Group B Streptococcus and Pregnancy

Towards an optimal prevention strategy for neonatal Group B Streptococcal Disease

Arijaan Valkenburg - van den Berg

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Be Thou my vision, O Lord of my heart;
Naught be all else to me, save that Thou art.
Thou my best thought, by day or by night,
Waking or sleeping, Thy presence my light.
(Traditional hymn, Eleanor Hull)

Aan mijn ouders

Voor Arco, Job, Sara, Mees en Noortje

Contents

List of Abbreviations

AF	Amniotic Fluid
CDC	Centers for Disease Control
CFU	Colony Forming Units
CI	Confidence Interval
ELISA	Enzyme-Linked Immunosorbent Assay
EOD	Early Onset Disease
EOS	Early Onset Sepsis
GA	Gestational Age
GBS	Group B Streptococcus
IAP	Intrapartum Antibiotic Prophylaxis
LOD	Late Onset Disease
LOS	Late Onset Sepsis
NM	Not Mentioned
NPV	Negative Predictive Value
NVOG	Nederlandse Vereniging voor Obstetrie en Gynaecologie (Dutch Society of Obstetrics and Gynecology)
NvK	Nederlandse Vereniging voor Kindergeneeskunde (Dutch Society of Paediatrics)
OIA	Optical Immunoassay
PCR	Polymerase Chain Reaction
PPROM	Premature Prolonged Rupture of Membranes
PPV	Positive Predictive Value
PROM	Prolonged Rupture of Membranes
RAPD	Randomly Amplified Polymorphic DNA

Chapter 1

General Introduction

1

Group B Streptococcus (GBS, Streptococcus agalactiae) has been recognized as an important cause of neonatal infection and early neonatal mortality within the first seven days of life.(1-3)

Vertical transmission of GBS from mother to child occurs during labor. The gastrointestinal tract of the mother has been recognized as the source of vaginal GBS colonization. The frequency of GBS colonization ranges from 10% to 35% in women of reproductive age.(4;5) Studies on vertical GBS transmission in colonized mothers during labor report incidences of colonization of the infant between 16 and 69%.(6-11) Early-onset group B streptococcal disease (GBS-EOD) occurs in approximately 1% of newborns who are colonized with GBS and typically presents with sepsis, pneumonia or meningitis.(12) Risk factors for acquiring GBS-EOD are prelabor rupture of membranes, preterm labor, intrapartum fever, GBS bacteriuria during pregnancy or a previous child with GBS.(13)

Clinical trials in the USA during the 1980s showed that GBS-EOD may be prevented by administering antibiotics during labor to mothers who are colonized with GBS.(14) After introduction of national guidelines in 2002, in which culture based screening of all pregnant women and intrapartum antibiotic prophylaxis (IAP) in all GBS carriers was recommended, the incidence of GBS-EOD in the USA has declined from 1.8 per 1000 live births to 0.32 cases per 1000 live births in 2003.(5;15) Overall mortality from GBS-EOD, as high as 50% in 1970s, fell to 5% in 2003.(1;16-18)

In Europe little data have been published on national incidence rates of GBS-EOD. The incidence of neonatal early-onset GBS disease in some European countries varies from 0.5 to 1.15 per 1000 live born infants.(19-21) In the United Kingdom, studies reported incidence rates of GBS-EOD of 0.5 per 1000 live births in the absence of screening,(19;22) with a case-fatality rate of 10.6%.(22)

In the Netherlands, the incidence of GBS-EOD before implementation of a nationwide guideline during a 2-year period (1997-1998) was 1.9 per 1000 live born infants. This is the total incidence of proven sepsis and probable sepsis. In proven sepsis, streptococci are isolated from blood and/or from cerebrospinal fluid combined with physical signs of infection in the neonate. In probable sepsis GBS is detected in serious ill children at various sites, but not in blood and/or cerebrospinal fluid. The incidence of proven GBS-EOD alone was 0.54 per 1000 live births. After the Dutch Society of Obstetrics and Gynecology and the Dutch Society of Paediatrics approved modified risk factor based guidelines for prevention in 1998, 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.(22) There was no decrease in the incidence of probable early-onset GBS sepsis, meningitis or case fatality rate. According to the Netherlands Perinatal Registry, incidences of (proven and probable) 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). Between 2000 and 2009 a case fatality rate for GBS-EOD of 6.3% was found.

Since the overall effect of the Dutch guideline on the incidence of GBS-EOD is disappointing, revision of the Dutch guidelines was considered in 2006. Because of the presumed lack of evidence to change towards an alternative strategy, the Dutch prevention strategy remained as it was. However, given the on-going burden of GBS-EOD, adaptation of the Dutch guidelines should be reconsidered, particularly concerning the fact that perinatal mortality in the Netherlands is high compared to other European countries.(23) The aim of this thesis is to contribute to the information needed for the establishment of an optimal prevention strategy for GBS-EOD.

BACKGROUND AND SCOPE

The Pathogen

Group B streptococcus (GBS, Streptococcus agalactiae) has been known as a human pathogen since 1938.(24) GBS are facultative anaerobic Gram-positive cocci growing in chains or as diplococci.(Figure 1) On sheep blood agar they cause a characteristic zone of beta-hemolysis around colonies, because of destruction of red blood cells.(Figure 2).

With serological techniques using capsular polysaccharides as type-specific antigens, GBS can be distinguished from other types Streptococci (A, C, D and G). When using surface proteins as additional antigenic markers, GBS can be divided into nine serotypes (Ia, Ib and II-VIII). Recently a tenth serotype has been proposed.(25)

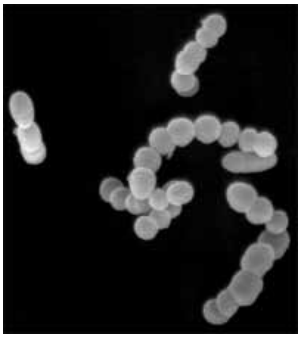

Figure 1 GBS: Gram-positive cocci growing in chains

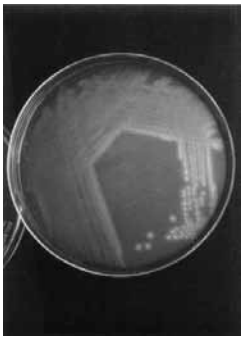

Figure 2 Blood Agar Plate with Streptococcus Agalactiae and typical haemolytic zone around colonies

Differences in the expression of polysaccharides and surface proteins account for differences in the pathogenesis of infections.(26) Factors playing a role in the development of an asymptomatic or invasive infection have not yet fully been elucidated. Capsular polysaccharides expressed by GBS assist in bacterial evasion of host defense by interfering with their ingestion by phagocytes. More virulent strains of GBS can produce increased amounts of polysaccharides. Another important virulence factor of GBS is related to its ability to attach to endothelium and epithelium, particularly of vaginal tissue and chorionic membranes and to the neonatal lungs.(27) The more virulent invasive strains of GBS have been found to have a greater capacity for adherence to endothelium and epithelium, and this has been particularly evident in studies of serotype III GBS.(27;28)

GBS disease is caused mainly by serotypes I, II and III.(27) Serotype III is the most prevalent serotype in asymptomatic carriers.(30-32)

Colonization and transmission

The gastrointestinal tract is the human reservoir of GBS. Women may carry GBS temporary, intermittent or persistent.(33-36) Colonization has not always been studied with the use of optimal microbiologic methods such as specific growth medium in a cohort that was studied over months. Detection methods for GBS that were used in earlier studies might have missed lightly colonized women.(28)

A cross-sectional study among healthy male and non-pregnant female students reported on colonization with group B Streptococcus. With adequate detection methods, GBS was isolated from one or more sites (vaginal, anal and urine specimens) in 34% of women and 31% of men. The prevalence was associated with sexual activity, tampon use, milk consumption, and hand washing done < 4 times per day.(29) Although GBS can be sexually transmitted, colonization has not been associated with frequency of sexual activity or numbers of partners.(30).

Since in the USA Caribbean Hispanics and black women were reported to be GBS carriers more frequently than white women, a role for ethnic or genetic factors is presumed. (33;40)

Colonization with GBS is described to occur in 10-35% of pregnant women.(4;5)

Studies on vertical GBS transmission in colonized mothers during delivery report incidences of colonization of the infant between 16 and 69%.(6-11) The majority of infants who are exposed to GBS are colonized on skin or mucous membranes but remain asymptomatic.

Of the colonized newborn infants, 1-2% develops serious neonatal infection.

Persistent carriage and high-level maternal colonization are important risk factors for vertical transmission.(31)

Intrauterine infection of the fetus results from ascending spread of GBS from the vagina of colonized women into the uterine cavity. This vertical transmission from mother to child usually occurs after rupture of the membranes, when GBS enters the amniotic fluid and colonizes the skin and mucocutaneous areas of the fetus. Aspiration of infected amniotic fluid may cause pneumonia, and when GBS entries the bloodstream, sepsis may occur. Entry in the cerebrospinal fluid after hematogenous spread may cause meningitis. (Figure 3)

The ability of GBS to attach and invade the chorioamniotic membranes has been demonstrated in vitro.(32) GBS may also penetrate the intact chorionic membranes, leading to cases of intra-amniotic infection or abortion.(33)

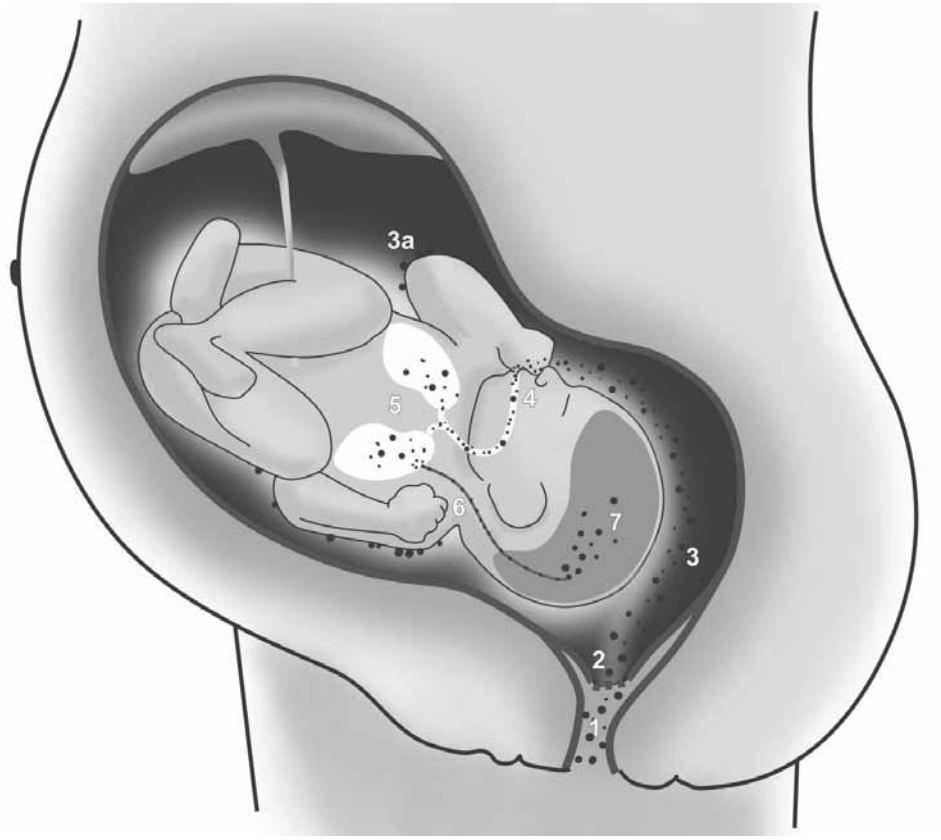

Figure 3: Hypothesized pathogenesis of GBS-EOD (Designed by Vincent Khouw, VMK- designs) 1 Colonization in the rectovaginal compartment; 2 Rupture of the membranes; 3 GBS enters the amniotic fluid; 3a GBS colonization of skin and mucocutaneous areas; 4 Aspiration of infected amniotic fluid; 5 Infected amniotic fluid causes pneumonia (if the bacterial load is high enough); 6 Entry of GBS in the bloodstream (sepsis or bacteraemia); 7 Entry in cerebrospinal fluid after hematogenous spread (meningitis). Derived from thesis A.E. Muller; Population pharmacokinetics of antibiotics to prevent group B streptococcal disease: from mother to neonate; 2009

Intra-amniotic bacterial colonization or progression to infection depends on the number and pathogenicity of the colonizing bacteria and the effectiveness of the amniotic fluid antibacterial mechanisms.(34) In addition, it is conceivable that maternal genetic variation plays a role in the response to occurrence and severity of intra-uterine infections. Romero et al. speculated that it is not the presence of the bacterial organism itself, but the response of the host that is the critical step in this chain of events. When the host defence system is inadequate, bacterial growth may become excessive and lead to an ascending infection into the uterus.(35)

GBS disease in the newborn

Neonatal GBS is diagnosed as *culture-proven* if streptococci are isolated from blood and/or from cerebrospinal fluid combined with physical signs of infection in the neonate. The diagnosis *probable* GBS-EOD is used for cases of serious neonatal disease when GBS is detected at various sites, but not in blood and/or cerebrospinal fluid.(36) A different group is the "asymptomatic" GBS bacteriemia, defined as positive blood cultures for GBS in neonates without clinical signs of infection.(37-39)

Most infections in newborns occur in the first week of life and are designated early-onset GBS disease (GBS-EOD). The majority of cases of GBS-EOD occur within 24 hours after delivery(22) and present as a rapidly progressive septicaemic illness (Figure 4).

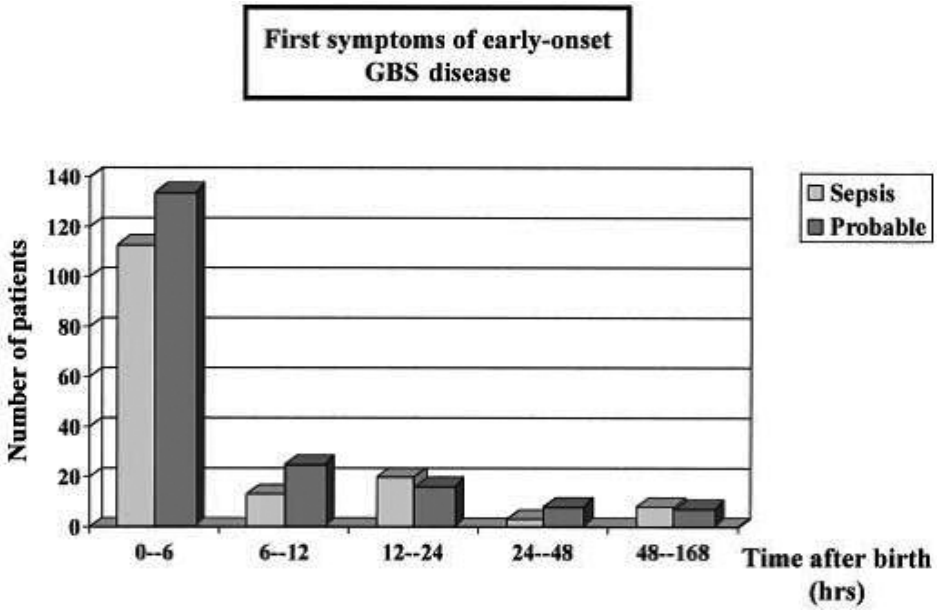

Figure 4: Onset of neonatal early-onset GBS disease(18)

Newborns with GBS-EOD usually present with sepsis or pneumonia, and less often contract meningitis, osteomyelitis, or septic arthritis.(18;27)

In late-onset neonatal GBS infections (GBS-LOD), illness occurs between 8 and 90 days after birth. In contrast to GBS-EOD, late-onset infection is not always acquired from the mother. Horizontal transmission during the perinatal period may occur from mother to infant or from nosocomial or community sources. GBS-LOD is more often associated with localized infections (especially meningitis and pneumonia), which are less rapidly progressive than GBS-EOD. The incidence of meningitis in late onset disease is approximately 30%.(15)

Case reports demonstrate that maternal milk, in cases of either clinical or subclinical mastitis, may be a source of GBS infection resulting in either late onset or recurrent neonatal GBS disease.(40-44) GBS may initially colonize the neonatal oropharynx mucosa during delivery, infecting maternal ducts during breastfeeding. The organism multiplies in the milk ducts and as the microbial concentration increases in the milk, the infant might be reinfected during breastfeeding.(40)

There is significant long-term morbidity after GBS-EOD and GBS-LOD.(45) Survivors may suffer from hearing or visual loss, uncontrolled seizures, impaired psychomotor development and/or mental retardation.(46;47) A prospective study with 5-year follow-up showed that GBS meningitis results in children with neurological deficiencies in 34.8% of cases ranging from partial sensory loss to profound mental retardation, blindness and deafness. (48)

Incidence and causes of neonatal sepsis

The reported incidence of overall neonatal sepsis varies from 7.1(49) to 38(50) per 1000 live births in Asia, from 6.5(51) to 23(52) per 1000 live births in Africa and from 3.5(53) to 8.9 per 1000 live births(54) in South America and the Caribbean. Incidence rates reported in the United States and Australia range from 1.5 to 3.5 per 1000 for early onset sepsis (EOS) and up to 6 per 1000 live births for late onset sepsis (LOS), a total of 6-9 per 1000 for neonatal sepsis.(55-58)

Neonatal surveillance in *developed* countries generally identifies GBS and E. coli as the dominant EOS pathogens and coagulase negative staphylococci (CONS) followed by GBS and Staphylococcus Aureus as the dominant LOS pathogens.(55;57) The pathogens most often implicated in neonatal sepsis in *developing* countries differ from those seen in developed countries. Overall, Gram-negative organisms are more common in developing countries and are mainly represented by Klebsiella, E.coli, Pseudomonas and Salmonella. Of the Gram-positive organisms in developing countries, Staphylococcus Aureus, coagulase

negative staphylococci, Streptococcus pneumoniae and Streptococcus pyogenes are most commonly isolated.(59;60)

The difference in occurrence of invasive pathogens in developed and developing countries might be explained by true differences in pathogens across the world, but might also be explained by an epidemiological bias linked to the fact that most EOS babies in developing countries die at home before reaching health care facilities and they do not appear in the statistics.(59) In a review of studies from developing countries reporting on etiology of community-acquired infections, authors stated that hospital-based studies suggest that most infections in the first week of life are due to Gram-negative pathogens, and many may be environmentally rather than maternally acquired, owing to unhygienic delivery practices. (60)

Risk factors for GBS-EOD

In general and for several reasons neonates are at risk for infections, and this is in particular for preterm neonates.(61;62) In the first place, preterm babies are at risk for infections because of decreased barrier function of skin and mucocutaneus tissue. Necessary invasive treatment of preterm neonates, such as intravenous and umbilical venous infusion, may contribute to infection. Secondly, the immune system in neonates is impaired. Considering the humoral immune response, adequate numbers of B lymphocytes are present, but antibody production is delayed compared with the adult. Decreased levels of complement components contribute to the increased vulnerability to infection of neonates. Infection is a major problem for infants born before 28 weeks. Their serum IgG antibody levels are low and the deficiencies in complement levels and chemotactic responses noted in full-term neonates are even more marked and persist for longer.(63)

For cellular immune response, compared with older children and adults, neonates have an intrinsic limitation in their capacity to produce neutrophils and a subsequent susceptibility to exhaustion of marrow reserves during times of increased use, such as sepsis. (64) In addition, the neutrophils have impairments of numerous functions important to the clearance of microbes, including marrow egress, adhesion to the microvascular endothelium, chemotaxis and antibacterial function.(61;64-67) Deficiencies in circulating levels of GBS-specific antibody in the context of neutrophil dysfunction heighten the neonatal susceptibility to GBS infection.(61)

Both host related factors and bacterial properties may increase the risk on GBS-EOD. A number of factors are known to increase the risk of neonatal early-onset infection in the presence of maternal GBS carriage. (Table 1)

Table 1 Risk Factors for GBS-EOD

Author	Country	Year	Studydesign	Prevalence	No of patients	OR for risk factor with 95% CI								
						Prematurity < 37 weeks	PROM > 18 hrs$	Fever	ROMBOL®	LBW%	IU-FM*	PProm^	Amnionitis	Frequent VE#
Oddie(13)	UK	1998-2000	Case Control	0.57/1000	37-147	10.4 (3.9-27.6)	25.8 (10.2-64.8)	10.0 (2.4-40.8)	11.1 (4.8-25.9)					
Benitz(74)	USA	1999	Review		NM	5.80 (2.15-15.7)	7.28 (4.42-12)	4.05 (2.17-7.56)		7.37 (4.48-12.1)			6.43 (2.32-17.8)	
Schuchat(56)	USA	1995-1996	Case Control	1.4/1000	41-200			4.1 (1.2-13.4)						2.9 (1.1-8.0)
Adair(73)	Canada	1993-1997	Case Control	0.25/1000	90-489	3.89 (2.08-7.27)		4.65 (2.48-8.69)		3.60 (1.68-7.65)	2.24 (1.22-4.13)	2.39 (1.38-4.14)	15.03 (5.58-41.89)	

