacteriuria during pregnancy or a previous child with GBS disease, as is performed worldwide in both screening based and risk factor based strategies. In women with preterm labor (< 37 weeks) or prolonged rupture of membranes (>24 hours) (PROM), a culture is taken, followed by IAP when the culture is GBS-positive. Culture results take 24 to 48 hours. If labor occurs before the result of the culture is available, the obstetrician should decide about IAP, based on the severity of the risk factor(s). After introduction of these guidelines, there only has been a limited decrease in the incidence of proven GBS-EOD (i.e.: streptococci are isolated from blood and/or from cerebrospinal fluid combined with physical signs of infection) in the Netherlands.(33) There is a continuous debate for improvement or change of guidelines, particularly with regard to perinatal mortality in the Netherlands, which is high compared to other European countries.(34)

Limited effectiveness of the present guideline might be explained by the fact that in case of occurrence of preterm labor or prolonged rupture of membranes, opportunities for prevention can be missed because of delay in obtaining culture results. If women with these risk factors are at higher risk to carry GBS, Dutch guidelines could be improved by advising direct treatment of women with these risk factors instead of waiting for culture results before start IAP.

In hospitals and midwifery practices in The Hague (the Netherlands), a prevalence study was performed on carriage of Group B streptococcus among pregnant women.(35) The present study

describes a secondary analysis of our cohort of 1702 women to evaluate whether labor before 37 weeks of gestation or prolonged rupture of membranes can predict prenatal GBS carriage.

METHODS

Between July 2000 and December 2002, physicians and midwives at their discretion, but without selecting specific groups, asked women at 35-37 weeks of pregnancy to participate in the study. All these women attended either the outpatient Department of Obstetrics and Gynecology at the Medical Centre Haaglanden, the Leyenburg Hospital, the Rode Kruis Hospital (nowadays together Haga Hospital) or one of the six participating midwifery practices in The Hague, the Netherlands.

After informed consent, the physician or midwife collected a rectovaginal swab for GBS culture by initially swabbing the vaginal introïtus and thereafter the rectum (through the anal sphincter). Swabs were placed in a transport medium (Amies transport medium with charcoal) and sent to one of the participating laboratories. Inoculation took place at 35-37°C for 18-24 hours into a selective broth medium (Todd-Hewitt supplemented with gentamycin (8 micrograms/ml) and nalidixic acid (15 micrograms/ml)). The broth was subcultured onto a blood agar under anaerobic circumstances and GBS suspected colonies were then Gram-stained. A catalase reaction was performed for all Gram-positive cocci. On all catalase negative colonies, a streptococcus grouping latex agglutination test (PathoDx group B, Diagnostic Products Corporation, Los Angeles, USA) was performed to identify GBS. The results were reported to the participating antenatal clinics and midwifery practices.

During labor, the main risk factors for GBS-EOD (Labor before 37 weeks of gestation, rupture of membranes for more than 24 hours, intrapartum temperature of > 38°C, maternal GBS bacteriuria during pregnancy and a history of a previous child with invasive neonatal GBS disease) were registered.

Local GBS protocol in all attending hospitals during the study advised to start IAP in case of intrapartum temperature above 37.8°C, GBS bacteriuria during pregnancy or a previous child with GBS-EOD.

In case of preterm labor or prolonged rupture of membranes (> 24 hours), IAP was given in both GBS colonized women and to women with unknown GBS culture results.

When registration was incomplete, the missing patient data were obtained from the National Obstetric Registration or the obstetric chart of the patient. To assess whether the occurrence of preterm labor or prolonged rupture of membranes was associated with GBS carriage, we calculated Odds Ratio's for frequency data by cross-tabulation with 95% confidence intervals based on binomial/ Poisson distributions.

RESULTS

During the study period a total of 1702 pregnant women were enrolled in the study. Of these women, 365 (21.4%) had GBS positive cultures. Table 1 presents patient characteristics in relation to GBS carriage at 35-37 weeks of gestation. Epidemiologic data from this cohort were previously reported by Valkenburg et al.(35)

Rupture of membranes for more than 24 hours and preterm labor (35-37 weeks of gestation) were registered in 6.5% and 1.5% of the study population respectively. Focusing on these risk factors in which the obstetrician must judge whether antibiotics should be started, we found that for preterm labor and for prolonged rupture of membranes odds ratios for GBS colonization were RR 1.35 (95% CI 0.77-2.37) and RR 0.82 (95% CI 0.55-1.21) respectively. (Table 2 and Table 3). Women with one of these risk factors alone or in combination do not show a higher risk on GBS colonization. (Table 4)

