Group B streptococcus and pregnancy : towards an optimal prevention strategy for neonatal Group B Streptococcal Disease

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Chapter 6

Timing of GBS screening in pregnancy: A systematic review

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ABSTRACT

Background Group B Streptococcus (GBS, Streptococcus agalactiae) is an important cause of early-onset neonatal sepsis. Guidelines include the advice to collect cultures at 35-37 weeks' gestation and to administer intrapartum antibiotic prophylaxis (IAP) in case of GBS-positive cultures, as well as in all preterm deliveries. Improved effectiveness of antenatal cultures might help to further decrease GBS-early onset disease (GBS-EOD).

Objectives The objective of our review was to determine the best timing of antenatal cultures, which may help to establish optimal prevention of perinatal GBS infection in both term and preterm neonates.

Search Strategy Pubmed and Embase databases and reference lists were searched for relevant articles published from 1966 to February 2009.

Selection criteria Nine articles were included. Information about study features and predictive values of antenatal cultures were abstracted.

Data collection and analysis From each study, study characteristics and inclusion and exclusion criteria were abstracted by two researchers. To assess the predictive value of the GBS test in each study, the researchers independently constructed four-fold prognostic tables.

Main results Positive predictive values for antenatal GBS cultures ranged from 43-100 % (mean 69%) and negative predictive values from 80-100% (mean 94%). GBS cultures collected in late pregnancy had high positive predictive values for colonization during delivery. The negative predictive value was high and relatively constant regardless of gestational age.

Conclusions This systematic review confirms recommendations to screen pregnant women for colonization of GBS at 35-37 weeks gestation, but one should be aware of the limitations of screening, with 6% of GBS carriers remaining undetected in antenatal cultures. There are two possible ways to prevent GBS-EOD in premature deliveries: either to give IAP in all premature deliveries or to screen all pregnant women both early in pregnancy and again later in pregnancy.

INTRODUCTION

Even with the increased use of intrapartum antibiotic prophylaxis, Group B Streptococcus (GBS, *Streptococcus agalactiae)* disease is an important cause of morbidity and mortality in newborn infants in developed countries.(1;2) For neonates, the source of colonization or GBS-infection is the mother. The maternal gastrointestinal tract is the source of vaginal GBS colonization. GBS has been found to be present in the rectovaginal compartment of 6-45% of pregnant women, (3-8) though in general it is asymptomatic.(9;10) The prevalence of positive GBS cultures varies due to the dynamics of GBS, culture techniques, sampling techniques, and the populations studied.(9;11)

Vertical transmission from colonized mothers to their infants during labor is 50-65%. (12;13) In GBS-colonized neonates, 1-2% of term infants and 8% of preterm infants will develop group B streptococcal early onset disease (GBS-EOD). Mortality rates vary from 5 to 20% and are higher in preterm infants.(3;12)

Intrapartum antibiotic prophylaxis (IAP) to GBS carriers reduces the incidence of GBS-EOD.(14-18) However, prevention strategies for GBS disease are currently based on two different approaches: risk factor based and screening based.

Since known risk factors for perinatal GBS infections (preterm labor, preterm or prolonged rupture of membranes, intrapartum fever, chorioamnionitis, and signs of heavy GBS colonization, such as a previous infant with GBS disease or GBS bacteriuria during the current pregnancy) only occur in 40-50% of all GBS cases, the Centers for Disease Control and Prevention in the United States advises rectovaginal cultures during the antenatal period at 35-37 weeks gestational age and offering IAP during delivery to all pregnant women with positive GBS cultures.(19) The choice to screen at this moment was based on studies by Yancey et al.(20) and Boyer et al.(12), who found that cultures accurately predicted GBS colonization status at delivery when obtained in the late antenatal period.