$Prolonged rupture of membranes
@Rupture of membranes before onset of labour
%Low birth weight
*Intrauterine fetal monitoring
^Premature Prelabour Rupture of Membranes
Frequent Vaginal Exam
NM Not Mentioned

Preterm delivery (before 37 weeks of gestation)

The excess risk of GBS-EOD in preterm and LBW infants has been well recognized for many years. Early reports noted that preterm and low- birth-weight infants were overrepresented among infants with early-onset disease.(68;69) This is confirmed by more recent case-control studies.(70;71)There is a progressive increase in risk for neonatal sepsis in general with decreasing gestational age.(72) Reported odds ratio's for GBS-EOD in prematurity differ from 3.89 (95% CI 2.08-7.27)(73;74) to 10.4 (95% CI 3.9-27.6).(13)

Prolonged rupture of the membranes (more than 18-24 hours)

Prolonged rupture of the amniotic membranes for > 18(72;75) to 20(76) hours before delivery substantially increases the risk of neonatal GBS-EOD.(77)

Odds for GBS-EOD in prolonged rupture of the membranes vary from 7.28 (95% CI 4.42-12) to 25.8 (95% CI 10.2-64.8).(13;74)

Intrapartum fever

Intrapartum temperature > 37.5°C(75) or fever without additional definition of temperature are associated with an increased risk of neonatal GBS infection.(27)There are no objective data to quantitate that higher maternal fever confers a higher risk. Odds of 4.1 (1.2-13.4) to 10.0 (95% CI 2.4-40.8) for GBS-EOD in patients with intrapartum fever were reported, but studies differ in definition of fever (either > 37.5°C or > 38°C).(13;56;73;74)

Chorioamnionitis

Intrapartum fever accompanied by two or more additional signs of chorioamnionitis, including fetal tachycardia, uterine tenderness, foul-smelling vaginal discharge, or maternal leukocytosis is associated with higher neonatal GBS attack rates.(72;78-81) One study provided sufficient data for estimation of OR, which was 6.42 (95% CI 2.32-17.8).(74)

One case control study reported that at least one of the risk factors preterm delivery, intrapartum fever and membrane rupture of at least 18 hours is found in 49% of GBS-EOD cases. (56)

Maternal GBS bacteriuria

The incidence of GBS in quantities $>10^5$ colony forming units (cfu) /ml urine in pregnant women has been reported to be between 0.4 and 7%.(82-84) Infants born to women with GBS bacteriuria during pregnancy are more frequently and more heavily colonized with GBS and may be at increased risk for invasive GBS disease.(85;86)

Two studies investigating the relation between bacteriuria and genital colonization reported a positive predictive value of GBS bacteriuria in the first trimester of pregnancy for positive GBS genital culture at the time of labor of 30.2%(87) and 61%.(88)

In another study urine was sampled at admission for labor. Of 1786 women whose urine was sampled during labor, GBS were isolated from 128 (7%), in 22 of whom (1% of the total) GBS were present in quantities greater than or equal to 10^4 colony forming units (cfu)/ml urine. Neonates born to women with greater than or equal to 10^4 cfu GBS/ml urine were apparently at greater risk for neonatal infection, as they were more commonly and more heavily colonized than were the newborns of women with lower quantities of GBS in urine. (84)

It has been shown that only 60% of bladder punctured pregnant women whose urine specimens contained $>10^5$ cfu/ml urine harboured GBS in the bladder.(84) Therefore, a high quantity of GBS in urine is assumed to reflect heavy colonization of urethra, vulva and vagina instead of cystitis. However, there are no studies with quantative cultures to confirm this assumption.

History of a previous child with invasive neonatal GBS disease.

Although having had a sibling with invasive GBS disease is widely accepted as a risk factor for GBS-EOD, only few reports show neonatal GBS infection followed more than one pregnancy in the same mother.(89-91) In some but not all of the cases, mothers received antibiotics during a subsequent pregnancy and delivery. Therefore it is difficult to determine what the exact risk for GBS-EOD in a subsequent pregnancy is.

Women may remain colonized with the same strain of a virulent subtype of GBS for prolonged periods and may fail to develop protective levels of type specific serum antibodies despite long term colonization.(92;93)

To conclude, there may be an increased risk of GBS-EOD in subsequent pregnancies in women who have had a child with GBS-EOD disease, but this risk has not been quantified.

Other factors

Bacterial virulence properties might influence the risk on GBS-EOD(94), as well as low levels of maternal antibodies.(95) Race or ethnicity,(96;97) maternal age,(96;97) neonate gender, multiple gestation, (98-101) internal monitoring> 12 hours, (72) increased number of vaginal exams, (56) meconium staining,(77) asphyxia(70) and fetal acidosis(102) may be associated with increased risk. These variables may be covariant with GBS colonization, gestational age at delivery, duration of ruptured membranes or other factors. Therefore, their independent contributions are not delineated readily.

However, 30-40% of GBS-EOD occurs in the absence of one of the five major risk factors (prelabor rupture of membranes, preterm labor, intrapartum fever, GBS bacteriuria during pregnancy or a previous child with GBS).(18;103)

GBS isolation and detection

The detection rate of GBS from clinical specimens depends on several factors. Culturing specimens from both the anorectum and the vaginal introitus increases the likelihood of GBS isolation by 5-27% over vaginal culture alone.(75;104;105) Internal examination or visualization of the cervix by speculum examination should not be performed for collection of screening cultures, since studies show much lower isolation rates from cervical swabs than low vaginal swabs.(5;106;107)

After collection of swabs, it is important that Group B streptococci from rectovaginal swabs will survive during shipment from satellite clinics to a central microbiology laboratory.

In 1967, Amies published about a transportation device that would preserve clinical samples from collection sites to the testing lab that could be many hours or even days away.(108) Until today, this "Amies transport medium" is internationally recommended for throat, wound and genital tract samples.(109) Amies broth with charcoal is a non-nutritional, phosphate buffered type medium used to maintain the viability of microorganisms without a significant increase in growth. Charcoal was added to the formulation to neutralize the toxic effects of fatty acids that are toxic to microorganisms.

The CDC guidelines state specifically that the viability of GBS can be maintained for up to 4 days in appropriate transport medium.(109) There are few data, which support this statement. One study showed that there will be a loss of positive culture results if the GBS colony density is low or if the room ambient temperature is relatively high (> 30^0C).(110) GBS was recovered from 92-100% of swabs containing 10 or more colony forming units (cfu) when stored either 3^0C or 24^0C for 4 days. However, GBS recovery decreased significantly when the swabs were stored at 30^0C. After 6 days, sensitivity of 96-100% was observed only for the swabs held at 4^0C and 24^0C and containing the high density of 100 or more cfu.(110)

Another study showed that among initially positive swabs kept at 21^0C in Amies transport medium, GBS were recovered after 24h, after 48 h, after 72 h and after 96 h in 95%, 88%, 85% and 71% of the specimens respectively.(111)

To conclude, viability of GBS is not fully preserved by storage of vaginorectal swabs in Amies transport medium. There are effects of time and temperature and these effects are greater for lower GBS concentrations.

When swabs arrive in a laboratory and culturing starts, the use of selective broth medium (i.e. a broth containing antimicrobial agents to inhibit competing organisms) is essential because it can increase the yield of screening cultures by as much as 50%.(112;113) Examples of selective enrichment broths include Todd-Hewitt broth supplemented either with gentamicin (8 microgram/ml) and nalidixic acid (15 microgram/ml) (called TransVag broth) or with colistin (10 microgram/ml and nalidixic acid (15 microgram/ml) (called Lim broth).(114)

Although TransVag and Lim broth media are often available without blood, the addition of 5% sheep blood can increase the recovery of GBS. Selective enrichment broth can also contain chromogenic substrates that provide for a change in color in the setting of beta-hemolytic GBS; however, nonhemolytic isolates will not be detected by these broths alone. (115-120)

Rapid tests

Nowadays, several non-culture-based tests are available which enable rapid point-of care diagnostics for intrapartum screening, allowing optimal targeting of IAP to women carrying GBS.

As well as being accurate, the ideal test should be rapid enough to allow adequate time for IAP to be effective, and should require minimal preparatory steps and be easily interpretable to enable routine use on busy delivery suites.

Polymerase chain reaction

Polymerase chain reaction (PCR) involves the logarithmic amplification of specific areas of the bacterial chromosome using an iterative process of hybridisation of replication primers, amplification from these primers of the target DNA and separation of the nascent DNA so that the process can be repeated. Real-time detection of the amplified DNA is by incorporation of a fluorescent marker, which is quantitatively measured within a PCR thermocycler. The net effect of this is to reduce the results turnaround time from 12–24 hours to less than 2 hours. One of the main disadvantages of current PCR technology is that laborious preparative steps are required to extract DNA before the thermocycling process can be undertaken.(121)

Optical immunoassay

In the optical immunoassay (OIA) an antibody specific to a GBS surface carbohydrate is coated on a sample well. In the presence of GBS carbohydrate the optical substrate of the test well reflects differently and can be detected visually using a luminometer. Again a preparative step is needed, to extract the carbohydrate antigen from GBS.(121)

DNA hybridisation

Nucleic acid hybridization tests are based on the ability of complementary nucleic acid strands to specifically align and associate to form stable double-stranded complexes. Commercially available kits use a single-stranded DNA probe with a chemiluminescent label that is complementary to GBS ribosomal RNA. A preparatory step releases the RNA from the organism, to which the labeled DNA probe combines to form a stable DNA:RNA hybrid. A specific reagent enables the differentiation of hybridized probe from unhybridized probe

and measurement in a luminometer, with a positive result being one that is greater than a predefined threshold.(121)

Enzyme-linked immunosorbent assay

Similar to the OIA, the enzyme-linked immunosorbent assay (ELISA) employs antibodies to GBS surface carbohydrate, both coated on a sample well and in soluble form linked to an enzyme. The GBS binds first to the sample well and then the soluble form of the antibody binds to the GBS. The enzyme then produces a reaction in a colored substrate, which can be detected by eye or quantitated in a luminometer.(121)

Latex agglutination

The most easy to use of all the available rapid tests is based on antibodies bound to latex particles. If GBS is present, the antibodies bind to its surface and the attached latex agglutinates into visible clumps.

Each of the tests currently available has advantages and disadvantages. Even laboratory-based use of these tests is limited, and there has been no proper evaluation of any of these tests in the point-of-care setting.(121)

Accuracy of rapid tests for GBS

In a recent systematic review on rapid tests for GBS colonization in laboring women 23 relevant papers of 29 test accuracy studies assessing a total of six tests were analyzed.(122)

This review shows that many of the GBS tests, with the exception of real-time PCR and optical immunoassay (OIA) either took too long to produce a result on time or were not of sufficient accuracy to be feasible for maternal intrapartum testing. The review focused on studies in which selective media were used for gold standard culture. PCR had a median sensitivity and specificity of 96% (Range 88–99%) and 98% (Range 96–98%) respectively. Median sensitivity for optical immunoassay (OIA) was 48% (Range 37–72%) and median specificity was 97% (Range 95–97%). Positive likelihood ratio for PCR was 38.80 (95% CI 6.05-248.720), negative likelihoodratio was 0.06 (95% CI 0.03-0.11). The positive likelihood ratio for OIA was 14.7 (95% CI 10.6-20.3) and negative likelihood ratio was 0.47 (95% CI 0.31-0.73).

Although OIA seems less accurate than PCR, it was more rapid (30 minutes compared to 40 minutes) and less complex to perform, making it more feasible as a near-patient test.

However, the real time PCR was only evaluated in 2 relatively small studies. Authors state that with regard to the poor methodological quality of the existing studies and the imprecision of the evidence for PCR, a robust technology assessment comparing the most promising tests (PCR and OIA) is needed before reaching recommendations for practice.(122)

Recently, in a primary test accuracy study swabs were obtained at the onset of labor from 1400 women from two large maternity units to compare the results of vaginal and rectal PCR and OIA (index tests) with the reference standard of enriched culture of combined vaginal and rectal swabs.(121) PCR was significantly more accurate than OIA for the detection of maternal GBS colonization. The sensitivity for PCR was 84% (95% CI 79-88%), with a specificity of 87% (95% CI 85-89%). Authors conclude that PCR performed better than OIA, but results of their economic analysis demonstrate that both rapid tests should not yet be used in practice, since both are not clearly cost-effective methods of screening women for GBS colonization.

Preventive measures

Vaccination

Vaccination of pregnant women offers the opportunity for primary prevention of GBS disease of the newborn by two mechanisms. First, a vaccine that induces mucosal immunity would decrease maternal colonization and consequently the risk of transmission to the fetus. Second, and potentially more important would be the transplacental transmission of protective antibodies to the baby. Babies with high concentrations of antibodies to GBS proteins have an OR of 0.002 (95% CI 0.000-0.57) of developing GBS-EOD compared with those with low levels.(123) Protective maternal antibodies are believed to persist in the fetus for about 3 months after birth affording additional passive protection against GBS late onset disease.(124)

The search for a suitable candidate molecule for vaccination has been ongoing for two decades, but a vaccine has yet to be licensed for use and evaluated for effectiveness in reducing neonatal GBS disease. Initial developments involved carbohydrate-based vaccines of which immunogenic efficacy has been demonstrated in women.(124) The problem with each vaccine is that there are five major, and several minor, serotypes of GBS, each with a different outer carbohydrate. The current vaccine preparations for GBS are based on the serotypes prevalent in the USA and Europe. However, these vaccine preparations are not as effective in women of other regions of the world because of the prevalence of different serotypes expressing a different repertoire of surface proteins. To ensure effective vaccine development, it will be important to monitor the distribution pattern of the prevalent serotypes and sequence types in all regions of the world, thereby ensuring the inclusion of the most relevant components in a global GBS vaccine.(124) Any vaccine would have to be multivalent and appropriate to the serotype prevalence within the population. Focus therefore shifted to an ubiquitous protein that is present on the outer surface of all GBS serotypes.(125) Protein-based antigens are inherently more immunogenic than carbohydrates, are less likely to cross-react with human tissues and can more readily be manipulated by molecular techniques.

Chlorhexidine

Vaginal disinfection with chlorhexidine during labor has been suggested as a simple, cheap and safe alternative for IAP to prevent vertical transmission and subsequent GBS-EOD. Chlorhexidine is without risk of bacterial resistance and with no risk of allergic complications.

In a systematic review in 2004, analysis of 5 studies (including 2190 term and preterm infants) comparing vaginal disinfection with chlorhexidine during labor versus no treatment or placebo resulted in a statistically significant reduction in GBS colonization of neonates (RR 0.72, 95% CI 0.56 to 0.91), but the studies were not large enough to draw conclusions regarding reduction of GBS infections.(126) There was no statistically significant reduction in EOD including GBS infection, GBS pneumonia, GBS meningitis or mortality.

In a randomized controlled study with 244 GBS colonized mothers at term (screened at 36-38 weeks), the efficacy of intrapartum vaginal flushings with chlorhexidine was compared with ampicillin intravenously (IV) in preventing GBS transmission to neonates. The rate of neonatal GBS colonization was not statistically different in both groups (chlorhexidine, 15.6%; ampicillin, 12%). However, colonization with Escherichia coli was significantly more prevalent in the ampicillin (7.4%) than in the chlorhexidine group (1.8%, $p < 0.05$).(127)

In a large trial in Soweto, South Africa, 8011 women were randomized to chlorhexidine vaginal wipes or external genitalia water wipes during active labor, and their babies were assigned to full body (intervention) or foot (control group) washes with chlorhexidine at birth, respectively.

Rates of neonatal sepsis did not differ between the groups. Rates of colonization with GBS in newborn babies born to mothers in chlorhexidine and control groups did not differ. (128)

In conclusion, studies with chlorhexidine showed promising results regarding reduction of transmission of GBS colonization but a definite conclusion on the effect of this treatment on the incidence of GBS-EOD cannot be drawn.(126;129;130)

Antibiotic treatment of the mother

Since vaginal re-colonization from the gut may occur, antibiotic treatment of GBS carriers during pregnancy is inadequate as prophylaxis.(5) In addition, prolonged prophylactic treatment can result in resistance of other microorganisms and disturbance of the intestinal and vaginal flora.

In a small double-blind randomized controlled trial, prenatal oral amoxicillin (500 mg 2 times daily during 5 days) or placebo was given to GBS carriers identified by rectovaginal culture at 35-37 weeks of gestation. Persistence of GBS colonization after treatment with

amoxicillin compared to placebo was 43% and 67% of the women at the time of labor (difference statistically not significant).(131)

Intrapartum antibiotic prophylaxis (IAP) of the mother during delivery is regarded as the most effective method to reduce the number of neonatal GBS infections.(14)

In the absence of IAP in vaginal deliveries, neonates born from GBS colonized mothers were colonized in 16%-69% at one or more surface areas.(6-11;132;133) After administration of IAP with ampicillin in randomized studies, a lower neonatal colonization rate has been found after vaginal delivery, varying from 0% to 10%.(9;14;133;134)

The most direct indicator for efficacy of IAP is the bacterial load in neonatal blood cultures.

Recently, the Cochrane collaboration conducted a systematic review on the impact of maternal intrapartum antibiotics for maternal Group B streptococcal colonization on neonatal GBS infection. Only three randomized controlled trials, evaluating the effects of IAP versus no treatment, conducted more than 20 years ago in three different countries and enrolling a total of 500 women have been published.(14;132;135)

Overall quality of the included studies was poor and the risk of bias high. No study reported on a pre-set sample size and no placebo was used in the three studies comparing one antibiotic versus no treatment; care-givers and researchers were not blinded to group assignment.(9)

Despite serious concerns about bias in the three included trials, studies were combined. A statistically significant reduction in GBS-EOD was found. (RR 0.17, 95% CI 0.04-0.74) The authors concluded that IAP reduces GBS-EOD, but there is lack of evidence from recent well designed and conducted trials to recommend IAP to reduce GBS-EOD.(11)

Antibiotics and dosing regimens

There are only a few well designed studies in which the efficacy and side effects of different antibiotics and dosing regimens have been examined. Adequate antibiotic concentrations in amniotic fluid are likely to be involved in eradication of GBS from surface areas. Since there is some time needed to achieve adequate amniotic fluid concentrations and eradicate GBS from these areas, the time interval between IAP and delivery is essential. De Cueto et al. found for ampicillin that when this interval is at least 2 hours, vertical transmission of GBS was minimized to 1.5%.(133)

Muller et al collected blood samples from mothers in labor, umbilical cord and neonates after administration of an intrapartum dose of amoxicillin of 2 gram. With these data a multicompartment model to describe the overall concentration versus time profile in maternal plasma, umbilical cord and neonatal plasma was developed. Peak concentrations in umbilical cord and neonatal serum were lower and delayed compared to the maternal peak concentration. Approximately one hour after the start of the antibiotic administration the

neonatal concentration reached its highest level, and thereafter exceeded the concentrations in venous umbilical cord. Simulation of a 2 gram infusion on basis of the developed pharmacokinetic model demonstrated that amoxicillin concentrations in maternal, venous umbilical cord and neonatal serum exceeded the minimal inhibitory concentration for > 90% of the dosing interval of 4 hours.(136)

The CDC guideline advises intravenous prophylaxis with 5 million IU penicillin G or 2 gram amoxicillin or ampicillin, followed by respectively 2.5 million IU penicillin or 1 gram amoxicillin or ampicillin every four hours until delivery.(5) Dutch guidelines deviate from this guideline, advising an initial dose of 2 million Units benzylpenicillin and subsequent doses of 1 million Units every four hours. (Table 2)

Muller et al. described in a simulation model in women with PPROM that a dosing regimen of bolus injections of 1 gram amoxicillin every 6 hours was predicted to be adequate for the prevention of GBS infection in pregnant patients.(137) This regimen was described as the usual regimen in a former review of the Cochrane Library(138), which now is withdrawn. The new Cochrane review on this topic doesn't describe recommendations for antibiotic dosing regimens anymore. A two gram loading dose does not seem to be beneficial and the 1 gram doses can safely be administered by bolus injection increasing the comfort of the patient and facilitating prophylaxis.(137)

Penicillin is the first choice because of the narrow spectrum and less risk of selection of resistant bacteria.(139) Resistance to penicillin in GBS has been described (140;141), but is very rare. Resistance to erythromycin and clindamycin has been reported in 7.4% and 3.4% of invasive GBS isolates respectively.(142;143) This has clinical consequence as these agents are recommended for intrapartum prophylaxis in women with a history of penicillin allergy. For this reason in the last report of the CDC the recommendation has been changed.