DISCUSSION

In the Netherlands, in women at labor with high risk of delivering a baby with GBS-EOD and unknown GBS status, in some cases the caregiver will decide whether or not to prescribe antibiotics. For risk factors such as intrapartum temperature of > 38°C, maternal GBS bacteriuria during pregnancy and a history of a previous child with invasive neonatal GBS disease, there is worldwide consensus to start IAP during labor. However, in case of preterm labor or prolonged rupture of the membranes there is no consensus. Therefore we focused on these risk factors. In our analysis of preterm labor and prolonged rupture of membranes in relation to prenatal GBS carriage in a Dutch cohort of pregnant women, we found that preterm labor and prolonged rupture of membranes do not predict maternal GBS carriage.

In the Dutch modified risk factor based strategy for prevention of GBS-EOD, opportunities for prevention can be missed in case of prolonged rupture of membranes or in case of preterm labor, because of delay in obtaining culture results. We hypothesized that if women with these risk factors are at higher risk to carry GBS, Dutch guidelines could be improved by advising direct treatment of women with these risk factors instead of waiting for culture results before start IAP.

However, occurrence of these two risk factors separately or combined does not show association with GBS carriage and is therefore not helpful in identifying mothers at higher risk for a baby with GBS-EOD. This has implications for a risk factor based prevention strategy. If all women with these risk factors during labor would receive antibiotics, this would result in the unnecessary exposure to antibiotics of a large group of women (eighty percent of these women are GBS negative and only twenty percent GBS positive). This is relevant,

Table 1 Patient characteristics of study population. Age, parity, history of abortions, continent of native country and presence of risk factors for GBS-EOD (risk factor alone or in combination with another risk factor) in relation to GBS carriage at 35-37 weeks of gestation

	N	% GBS positive	95% CI
Total Population	**1702**	**21**	**0.19-0.23**
Age			
< 20	41	32	0.18-0.46
20-29	663	17	0.14-0.20
30-39	905	24	0.21-0.27
>= 40	92	25	0.16-0.34
Unknown	1	100	
Parity			
0	663	21	0.18-0.24
1	645	19	0.16-0.22
2	232	29	0.23-0.35
3 or more	181	22	0.16-0.28
Unknown	11	18	
History of Abortions			
0	1163	21	0.20-0.21
1 or 2	470	22	0.18-0.26
3 or more	58	22	0.11-0.33
Unknown	11	18	
Native country in:			
Africa	240	29	0.23-0.35
Asia	256	13	0.09-0.17
Latin America	245	22	0.17-0.27
Europe	907	21	0.18-0.24
Other	10	30	0.015-0.58
Unknown	44	27	
Risk factor for GBS-EOD			
Rupture of Membranes > 24 hrs	123	18	0.12-0.26
Preterm labor (< 35 weeks'gestation)	31	29	0.16-0.47
GBS-bacteriuria	27	67	0.48-0.81
Fever during labor	25	32	0.17-0.51
Sibling with GBS-EOD	15	47	0.25-0.70
No risk factor present	1466	21	0.18-0.22
Risk Factor unknown	33	15	

Thirty-three (1.9%) women of the study population were excluded because of missing data.

Table 2 PROM > 24 hrs alone or in combination with another risk factor.
Presence of rupture of membranes for > 24 hours (prolonged rupture of membranes, PROM) during delivery in relation to GBS carriage at 35-37 weeks gestation

	GBS +	GBS -	Total
PROM	22	101	123
No PROM	338	1208	1546
Total	360	1309	1669

RR 0.82 95% CI 0.55-1.21

Table 3 Preterm Labor (PL) alone or in combination with another risk factor.
Presence of preterm labor in relation to GBS carriage at 35-37 weeks gestation

	GBS +	GBS -	Total
Preterm Labor	9	22	31
No Preterm Labor	351	1287	1638
Total	360	1309	1669

RR 1.35 95% CI 0.77-2.37

Table 4 Prolonged rupture of membranes (> 24 hours) (PROM), Preterm labor (gestational age < 37 weeks of gestation) and combination of both in relation to GBS carriage at 35-37 weeks gestation in patients were there is no other risk factor for GBS-EOD