In cases of preterm labor, prevention strategies advise antibiotic prophylaxis. By the end of the last decade, 30% of women delivering in US maternity units involved in a large multicenter study received intravenous antibiotics during labor.(21) 24% of women received antibiotics for vaginal colonization of group B streptococci, in order to reduce the risk of GBS-EOD. Screening for GBS and intrapartum prophylactic antibiotics contributed to a decline of the incidence of GBS-EOD during the 1990s, but this stabilised in the US at 0.2 to 0.5/1000 live births in the mid to late 1990s.(22;23)

Thus, despite the considerable effort and economic resources spent on IAP for GBS-EOD, cases continue to occur. Puopolo reported that the majority of remaining GBS-EOD occurred in infants whose mothers screened negative for GBS colonization.(24) Predictive values of GBS cultures at gestational age of 35-37 weeks have never been reported to be 100%, and screening in this period will not provide information about GBS colonization in the preterm period, when

GBS-disease in neonates is most dangerous.(25;26) Improving the effectiveness of GBS screening and awareness of its limitations might help to further decrease the prevalence of GBS-EOD.

Our objective was to review the literature on the timing of GBS screening in pregnancy to determine the best moment to screen for GBS colonization, which may help to establish optimal prevention of perinatal GBS infection both in term and preterm neonates.

METHODS

The review process, including the method of reporting outcomes, was based on recommendations given by Stroup et al(27) in their article "Meta-analysis of Observational Studies in Epidemiology."

Search for studies

Relevant articles were selected in several steps, following the guidelines provided by *Systematic Reviews in Health Care*.(28) First, Pubmed and Embase databases were searched for potentially relevant articles published from 1966 to February 2009. The search strategy is presented in Table 1.

Selection process, selected studies and validity

Articles were selected on the basis of title and abstract by two researchers (AV, RR) and were retrieved for more detailed examination, based on the following criteria:

1) The article represented original research.
2) The article reported the outcome of maternal antenatal and intrapartum GBS-cultures.
2) The results allowed a positive and negative predictive value to be calculated.

Studies were excluded when the study population received antibiotics prior to cultures being taken (i.e., during pregnancy or labor), or when it was unclear whether antibiotics were administered.

All selected articles were searched for additional references. Both researchers screened all retrieved articles to ensure they met the inclusion criteria mentioned above. In case of disagreement, articles or abstracts were re-examined and discussed until consensus was achieved.

To determine the validity of selected studies, each study was graded by the two researchers (AV, RR) on the basis of eight criteria (see Table 3). A validity score was calculated (range:0-9) according to the criteria for prognostic studies described by the Evidence-Based Medicine Working Group (29). The following validity criteria were used: adequate description of study population, well-defined point of inclusion in study, well-defined moment of antenatal cultures, use of selective medium and chosen culture site(s), completeness of follow-up and/or clear description of dropouts, and the possibility to formulate a fourfold

table. Poor validity is defined as a validity score below five and good validity as a score of five or higher, with a maximum possible score of nine.

Data extraction & statistical analysis

The two researchers independently extracted information on study design, methods of GBS screening, culture sampling, timing of antenatal culture(s), prevalence and numerical follow-up data from each study. To assess the predictive values of the GBS test in each study, a fourfold prognostic table was constructed to show the relation between antenatal test results and GBS culture outcome at delivery for several points in gestation. Positive predictive value (PPV) is defined as the proportion of pregnant women with a positive antenatal GBS culture in whom

Table 1 Search strategy in Medline and Embase (up to February 2009)

Search	Query
1	Group B Streptococcus (Textword) Streptococcus agalactiae (Mesh)
2	Pregnancy
3	Pregnant
4	Pregnant women
5	Early pregnancy
6	Late pregnancy
7	Antenatal
8	#2 OR #3 OR #4 OR #5 OR #6 OR #7
9	Colonisation
10	Colonization
11	Carriage
12	Carriership
13	Carrier state
14	Carrier
15	#9 OR #10 OR #11 OR #12 OR #13 OR #14
16	Screening
17	Screening Cultures
18	Cultures
19	Detection
20	#16 OR #17 OR #18 OR #19
21	Colonised OR colonized
22	#15 OR #21
23	#22 AND #8 AND # 1 AND #20

* in Embase-search: only one additional article was found

Table 2a Results of original prospective studies including positive and negative predictive values for GBS colonization during delivery