In case of penicillin allergy with low risk of anaphylaxis, cefazolin instead of erythromycin or clindamycin is recommended. In case of allergy to penicillin with high risk of anaphylaxis, clindamycin or erythromycin is given after susceptibility to one of these agents is proven. In case of allergy to penicillin with high risk of anaphylaxis and resistance to clindamycin and erythromycin, vancomycin can be given.

Dutch guidelines advise either clindamycin or erythromycin in case of history of penicillin allergy without establishing low or high risk of anaphylaxis or the susceptibility of GBS to one of these antibiotics. (Table 2)

Antibiotic treatment of the neonate

Complete absence of GBS-EOD was reported as an unexpected benefit of a policy of routine administration of intramuscular penicillin to neonates to prevent gonococcal ophthalmia.

Table 2 Antibiotic Dosing regimen as recommended by the CDC(5)

Antibiotic	Initial Dose	Subsequent Dose	Dosing Interval	Patients
Benzylpenicillin	5 million Units*	2.5 million Units*	4 hours	Not penicillin allergic
Ampicillin	2 g	1 g	4 hours	Not penicillin allergic
Cefazolin**	2 g	1 g	8 hours	Allergic to Penicillin; Low risk of anaphylaxis
Clindamycin	-	900 mg	8 hours	Allergic to Penicillin; High risk of anaphylaxis, susceptibility to clindamycin proven
Erythromycin	-	600 mg	6 hours	Allergic to Penicillin; High risk of anaphylaxis, susceptibility to erythromycin proven
Vancomycin**		1g	12 hours	Allergic to Penicillin; High risk of anaphylaxis, resistant to clindamycin and erythromycin

* Dutch guidelines differ from these CDC guidelines, advising an initial dose of 2 million Units and subsequent doses of 1 million Units

** Dutch guidelines do not mention cefazolin nor vancomycin as alternatives for Benzylpenicillin in case of allergy

(144;145) Subsequent observational studies have suggested that the administration of intramuscular penicillin to the newborn immediately following delivery may be an effective strategy to reduce the incidence of GBS-EOD. However, these studies were uncontrolled, retrospective and non-randomized.(146-149) A Cochrane review on intramuscular penicillin for the prevention of early onset group B streptococcal infection in newborn infants included only one study. In this randomized controlled trial of 1187 infants of birth weight 501 to 2000 grams, there were no significant differences found for the outcomes of GBS-EOD (RR 0.73, 95% CI 0.32-1.62) or neonatal mortality (RR 0.78, 955 CI 0.55-1.11). Other outcomes such as GBS-LOD, neonatal sepsis and secondary outcomes such as neurodevelopmental status and length of hospital stay could not be assessed.(150)

Adverse effects of antibiotics

The administration of antibiotics as prophylaxis against GBS-EOD should have minimal risks for both mother and child. For the mothers, an important adverse effect of an increased use of antibiotics is the increasing incidence of potential severe adverse reactions including anaphylaxis to penicillin.(151;152) The incidence of anaphylaxis after administration of penicillin is estimated to be 0.01% with a mortality rate of 9%.(153;154)

Neonatal risks include an increase in incidence of non-GBS-EOD. The use of ampicillin rather than penicillin for intrapartum GBS prophylaxis has been reported to be associated with an increase in the incidence of neonatal sepsis caused by ampicillin-resistant Gram-negative micro-organisms.(55;155;156)

One study reported an association between the use of intrapartum antibiotics and LOD.(157) The incidence of postnatal yeast infections may increase with the use of intrapartum antibiotics(158) and possibly acquired abnormalities in early-life bacterial colonization may affect the development of the immune system and change the pattern of initial colonization of the gut in the first days of life which may be linked to later development of allergic disease.(157;159-161)

Burden of the disease

The incidence of GBS-EOD *before* implementation of prevention strategies ranged from 0.2 to 3 or even more cases per 1000 live births with substantial geographical variations.(162) In Europe, prior to 2000, incidence varied between 0.2 and 0.3 in Denmark(21) to 0.76 in Finland(163), 0.69 to 4.5 in France(164), 1.9 in the Netherlands(18), 3.25 in the Czech Republic(165) and 2.4 in Spain.(166)

Wide variations in incidence could be correlated with differences in women's GBS carriage rate, with differences of ethnic or racial susceptibility to GBS infection, with differences in definition of diagnosis of GBS-EOD and with differences in virulence among the prevalent GBS strains.

Evolution of Guidelines for prevention of GBS-EOD

During the past two decades, various initiatives have been established to prevent GBS-EOD. These were mainly promoted in the USA and transferred and adapted into national guidelines in some European countries.

Clinical trials in the 1980s showed that GBS-EOD can be prevented by administering intrapartum antibiotic prophylaxis (IAP) to mothers who are colonized with GBS.(14;17)

Prevention starts with a strategy to identify mothers at risk for having a baby with GBS-EOD.

The simplest strategy, IAP in all deliveries, has not been considered because of unnecessary exposure to antibiotics.

In the USA, two different options of IAP, either based on the presence of maternal factors associated with increased risk of GBS-EOD (risk factor based screening) or on maternal antenatal GBS-positive screening cultures (culture based screening), were established in 1996.(46) Although neither option was optimal or properly implemented, surveillance studies already documented from the early 1990s to 1999 a decline in GBS-EOD of 65%.(17)

In the risk factor based approach, women presenting at the time of labor with clinical risk factors for disease (ie preterm delivery before 37 weeks of gestation, prolonged rupture of the membranes, intrapartum temperature > 37.5°C, maternal GBS bacteriuria during pregnancy and a history of a previous child with GBS-EOD) are offered intrapartum antibiotic prophylaxis.

In the screening approach, women are screened for carriage of group B streptococcus between 35 and 37 weeks of gestation, and IAP is offered to all carriers as well as in case of unknown GBS carriage and delivery at < 37 weeks gestation or amniotic membrane rupture > 18 hours.

In both strategies, antibiotics are given during labor to women who had group B streptococcal bacteriuria during their current pregnancy, or who have had an infant with GBS-EOD previously.(46)

In 2002, a population-based retrospective study of 5144 births, including 312 in which the newborn had GBS-EOD, showed that culture based screening was 50% more effective in prevention of GBS-EOD compared to risk factor based screening.(167) In this study, to identify candidates for intrapartum prophylaxis, either screening of pregnant women for GBS colonization by means of cultures (screening approach) or assessing clinical risk factors (risk factor approach) was used as both recommended by the former CDC guidelines in the USA.(46) Antenatal screening was documented for 52 percent of the mothers in the study. The risk of GBS-EOD was significantly lower among the infants of screened women than among those in the risk factor group (RR 0.46, 95% CI 0.36-0.60).

Thereafter, national guidelines in the USA were changed, shifting from a recommendation of either of these strategies to a recommendation of only culture based screening at 35-37 weeks of gestation for all pregnant women and IAP for any woman with GBS colonization. The risk factor based approach was reserved for women in labor with an unknown maternal colonization status.(5) Culture based screening was expected to result in further declines in the incidence of GBS-EOD.(167)

Since the end of the 1990's, in several European countries a culture based screening strategy has been recommended, including Spain (1998 and 2003), Italy (1996), France (2001), Belgium (2003), Germany (1996, 2008) Switzerland (2007), Poland(2008) and Czech Republic (2008). The risk factor based strategy has been recommended in the UK and in the Netherlands. In some other European countries, for example in Bulgaria and Denmark, there are no guidelines.(168)

Epidemiology

In the USA, after widespread implementation of prevention strategies, the incidence decreased from 1.8 cases per 1000 live births in 1993 to 0.6 per 1000 live births in 1998 and 0.32 cases per 1000 live births in 2003.(17;109;169)

In European countries in which a prevention strategy was adopted, an important drop of the incidence of GBS-EOD was observed as well. In Spain for example, incidence declined from 2.4 cases per 1000 live births in 1996 to 0.59 in 2005.(166) Table 3 shows GBS colonization during pregnancy and incidence of GBS-EOD in various European countries after 2000.

The initial reported case fatality rate associated with GBS-EOD in the USA dropped from > 50% in the 1970s to 4-10% in recent years.(1;16-18;109;170-173)

Intrapartum administration of antibiotic prophylaxis (IAP) to the mother may have contributed to above named declines, by the antibiotic effect on the infant and by decreasing the severity of the disease. It is unclear to what extent the decrease in GBS-EOD can be attributed to the administration of antibiotics. Other factors may contribute as well, among which are early recognition of infection and improved neonatal care(174), as well as natural changes in prevalence of maternal colonization and variation in GBS subtype distribution.

From Norway an, unexplained, marked increase in case fatality was reported. In this country a risk factor based strategy is applied. From an average of 5.8% in 2000-2005 a significant increase to 33% in the first 6 months of 2006 and a slightly increased incidence of invasive GBS disease in neonates using a risk factor based strategy has been reported.(175) Such changes in case fatality rates without alterations in antibiotic policy might be explained by changes in the virulence characteristics of circulating GBS.

In all countries the case fatality rate in preterm born infants remains substantially higher than in term born infants, with case-fatality rates of approximately 20% - 30% among infants born before 33 weeks' gestation, compared with 2%-3% among term born infants.(173;176;177)

Remaining burden of the disease

In 2009, evaluation of the implementation of the screening guidelines in the USA was performed over the period 2003-2004. This revealed that the rate of screening for GBS during pregnancy increased from 48.1% in 1998-99 to 85% in 2003-2004; the percentage of infants exposed to IAP increased from 26.8% to 31.7%.(169)

IAP was given in 87.0% of the women who were screened positive for GBS and who delivered at term, but in only 63.4% of women with an unknown colonization status who delivered preterm.

Table 3 GBS colonization during pregnancy and incidence of GBS-EOD in various European countries after 2000. Derived from Trijbels-Smeulders et al(168), Barcaite et al(4) and Edmond et al(3)

		GBS colonization (% of Pregnant Women)		Incidence of GBS-EOD/1000 Live Births
Eastern Europe				
Lithuania	2012	15.3(179)		
Czech Republic	2004	29.3(180)	2004	0.80(181)
Poland	2003	19.7(182)		
Western Europe				
France	2001	14.3(183)		
France	2003	15.4(184)		
France			2010	0.75(185)
Germany	2006	16(186)	2005	0.21(171)
United Kingdom	2006	21.3(187)	2011	0.67(188)
The Netherlands	2002	21(189)	2007	0.36(22)
			2010	0.70(190)
Ireland	2004	11.8(191)		
Scandinavia				
Denmark	2004	36(192)	2004	0.34(193)
Iceland	2003	24.3(194)		
Sweden	2008	25.4(195)	2004	0.69(196)
Norway			2006	0.85(175)
Southern Europe				
Greece	2003	6.6(197)		
Italy	2007	17.9(198)	2007	0.50(199)
Spain			2005	0.59(166)
Turkey	2003	10.6(200)		
Turkey	2004	6.5(201)		
Turkey	2005	32(202)		
Turkey	2005	9.2(203)		

The overall incidence of GBS-EOD in the USA in 2004 was 0.31 cases per 1000 live births. Preterm infants had a higher incidence of GBS-EOD than term infants (0.73 vs. 0.26 cases per 1000 live births). However, 74.4% of the cases of GBS disease occurred in term infants. Missed screening (i.e. "forgot to screen" at 35-37 weeks of gestation and no IAP) among mothers who delivered at term accounted for 13.4% of group B streptococcal disease. (34 of the 254 cases) A total of 61.4% of the term infants with GBS disease were born to women who had tested negative for GBS before delivery.(169)

From 2003 to 2006, an increase in GBS-EOD in the USA was seen towards 0.40 per 1000 live births. When stratified by race, incidence among black infants increased significantly (0.53 to 0.86 cases per 1000 live births), whereas incidence among white infants did not change significantly (0.26 to 0.29 cases per 1000 live births.(178) The reason for this difference remains unexplained.

Strategy for prevention and incidence of GBS-EOD in the Netherlands

In the Netherlands, the Dutch Society of Obstetrics and Gynecology (NVOG) and the Dutch Society of Pediatrics (NVK) approved the guidelines for prevention of GBS-EOD in 1998. These guidelines do not recommend universal screening nor prophylaxis in case of risk factors for GBS-EOD alone, but were based on a sort of the risk factor based approach. (46) IAP is recommended following a previous delivery of an infant with GBS-EOD, or heavy maternal GBS colonization (which may present as GBS urinary tract infection or GBS bacteriuria during current pregnancy). In the case of onset of labor before 37 weeks of gestation or prolonged rupture of membranes (>18 hours before delivery), screening for GBS carriage is performed first, followed by prophylaxis when the culture is positive. When delivery occurs before the result of the culture is available, the gynecologist should decide about antibiotic prophylaxis, based on the severity of the risk factor(s). (Figure 5) In this approach, the Dutch strategy differs from the risk factor based strategy. The choice for this risk factor-based strategy in 1998 was made with the intention to reduce the number of women that receives prophylactic antibiotics, taking into account the Dutch organisation of obstetrical care with approximately 30% home deliveries.

The Dutch guidelines advise to discontinue prophylactic administration of antibiotics to the mother after delivery, unless symptoms of maternal infection persist. In that case prophylaxis is changed to therapy with a change of antibiotic strategy.

A differentiated sequential management of newborn infants of GBS carriers who had an indication for antibiotic prophylaxis seems to be justified. It should be established whether adequate prophylaxis was given during delivery. Despite lack of evidence for existing dosing schedules, IAP is regarded as adequate if the antibiotics were given intravenously in the right dosage and at least 4 hours before delivery, so that two doses have been given. After adequate prophylaxis, observation during 48 hours, of which at least 24 hours in hospital, is recommended. If no or inadequate prophylaxis was given and gestation was more than 35 weeks, the same strategy is followed. If no or inadequate prophylaxis was given and gestation was less than 35 weeks, a culture is taken from blood and cerebrospinal fluid and treatment for sepsis is started. If the cultures of blood and of cerebrospinal fluid are negative and no clinical signs of infection are present, treatment can be stopped.

If clinical signs of infection exist, an extensive diagnostic approach for infection is indicated and the infant is treated as in sepsis, independently of the prophylaxis and the gestational age.(22) (Figure 6)

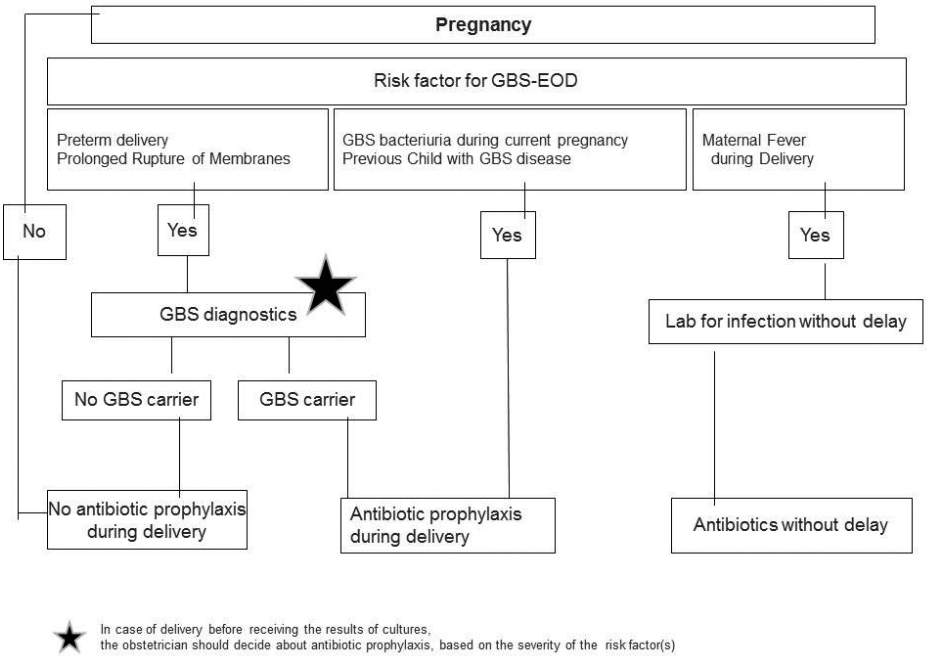

Figure 5: Scheme on prevention strategy of GBS-EOD in the Netherlands

After the introduction of above named prevention guidelines based on risk factors in 1999, there has only been a limited decrease in the incidence of proven GBS-EOD from 0.54 per 1000 live births to 0.36 per 1000 live birth in the Netherlands.(22)

There was no decrease in the incidence of probable early-onset GBS sepsis, respectively 1.3 and 1.4 per 1000 live births. In the small category of late onset GBS sepsis (> 7 days after birth), there was no decrease in the incidence of proven cases.(22)

Table 4 shows incidence figures of GBS meningitis and GBS sepsis and Table 5 shows deaths due to perinatal GBS infections in the Netherlands between 2000 and 2009, as registered by the Netherlands Perinatal Registry. This registration is estimated to cover 70% of the total population of the Netherlands and data therefore only show a trend over years. Incidences of (proven and probable) 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). Between 2000 and 2009 a case fatality rate for GBS-EOD of 6.3% was found.

Revision of the Dutch guidelines was considered in 2006, but recommended prevention strategy remained as it was. Because of the ongoing burden of GBS-EOD, adaptation of the Dutch guidelines should be reconsidered, particularly with regard to the fact that perinatal mortality in the Netherlands is high compared to other European countries.(23)

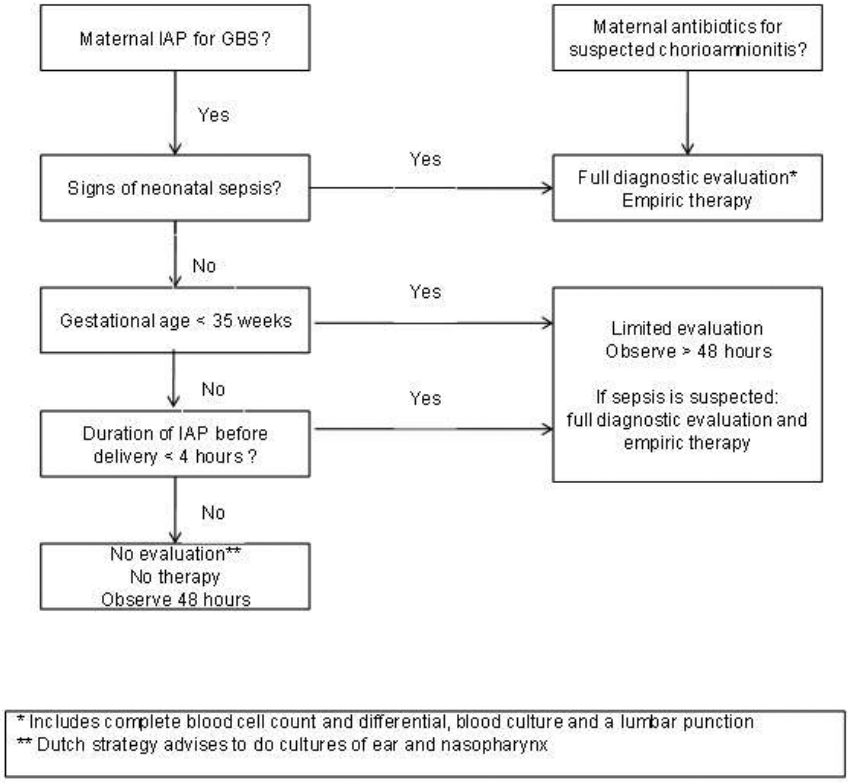

Figure 6: Postdelivery management of newborn infants of GBS carriers who received IAP as recommended by the CDC(5)

OUTLINE OF THE THESIS

The aim of this thesis is to contribute to the information needed for the establishment of an optimal preventive strategy for GBS-EOD.

In **chapter 2** a study is described that was performed to determine the prevalence of GBS and to identify risk factors for GBS carriage in a multicultural population of pregnant women in The Hague in the Netherlands. Several factors are known to increase the risk of perinatal GBS-infection in women that carry GBS. In **chapter 3** we report on the relationship between prolonged rupture of membranes (PROM, >24 hours) and labor before 37 weeks of gestation and GBS, to evaluate whether occurrence of these risk factors can predict prenatal GBS status. In GBS strains from the studied multicultural obstetric population, phenotypic and genotypic antibiotic susceptibility patterns and putative epidemicity was assessed, which is described in **chapter 4**.