PROM	**PL**	**GBS +**	**GBS-**	**Total**	**OR (95% CI)**
No	No	334	1196	1530	Reference
No	Yes	5	20	25	0.89 (0.33-2.40)
Yes	No	18	91	109	0.71 (0.42-1.19)
Yes	Yes	3	2	5	5.3 (0.90-32.28)
Total PROM and/or PL		26	113	139	**0.82 (0.53-1.28)**
Total		**360**	**1309**	**1669**	

since particularly in case of preventive interventions, it is necessary to pay attention to the increasing potential maternal and neonatal risks and side effects of antibiotics and the emergence of resistant GBS strains.(36-39) For mothers, an important adverse effect of an increased use of antibiotics is the increasing incidence of potential severe adverse reactions including anaphylaxis to penicillin.(40;41) Neonatal risks include an increase in incidence of non-GBS-EOD.(42-44)

In a previous report we showed non-significant ethnical differences between GBS colonized and non-colonized women, but we could not demonstrate differences between colonized and non-colonized women with respect to age, parity or socio-economic background. Results of this study show that it is not possible to identify a subgroup of pregnant women that is at higher risk for GBS colonization.(35) If it was, defining riskgroups for GBS

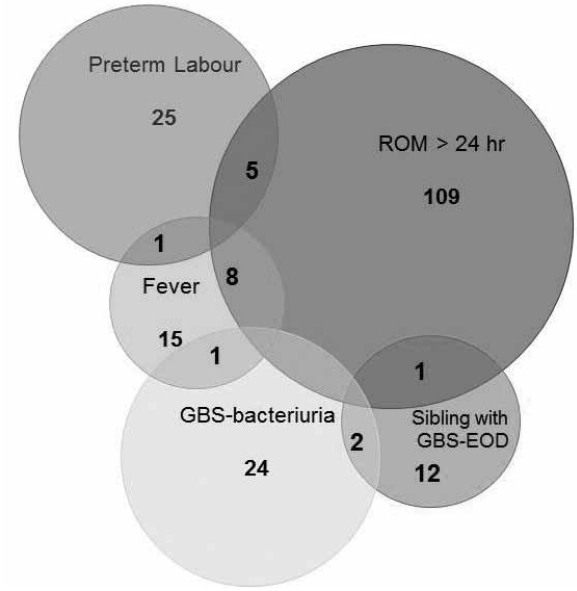

Figure 1 Risk factors for GBS-EOD during delivery

carriage could be usefull in daily laborroom decisionmaking to start IAP in case screening results were not available yet.

Although our study shows interesting results, there are some limitations. First, bacterial cultures were taken at 35 to 37 weeks' gestation, with the assumption that GBS carriage at 35-37 weeks is a good indicator for GBS status during labor. In a systematic review we confirmed the recommendations to screen pregnant women for colonization of GBS at 35-37 weeks gestation(32), since the positive predictive value (PPV) of GBS cultures for GBS carriage during labor decreases when the interval between antenatal culture and delivery culture increases, especially when it is more than six weeks.(11) Negative predictive values (NPV) remain constant and are therefore unrelated to the gestational age at which the culture is performed. However, predictive values of GBS cultures at gestational age of 35-37 weeks have never been reported to be 100%.

Second, women who delivered before 35 weeks of gestation were not included in the analysis, which makes the present rate of preterm birth low. Third, we have studied the risk for, but not the true incidence of GBS-EOD. Finally, we need to mention that international definitions define PROM as rupture of membranes for more than 18 hours,(19-22;32) while Dutch guidelines during current study used to define PROM as more than 24 hours. In international guidelines on GBS prevention, intrapartum temperature of > 38°C is a reason to start intrapartum antibiotic therapy, whereas Dutch guidelines at time of study advised to start antibiotics in women with an intrapartum temperature of 37.8°C.

Since the introduction in 1998 of a Dutch national guideline on prevention of GBS-EOD there has been a limited decrease in the incidence of proven GBS-EOD in the Netherlands from 0.54 per 1000 live births to 0.36 per 1000 live births.(33) There was no decrease in the incidence of probable early-onset GBS sepsis, meningitis or case fatality rate. According to the Netherlands Perinatal Registry, GBS sepsis and GBS meningitis seemed to be stable until 2008, with respectively 108 and 15 reported cases in 2008. In 2009 an unexplained increase was seen, with 172 cases of GBS-EOD (0.93 per 1000 live births).

It is clear that the current Dutch guideline is not effective and a new strategy to prevent GBS-EOD is justified, particularly with regard to perinatal mortality in the Netherlands, which is high compared to other European countries.(34) The present study showed that occurrence of labor before 37 weeks of gestation or prolonged rupture of membranes do not predict GBS colonization of the mother.

Depending the results of a bedside screening test during delivery, further cost-effectiveness-and implementation studies are needed to compare different prevention strategies for the Netherlands, in order to further reduce the burden of GBS-EOD.

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