Author	N	Methods		Prevalence		Follow-up	GA	PPV	PPV-CI	NPV	NPV-CI	Sens	Spec
		Swabs	Selective	antenatal	delivery								
Kubota '98	615	vaginal	no	11.4	13.8	100	22-26	71.4	0.68-0.75	93.6	0.92-0.95	58.8	96.2
Regan '96	2613	vaginal,	yes	15.3	18.9	unclear	23-26	53.1	0.51-0.55	87.2	0.87-0.89	42.8	91.2
	439	endocervical,		20.3	20.7		31-36	68.5	0.64-0.73	91.4	0.89-0.94	67	92
		vaginal wash											
Persson '87	152	urethra,rectal		24.3	25.7	100	37	89.2	0.84-0.94	94.8	0.91-0.98	84.6	96.5
		and urine											
Easmon '85		anorectal	yes	17		96.8	total						
	1116	and		21	16.9	67.9	28	57.9	0.54-0.61	94	0.92-0.96	71.9	89.4
	895	low-vaginal		20.7	16.5	73	36	67.4	0.64-0.71	96.7	0.95-0.98	84.3	91.9
	2011					31.4	28+36	60.8	0.57-0.65	97.1	0.96-0.98	91.7	82.6
	2829					15.5	28+36+1st	53.8	0.52-0.56	96	0.95-0.97	94.1	64
Allardice '82	524	vaginal	yes	10.3	7.6	74.2	28-39	54.7	0.51-0.59	96	0.95-0.97	60.4	95
				10.6			28-34						
				6			36-37						
				15.2			39-40						
Goodman '97	735	vaginal	yes		12.1	75.5							
		and		13.2			1st visit	45.5	0.36-0.55	92.9	0.91-0.95	49.5	91.8
		peri-anal		14			27.6	60.4	0.51-0.70	95.6	0.94-0.97	68.4	93.9
				12.5			37.3	61.3	0.51-0.71	95	0.93-0.97	63.3	94.5
Valkenburg '06	1702	rectovaginal		21.5	22.9	44.7	35-37	78.6	0.77-0.81	93.5	0.92-0.95	78.2	93.7

GA: Gestational age
PPV: Positive Predictive Value
NPV: Negative Predictive Value
CI: Confidence Interval

Table 2b Results of original retrospective studies including positive and negative predictive values for GBS colonization during delivery

Author	N	Methods		Prevalence		follow-up	Interval	PPV	PPV-CI	NPV	NPV-CI	sens	spec
		swabs	selective	antenatal	delivery		weeks						
Yancey '96	826	anal	no	23.4	23.5	100	total	87.1	0.85-0.90	95.9	0.95-0.97	86.6	96
	50	and		20	22		-1	100		97.5	0.96-1.00	90.9	100
	136	low-vaginal		24.3	25		-2	90.9	0.86-0.96	96.1	0.95-0.97	88.2	97.1
	204			16.7	17.2		-3	88.2	0.81-0.95	97.1	0.94-1.00	85.7	97.6
	265			28.7	27.2		-4	86.8	0.81-0.93	96.8	0.94-1.00	91.7	94.8
	139			23.7	24.5		-5	87.9	0.83-0.93	95.3	0.91-0.99	85.3	96.2
	32			21.9	25		<-6	42.9	0.35-0.51	80	0.73-0.87	37.5	83.3
Boyer '83	775	vagina	yes	22.8		76.5							
	26	and					<6	100		100		100	100
	66	rectal					6-10	72.3	0.62-0.83	100		100	59.4
	107						11-15	67.5	0.59-0.76	92.6	0.88-0.98	96.4	49
	140						16-20	66.3	0.59-0.74	93.3	0.90-0.98	95.5	56.8
	162						21-25	65.6	0.59-0.73	87.9	0.85-0.94	88.7	63.7
	72						26-30	62.2	0.51-0.73	88.9	0.83-0.97	90.3	58.5
	20						>30	42.9	0.22-0.64	83.3	0.71-0.10	85.7	38.5

GA: Gestational age
PPV: Positive Predictive Value
NPV: Negative Predictive Value
CI: Confidence Interval

Table 3 Characteristics and results of original studies according to the validity