Chapter 5 describes the results of a systematic review in which the relation between maternal colonization with Group B Streptococcus and preterm birth was determined and

Table 4 Incidence of GBS meningitis and GBS sepsis in the Netherlands, as registered by the Netherlands Perinatal Registry

Year	Number of cases	
	GBS meningitis	GBS sepsis
2000	15	158
2001	18	132
2002	19	137
2003	27	133
2004	28	151
2005	24	121
2006	18	117
2007	25	115
2008	15	108
2009	20	172
Total 2000-2009	209	1344

Table 5 Deaths due to perinatal GBS infections in the Netherlands between 2000 and 2009, as registered by the Netherlands Perinatal Registry

Diagnosis	Number of deaths	Percentage
GBS meningitis (n=209)	12	5.7%
GBS sepsis (n=1344)	87	6.5%
GBS meningitis or GBS sepsis (n=1171)	92	6.3%

in **chapter 6** we present results of a meta-analysis to assess the best timing of antenatal cultures, which may help to establish optimal prevention of GBS-EOD in neonates. With regard to the remaining burden of disease in the world, we list opportunities for improvement of prevention of GBS-EOD in **chapter 7**, followed by considerations in finding an optimal prevention strategy for the Netherlands in **chapter 8**. Finally, conclusions of earlier chapters are summarized and future perspectives and directions of research in the prevention of GBS-EOD are discussed in **chapter 9.**

REFERENCE LIST

1. Schuchat A. Epidemiology of group B streptococcal disease in the United States: shifting paradigms. Clin Microbiol Rev 1998 Jul;11(3.:497-513.
2. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. Pediatr Infect Dis J 2011 Nov;30(11.:937-41.
3. Edmond KM, Kortsalioudaki C, Scott S, Schrag SJ, Zaidi AK, Cousens S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. Lancet 2012 Feb 11;379(9815.:547-56.
4. Barcaite E, Bartusevicius A, Tameliene R, Kliucinskas M, Maleckiene L, Nadisauskiene R. Prevalence of maternal group B streptococcal colonisation in European countries. Acta Obstet Gynecol Scand 2008;87(3.:260-71.
5. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. MMWR Recomm Rep 2002 Aug 16;51(RR-11.:1-22.
6. Pylipow M, Gaddis M, Kinney JS. Selective intrapartum prophylaxis for group B streptococcus colonization: management and outcome of newborns. Pediatrics 1994 Apr;93(4.:631-5.
7. de Cueto M, Sanchez MJ, Molto L, Miranda JA, Herruzo AJ, Ruiz-Bravo A, et al. Efficacy of a universal screening program for the prevention of neonatal group B streptococcal disease. Eur J Clin Microbiol Infect Dis 1995 Sep;14(9.:810-2.
8. Hickman ME, Rench MA, Ferrieri P, Baker CJ. Changing epidemiology of group B streptococcal colonization. Pediatrics 1999 Aug;104(2 Pt 1.:203-9.
9. Lim DV, Morales WJ, Walsh AF, Kazanis D. Reduction of morbidity and mortality rates for neonatal group B streptococcal disease through early diagnosis and chemoprophylaxis. J Clin Microbiol 1986 Mar;23(3.:489-92.
10. Adriaanse AH, Kollee LA, Muytjens HL, Nijhuis JG, de Haan AF, Eskes TK. Randomized study of vaginal chlorhexidine disinfection during labor to prevent vertical transmission of group B streptococci. Eur J Obstet Gynecol Reprod Biol 1995 Aug;61(2.:135-41.
11. Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. Cochrane Database Syst Rev 2009;(3.:CD007467.
12. Itakura A, Kurauchi O, Morikawa S, Matsuzawa K, Mizutani S, Tomoda Y. A prospective study on the relationship between intrapartum maternal group-B streptococcal concentration and signs of infection in neonates. J Obstet Gynaecol Res 1996 Apr;22(2.:101-5.
13. Oddie S, Embleton ND. Risk factors for early onset neonatal group B streptococcal sepsis: case-control study. BMJ 2002 Aug 10;325(7359.:308.
14. Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. N Engl J Med 1986 Jun 26;314(26.:1665-9.
15. Zangwill KM, Schuchat A, Wenger JD. Group B streptococcal disease in the United States, 1990: report from a multistate active surveillance system. MMWR CDC Surveill Summ 1992 Nov .20;41(6.:25-32.
16. Diminishing racial disparities in early-onset neonatal group B streptococcal disease--United States, 2000-2003. MMWR Morb Mortal Wkly Rep 2004 Jun 18;53(23.:502-5.
17. Schrag SJ, Zywicki S, Farley MM, Reingold AL, Harrison LH, Lefkowitz LB, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. N Engl J Med 2000 Jan 6;342(1.:15-20.
18. Trijbels-Smeulders M, Gerards LJ, PC M, de Jong P, van Lingen RA, Adriaanse AH, et al. Epidemiology of neonatal group B streptococcal disease in The Netherlands 1997-98. Paediatr Perinat Epidemiol 2002 Oct;16(4.:334-41.
19. Moses LM, Heath PT, Wilkinson AR, Jeffery HE, Isaacs D. Early onset group B streptococcal neonatal infection in Oxford 1985-96. Arch Dis Child Fetal Neonatal Ed 1998 Sep;79(2.:F148-F149.

20. Aavitsland P, Hoiby EA, Lystad A. Systemic group B streptococcal disease in neonates and young infants in Norway 1985-94. Acta Paediatr 1996 Jan;85(1.:104-5.
21. Mayon-White RT. The incidence of GBS disease in neonates in different countries. Antibiot Chemother 1985;35:17-27.
22. Trijbels-Smeulders M, de Jonge GA, Pasker-de Jong PC, Gerards LJ, Adriaanse AH, van Lingen RA, et al. Epidemiology of neonatal group B streptococcal disease in the Netherlands before and after introduction of guidelines for prevention. Arch Dis Child Fetal Neonatal Ed 2007 Jul;92(4.:F271-F276.
23. Mohangoo AD, Buitendijk SE, Hukkelhoven CW, Ravelli AC, Rijninks-van Driel GC, Tamminga P, et al. [Higher perinatal mortality in The Netherlands than in other European countries: the Peristat-II study]. Ned Tijdschr Geneeskd 2008 Dec 13;152(50.:2718-27.
24. Fry R. Fatal infections caused by heamolytic Streptococcus group B. Lancet 1, 199-201. 1938.
25. Slotved HC, Kong F, Lambertsen L, Sauer S, Gilbert GL. Serotype IX, a Proposed New Streptococcus agalactiae Serotype. J Clin Microbiol 2007 Sep;45(9.:2929-36.
26. Michon F, Katzenellenbogen E, Kasper DL, Jennings HJ. Structure of the complex group-specific polysaccharide of group B Streptococcus. Biochemistry 1987 Jan 27;26(2.:476-86.
27. Schuchat A, Wenger JD. Epidemiology of group B streptococcal disease. Risk factors, prevention strategies, and vaccine development. Epidemiol Rev 1994;16(2.:374-402.
28. Larsen JW, Sever JL. Group B Streptococcus and pregnancy: a review. Am J Obstet Gynecol 2008 Jan 15.
29. Bliss SJ, Manning SD, Tallman P, Baker CJ, Pearlman MD, Marrs CF, et al. Group B Streptococcus colonization in male and nonpregnant female university students: a cross-sectional prevalence study. Clin Infect Dis 2002 Jan 15;34(2.:184-90.
30. Edwards MS, Baker CJ. Group B Streptococcal infections. In: Remington J.S., Klein J.O., editors. Infectious Diseases of the Fetus and Newborn Infant.Philadelphia: W.B. Saunders; 2001. p. 1091-156.
31. Adriaanse AH. Prevention of neonatal septicaemia due to group B streptococci. Baillieres Clin Obstet Gynaecol 1995 Sep;9(3.:545-52.
32. Galask RP, Varner MW, Petzold CR, Wilbur SL. Bacterial attachment to the chorioamniotic membranes. Am J Obstet Gynecol 1984 Apr 1;148(7.:915-28.
33. Naeye RL, Peters EC. Amniotic fluid infections with intact membranes leading to perinatal death: a prospective study. Pediatrics 1978 Feb;61(2.:171-7.
34. Wahbeh CJ, Hill GB, Eden RD, Gall SA. Intra-amniotic bacterial colonization in premature labor. Am J Obstet Gynecol 1984 Mar 15;148(6.:739-43.
35. Romero R, Mazor M, Oyarzun E, Sirtori M, Wu YK, Hobbins JC. Is there an association between colonization with group B Streptococcus and prematurity? J Reprod Med 1989 Oct;34(10.:797-801.
36. Gerdes JS. Clinicopathologic approach to the diagnosis of neonatal sepsis. Clin Perinatol 1991 Jun;18(2.:361-81.
37. Weisman LE, Stoll BJ, Cruess DF, Hall RT, Merenstein GB, Hemming VG, et al. Early-onset group B streptococcal sepsis: a current assessment. J Pediatr 1992 Sep;121(3.:428-33.
38. Roberts KB. Letter: Persistent group B Streptococcus bacteremia without clinical "sepsis" in infants. J Pediatr 1976 Jun;88(6.:1059-60.
39. Howard JB, McCracken GH, Jr. The spectrum of group B streptococcal infections in infancy. Am J Dis Child 1974 Dec;128(6.:815-8.
40. Kotiw M, Zhang GW, Daggard G, Reiss-Levy E, Tapsall JW, Numa A. Late-onset and recurrent neonatal Group B streptococcal disease associated with breast-milk transmission. Pediatr Dev Pathol 2003 May;6(3.:251-6.
41. Atkins JT, Heresi GP, Coque TM, Baker CJ. Recurrent group B streptococcal disease in infants: Who should receive rifampin? J Pediatr 1998 Mar;132(3 Pt 1.:537-9.

42. Byrne PA, Miller C, Justus K. Neonatal group B streptococcal infection related to breast milk. Breastfeed Med 2006;1(4.:263-70.
43. Olver WJ, Bond DW, Boswell TC, Watkin SL. Neonatal group B streptococcal disease associated with infected breast milk. Arch Dis Child Fetal Neonatal Ed 2000 Jul;83(1.:F48-F49.
44. Wang LY, Chen CT, Liu WH, Wang YH. Recurrent neonatal group B streptococcal disease associated with infected breast milk. Clin Pediatr (Phila. 2007 Jul;46(6.:547-9.
45. Adriaanse AH, Lagendijk I, Muytjens HL, Nijhuis JG, Kollee LA. Neonatal early onset group B streptococcal infection. A nine-year retrospective study in a tertiary care hospital. J Perinat Med 1996;24(5.:531-8.
46. Prevention of perinatal group B streptococcal disease: a public health perspective. Centers for Disease Control and Prevention. MMWR Recomm Rep 1996 May 31;45(RR-7.:1-24.
47. Schroder H, Tessmar J, Paust H, Keller P, Hanefeld F. [Long-term sequelae of neonatal group B streptococcal septicemia/meningitis (author's transl.]. Monatsschr Kinderheilkd 1982 Mar;130(3.:153-6.
48. Harvey D, Holt DE, Bedford H. Bacterial meningitis in the newborn: a prospective study of mortality and morbidity. Semin Perinatol 1999 Jun;23(3.:218-25.
49. Lim NL, Wong YH, Boo NY, Kasim MS, Chor CY. Bacteraemic infections in a neonatal intensive care unit--a nine-month survey. Med J Malaysia 1995 Mar;50(1.:59-63.
50. Tallur SS, Kasturi AV, Nadgir SD, Krishna BV. Clinico-bacteriological study of neonatal septicemia in Hubli. Indian J Pediatr 2000 Mar;67(3.:169-74.
51. Airede AI. Neonatal septicaemia in an African city of high altitude. J Trop Pediatr 1992 Aug;38(4.:189-91.
52. Clinical prediction of serious bacterial infections in young infants in developing countries. The WHO Young Infants Study Group. Pediatr Infect Dis J 1999 Oct;18(10 Suppl.:S23-S31.
53. Moreno MT, Vargas S, Poveda R, Saez-Llorens X. Neonatal sepsis and meningitis in a developing Latin American country. Pediatr Infect Dis J 1994 Jun;13(6.:516-20.
54. Robillard PY, Nabeth P, Hulsey TC, Sergent MP, Perianin J, Janky E. Neonatal bacterial septicemia in a tropical area. Four-year experience in Guadeloupe (French West Indies.. Acta Paediatr 1993 Aug;82(8.:687-9.
55. Hyde TB, Hilger TM, Reingold A, Farley MM, O'Brien KL, Schuchat A. Trends in incidence and antimicrobial resistance of early-onset sepsis: population-based surveillance in San Francisco and Atlanta. Pediatrics 2002 Oct;110(4.:690-5.
56. Schuchat A, Zywicki SS, Dinsmoor MJ, Mercer B, Romaguera J, O'Sullivan MJ, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case-control study. Pediatrics 2000 Jan;105(1 Pt 1.:21-6.
57. Isaacs D. A ten year, multicentre study of coagulase negative staphylococcal infections in Australasian neonatal units. Arch Dis Child Fetal Neonatal Ed 2003 Mar;88(2.:F89-F93.
58. Isaacs D, Royle JA. Intrapartum antibiotics and early onset neonatal sepsis caused by group B Streptococcus and by other organisms in Australia. Australasian Study Group for Neonatal Infections. Pediatr Infect Dis J 1999 Jun;18(6.:524-8.
59. Vergnano S, Sharland M, Kazembe P, Mwansambo C, Heath PT. Neonatal sepsis: an international perspective. Arch Dis Child Fetal Neonatal Ed 2005 May;90(3.:F220-F224.
60. Zaidi AK, Thaver D, Ali SA, Khan TA. Pathogens associated with sepsis in newborns and young infants in developing countries. Pediatr Infect Dis J 2009 Jan;28(1 Suppl.:S10-S18.
61. Wilson CB. Immunologic basis for increased susceptibility of the neonate to infection. J Pediatr 1986 Jan;108(1.:1-12.
62. Koenig JM, Yoder MC. Neonatal neutrophils: the good, the bad, and the ugly. Clin Perinatol 2004 Mar;31(1.:39-51.
63. Haeney M. Infection determinants at extremes of age. J Antimicrob Chemother 1994 Aug;34 Suppl A:1-9.

64. Christensen RD, Rothstein G. Exhaustion of mature marrow neutrophils in neonates with sepsis. J Pediatr 1980 Feb;96(2.:316-8.
65. Shigeoka AO, Santos JI, Hill HR. Functional analysis of neutrophil granulocytes from healthy, infected, and stressed neonates. J Pediatr 1979 Sep;95(3.:454-60.
66. Kallman J, Schollin J, Schalen C, Erlandsson A, Kihlstrom E. Impaired phagocytosis and opsonisation towards group B streptococci in preterm neonates. Arch Dis Child Fetal Neonatal Ed 1998 Jan;78(1.:F46-F50.
67. Stroobant J, Harris MC, Cody CS, Polin RA, Douglas SD. Diminished bactericidal capacity for group B Streptococcus in neutrophils from "stressed" and healthy neonates. Pediatr Res 1984 Jul;18(7.:634-7.
68. Quirante J, Ceballos R, Cassady G. Group B beta-hemolytic streptococcal infection in the newborn. I. Early onset infection. Am J Dis Child 1974 Nov;128(5.:659-65.
69. Tseng PI, Kandall SR. Group B streptococcal disease. In neonates and infants. N Y State J Med 1974 Nov;74(12.:2169-73.
70. Yagupsky P, Menegus MA, Powell KR. The changing spectrum of group B streptococcal disease in infants: an eleven-year experience in a tertiary care hospital. Pediatr Infect Dis J 1991 Nov;10(11.:801-8.
71. Garland SM. Early onset neonatal group B streptococcus (GBS. infection: associated obstetric risk factors. Aust N Z J Obstet Gynaecol 1991 May;31(2.:117-8.
72. Yancey MK, Duff P, Kubilis P, Clark P, Frentzen BH. Risk factors for neonatal sepsis. Obstet Gynecol 1996 Feb;87(2.:188-94.
73. Adair CE, Kowalsky L, Quon H, Ma D, Stoffman J, McGeer A, et al. Risk factors for early-onset group B streptococcal disease in neonates: a population-based case-control study. CMAJ 2003 Aug 5;169(3.:198-203.
74. Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics 1999 Jun;103(6.:e77.
75. Boyer KM, Gadzala CA, Kelly PD, Burd LI, Gotoff SP. Selective intrapartum chemoprophylaxis of neonatal group B streptococcal early-onset disease. II. Predictive value of prenatal cultures. J Infect Dis 1983 Nov;148(5.:802-9.
76. Stewardson-Krieger PB, Gotoff SP. Risk factors in early-onset neonatal group b streptococcal infections. Infection 1978;6(2.:50-3.
77. Spaans WA, Knox AJ, Koya HB, Mantell CD. Risk factors for neonatal infection. Aust N Z J Obstet Gynaecol 1990 Nov;30(4.:327-30.
78. Yoder PR, Gibbs RS, Blanco JD, Castaneda YS, St Clair PJ. A prospective, controlled study of maternal and perinatal outcome after intra-amniotic infection at term. Am J Obstet Gynecol 1983 Mar 15;145(6.:695-701.
79. Sperling RS, Ramamurthy RS, Gibbs RS. A comparison of intrapartum versus immediate postpartum treatment of intra-amniotic infection. Obstet Gynecol 1987 Dec;70(6.:861-5.
80. Gibbs RS, Dinsmoor MJ, Newton ER, Ramamurthy RS. A randomized trial of intrapartum versus immediate postpartum treatment of women with intra-amniotic infection. Obstet Gynecol 1988 Dec;72(6.:823-8.
81. Gilstrap LC, III, Leveno KJ, Cox SM, Burris JS, Mashburn M, Rosenfeld CR. Intrapartum treatment of acute chorioamnionitis: impact on neonatal sepsis. Am J Obstet Gynecol 1988 Sep;159(3.:579-83.
82. Mead PJ, Harris RE. The incidence of group B beta hemolytic streptococcus in antepartum urinary tract infections. Obstet Gynecol 1978 Apr;51(4.:412-4.
83. McFadyen IR, Eykyn SJ, Gardner NH, Vanier TM, Bennett AE, Mayo ME, et al. Bacteriuria in pregnancy. J Obstet Gynaecol Br Commonw 1973 May;80(5.:385-405.
84. Persson K, Bjerre B, Elfstrom L, Polberger S, Forsgren A. Group B streptococci at delivery: high count in urine increases risk for neonatal colonization. Scand J Infect Dis 1986;18(6.:525-31.