Author	**Study population**	**GA δ**		**Methods**		**Follow-up**	**Forfould**		**Validity**
	Well defined point of start of study-participation Yes=1, No=0	*Identification of population defined Yes=1, No=0*	*Spread of antenatal cultures <2 wks=1 >2 wks=0*	*Swabs; number of sites*	*Used selective broth medium Yes=1 No=0*	*Complete Follow-up (100%) Yes=1 No=0*	*Description of incom-pleteness in follow-up Yes=1 No=0*	*Possible to construct 2x2matrix Yes=1 No=0*	***Score Min 0 Max 9***
Kubota	1	1	0	1	0	0	1	1	**5**
Regan	1	0	0	1	1	0*	0	1	**4**
Yancey	1	1	1	2	0	1	1	1	**8**
Persson	1	0	1	1	1	1	1	1	**7**
Easmon	1	0	1	2	1	0	0	1	**6**
Boyer	1	0	0	2	1	0	1	1	**6**
Allardice	1	1	0	1	1	0	1	1	**6**
Goodman	1	1	1	2	1	0	1	1	**8**
Valkenburg	1	1	1	2	1	0	0	1	**7**

δ GA=gestational age at time of antenatal screening

* follow-up only for a randomly selected subgroup

the GBS culture remained positive during labor. Negative predictive value (NPV) is defined as the proportion of pregnant women with negative GBS cultures, both antenatal and intrapartum. For studies which included more than one antenatal culture sample, several fourfold prognostic tables were constructed. The following numerical data was considered: positive and negative predictive values, sensitivity, and specificity, all at 95% confidence intervals.

RESULTS

Selection

Medline and Embase searches yielded 365 and 53 potentially relevant references, respectively (Table 1). After assessing these articles on the basis of title and abstracts, twenty-five of these publications were retrieved for more detailed examination. Searching the reference lists of these articles resulted in eight additional articles. Of these 33 articles, nine studies met our inclusion criteria.(3;12;20;25;26;30-33) Twenty-four articles were excluded, eight because they did not include original research,(13;34-40) five because no culture was performed at delivery,(5;11;41-43) one because the cultures taken early in pregnancy were not from same site as those taken during labor,(44) nine because it was impossible to construct a fourfold prognostic table using the data presented in the article,(4;17;45-51) and one because antibiotics were used during labor before an intrapartum GBS culture was taken (n=1).(52) The remaining nine articles were used for data extraction and analysis.

Description

The nine remaining articles studied a total of 25,664 women, 8,898 of whom were cultured for GBS both in the antenatal period and during delivery. Results of data extraction are listed in Tables 2a and 2b. Positive predictive values for all GBS cultures ranged from 43-100 % (mean 69%) and negative predictive values from 80-100% (mean 94%). All data were separated into prospective studies (Group A, n=7) and retrospective studies (Group B, n=2). In Group A, GBS cultures were taken at one or more points during gestation and were repeated during delivery. All seven of these studies identify the gestational age at which antenatal cultures were taken.(3;25;26;30-33) The mean positive and negative predictive values (PPV and NPV) for the studies in Group A were 63.3% (range: 46-89%) and 94.2% (range: 87-97%), respectively, with medians of 61% and 95% (Table 2a). Dividing these results into early cultures (collected before 35 weeks gestational age [GA] and delivered at term) and late cultures (collected after 35 weeks GA and delivered at term), these results are 58.8% and 70.2% for PPV (mean), respectively, and 93.0% and 95.2% for NPV (mean), respectively.

In group B, study data were collected according to the interval (in weeks) between antenatal culture and the culture taken during delivery (counted retrospectively).(12;20) The mean PPV and NPV were 74.9% (range 43-100%) and 92.9% (range 80-100%), respectively, with

medians of 72% and 95% (Table 2b). Dividing into early and late cultures, mean PPV was 63.5% and 93.2%, respectively, and mean NPV 90.2% and 97.5%.