85. Wood EG, Dillon HC, Jr. A prospective study of group B streptococcal bacteriuria in pregnancy. Am J Obstet Gynecol 1981 Jul 1;140(5.:515-20.
86. Persson K, Christensen KK, Christensen P, Forsgren A, Jorgensen C, Persson PH. Asymptomatic bacteriuria during pregnancy with special reference to group B streptococci. Scand J Infect Dis 1985;17(2.:195-9.
87. McKenna DS, Matson S, Northern I. Maternal group B streptococcal (GBS. genital tract colonization at term in women who have asymptomatic GBS bacteriuria. Infect Dis Obstet Gynecol 2003;11(4.:203-7.
88. Edwards RK, Clark P, Duff P. Intrapartum antibiotic prophylaxis 2: positive predictive value of antenatal group B streptococci cultures and antibiotic susceptibility of clinical isolates. Obstet Gynecol 2002 Sep;100(3.:540-4.
89. Carstensen H, Christensen KK, Grennert L, Persson K, Polberger S. Early-onset neonatal group B streptococcal septicaemia in siblings. J Infect 1988 Nov;17(3.:201-4.
90. Faxelius G, Bremme K, Kvist-Christensen K, Christensen P, Ringertz S. Neonatal septicemia due to group B streptococci--perinatal risk factors and outcome of subsequent pregnancies. J Perinat Med 1988;16(5-6.:423-30.
91. Philipson EH, Herson VC. Intrapartum chemoprophylaxis for group B streptococcus infection to prevent neonatal disease: who should be treated? Am J Perinatol 1996 Nov;13(8.:487-90.
92. Dykes AK, Christensen KK, Christensen P. Chronic carrier state in mothers of infants with group B streptococcal infections. Obstet Gynecol 1985 Jul;66(1.:84-8.
93. Christensen KK, Dahlander K, Linden V, Svenningsen N, Christensen P. Obstetrical care in future pregnancies after fetal loss in group B streptococcal septicemia. A prevention program based on bacteriological and immunological follow-up. Eur J Obstet Gynecol Reprod Biol 1981 Sep;12(3.:143-50.
94. Tenenbaum T, Spellerberg B, Adam R, Vogel M, Kim KS, Schroten H. Streptococcus agalactiae invasion of human brain microvascular endothelial cells is promoted by the laminin-binding protein Lmb. Microbes Infect 2007 May;9(6.:714-20.
95. Lin FY, Weisman LE, Azimi PH, Philips JB, III, Clark P, Regan J, et al. Level of maternal IgG anti-group B streptococcus type III antibody correlated with protection of neonates against early-onset disease caused by this pathogen. J Infect Dis 2004 Sep 1;190(5.:928-34.
96. Schuchat A, Deaver-Robinson K, Plikaytis BD, Zangwill KM, Mohle-Boetani J, Wenger JD. Multistate case-control study of maternal risk factors for neonatal group B streptococcal disease. The Active Surveillance Study Group. Pediatr Infect Dis J 1994 Jul;13(7.:623-9.
97. Schuchat A, Oxtoby M, Cochi S, Sikes RK, Hightower A, Plikaytis B, et al. Population-based risk factors for neonatal group B streptococcal disease: results of a cohort study in metropolitan Atlanta. J Infect Dis 1990 Sep;162(3.:672-7.
98. Katz VL. Management of group B streptococcal disease in pregnancy. Clin Obstet Gynecol 1993 Dec;36(4.:832-42.
99. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn: Guidelines for prevention of group B streptococcal (GBS. infection by chemoprophylaxis. Pediatrics 1992 Nov;90(5.:775-8.
100. Noya FJ, Baker CJ. Prevention of group B streptococcal infection. Infect Dis Clin North Am 1992 Mar;6(1.:41-55.
101. Gilbert GL, Isaacs D, Burgess MA, Garland SM, Grimwood K, Hogg GG, et al. Prevention of neonatal group B streptococcal sepsis: is routine antenatal screening appropriate. Aust N Z J Obstet Gynaecol 1995 May;35(2.:120-6.
102. Montgomery DM, Stedman CM, Robichaux AG, III, Joyner JC, Scariano SM. Cord blood gas patterns identifying newborns at increased risk of group B streptococcal sepsis. Obstet Gynecol 1991 Nov;78(5 Pt 1.:774-7.

103. Heath PT, Balfour GF, Tighe H, Verlander NQ, Lamagni TL, Efstratiou A. Group B streptococcal disease in infants: a case control study. Arch Dis Child 2009 Sep;94(9.:674-80.
104. Dillon HC, Jr., Gray E, Pass MA, Gray BM. Anorectal and vaginal carriage of group B streptococci during pregnancy. J Infect Dis 1982 Jun;145(6.:794-9.
105. Badri MS, Zawaneh S, Cruz AC, Mantilla G, Baer H, Spellacy WN, et al. Rectal colonization with group B streptococcus: relation to vaginal colonization of pregnant women. J Infect Dis 1977 Feb;135(2.:308-12.
106. Hoogkamp-Korstanje JA, Gerards LJ, Cats BP. Maternal carriage and neonatal acquisition of group B streptococci. J Infect Dis 1982 Jun;145(6.:800-3.
107. MacDonald SW, Manuel FR, Embil JA. Localization of group B beta-hemolytic streptococci in the female urogenital tract. Am J Obstet Gynecol 1979 Jan 1;133(1.:57-9.
108. Amies CR. A modified formula for the preparation of Stuart's Transport Medium. Can J Public Health 1967 Jul;58(7.:296-300.
109. Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep 2010 Nov 19;59(RR-10.:1-36.
110. Stoner KA, Rabe LK, Hillier SL. Effect of transport time, temperature, and concentration on the survival of group B streptococci in amies transport medium. J Clin Microbiol 2004 Nov;42(11.:5385-7.
111. Rosa-Fraile M, Camacho-Munoz E, Rodriguez-Granger J, Liebana-Martos C. Specimen storage in transport medium and detection of group B streptococci by culture. J Clin Microbiol 2005 Feb;43(2.:928-30.
112. Baker CJ, Goroff DK, Alpert S, Crockett VA, Zinner SH, Evrard JR, et al. Vaginal colonization with group B streptococcus: a study in college women. J Infect Dis 1977 Mar;135(3.:392-7.
113. Ferrieri P, Cleary PP, Seeds AE. Epidemiology of group-B streptococcal carriage in pregnant women and newborn infants. J Med Microbiol 1977 Feb;10(1.:103-14.
114. Fenton LJ, Harper MH. Evaluation of colistin and nalidixic acid in Todd-Hewitt broth for selective isolation of group B streptococci. J Clin Microbiol 1979 Feb;9(2.:167-9.
115. de la Rosa M, Perez M, Carazo C, Pareja L, Peis JI, Hernandez F. New Granada Medium for detection and identification of group B streptococci. J Clin Microbiol 1992 Apr;30(4.:1019-21.
116. Rosa-Fraile M, Rodriguez-Granger J, Cueto-Lopez M, Sampedro A, Gaye EB, Haro JM, et al. Use of Granada medium to detect group B streptococcal colonization in pregnant women. J Clin Microbiol 1999 Aug;37(8.:2674-7.
117. Church DL, Baxter H, Lloyd T, Miller B, Elsayed S. Evaluation of StrepB carrot broth versus Lim broth for detection of group B Streptococcus colonization status of near-term pregnant women. J Clin Microbiol 2008 Aug;46(8.:2780-2.
118. Martinho F, Prieto E, Pinto D, Castro RM, Morais AM, Salgado L, et al. Evaluation of liquid biphasic Granada medium and instant liquid biphasic Granada medium for group B streptococcus detection. Enferm Infecc Microbiol Clin 2008 Feb;26(2.:69-71.
119. Adler A, Block C, Engelstein D, Hochner-Celnikcier D, Drai-Hassid R, Moses AE. Culture-based methods for detection and identification of Streptococcus agalactiae in pregnant women--what are we missing? Eur J Clin Microbiol Infect Dis 2008 Mar;27(3.:241-3.
120. Smith D, Perry JD, Laine L, Galloway A, Gould FK. Comparison of BD GeneOhm real-time polymerase chain reaction with chromogenic and conventional culture methods for detection of group B Streptococcus in clinical samples. Diagn Microbiol Infect Dis 2008 Aug;61(4.:369-72.
121. Daniels J, Gray J, Pattison H, Roberts T, Edwards E, Milner P, et al. Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness. Health Technol Assess 2009 Sep;13(42.:1-iv.
122. Honest H, Sharma S, Khan KS. Rapid tests for group B Streptococcus colonization in laboring women: a systematic review. Pediatrics 2006 Apr;117(4.:1055-66.

123. Larsson C, Lindroth M, Nordin P, Stalhammar-Carlemalm M, Lindahl G, Krantz I. Association between low concentrations of antibodies to protein alpha and Rib and invasive neonatal group B streptococcal infection. Arch Dis Child Fetal Neonatal Ed 2006 Nov;91(6.:F403-F408.
124. Johri AK, Paoletti LC, Glaser P, Dua M, Sharma PK, Grandi G, et al. Group B Streptococcus: global incidence and vaccine development. Nat Rev Microbiol 2006 Dec;4(12.:932-42.
125. Hughes MJ, Wilson R, Moore JC, Lane JD, Dobson RJ, Muckett P, et al. Novel protein vaccine candidates against Group B streptococcal infection identified using alkaline phosphatase fusions. FEMS Microbiol Lett 2003 May 28;222(2.:263-71.
126. Stade B, Shah V, Ohlsson A. Vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection. Cochrane Database Syst Rev 2004;(3.:CD003520.
127. Facchinetti F, Piccinini F, Mordini B, Volpe A. Chlorhexidine vaginal flushings versus systemic ampicillin in the prevention of vertical transmission of neonatal group B streptococcus, at term. J Matern Fetal Neonatal Med 2002 Feb;11(2.:84-8.
128. Cutland CL, Madhi SA, Zell ER, Kuwanda L, Laque M, Groome M, et al. Chlorhexidine maternal-vaginal and neonate body wipes in sepsis and vertical transmission of pathogenic bacteria in South Africa: a randomised, controlled trial. Lancet 2009 Dec 5;374(9705.:1909-16.
129. Taha TE, Biggar RJ, Broadhead RL, Mtimavalye LA, Justesen AB, Liomba GN, et al. Effect of cleansing the birth canal with antiseptic solution on maternal and newborn morbidity and mortality in Malawi: clinical trial. BMJ 1997 Jul 26;315(7102.:216-9.
130. Burman LG, Christensen P, Christensen K, Fryklund B, Helgesson AM, Svenningsen NW, et al. Prevention of excess neonatal morbidity associated with group B streptococci by vaginal chlorhexidine disinfection during labour. The Swedish Chlorhexidine Study Group. Lancet 1992 Jul 11;340(8811.:65-9.
131. Baecher L, Grobman W. Prenatal antibiotic treatment does not decrease group B streptococcus colonization at delivery. Int J Gynaecol Obstet 2008 May;101(2.:125-8.
132. Matorras R, Garcia-Perea A, Omenaca F, Diez-Enciso M, Madero R, Usandizaga JA. Intrapartum chemoprophylaxis of early-onset group B streptococcal disease. Eur J Obstet Gynecol Reprod Biol 1991 Jun 5;40(1.:57-62.
133. de Cueto M, Sanchez MJ, Sampedro A, Miranda JA, Herruzo AJ, Rosa-Fraile M. Timing of intrapartum ampicillin and prevention of vertical transmission of group B streptococcus. Obstet Gynecol 1998 Jan;91(1.:112-4.
13. Yow MD, Mason EO, Leeds LJ, Thompson PK, Clark DJ, Gardner SE. Ampicillin prevents intrapartum transmission of group B streptococcus. JAMA 1979 Mar 23;241(12.:1245-7.
135. Tuppurainen N, Hallman M. Prevention of neonatal group B streptococcal disease: intrapartum detection and chemoprophylaxis of heavily colonized parturients. Obstet Gynecol 1989 Apr;73(4.:583-7.
136. Muller AE, Oostvogel PM, DeJongh J, Mouton JW, Steegers EA, Dorr PJ, et al. Pharmacokinetics of amoxicillin in maternal, umbilical cord, and neonatal sera. Antimicrob Agents Chemother 2009 Apr;53(4.:1574-80.
137. Muller AE, DeJongh J, Oostvogel PM, Voskuyl RA, Dorr PJ, Danhof M, et al. Amoxicillin pharmacokinetics in pregnant women with preterm premature rupture of the membranes. Am J Obstet Gynecol 2008 Jan;198(1.:108-6.
138. Smaill F. Intrapartum antibiotics for group B streptococcal colonisation. Cochrane Database Syst Rev 2000;(2.:CD000115.
139. Amstey MS, Gibbs RS. Is penicillin G a better choice than ampicillin for prophylaxis of neonatal group B streptococcal infections? Obstet Gynecol 1994 Dec;84(6.:1058-9.
140. Betriu C, Culebras E, Gomez M, Rodriguez-Avial I, Sanchez BA, Agreda MC, et al. Erythromycin and Clindamycin Resistance and Telithromycin Susceptibility in Streptococcus agalactiae. Antimicrob Agents Chemother 2003 Mar;47(3.:1112-4.

141. Betriu C, Gomez M, Sanchez A, Cruceyra A, Romero J, Picazo JJ. Antibiotic resistance and penicillin tolerance in clinical isolates of group B streptococci. Antimicrob Agents Chemother 1994 Sep;38(9.:2183-6.
142. Fernandez M, Hickman ME, Baker CJ. Antimicrobial susceptibilities of group B streptococci isolated between 1992 and 1996 from patients with bacteremia or meningitis. Antimicrob Agents Chemother 1998 Jun;42(6.:1517-9.
143. Bland ML, Vermillion ST, Soper DE, Austin M. Antibiotic resistance patterns of group B streptococci in late third-trimester rectovaginal cultures. Am J Obstet Gynecol 2001 May;184(6.:1125-6.
144. Steigman AJ, Bottone EJ, Hanna BA. Letter: Does intramuscular penicillin at delivery prevent group B beta hemolytic streptococcal disease of the newborn infant? J Pediatr 1975 Sep;87(3.:496.
145. Steigman AJ, Bottone EJ, Hanna BA. Intramuscular penicillin administration at birth: prevention of early-onset group B streptococcal disease. Pediatrics 1978 Nov;62(5.:842-4.
146. Steigman AJ, Bottone EJ, Hanna BA. Control of perinatal group B streptococcal sepsis: efficacy of single injection of aqueous penicillin at birth. Mt Sinai J Med 1978 Nov;45(6.:685-93.
147. Lloyd DJ, Belgaumkar TK, Scott KE, Wort AJ, Aterman K, Krause VW. Prevention of group-B beta-haemolytic streptococcal septicaemia in low-birth-weight neonates by penicillin administered within two hours of birth. Lancet 1979 Mar 31;1(8118.:713-5.
148. Patel DM, Leblanc MH, Morrison JC, Graves GR, Glick CG, Martin JN, Jr., et al. Postnatal penicillin prophylaxis and the incidence of group B streptococcal sepsis in neonates. South Med J 1994 Nov;87(11.:1117-20.
149. Siegel JD, Cushion NB. Prevention of early-onset group B streptococcal disease: another look at single-dose penicillin at birth. Obstet Gynecol 1996 May;87(5 Pt 1.:692-8.
150. Woodgate P, Flenady V, Steer P. Intramuscular penicillin for the prevention of early onset group B streptococcal infection in newborn infants. Cochrane Database Syst Rev 2004;(3.:CD003667.
151. Rouse DJ, Goldenberg RL, Cliver SP, Cutter GR, Mennemeyer ST, Fargason CA, Jr. Strategies for the prevention of early-onset neonatal group B streptococcal sepsis: a decision analysis. Obstet Gynecol 1994 Apr;83(4.:483-94.
152. Mohle-Boetani JC, Schuchat A, Plikaytis BD, Smith JD, Broome CV. Comparison of prevention strategies for neonatal group B streptococcal infection. A population-based economic analysis. JAMA 1993 Sep 22;270(12.:1442-8.
153. Luskin AT, Luskin SS. Anaphylaxis and Anaphylactoid Reactions: Diagnosis and Management. Am J Ther 1996 Jul;3(7.:515-20.
154. Haupt MTCR. Anaphylactic reactions. In: Grenvik A.S. HPRSWC, editor. Textbook of Critical Care.Philadelphia, Pennsylvania: WB Saunders Compagny; 2000. p. 246-58.
155. Baltimore RS, Huie SM, Meek JI, Schuchat A, O'Brien KL. Early-onset neonatal sepsis in the era of group B streptococcal prevention. Pediatrics 2001 Nov;108(5.:1094-8.
156. Stoll BJ, Hansen NI, Higgins RD, Fanaroff AA, Duara S, Goldberg R, et al. Very low birth weight preterm infants with early onset neonatal sepsis: the predominance of gram-negative infections continues in the National Institute of Child Health and Human Development Neonatal Research Network, 2002-2003. Pediatr Infect Dis J 2005 Jul;24(7.:635-9.
157. Glasgow TS, Young PC, Wallin J, Kwok C, Stoddard G, Firth S, et al. Association of intrapartum antibiotic exposure and late-onset serious bacterial infections in infants. Pediatrics 2005 Sep;116(3.:696-702.
158. Dinsmoor MJ, Viloria R, Lief L, Elder S. Use of intrapartum antibiotics and the incidence of postnatal maternal and neonatal yeast infections. Obstet Gynecol 2005 Jul;106(1.:19-22.
159. Bedford-Russell AR. New modalities for treating neonatal infection. Eur J Pediatr 1996 Aug;155 Suppl 2:S21-S24.
160. Murch SH. Toll of allergy reduced by probiotics. Lancet 2001 Apr 7;357(9262.:1057-9.

161. Jaureguy F, Carton M, Panel P, Foucaud P, Butel MJ, Doucet-Populaire F. Effects of intrapartum penicillin prophylaxis on intestinal bacterial colonization in infants. J Clin Microbiol 2004 Nov;42(11.:5184-8.
162. Decreasing incidence of perinatal Group B streptococcal disease--United States, 1993-1995. MMWR Morb Mortal Wkly Rep 1997 May 30;46(21.:473-7.
163. Kalliola S, Vuopio-Varkila J, Takala AK, Eskola J. Neonatal group B streptococcal disease in Finland: a ten-year nationwide study. Pediatr Infect Dis J 1999 Sep;18(9.:806-10.
164. Poulain P, Betremieux P, Donnio PY, Proudhon JF, Karege G, Giraud JR. Selective intrapartum anti-bioprophylaxy of group B streptococci infection of neonates: a prospective study in 2454 subsequent deliveries. Eur J Obstet Gynecol Reprod Biol 1997 Apr;72(2.:137-40.
165. Simetka O, Petros M, Podesvova H. [Prevention of early-onset neonatal group B streptococcal infection: neonatal outcome after introduction of national screening guideline]. Ceska Gynekol 2010 Feb;75(1.:41-6.
166. Lopez Sastre JB, Fernandez CB, Coto Cotallo GD, Ramos AA. Trends in the epidemiology of neonatal sepsis of vertical transmission in the era of group B streptococcal prevention. Acta Paediatr 2005 Apr;94(4.:451-7.
167. Schrag SJ, Zell ER, Lynfield R, Roome A, Arnold KE, Craig AS, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. N Engl J Med 2002 Jul 25;347(4.:233-9.
168. Trijbels-Smeulders MA, Kollee LA, Adriaanse AH, Kimpen JL, Gerards LJ. Neonatal group B streptococcal infection: incidence and strategies for prevention in Europe. Pediatr Infect Dis J 2004 Feb;23(2.:172-3.
169. Van Dyke MK, Phares CR, Lynfield R, Thomas AR, Arnold KE, Craig AS, et al. Evaluation of universal antenatal screening for group B streptococcus. N Engl J Med 2009 Jun 18;360(25.:2626-36.
170. Heath PT, Schuchat A. Perinatal group B streptococcal disease. Best Pract Res Clin Obstet Gynaecol 2007 Jun;21(3.:411-24.
171. Fluegge K, Siedler A, Heinrich B, Schulte-Moenting J, Moennig MJ, Bartels DB, et al. Incidence and clinical presentation of invasive neonatal group B streptococcal infections in Germany. Pediatrics 2006 Jun;117(6.:e1139-e1145.
172. Phares CR, Lynfield R, Farley MM, Mohle-Boetani J, Harrison LH, Petit S, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. JAMA 2008 May 7;299(17.:2056-65.
173. Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. Pediatrics 2005 May;115(5.:1240-6.
174. Gilbert R. Prenatal screening for group B streptococcal infection: gaps in the evidence. Int J Epidemiol 2004 Feb;33(1.:2-8.
175. Hajdu A, Blystad H, Hoiby EA, Klouman E, Schimmer B, Nygard K. Unexpected increase in case fatality of invasive group B streptococcal infections in infants in Norway, January-July 2006. Euro Surveill 2006;11(7.:E060727.
176. Verani JR, Schrag SJ. Group B streptococcal disease in infants: progress in prevention and continued challenges. Clin Perinatol 2010 Jun;37(2.:375-92.
177. Schuchat A. Group B streptococcus. Lancet 1999 Jan 2;353(9146.:51-6.
178. Trends in perinatal group B streptococcal disease - United States, 2000-2006. MMWR Morb Mortal Wkly Rep 2009 Feb 13;58(5.:109-12.
179. Barcaite E, Bartusevicius A, Tameliene R, Maleckiene L, Vitkauskiene A, Nadisauskiene R. Group B streptococcus and Escherichia coli colonization in pregnant women and neonates in Lithuania. Int J Gynaecol Obstet 2012 Apr;117(1.:69-73.
180. Motlova J, Strakova L, Urbaskova P, Sak P, Sever T. Vaginal & rectal carriage of Streptococcus agalactiae in the Czech Republic: incidence, serotypes distribution & susceptibility to antibiotics. Indian J Med Res 2004 May;119 Suppl:84-7.