Antenatal cultures in the studies in Group A were performed at a mean gestational age of 30.6 weeks (range: 10-40 weeks). Term delivery occurred in >90% in studies which reported gestational age at delivery (four out of six studies).(3;20;26;32) The prevalence of GBS colonization varied from 6-29% (mean 18%) in the antenatal period, and 8-27% (mean 20%) at delivery (Tables 2a and 2b), based on data from eight studies.(3;20;25;26;30-33) Data on prevalence from Boyer et al. could not be taken into account, because they did not distinguish between antenatal prevalence and prevalence at delivery.(12) In 7 out of 9 studies, GBS was cultured on a selective broth medium, which is reported to be an important factor for adequate detection of GBS.(20;53;54) In two studies, only vaginal cultures were taken,(30;31) and in five studies vaginal cultures were combined with rectal cultures.(3;12;20;25;26)(Tables 2a and 2b). Five studies reported follow-up data of the study population;(12;20;30-32) in three

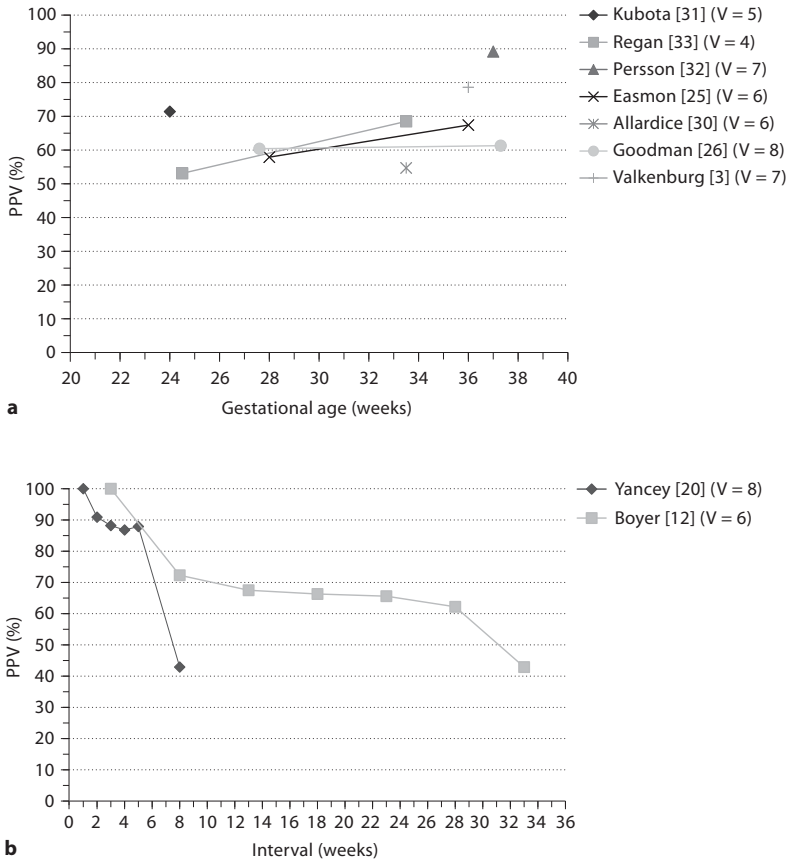

Figure 1: Positive Predictive Values in prospective (a) and retrospective (b) studies.V= validity score

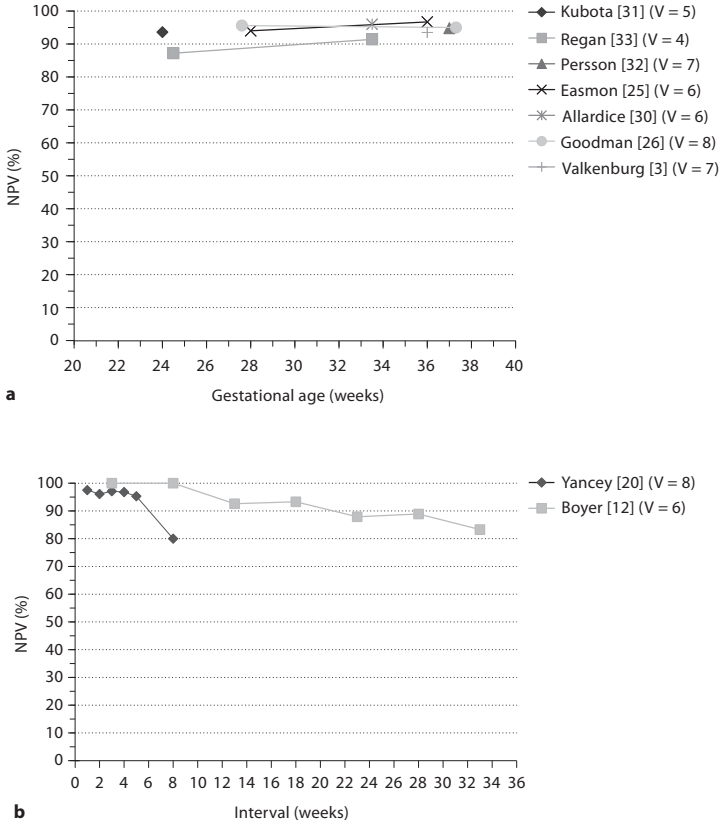

Figure 2 Negative Predictive Values in prospective (a) and retrospective (b) studies. V= validity score

studies, follow-up data could be extracted using information in text or tables, (3;25;26) while no follow-up data could be extracted from one study.(33) Of the eight studies with follow-up data, three contained a complete follow-up.(20;31;32) Persson et al.(32) followed a randomly selected subgroup of the study population from the start of antenatal screening until delivery. The mean follow-up percentage of all eight studies was 83.5% (range: 45-100%) (Tables 2a and 2b). Total validity scores of the included studies are shown in Table 3.

All studies were found to have methodological limitations, with a range of 4-8 (with a maximum possible validity score of nine). The study of Regan et al. showed serious limitations, with a validity score less than five.(33)

Data synthesis

Figures 1 and 2 show positive and negative predictive values of each study in relation to the mean antenatal gestational age at the time of GBS cultures. The figures also give the valid-

ity score per study. GBS cultures taken late in pregnancy correspond with higher positive predictive values. The negative predictive value remains constant regardless of gestational age.

DISCUSSION

We reviewed the literature on the predictive value of antenatal cultures during gestation to find the optimal timing for collecting antenatal GBS cultures. After primary assessment, nine studies were included. Meta-analysis was not conducted; studies were analyzed separately because of differences in study design. In seven studies (Group A), culture intervals were calculated from gestational age at which the culture was take, to birth. In two studies (Group B), culture intervals were calculated retrospectively from birth to the time the culture was taken (irrespective of gestational age). Positive predictive values for GBS cultures ranged from 43-100 % (mean 69%) and negative predictive values ranged from 80-100% (mean 94%). The positive predictive values (PPVs) correlate positively with increasing gestational age at time of GBS culture. The results of the studies in Group B show that PPV decreases when the interval between antenatal culture and delivery culture increases, especially when it is more than six weeks. Negative predictive values remain constant and are therefore unrelated to the gestational age at which the culture is performed.

GBS disease remains a problem despite IAP, causing significant neonatal morbidity and mortality. Inaccurate screening results, improper implementation of IAP or antibiotic failure may all contribute to persistent disease. Procedural factors may contribute to false negative culture results; these may include improper sampling and culturing, poor swab storage and transfer practices, or inappropriate culture media. Furthermore, it is possible that women who screened negative early in pregnancy acquired GBS later, since GBS colonization is not constant and varies during pregnancy.(5;45;51)

Limits

This systematic review is subject to several methodological limitations. Almost all the reviewed studies were published before 2003, which means that recently available highly sensitive rapid microbiological diagnostics (PCR) were not taken into account.(55;56) In addition, little information about antenatal cultures in the first trimester of pregnancy is available.

It is difficult to compare the studies, due to the wide variety of study methods and incomplete information on follow up. Some studies reported predictive values in a non-representative subgroup of the original cohort. Such a selection of patients could result in over or underestimation of the true prevalence of GBS. Prevalence rates were also different in the studies, making it difficult to compare them, since PPV is dependent on the prevalence. The type of broth medium used and the culture site(s) can influence the prevalence.

Using selective broth media and sampling several culture sites (i.e., both vagina and rectum) improves recovery of GBS up to 50%.(37) Other factors could also affect prevalence and predictive values: e.g., ethnicity, socio-economic status, age at beginning of pregnancy, duration of pregnancy, or multiparity. In other words, differences in the prevalence of GBS could be a reflection of the different risk profiles in the study population.(3;9;13;37;45)

The differences mentioned above are reflected in the differences in the validity of the studies (Table 3, Figures 1a and 1b). The validity score reflects both the quality of the specific studies and the comparability between the studies. All studies showed methodological limitations, with validity varying from four to eight (with nine being the maximum score). A strong correlation between validity scores and predictive values was not found.