181. Strakova L, Motlova J. Active surveillance of early onset disease due to group B streptococci in newborns. Indian J Med Res 2004 May;119 Suppl:205-7.
182. Kowalska B, Niemiec KT, Drejewicz H, Polak K, Kubik P, Elmidaoui A, et al. [Prevalence of group B streptococcal colonization in pregnant women and their newborns based on the results of examination of patients in the Obstetric and Gynecology Department of the National Research Institute of Mother and Child--a pilot study]. Ginekol Pol 2003 Oct;74(10.:1223-7.
183. Volumenie JL, Fernandez H, Vial M, Lebrun L, Frydman R. Neonatal group B streptococcal infection. Results of 33 months of universal maternal screening and antibioprophylaxis. Eur J Obstet Gynecol Reprod Biol 2001 Jan;94(1.:79-85.
184. Jaureguy F, Carton M, Teboul J, Butel MJ, Panel P, Ghnassia JC, et al. [Risk factors and screening strategy for group B streptococcal colonization in pregnant women: results of a prospective study]. J Gynecol Obstet Biol Reprod (Paris. 2003 Apr;32(2.:132-8.
185. Kuhn P, Dheu C, Bolender C, Chognot D, Keller L, Demil H, et al. Incidence and distribution of pathogens in early-onset neonatal sepsis in the era of antenatal antibiotics. Paediatr Perinat Epidemiol 2010 Sep;24(5.:479-87.
186. Brimil N, Barthell E, Heindrichs U, Kuhn M, Lutticken R, Spellerberg B. Epidemiology of Streptococcus agalactiae colonization in Germany. Int J Med Microbiol 2006 Feb;296(1.:39-44.
187. Jones N, Oliver K, Jones Y, Haines A, Crook D. Carriage of group B streptococcus in pregnant women from Oxford, UK. J Clin Pathol 2006 Apr;59(4.:363-6.
188. Vergnano S, Menson E, Kennea N, Embleton N, Russell AB, Watts T, et al. Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed 2011 Jan;96(1.:F9-F14.
189. Valkenburg-van den Berg AW, Sprij AJ, Oostvogel PM, Mutsaers JA, Renes WB, Rosendaal FR, et al. Prevalence of colonisation with group B Streptococci in pregnant women of a multi-ethnic population in The Netherlands. Eur J Obstet Gynecol Reprod Biol 2006 Feb 1;124(2.:178-83.
190. van den Hoogen A, Gerards LJ, Verboon-Maciolek MA, Fleer A, Krediet TG. Long-term trends in the epidemiology of neonatal sepsis and antibiotic susceptibility of causative agents. Neonatology 2010;97(1.:22-8.
191. Whitney CG, Daly S, Limpongsanurak S, Festin MR, Thinn KK, Chipato T, et al. The international infections in pregnancy study: group B streptococcal colonization in pregnant women. J Matern Fetal Neonatal Med 2004 Apr;15(4.:267-74.
192. Hansen SM, Uldbjerg N, Kilian M, Sorensen UB. Dynamics of Streptococcus agalactiae colonization in women during and after pregnancy and in their infants. J Clin Microbiol 2004 Jan;42(1.:83-9.
193. Ekelund K, Konradsen HB. Invasive group B streptococcal disease in infants: a 19-year nationwide study. Serotype distribution, incidence and recurrent infection. Epidemiol Infect 2004 Dec;132(6.:1083-90.
194. Bjarnadottir I, Kristinsson KG, Hauksson A, Vilbergsson G, Palsson G, Dagbjartsson A. [Carriage of group B beta-haemolytic streptococci among pregnant women in Iceland and colonisation of their newborn infants.]. Laeknabladid 2003 Feb;89(2.:111-5.
195. Hakansson S, Axemo P, Bremme K, Bryngelsson AL, Wallin MC, Ekstrom CM, et al. Group B streptococcal carriage in Sweden: a national study on risk factors for mother and infant colonisation. Acta Obstet Gynecol Scand 2008;87(1.:50-8.
196. Persson E, Berg S, Trollfors B, Larsson P, Ek E, Backhaus E, et al. Serotypes and clinical manifestations of invasive group B streptococcal infections in western Sweden 1998-2001. Clin Microbiol Infect 2004 Sep;10(9.:791-6.
197. Tsolia M, Psoma M, Gavrili S, Petrochilou V, Michalas S, Legakis N, et al. Group B streptococcus colonization of Greek pregnant women and neonates: prevalence, risk factors and serotypes. Clin Microbiol Infect 2003 Aug;9(8.:832-8.

198. Busetti M, D'Agaro P, Campello C. Group B streptococcus prevalence in pregnant women from North-Eastern Italy: advantages of a screening strategy based on direct plating plus broth enrichment. J Clin Pathol 2007 Oct;60(10.:1140-3.
199. Berardi A, Lugli L, Baronciani D, Creti R, Rossi K, Ciccia M, et al. Group B streptococcal infections in a northern region of Italy. Pediatrics 2007 Sep;120(3.:e487-e493.
200. Arisoy AS, Altinisik B, Tunger O, Kurutepe S, Ispahi C. Maternal carriage and antimicrobial resistance profile of group B Streptococcus. Infection 2003 Aug;31(4.:244-6.
201. Yucesoy G, Caliskan E, Karadenizli A, Corakci A, Yucesoy I, Huseyinoglu N, et al. Maternal colonisation with group B streptococcus and effectiveness of a culture-based protocol to prevent early-onset neonatal sepsis. Int J Clin Pract 2004 Aug;58(8.:735-9.
202. Kadanali A, Altoparlak U, Kadanali S. Maternal carriage and neonatal colonisation of group B streptococcus in eastern Turkey: prevalence, risk factors and antimicrobial resistance. Int J Clin Pract 2005 Apr;59(4.:437-40.
203. Eren A, Kucukercan M, Oguzoglu N, Unal N, Karateke A. The carriage of group B streptococci in Turkish pregnant women and its transmission rate in newborns and serotype distribution. Turk J Pediatr 2005 Jan;47(1.:28-33.

Chapter 2

Prevalence of colonization with Group B Streptococci in pregnant women of a multi-ethnic population in the Netherlands

2

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ABSTRACT

Objective This study was performed to determine the prevalence of GBS and to identify GBS colonization risk factors in a multicultural population of pregnant women in the Netherlands. We calculated predictive values of cultures in pregnancy for intrapartum GBS carriage.

Study Design From a total of 1702 women visiting several antenatal outpatient departments, rectovaginal swabs were collected at 35-37 weeks' gestation. In 761 women swabs were repeated at time of delivery. Carriage of GBS late in third trimester and at time of delivery was analysed in relation to age, parity, ethnicity and socio-economic status.

Results Twenty-one percent was GBS carrier late in pregnancy. Compared to Europeans, African women were at a higher risk (29%) and Asian women were at lower risk (13%) for GBS carriage. No differences in colonization were found between women with respect to age, parity or socio-economic background. Positive predictive value of GBS carriage at 35-37 weeks' gestation for carriage at time of parturition was 79% and negative predictive value was 93%.

Conclusions It is impossible to identify a group of pregnant women at high risk for GBS colonization. Predictive values of antenatal genital group B streptococci cultures at 35-37 weeks' gestation for intrapartum GBS carriage are lower than previously reported.

INTRODUCTION

Since the 1970s, Group B Streptococcus (GBS, *Streptococcus agalactiae)* has been recognized as the most important infectious cause of morbidity and mortality in newborn infants. Despite the decrease in mortality during the last decades, early-onset GBS disease remains a serious neonatal condition, which may cause severe neurological damage. In the Netherlands, the incidence of early-onset GBS disease in 1997-1998 was estimated at 1.9 per 1000 live births, with a case fatality rate of 5%(1). GBS transmission is vertical from mother to child. The gastrointestinal tract is the source of vaginal GBS colonization and many adults are colonized with GBS without showing symptoms. Approximately 10%-30% of women of childbearing age carries GBS in the rectovaginal compartment(2-4). The prevalence may vary due to differences in the culture technique, the location and number of sites cultured and the population studied(2). A role for ethnic or genetic factors is presumed, since Caribbean Hispanics and black women were reported to be GBS carriers more frequently(2;5;6).

Dutch data originate from studies by Gerards in 1985 and Adriaanse in 1995, in which overall carrier rates of 14% in the 16-20th week of pregnancy(7) and 20% at delivery(8) have been described.

In the United States, revised consensus guidelines regarding the management of GBS were published in 2002. These guidelines recommend screening of all pregnant women for GBS carriage at 35 to 37 weeks' gestation and intrapartum treatment of those women with positive cultures(9).

The Dutch Society of Obstetrics and Gynaecology and the Dutch Society of Pediatrics(10) recommend intrapartum maternal administration of antibiotics in women with intrapartum temperature > 38ºC, in women with GBS bacteriuria during current pregnancy and in women who previously gave birth to an infant with early-onset GBS disease, irrespective to their GBS status. In women presenting with any of the other risk factors associated with early onset GBS disease, i.e. delivery at <37 weeks' gestation or rupture of membranes for more then 24 hrs, screening for GBS carriage is performed first, followed by chemoprophylaxis when the culture is positive. In case the delivery occurs before the result is available, the obstetrician should decide about antibiotic prophylaxis, based on the severity of the risk factor(11). The choice for this risk factor-based strategy was made in 1998, with the intention to reduce the number of women that receives prophylactic antibiotics(11), taking account of the Dutch organisation of obstetrical care with approximately 30% home deliveries. The disadvantages of this strategy are, that 30%-40% of neonatal early-onset GBS infections may occur in the absence of risk factors(1) and that in most cases delivery occurs before culture results are available.

The best preventive strategy maximises treatment in women who need it, and minimises treatment in women who do not need it. To be able to optimise the strategy it is essential to know the prevalence of GBS colonization of pregnant women in the Netherlands, which

may have changed due to recent changes in demographics, in particular with regard to ethnic background of women living in major cities. The aim of this study was to ascertain GBS carrier-rate late in pregnancy in a multicultural, urban population in the Netherlands, to find out if a group of high risk for GBS colonization could be identified and to calculate positive and negative predictive values for intrapartum carriage, based on results of the cultures at 35-37 weeks' gestation.

METHODS

In The Hague, approximately 8000 deliveries take place annually. Almost all hospitals and a part of midwifery practices joined this study. Between July 2000 and December 2002, physicians and midwives at their discretion non-selectively asked women at 35-37 weeks of pregnancy to participate in the study. All these women attended either the outpatient department of obstetrics and gynaecology at the Medisch Centrum Haaglanden, the Leyenburg Hospital, the Rode Kruis 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 nalidixid 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. Colonized women received intrapartum antibiotics only when one or more of the risk factors associated with early onset GBS disease was present. The initial intention was to repeat GBS cultures during labour in all GBS positive women and in 400 of GBS negative women.

All women were asked to complete a questionnaire about ethnic, demographic and socio-economic factors and obstetric details. Age, parity, postal code and the country of birth of both the woman and her parents were registered. The participants were grouped into different demographic and socio-economic categories by using the classification systems of the Municipal Information Centre of The Hague and the Central Commission for Statistics in the Netherlands (Statistics Netherlands/CBS) and into different ethnic categories by using publications published by the Ministry of the Interior and Kingdom Relations (BZK) and information acquired from the United Nations. The country of birth was used to classify the

women into ethnic groups according to the Dutch standard identification method(12). These ethnic groups are Class A: Born in the Netherlands or coming from one of the developed countries; Class B: Coming from any less developed country (Table 2B).

A protocol was formulated to screen 2100 women from The Hague, classified into different ethnic and socio-economic groups:

Group 1: Class A and living in the inner city (lower socio-economic group),
Group 2: Class B and living in the inner city,
Group 3: Class A and living in the suburbs (higher socio-economic group) and
Group 4: Class B and living in the suburbs.

Although we initially planned to include 2100 women, we found that after 2 years and 5 months 1700 women were included, and that no additional information would be gained by continuation of the inclusion period.

We estimated the prevalence of positive cultures as the proportion of positive testing women over all women, with 95%-confidence intervals based on a binomial distribution. These calculations were performed for various subgroups, and prevalences were compared by calculating relative risks (prevalence ratios), with 95%-confidence intervals based on a Poisson distribution of the positive tests.

Positive and negative predictive values for intrapartum carriage, based on the results of the cultures collected at 35-37 weeks pregnancy, were calculated.

The medical ethics committees of the participating hospitals approved the protocol for this study.

RESULTS

During the study period, a total of 1702 pregnant women were enrolled. Mean age was 30.5 years, median was 31 years (range 14 to 45 years). Four hundred and sixty-six women were primigravida and 1225 women were multigravida, while data about parity were missing in 11 cases. Six hundred and ninety-two women were Dutch and had parents who were both born in the Netherlands, the remaining women had at least one parent born in a foreign country or were born in another country themselves. The ethnic origin of 53 women was unknown. Of the 1702 women, 365 (21%) had positive cultures for Group B Streptococcus at 35-37 weeks of gestation. There was no relationship between colonization and age, parity or miscarriages (Table 1). Table 2 shows the breakdown of women by classification in group A or B, living in the inner city or the suburbs and the percentage of GBS carriage found per group. The prevalence of GBS carriage in Classes A and B were identical: 21%. We then analysed whether the place where women lived (inner city or the suburbs) affected the prevalence of GBS colonization. Of the 1702 women, 657 lived in the inner city and 1032

Table 1 Age, parity, history of abortions and GBS culture results

Age	N	% GBS positive	95% CI
< 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	

Table 2A GBS carrier rates according to origin and where people lived in The Hague (The Netherlands)

		Rate	%	95% CI
Class A	Inner City	29/174	17	0.11-0.23
	Suburb	129/569	23	0.19-0.26
	Unknown	1/2		
	Total	159/745	21	0.18-0.24
Class B	Inner City	104/471	22	0.18-0.26
	Suburb	88/427	21	0.17-0.25
	Unknown	2/6		
	Total	194/904	21	0.18-0.24
Unknown	Inner City	1/12		
	Suburb	8/36		
	Unknown	3/5		
	Total	12/53		
Total	Inner City	134/657	20	0.17-0.23
	Suburb	225/1032	22	0.19-0.23
	Unknown	6/13		
	Total	365/1702	21	0.19-0.23

Table 2B Classification in Class A or B according to country of birth

	Country
Class A	Netherlands, Belgium, Canada, Denmark, Germany, Finland, France, Greenland, United Kingdom, Ireland, Iceland, Israel, Japan, Channel Islands, Liechtenstein, Luxembourg, Monaco, Dutch East Indies, Dutch Newguinea, Newfoundland, New-Zealand, Norway, Austria,United States of America, Sweden, Switzerland.
Class B	All other countries
Class A:	Women of Dutch origin or coming from one of the developed countries
Class B:	women coming from one of the other countries

lived in the suburbs. Prevalence in these groups was 20% and 22%, respectively. The place of residence of 13 women was unknown.

Participating women originated from 72 different countries. When using United Nations world region classifications to cluster these countries, differences in GBS carriage between the women of these various countries of birth become apparent. (Table 3). In women originating from countries in Europe and Latin America we found a colonization rate of 21% compared to colonization rates of 29% in African women and 13% in Asian women. Women born in Africa had an increased risk for colonization compared with European women (RR 1.4, CI 1.1 – 1.7), whereas Asian women had a reduced risk for GBS carriage compared to European women (RR 0.6, CI 0.4 - 0.8). In 173 of the 365 GBS positive women and in 588 of the 1337 GBS negative women, cultures were repeated at delivery. In 174 (23%) of these 761 women, cultures were positive at this time.

Table 4 shows the proportion of women with positive and negative intrapartum cultures in relation to the results of the first swab taken between 35 - 37 weeks' pregnancy. Of all the pairs of cultures, 136 of 173 women who were positive at 35-37 weeks gestation were also positive at delivery (Positive Predictive Value 79%) and 550 of 588 women who were initially negative, remained negative at delivery (Negative Predictive Value 93%). Thirty-eight women acquired GBS in the last weeks of pregnancy, whereas cultures in 37 previously positive women were negative at delivery.

COMMENT

In this study we show that in the multicultural, urban population of pregnant women in The Hague, the Netherlands, the GBS carrier rate is 21%. We showed differences between colonized and non-colonized women in ethnicity, but we could not demonstrate differences between colonized and non-colonized women with respect to age, parity or socio-economic background. Positive predictive value of GBS carriage at 35-37 weeks' gestation for carriage at time of parturition was 79% and negative predictive value was 93%.

Table 3 World regions and GBS culture results

Continent of Native Country	N	% GBS positive	95% CI
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	0.14-0.40
Total	1702	27	

Table 4 Cultures at 35-37 weeks' gestation compared to intrapartum cultures*

Culture at 35-37 weeks	Intrapartum	Intrapartum	Total
	Positive	Negative	
Positive	136	37	173
Negative	38	550	588
Total	174	587	761

* In 761 of 1702 cases intrapartum GBS cultures were performed

PPV was 79%, NPV was 93%

Table 5 Studies with Rectovaginal GBS cultures on selective broth medium in third trimester of pregnancy

Author	Year	Country	N	Prevalence GBS
Dillon et al	1982	United States	754	28%
Easmon et al	1985	United Kingdom	895	19.8%
Sunna et al	1991	Jordan	500	30.4%
Yancey et al	1996	United States	826	26.5%
Grimwood et al	2002	New Zealand	240	22%
This study	2003	The Netherlands	1702	21%

The large number of women in our study distinguishes this study from other GBS prevalence studies. Table 5 presents other studies in which pregnant women were cultured rectovaginal at about 35-37 weeks' gestation with the use of selective broth media.

In previous studies, GBS carriage prevalences between 1,6% and 30,4% have been described(2-5;7;8;13-26). The differences in these prevalences can probably be explained by the different gestational ages at culturing, differences in culture site and in the use of different culture techniques.

Characteristics of the population studied can also explain differences in prevalence rates. Women of Caribbean origin and black women were previously reported to be at greater risk of colonization than those of Mexican origin and white women(2;5;6), which suggests a role for ethnic or genetic factors. However, other small studies(27-29) have reported no differences in group B streptococcal prevalence between any ethnic groups. The women in our study originated from 72 different countries. Differences were found in the prevalence rates between European, Asian and African women. These results are in accordance with the findings of others(2;5;6).

Differences in GBS carriage rates may also be explained by differences in the socio-economic status of the study group. A study in New Zealand women showed an increased risk for GBS carriage in the socially advantaged(3), whereas Regan et al(2) found GBS was less common among women with a higher education. In our study, we registered postal codes and related socio-economic status to the neighbourhood. Even when calculating prevalences for the poor and wealthy neighbourhoods separately and using different levels of income, we could not find any relation between socio-economic status and GBS carriage. An explanation for this might be that in our population the higher income group was quite small compared to the other groups.

Numerous studies have documented that the accuracy of prenatal screening cultures in identifying intrapartum colonization status can be enhanced by careful attention to the timing of cultures, the anatomic sites swabbed and the laboratory procedures used for culture and detection of the organisms(9). Swabbing both the lower vagina and the rectum (through the anal sphincter) substantially increases the yield compared with sampling only the cervix or sampling the vagina without swabbing the rectum(30). Isolation rates will be increased by approximately 10%-15% if the lower genital and anorectal areas are sampled rather than only the upper vagina and cervix(31).

Yow(14), Kubota(23) and others(15;25) performed only vaginal or cervicovaginal swabs and found prevalences between 6% and 14.2%, whereas rectovaginal cultures done in several other studies(3;8;16;21;24;26) revealed higher rates between 19.4% and 31%, similar to the 21% found in our study.

Since vaginal and in particular rectal flora contains numerous micro-organisms, the use of selective enrichment broth is recommended to maximise the isolation of GBS and to avoid the overgrowth of other organisms. When direct agar plating is used instead of selective enrichment broth, as many as 50% of woman who are GBS carriers have false-negative culture results(32). Ferrieri(13) and Kubota(23) did not use selective culture medium and only found prevalence rates of 5,6% and 11.4% respectively, whereas studies that used selective medium reported rates of 19,8%(16) and 18,6%(2).

Discordant results are reported regarding the effects of age and parity on GBS prevalence(5;14;27;28;33;34). In various studies(27;29;35;36) no significant differences in colonization rates were noted on the basis of age or parity, but increasing age(5) and parity(5;14) have also sometimes been associated with lower rates of carriage. However, Regan(2) described GBS carriage as being more common among older women and women of lower parity. In our study we found no association between colonization and age or parity.

Although the importance of infection as a cause of preterm delivery is gaining recognition, little is known about the role of GBS infection in miscarriages. McDonald et al.(37) stated that GBS was a key pathogen in unsuspected intrauterine infections underlying spontaneous midgestation abortions. The study of Daugaard(38) demonstrated an association between the occurrence of group B streptococci in the urine and cervix and late spontaneous abortions, but El Kersh et al.(24) found no correlation with a history of repeated spontaneous miscarriages. We did not find any relation between women who had a history of miscarriages and GBS carriage, but at this point our population is selected since we only screened almost term pregnant women.