To compare these studies, we divided them into two groups: Group A (prospective studies) and Group B (retrospective studies). In Group A, the gestational age at birth was not always clearly stated, so the exact interval between antenatal culture and delivery culture can not be calculated. In Group B, the interval is known (calculated afterwards), but since one can not know in advance exactly when the delivery will take place, it is impossible to determine precisely when to collect the antenatal culture.

Interpretation of results

The positive relationship between gestational age and predictive values of GBS cultures found in this review corresponds with the results of earlier retrospective studies by Yancey et al.(20) and Boyer et al.(12) Based on these studies, the Centers for Disease Control and Prevention in the United States advises collecting rectovaginal cultures during the antenatal period at 35-37 weeks gestational age.

Based on this systematic review, the overall chance of a positive GBS result in pregnant women is 19%. Pregnant women with antenatal GBS colonization (i.e., a positive GBS test) have an approximately 70% chance (PPV) of being colonized during delivery. This implies that the 19% a-priori chance of GPS increases to 70% with a positive test result for GBS. On the other hand, the 19% a-priori chance of GBS decreases to 6% with an initial negative antenatal test result for GBS.

A high NPV is needed in order not to miss the chance to treat women with GBS colonization during delivery and a high PPV is needed in order not to overtreat pregnant women for GBS. Accordingly, it is fair to say that an NPV of 94% is sufficiently accurate for clinical policy: i.e. in the dilution in the GBS-population, according to prevalence, transmission and actual early-onset disease a NPV of 94% (and not 100%) can be accepted. The NPV is surprisingly constant, and unrelated to prevalence or gestational age at time of culture.

Screening for GBS between 35 and 37 weeks will predict GBS colonization at term delivery, but this screening misses the pre-term neonatal group, in which GBS sepsis is most dangerous. Therefore, all different prevention strategies advise antibiotic prophylaxis in cases of preterm labor where GBS status is not known. However, large scale IAP may

result in unwanted side-effects, such as decreased susceptibility or resistance to other micro-organisms(57) and disturbance of both the mother's and the neonate's intestinal and vaginal flora.(58) While IAP during delivery is associated with declines in GBS streptococcal infections, there have also been reports of clusters or increases in gram-negative infections among newborns as a result of increasing prophylactic treatment.(59-62) In addition, the incidence of penicillin allergy (allergic reactions of all severities), specifically in an obstetric population, has been reported to vary from 0.7–10%.(63-66)

In order to minimize IAP while still providing optimal prevention of perinatal GBS infection in preterm neonates, it would be beneficial to screen for GBS colonization early in pregnancy, as the American Academy of Pediatrics recommended in 1992.(67;68) However, the results of early screening are not predictive of colonization during delivery after six weeks, which means that when early screening is performed, cultures should be repeated later in pregnancy. Because NPV remains high and constant during pregnancy and PPV decreases as the interval between antenatal culture and delivery increases beyond six weeks, cultures should only be repeated at 35-37 weeks gestation in women who tested positive at 29-31 weeks gestation.

CONCLUSION

This systematic review confirms the recommendations to screen pregnant women for colonization of GBS at 35-37 weeks gestation, but one should be aware of the limitations of screening, because 6% of GBS carriers during delivery remain undetected in antenatal cultures. There are two options for preventing GBS-EOD in preterm infants: either giving IAP in all premature deliveries or screening all pregnant women early in pregnancy and culturing again later in pregnancy.

Because the studies reviewed for this article had serious methodological limitations, we recommend new, well-designed and well-executed studies to determine the best timing of antenatal culturing for GBS. These could include longitudinal prospective cohort studies with cultures taken at different gestational ages. This would provide more reliable data to compare individual differences in GBS colonization, and understand its dynamics, thus permitting practitioners to draw more dependable conclusions from culture results.

Rapid molecular diagnostics such as PCR will fill an important need in the near future, since bedside testing will help to identify every GBS carrier during delivery.(6;7;56)

To reduce the serious problem of perinatal GBS disease, a highly-accurate, rapid diagnostic test for GBS, as well as the development of a polyvalent GBS vaccine and rapid implementation should be high public health priorities.

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