Collection of cultures between 35 and 37 weeks' gestation is recommended to improve the sensitivity and specificity of the identification of women who are colonized at the time of delivery(4;31).

Serial cultures done in antenatal patients suggest that women may be intermittent carriers of Group B streptococci and demonstrate that concordance with intrapartum culture status improves as the interval between antenatal cultures and delivery is shortened(4). Yancey et al(4) found in a population with 26,5% carriage a positive predictive value of 87% and a negative predictive value of 96%, when cultures were done within six weeks before delivery. To improve the accuracy of antenatal cultures, the Centres for Disease Control and Prevention has suggested that the collection of these cultures should occur at 35-37 weeks' gestation instead of earlier in pregnancy(39). In our study we cultured 761 women again on admission for delivery and then calculated the positive and negative predictive values of the first culture for carriage during labour. The intention to reculture all GBS positive women and 400 of GBS negative women during labour was not fulfilled, probably because of hectic in the labourrooms and lack of attention to the studyprotocol.

The PPV of 79% and the NPV of 93% in our study is low compared to other studies and probably would have been higher if we recultured all initially GBS positive women during labour. Both our results and the somewhat higher but still low predictive values of others underline the need for rapid tests to detect GBS colonization status. These bedside-tests might obviate the need for antenatal culture based screening if their sensitivity and specitivity are comparable to culture in selective broth media and they yield results rapidly enough to permit the administration of adequate intrapartum antibiotic prophylaxis to women detected as carriers(9). Thus far, these tests have not been reliable enough to be used as an alternative to rectovaginal cultures.

In the USA, the screening based strategy is recommended since 2002(9). This recommendation is based on data found in a recent study of comparison of screening based and risk factor based strategies. The conclusion of this study was that the screening based strategy was over 50% more effective than the risk-factor based strategy(40). Management strategy depends on local factors like the percentage of GBS carriers and the percentage of pregnant women with perinatal risk-factors within the population, the organisation of perinatal care and the local availability of laboratory facilities.

The choice for a preventive strategy should be based on rationality, cost-effectiveness and the current knowledge and possibilities(11). Since the GBS prevalence found in our Dutch studypopulation is more or less similar to prevalences in the USA, the present Dutch recommended risk factor based strategy for GBS disease prevention should be reconsidered.

We show that it is not possible to identify a group of pregnant women at high risk for GBS colonization with regard to age, parity or socio-economic factors. There are ethnic differences between colonized and noncolonized women. We demonstrated that positive and negative predictive values of antenatal genital group B streptococci cultures at 35-37 weeks' gestation for intrapartum GBS carriage are lower than previously reported.

Results of this study can be useful in the process of finding the best preventive strategy for neonatal GBS-disease in the Netherlands.

REFERENCE LIST

1. Trijbels-Smeulders M, Gerards LJ, PC M, de Jong P, van Lingen RA, Adriaanse AH, et al. Epidemiology of neonatal group B streptococcal disease in The Netherlands 1997-98. Paediatr Perinat Epidemiol 2002 Oct;16(4.:334-41.
2. Regan JA, Klebanoff MA, Nugent RP. The epidemiology of group B streptococcal colonization in pregnancy. Vaginal Infections and Prematurity Study Group. Obstet Gynecol 1991 Apr;77(4.:604-10.
3. Grimwood K, Stone PR, Gosling IA, Green R, Darlow BA, Lennon DR, et al. Late antenatal carriage of group B Streptococcus by New Zealand women. Aust N Z J Obstet Gynaecol 2002 May;42(2.:182-6.
4. Yancey MK, Schuchat A, Brown LK, Ventura VL, Markenson GR. The accuracy of late antenatal screening cultures in predicting genital group B streptococcal colonization at delivery. Obstet Gynecol 1996 Nov;88(5.:811-5.
5. Anthony BF, Okada DM, Hobel CJ. Epidemiology of group B Streptococcus: longitudinal observations during pregnancy. J Infect Dis 1978 May;137(5.:524-30.
6. Aber RC, Allen N, Howell JT, Wilkenson HW, Facklam RR. Nosocomial transmission of group B streptococci. Pediatrics 1976 Sep;58(3.:346-53.
7. Hoogkamp-Korstanje JA, Gerards LJ, Cats BP. Maternal carriage and neonatal acquisition of group B streptococci. J Infect Dis 1982 Jun;145(6.:800-3.
8. Adriaanse AH, Kollee LA, Muytjens HL, Nijhuis JG, de Haan AF, Eskes TK. Randomized study of vaginal chlorhexidine disinfection during labor to prevent vertical transmission of group B streptococci. Eur J Obstet Gynecol Reprod Biol 1995 Aug;61(2.:135-41.
9. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. MMWR Recomm Rep 2002 Aug 16;51(RR-11.:1-22.
10. Dutch Society of Obstetrics and Gynaecology (NVOG., Adriaanse AH, Schutte MF, Gerards LJ. Preventie van perinatale groep-B-streptokokkenziekte. NVOG guidelines 1998 Oct;12.
11. Trijbels-Smeulders M, Adriaanse AH, Gerards LJ, Kimpen JL. Strategy to prevent neonatal early-onset group B streptococcal (GBS. disease in the Netherlands. Reviews in Medical Microbiology 2003;14:35-9.
12. den Heeren J, Verwij AO. Identificatie en registratie van etnische herkomst. 1993.
13. Ferrieri P, Cleary PP, Seeds AE. Epidemiology of group-B streptococcal carriage in pregnant women and newborn infants. J Med Microbiol 1977 Feb;10(1.:103-14.
14. Yow MD, Leeds LJ, Thompson PK, Mason EO, Jr., Clark DJ, Beachler CW. The natural history of group B streptococcal colonization in the pregnant woman and her offspring. I. Colonization studies. Am J Obstet Gynecol 1980 May 1;137(1.:34-8.
15. Lewin EB, Amstey MS. Natural history of group B streptococcus colonization and its therapy during pregnancy. Am J Obstet Gynecol 1981 Mar 1;139(5.:512-5.
16. Easmon CS, Hastings MJ, Neill J, Bloxham B, Rivers RP. Is group B streptococcal screening during pregnancy justified? Br J Obstet Gynaecol 1985 Mar;92(3.:197-201.
17. Visconti A, Orefici G, Notarnicola AM. Colonization and infection of mothers and neonates with group B streptococci in three Italian hospitals. J Hosp Infect 1985 Sep;6(3.:265-76.
18. Persson K, Bjerre B, Elfstrom L, Forsgren A. Longitudinal study of group B streptococcal carriage during late pregnancy. Scand J Infect Dis 1987;19(3.:325-9.
19. Eidelman AI, Rudensky B, Ferne M, Weintraub G, Isacshon M. Epidemiology of group B streptococci in an Israeli hospital. Isr J Med Sci 1983 Oct;19(10.:903-5.
20. Regan JA, Klebanoff MA, Nugent RP, Eschenbach DA, Blackwelder WC, Lou Y, et al. Colonization with group B streptococci in pregnancy and adverse outcome. VIP Study Group. Am J Obstet Gynecol 1996 Apr;174(4.:1354-60.

21. Sunna E, el Daher N, Bustami K, Na'was T. A study of group B streptococcal carrier state during late pregnancy. Trop Geogr Med 1991 Jan;43(1-2.:161-4.
22. Yancey MK, Duff P. Group B streptococcal infections during pregnancy. Curr Opin Obstet Gynecol 1993 Aug;5(4.:508-12.
23. Kubota T. Relationship between maternal group B streptococcal colonization and pregnancy outcome. Obstet Gynecol 1998 Dec;92(6.:926-30.
24. El Kersh TA, Al Nuaim LA, Kharfy TA, Al Shammary FJ, Al Saleh SS, Al Zamel FA. Detection of genital colonization of group B streptococci during late pregnancy. Saudi Med J 2002 Jan;23(1.:56-61.
25. Allardice JG, Baskett TF, Seshia MM, Bowman N, Malazdrewicz R. Perinatal group B streptococcal colonization and infection. Am J Obstet Gynecol 1982 Mar 15;142(6 Pt 1.:617-20.
26. Dillon HC, Jr., Gray E, Pass MA, Gray BM. Anorectal and vaginal carriage of group B streptococci during pregnancy. J Infect Dis 1982 Jun;145(6.:794-9.
27. Baker CJ, Barrett FF, Yow MD. The influence of advancing gestation on group B streptococcal colonization in pregnant women. Am J Obstet Gynecol 1975 Aug 1;122(7.:820-3.
28. Schauf V, Hlaing V. Group B streptococcal colonization in pregnancy. Obstet Gynecol 1976 Jun;47(6.:719-21.
29. Jaureguy F, Carton M, Teboul J, Butel MJ, Panel P, Ghnassia JC, et al. [Risk factors and screening strategy for group B streptococcal colonization in pregnant women: results of a prospective study]. J Gynecol Obstet Biol Reprod (Paris. 2003 Apr;32(2.:132-8.
30. Badri MS, Zawaneh S, Cruz AC, Mantilla G, Baer H, Spellacy WN, et al. Rectal colonization with group B streptococcus: relation to vaginal colonization of pregnant women. J Infect Dis 1977 Feb;135(2.:308-12.
31. Boyer KM, Gadzala CA, Kelly PD, Burd LI, Gotoff SP. Selective intrapartum chemoprophylaxis of neonatal group B streptococcal early-onset disease. II. Predictive value of prenatal cultures. J Infect Dis 1983 Nov;148(5.:802-9.
32. Laboratory practices for prenatal Group B streptococcal screening and reporting--Connecticut, Georgia, and Minnesota, 1997-1998. MMWR Morb Mortal Wkly Rep 1999 May 28;48(20.:426-8.
33. Papapetropoulou M, Kondakis XG. A study of risk factors of vaginal colonization with group B streptococci in pregnancy. Eur J Epidemiol 1987 Dec;3(4.:419-22.
34. Dawodu AH, Damole IO, Onile BA. Epidemiology of group B streptococcal carriage among pregnant women and their neonates: an African experience. Trop Geogr Med 1983 Jun;35(2.:145-50.
35. Hastings MJ, Easmon CS, Neill J, Bloxham B, Rivers RP. Group B streptococcal colonisation and the outcome of pregnancy. J Infect 1986 Jan;12(1.:23-9.
36. Beachler CW, Baker CJ, Kasper DL, Fleming DK, Webb BJ, Yow MD. Group B streptococcal colonization and antibody status in lower socioeconomic parturient women. Am J Obstet Gynecol 1979 Jan 15;133(2.:171-3.
37. McDonald HM, Chambers HM. Intrauterine infection and spontaneous midgestation abortion: is the spectrum of microorganisms similar to that in preterm labor? Infect Dis Obstet Gynecol 2000;8(5-6.:220-7.
38. Daugaard HO, Thomsen AC, Henriques U, Ostergaard A. Group B streptococci in the lower urogenital tract and late abortions. Am J Obstet Gynecol 1988 Jan;158(1.:28-31.
39. Prevention of perinatal group B streptococcal disease: a public health perspective. Centers for Disease Control and Prevention. MMWR Recomm Rep 1996 May 31;45(RR-7.:1-24.
40. Schrag SJ, Zell ER, Lynfield R, Roome A, Arnold KE, Craig AS, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. N Engl J Med 2002 Jul 25;347(4.:233-9.

Chapter 3

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

3

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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

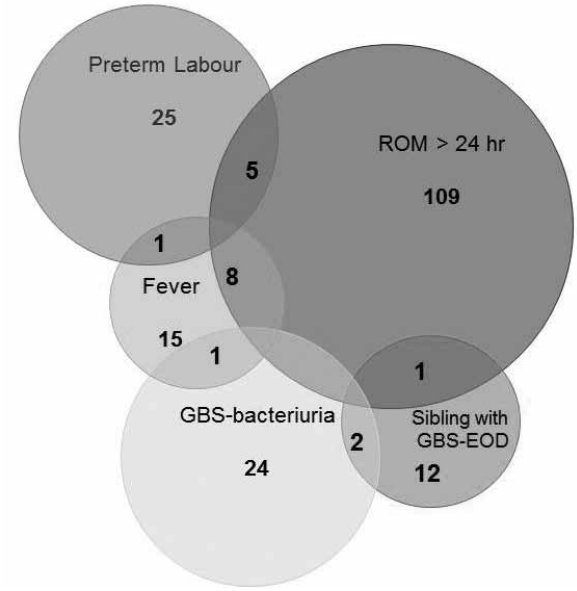

Figure 1 Risk factors for GBS-EOD during delivery

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.

REFERENCE LIST

1. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. Pediatr Infect Dis J 2011 Nov;30(11.:937-41.
2. Schuchat A. Epidemiology of group B streptococcal disease in the United States: shifting paradigms. Clin Microbiol Rev 1998 Jul;11(3.:497-513.
3. Stoll BJ, Hansen NI, Sanchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics 2011 May;127(5.:817-26.
4. Edmond KM, Kortsalioudaki C, Scott S, Schrag SJ, Zaidi AK, Cousens S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. Lancet 2012 Feb 11;379(9815.:547-56.
5. Barcaite E, Bartusevicius A, Tameliene R, Kliucinskas M, Maleckiene L, Nadisauskiene R. Prevalence of maternal group B streptococcal colonisation in European countries. Acta Obstet Gynecol Scand 2008;87(3.:260-71.
6. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. MMWR Recomm Rep 2002 Aug 16;51(RR-11.:1-22.
7. Lewin EB, Amstey MS. Natural history of group B streptococcus colonization and its therapy during pregnancy. Am J Obstet Gynecol 1981 Mar 1;139(5.:512-5.
8. Hoogkamp-Korstanje JA, Gerards LJ, Cats BP. Maternal carriage and neonatal acquisition of group B streptococci. J Infect Dis 1982 Jun;145(6.:800-3.
9. Hansen SM, Uldbjerg N, Kilian M, Sorensen UB. Dynamics of Streptococcus agalactiae colonization in women during and after pregnancy and in their infants. J Clin Microbiol 2004 Jan;42(1.:83-9.
10. Yancey MK, Schuchat A, Brown LK, Ventura VL, Markenson GR. The accuracy of late antenatal screening cultures in predicting genital group B streptococcal colonization at delivery. Obstet Gynecol 1996 Nov;88(5.:811-5.
11. Valkenburg-van den Berg AW, Houtman-Roelofsen RL, Oostvogel PM, Dekker FW, Dorr PJ, Sprij AJ. Timing of group B streptococcus screening in pregnancy: a systematic review. Gynecol Obstet Invest 2010;69(3.:174-83.
12. Quirante J, Ceballos R, Cassady G. Group B beta-hemolytic streptococcal infection in the newborn. I. Early onset infection. Am J Dis Child 1974 Nov;128(5.:659-65.
13. Tseng PI, Kandall SR. Group B streptococcal disease. In neonates and infants. N Y State J Med 1974 Nov;74(12.:2169-73.
14. Yagupsky P, Menegus MA, Powell KR. The changing spectrum of group B streptococcal disease in infants: an eleven-year experience in a tertiary care hospital. Pediatr Infect Dis J 1991 Nov;10(11.:801-8.
15. Garland SM. Early onset neonatal group B streptococcus (GBS. infection: associated obstetric risk factors. Aust N Z J Obstet Gynaecol 1991 May;31(2.:117-8.
16. Adair CE, Kowalsky L, Quon H, Ma D, Stoffman J, McGeer A, et al. Risk factors for early-onset group B streptococcal disease in neonates: a population-based case-control study. CMAJ 2003 Aug 5;169(3.:198-203.
17. Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics 1999 Jun;103(6.:e77.
18. Oddie S, Embleton ND. Risk factors for early onset neonatal group B streptococcal sepsis: case-control study. BMJ 2002 Aug 10;325(7359.:308.
19. Spaans WA, Knox AJ, Koya HB, Mantell CD. Risk factors for neonatal infection. Aust N Z J Obstet Gynaecol 1990 Nov;30(4.:327-30.
20. Yancey MK, Duff P, Kubilis P, Clark P, Frentzen BH. Risk factors for neonatal sepsis. Obstet Gynecol 1996 Feb;87(2.:188-94.

21. Boyer KM, Gadzala CA, Kelly PD, Burd LI, Gotoff SP. Selective intrapartum chemoprophylaxis of neonatal group B streptococcal early-onset disease. II. Predictive value of prenatal cultures. J Infect Dis 1983 Nov;148(5.:802-9.
22. Stewardson-Krieger PB, Gotoff SP. Risk factors in early-onset neonatal group b streptococcal infections. Infection 1978;6(2.:50-3.
23. Schuchat A, Wenger JD. Epidemiology of group B streptococcal disease. Risk factors, prevention strategies, and vaccine development. Epidemiol Rev 1994;16(2.:374-402.
24. Schuchat A, Zywicki SS, Dinsmoor MJ, Mercer B, Romaguera J, O'Sullivan MJ, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case-control study. Pediatrics 2000 Jan;105(1 Pt 1.:21-6.
25. Wood EG, Dillon HC, Jr. A prospective study of group B streptococcal bacteriuria in pregnancy. Am J Obstet Gynecol 1981 Jul 1;140(5.:515-20.
26. Persson K, Christensen KK, Christensen P, Forsgren A, Jorgensen C, Persson PH. Asymptomatic bacteriuria during pregnancy with special reference to group B streptococci. Scand J Infect Dis 1985;17(2.:195-9.
27. Carstensen H, Christensen KK, Grennert L, Persson K, Polberger S. Early-onset neonatal group B streptococcal septicaemia in siblings. J Infect 1988 Nov;17(3.:201-4.
28. Faxelius G, Bremme K, Kvist-Christensen K, Christensen P, Ringertz S. Neonatal septicemia due to group B streptococci--perinatal risk factors and outcome of subsequent pregnancies. J Perinat Med 1988;16(5-6.:423-30.
29. Philipson EH, Herson VC. Intrapartum chemoprophylaxis for group B streptococcus infection to prevent neonatal disease: who should be treated? Am J Perinatol 1996 Nov;13(8.:487-90.
30. Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. N Engl J Med 1986 Jun 26;314(26.:1665-9.
31. Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. Cochrane Database Syst Rev 2009;(3.:CD007467.
32. Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep 2010 Nov 19;59(RR-10.:1-36.
33. Trijbels-Smeulders M, de Jonge GA, Pasker-de Jong PC, Gerards LJ, Adriaanse AH, van Lingen RA, et al. Epidemiology of neonatal group B streptococcal disease in the Netherlands before and after introduction of guidelines for prevention. Arch Dis Child Fetal Neonatal Ed 2007 Jul;92(4.:F271-F276.
34. Mohangoo AD, Buitendijk SE, Hukkelhoven CW, Ravelli AC, Rijninks-van Driel GC, Tamminga P, et al. [Higher perinatal mortality in The Netherlands than in other European countries: the Peristat-II study]. Ned Tijdschr Geneeskd 2008 Dec 13;152(50.:2718-27.
35. Valkenburg-van den Berg AW, Sprij AJ, Oostvogel PM, Mutsaers JA, Renes WB, Rosendaal FR, et al. Prevalence of colonisation with group B Streptococci in pregnant women of a multi-ethnic population in The Netherlands. Eur J Obstet Gynecol Reprod Biol 2006 Feb 1;124(2.:178-83.
36. Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy 1988 Nov;18(6.:515-40.
37. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. N Engl J Med 2002 Jul 25;347(4.:240-7.
38. Moore MR, Schrag SJ, Schuchat A. Effects of intrapartum antimicrobial prophylaxis for prevention of group-B-streptococcal disease on the incidence and ecology of early-onset neonatal sepsis. Lancet Infect Dis 2003 Apr;3(4.:201-13.
39. Murch SH. Toll of allergy reduced by probiotics. Lancet 2001 Apr 7;357(9262.:1057-9.
40. Rouse DJ, Goldenberg RL, Cliver SP, Cutter GR, Mennemeyer ST, Fargason CA, Jr. Strategies for the prevention of early-onset neonatal group B streptococcal sepsis: a decision analysis. Obstet Gynecol 1994 Apr;83(4.:483-94.
41. Mohle-Boetani JC, Schuchat A, Plikaytis BD, Smith JD, Broome CV. Comparison of prevention strategies for neonatal group B streptococcal infection. A population-based economic analysis. JAMA 1993 Sep 22;270(12.:1442-8.

42. Hyde TB, Hilger TM, Reingold A, Farley MM, O'Brien KL, Schuchat A. Trends in incidence and antimicrobial resistance of early-onset sepsis: population-based surveillance in San Francisco and Atlanta. Pediatrics 2002 Oct;110(4.:690-5.
43. Baltimore RS, Huie SM, Meek JI, Schuchat A, O'Brien KL. Early-onset neonatal sepsis in the era of group B streptococcal prevention. Pediatrics 2001 Nov;108(5.:1094-8.
44. Stoll BJ, Hansen NI, Higgins RD, Fanaroff AA, Duara S, Goldberg R, et al. Very low birth weight preterm infants with early onset neonatal sepsis: the predominance of gram-negative infections continues in the National Institute of Child Health and Human Development Neonatal Research Network, 2002-2003. Pediatr Infect Dis J 2005 Jul;24(7.:635-9.

Chapter 4

Low rate of carriage of macrolide-resistant group B streptococci in pregnant women in the Netherlands

4

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ABSTRACT

Objectives To describe prevalence of phenotypic and genotypic macrolide-resistance among GBS isolates in pregnant women and explore the possibility of clonal spread of resistant GBS isolates in a multicultural population.

Study design Antimicrobial resistance patterns of 107 GBS isolates obtained from asymptomatic pregnant women were determined using Etests.
Macrolide resistance genes *mef*(A), *erm*(TR) and *erm*(B) were determined with PCR and a subset of 39 isolates, including the 8 isolates harbouring macrolide resistance genes, was subjected to RAPD analysis to detect clonal spreading.

Results Resistance to erythromycin and clindamycin was found in 8% and 7%, respectively. Macrolide resistance genes *mef*(A), *erm*(TR) and *erm*(B) were found in 1, 2 and 5 isolates, respectively; only five of these eight isolates exhibited both genotypic as well as phenotypic resistance. One genotype occurred in 36% of the subset.

Conclusions Earlier reports on prevalence of phenotypic resistance were confirmed. Among the susceptible isolates one clonal type of GBS was clearly predominant; one of the resistant isolates shared its genotype. When such clonal types acquire resistance traits in the future, GBS disease may become harder to control.

INTRODUCTION

Neonatal infection with group B streptococci (GBS, *Streptococcus agalactiae)* is a universal cause of neonatal morbidity and mortality. To prevent GBS acquisition of the child during labor and delivery, intrapartum antibiotic prophylaxis is applied, usually with benzylpenicillin or, otherwise, with cefazolin, clindamycin, erythromycin or vancomycin. Emergence of resistance against these antimicrobials would decrease prophylactic efficacy. Resistance against erythromycin and clindamycin has been found in 0.7%-29% and 1.7%-21% of the strains, depending on geographical origin and temporal trends.(1-4) Fortunately, decreased susceptibility to benzylpenicillin has been scarcely reported(4;5), but clonal dissemination of such strains of decreased susceptibility would be worriesome.(6) Clonal diversity of erythromycin-resistant strains was documented in Portugal(3) and Spain.(7) Purpose of the present study was to assess phenotypic and genotypic antibiotic susceptibility patterns and putative epidemicity of GBS strains from a multicultural obstetric population in The Hague (the Netherlands).

MATERIALS AND METHODS

GBS isolates were obtained from rectovaginal cultures from asymptomatic women in the third trimester of pregnancy (January 2002 - February 2003). Isolates were kept in Amies transport medium. Incubation took place at 35-37°C for 18-24 hours in Todd-Hewitt broth with gentamycin (8 µg/ml) and nalidixic acid (15 µg/ml). Bacterial isolates were subcultured on 5% sheep blood agar in 5% CO_2. Suspect GBS colonies were subjected to Gram-staining. Catalase activity was assayed for Gram-positive cocci. GBS strains were identified by PathoDx group B® (DPC, Los Angeles, USA) and stored at -80°C in glycerol containing media.

Antibiotic susceptibility and presence of macrolide resistance genes were determined for 107 isolates from as many women. A subset of 39 strains was included in RAPD genotyping. This selection included all 8 isolates showing phenotypic macrolide resistance and 31 randomly selected isolates. Patient records revealed the countries of birth of the women.

Prior to susceptibility testing, GBS isolates were grown on 5% sheep blood agar plates for 18-24 hours in 5% CO_2. Dilutions of 0.5 McFarland were swabbed on Mueller-Hinton agar plates with 5% horse blood. E-tests (AB Biodisk, Solna, Sweden) for benzylpenicillin, cephalothin, erythromycin and clindamycin were performed according to the manufacturers' instructions. Cephalothin was tested as a representative first-generation cephalosporin. Cultures were incubated for 24 hours at 35-37°C in 5% CO_2. The MIC was recorded as indicated by the NCCLS guidelines for streptococci.

For molecular typing, bacterial DNA was extracted using lysostaphin treatment, the Bacterial DNA kit III and the MagnaPure Robot (Roche Diagnostics, Almere, The Netherlands). Macrolide resistance genes *mef*(A), *erm*(B) and *erm*(TR) were amplified from 50 ng DNA

using primers and protocols as described by Sutcliffe et al.(8) and Seppala et al.(9) PCR results were scored on the basis of the absence or presence of the correctly sized amplicon after agarose gel electrophoresis. No positive control isolates were included, allthough all of the individual PCR runs showed positive results. Negative controls involved water samples. Genotyping by RAPD was performed according to Ahmed et al.(10) using primers 12/13 (AAGTAAGTG-ACTGGGGTGAGCG), 46 (GGTTGGGTGAGAA-TTGCACG). 48 (GGCCATAGAGTG-TTGCAGACAAACTGC), 50 (GCGATCCCA) and 52 (GTGGATGCGA) DNA fingerprints were scored by two independent individuals and any change in banding pattern led to definition of a novel genotype. In case of discrepant interpretations consensus was sought through intervention of a third examiner. This resolved all discrepancies. Genotypes were defined for all separate RAPD tests, the combination of all five types led to the composite, overall RAPD genotype.(11) Finally, PCR ribotyping was performed according to Martirosian et al.(12)

RESULTS AND DISCUSSION

Samples were obtained from 1702 pregnant women between 35 and 37 weeks of pregnancy. In 365 (21%) samples GBS was cultured. From this isolate collection, we randomly selected 107 isolates. Of all 107 isolates, over 84% were susceptible to all antimicrobials tested (Table 1). Of the 9 isolates not susceptible to erythromycin, resistance or intermediate susceptibility to clindamycin was present in seven cases. Macrolide resistance genes were detected in 8 of 107 strains. Phenotypic and genotypic data for the subset of 39 strains are summarized in Table 2. No strain contained more than one macrolide resistance gene. Out of these 8 strains, 5 showed phenotypic resistance towards macrolides on lincosamides. In two phenotypically macrolide-resistant or -intermediate strains resistance genes were not detected. PCR ribotyping produced a single PCR fragment of which the nucleotide sequence precisely matched the sequence of the reference strain 2603 V/R (results not shown), confirming GBS identity. Per GBS-isolate 5 separate RAPD reactions were performed. When

Table 1 Susceptibility patterns of 107 tested GBS strains

Antibiotic*	**Susceptible (S)**		**Intermediate (I)**		**Resistant (R)**	
Benzylpenicillin	107	(100%)	0	(0%)	0	(0%)
Cephalothin	107	(100%)	0	(0%)	0	(0%)
Erythromycin	98	(92%)	2	(2%)	7	(6%)
Clindamycin	100	(93%)		(1%)	6	(6%)

*MIC breakpoints (µg/mL) used in our study are as recommended by NCCLS(8) for benzylpenicillin: S =< 0.12, I = 0.25-2, R >= 4, cephalothin: S =< 8, I = 16, R >= 32, erythromycin: S=< 0.25, I = 0.38-0.75, R >= 1, clindamycin: S =< 0.25, I = 0.38-0.75, R >= 1.

Table 2 Summary of typing data obtained from a subset of GBS isolates from The Hague

E tests (MIC values in µg/ml)					Resistance Genes			RAPD Types					Overall RAPD genotype
	penicillin G	Cephalothin	Erythromycin	Clindamycin	*mef*(A)	*erm*(B)	*erm*(TR)	12/13	46	48	50	52	
1	0.032	0.094	0.064	0.064				A	A	A	A	B	*
2	0.047	0.064	0.047	0.094				B	B	B	B	G	*
3	0.032	0.094	0.047	0.047				A	A	C	A	H	*
4	0.032	0.094	0.047	0.047				A	A	C	A	A	*
5	0.047	0.094	0.047	0.094				A	A	D	A	A	I
6	0.047	0.125	0.094	0.19				A	A	E	A	A	*
7	0.032	0.125	0.094	0.064				A	A	F	A	A	II
8	0.064	0.125	0.125	0.125				A	A	G	A	A	*
9	0.032	0.094	0.125	0.19				A	A	F	A	A	II
10	0.047	0.094	0.125	0.094				A	C	*	A	A	*
11	0.047	0.094	**2**	0.064	+			A	C	H	A	A	*
13	0.047	0.064	0.016	0.047				A	A	F	A	A	II
14	0.032	0.094	0.125	0.094				A	A	D	A	B	III
15	0.047	0.064	0.047	0.064				A	A	D	C	A	*
16	0.047	0.094	0.064	0.094				A	A	D	C	B	*
23	0.047	0.094	0.064	0.094		+		A	A	D	A	B	III
36	0.064	0.094	**>256**	**>256**			+	A	D	F	A	A	*
44	0.064	0.094	***0.50***	***12***				A	A	D	A	A	I
45	0.047	0.064	**4**	**>256**				A	E	D	A	A	IV
59	0.032	0.094	**1.5**	0.19			+	B	F	*	B	C	*
68	0.023	0.047	**>256**	*R*[a]		+		A	A	D	A	D	*
72	0.047	0.094	**>256**	**>256**		+		A	G	D	A	E	*
76	0.064	0.064	*0.50*	*0.50*				C	D	F	A	F	*
78	0.064	0.064	0.19	0.094		+		C	H	F	A	C	*
91	0.047	0.094	0.016	0.064		+		D	H	*	D	G	*
92	0.094	0.094	0.094	0.094				E	A	F	A	A	*
96	0.064	0.064	0.094	0.19				F	A	D	E	A	*
97	0.047	0.125	0.016	0.032				G	F	*	E	C	*
98	0.032	0.094	0.064	0.064				C	A	D	A	A	V
99	0.032	0.094	0.047	0.047				A	A	D	A	A	I
100	0.047	0.125	0.094	0.094				A	A	D	A	A	I

E tests (MIC values in µg/ml)					Resistance Genes			RAPD Types					Overall RAPD genotype
	penicillin G	Cephalothin	Erythromycin	Clindamycin	*mef*(A)	*erm*(B)	*erm*(TR)	12/13	46	48	50	52	
101	0.064	0.125	0.047	0.094				C	A	D	A	A	V
102	0.094	0.19	0.047	0.094				A	C	D	A	E	*
103	0.094	0.125	0.047	0.094				A	A	D	A	A	I
104	0.064	0.125	0.032	0.094				A	A	D	A	A	I
105	0.094	0.125	0.047	0.064				A	E	D	A	A	IV
106	0.094	0.125	0.047	0.064				A	A	D	A	A	I
107	0.094	0.125	0.064	0.094				A	A	D	A	A	I
108	0.064	0.125	0.047	0.094				H	A	D	A	A	*

The overall RAPD genotype combines the outcome of the five assays as defined by the different primers listed in Methods. This led to the identification of 27 genotypes. Note that strains sharing the AA*AA genotype (* any other type) may also form a clonal cluster. Only types occurring more than once have been given a serial Roman cluster code, all others are unique. Resistant isolates are marked in bold and intermediate susceptible isolates in italic.
a Resistance to clindamycin was inducible

the amplimers were analysed by gel electrophoresis on avarage 5 DNA fragments were visible per fingerprint. This amounts to an approximate number of 25 scorable fragments per isolate. Per RAPD assay a type was assigned and a single band difference led to another type designation.

Overall, 27 RAPD genotypes were identified (Table 2), 5 of which occurred more than once (I: 8/39 (21%) ; II: 3/39 (8%) ; III: 2/39 (5%) ; IV: 2/39 (5%) ; V: 2/39 (5%)). The AA*AA type occurs 14 times (36%), showing that certain (sub)clones may spread more efficiently than others. These subclonal types, sharing 4 out of 5 individual RAPD test results, shared >80% band identity. Data on the countries of birth of the patients in the subset were obtained: 18 were born in the Netherlands and the others were from 10 different countries, showing the heterogeneity of the population. As expected in this small study group, no association between country of birth and phenotypic resistance or RAPD type was found.

All phenotypically macrolide-resistant isolates were RAPD-unique, but isolate 44 shared the epidemic genotype AA*AA with antibiotic susceptible GBS isolates.

CONCLUSIONS

The prevalence of macrolide resistance among our isolates agrees with recent reports.(2;4;5) Several discrepancies between the phenotypic resistance and the presence of resistance genes are identified. Phenotypic resistance without *erm* or *mef* genes may be due to the fact that also other genes are involved in macrolide resistance.(9;13) In addition, *erm*(B) expression, often needs to be induced.(14) Furthermore, genetic variation in the *erm* and *mef* genes may also lead to false-negative PCR results. All phenotypically macrolide resistant strains were RAPD typed as unique genotypes. But among the susceptible isolates, we found a predominant GBS clone. One of the resistant isolates shared the genotype with this predominant clone, but the presence of resistance within the predominant clone is still limited to a single GBS isolate. The existence of a major antibiotic-susceptible GBS clone indicates that epidemic expansion of resistant variants could easily happen even in a heterogenous population. When resistance would expand in such epidemic isolates, efficient spread of antimicrobial resistance could take place. Continuous surveillance for resistance and its clonal spread is therefore needed, especially in the light of the increased use of antibiotics for prophylactic indications. In addition, the spread of this clone beyond the limited geographic area we analyzed in this study should be monitored by modern genotyping methods including multi locus sequence typing to better estimate its possible clinical impact.

REFERENCE LIST

1. Al-Sweih N, Jamal M, Kurdia M, Abduljabar R, Rotimi V. Antibiotic susceptibility profile of group B streptococcus (Streptococcus agalactiae. at the Maternity Hospital, Kuwait. Med Princ Pract 2005 Jul;14(4.:260-3.
2. Manning SD, Foxman B, Pierson CL, Tallman P, Baker CJ, Pearlman MD. Correlates of antibiotic-resistant group B streptococcus isolated from pregnant women. Obstet Gynecol 2003 Jan;101(1.:74-9.
3. Figueira-Coelho J, Ramirez M, Salgado MJ, Melo-Cristino J. Streptococcus agalactiae in a large Portuguese teaching hospital: antimicrobial susceptibility, serotype distribution, and clonal analysis of macrolide-resistant isolates. Microb Drug Resist 2004;10(1.:31-6.
4. Bland ML, Vermillion ST, Soper DE, Austin M. Antibiotic resistance patterns of group B streptococci in late third-trimester rectovaginal cultures. Am J Obstet Gynecol 2001 May;184(6.:1125-6.
5. Simoes JA, Aroutcheva AA, Heimler I, Faro S. Antibiotic resistance patterns of group B streptococcal clinical isolates. Infect Dis Obstet Gynecol 2004;12(1.:1-8.
6. Diekema DJ, Andrews JI, Huynh H, Rhomberg PR, Doktor SR, Beyer J, et al. Molecular epidemiology of macrolide resistance in neonatal bloodstream isolates of group B streptococci. J Clin Microbiol 2003 Jun;41(6.:2659-61.
7. Gonzalez JJ, Andreu A. Multicenter study of the mechanisms of resistance and clonal relationships of Streptococcus agalactiae isolates resistant to macrolides, lincosamides, and ketolides in Spain. Antimicrob Agents Chemother 2005 Jun;49(6.:2525-7.
8. Sutcliffe J, Grebe T, Tait-Kamradt A, Wondrack L. Detection of erythromycin-resistant determinants by PCR. Antimicrob Agents Chemother 1996 Nov;40(11.:2562-6.
9. Seppala H, Haanpera M, Al-Juhaish M, Jarvinen H, Jalava J, Huovinen P. Antimicrobial susceptibility patterns and macrolide resistance genes of viridans group streptococci from normal flora. J Antimicrob Chemother 2003 Oct;52(4.:636-44.
10. Ahmed A, van de Sande W, Verbrugh H, Fahal A, van BA. Madurella mycetomatis strains from mycetoma lesions in Sudanese patients are clonal. J Clin Microbiol 2003 Oct;41(10.:4537-41.
11. Chatellier S, Ramanantsoa C, Harriau P, Rolland K, Rosenau A, Quentin R. Characterization of Streptococcus agalactiae strains by randomly amplified polymorphic DNA analysis. J Clin Microbiol 1997 Oct;35(10.:2573-9.
12. Martirosian G, van BA, Van LW, Meisel-Mikolajczyk F, Verbrugh H. PCR ribotyping and arbitrarily primed PCR for the comparison of enterotoxigenic Bacteroides fragilis strains from two Polish university hospitals. Clin Microbiol Infect 1997 Feb;3(1.:102-8.
13. Zeng X, Kong F, Wang H, Darbar A, Gilbert GL. Simultaneous detection of nine antibiotic resistance-related genes in Streptococcus agalactiae using multiplex PCR and reverse line blot hybridization assay. Antimicrob Agents Chemother 2006 Jan;50(1.:204-9.
14. Desjardins M, Delgaty KL, Ramotar K, Seetaram C, Toye B. Prevalence and mechanisms of erythromycin resistance in group A and group B Streptococcus: implications for reporting susceptibility results. J Clin Microbiol 2004 Dec;42(12.:5620-3.

Chapter 5

Association between colonization with Group B Streptococcus and preterm delivery:

A systematic review of the literature

5

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ABSTRACT

Background Up to 36% of pregnant women is colonized with GBS, most often without having symptoms. Preterm delivery in GBS colonized mothers is a recognized risk factor for early onset neonatal GBS disease (GBS-EOD), but whether maternal GBS genital colonization is related to preterm delivery is unclear.

Objective The objective of this review was to determine the relationship between maternal colonization with Group B Streptococcus and preterm delivery.

Study Design Pubmed searches and reference lists of all selected publications were used to find studies reporting on the relationship between maternal GBS colonization and preterm delivery. Study characteristics were abstracted, and validity scores were performed. To assess the relationship between GBS colonization and pregnancy outcome, four-fold prognostic tables were constructed for each study.

Results Out of more than 60 full-text articles, 16 follow-up studies and four case control studies were included in this review. Follow-up studies were divided into 'cohort studies', in which cultures were taken early in pregnancy and which reported on pregnancy outcome, and 'cross-sectional studies', in which cultures were collected during delivery. Studies differed widely in methods, validity score and GBS prevalence. The combined estimate from a random effect meta-analysis of the eleven cohort studies was 1.06 (95%CI 0.95-1.19) and for the five cross-sectional studies 1.75 (95%CI 1.43-2.14). For the case control studies the pooled odds ratio was 1.59 (95% CI 1.03-2.44).

Conclusions This systematic review did not show an association between maternal GBS colonization during pregnancy and preterm delivery. However, in case of preterm delivery, there is an increased risk of subsequent maternal GBS colonization.

INTRODUCTION

Despite major advances in perinatal care, preterm delivery is still the predominant cause of perinatal mortality and a major cause of neurological morbidity in surviving infants. Although the determinants of preterm delivery are uncertain, evidence suggests maternal genital tract colonization with specific organisms can play a role in preterm rupture of membranes and preterm delivery. Bacterial products such as phospholipases A_2 and C, endotoxin, and induction of the cytokine cascade can stimulate the prostaglandin pathway and initiate labour. (1;2) Reproductive tract infections or colonization associated with preterm delivery include Chlamydia trachomatis (3) and bacterial vaginosis. (4-6)

Up to 36% of pregnant women is colonized with GBS, most often without having symptoms.(7-10) Preterm delivery in GBS colonized mothers is a recognized risk factor for early onset neonatal GBS disease (GBS-EOD)(11), but whether maternal GBS genital colonization is related to preterm delivery is unclear.

The objective of this study was to critically review the literature to find any association between maternal GBS colonization and preterm delivery.

METHODS

The review process of our study, including methods of reporting outcomes was based on recommendations of Stroup et al.(12)

Search for studies

The selection process for studies reporting on GBS colonization and the outcome of pregnancy involved several steps following the guidelines provided by the book *Systematic Reviews in Health Care*.(13) Pubmed was searched for potentially relevant articles on the predictive value of positive GBS-cultures for preterm delivery published from 1966 to December 2008.

The search strategy included the terms Streptococcus *agalactiae*, streptococcus group B, premature, preterm, labor, labour, delivery, birth, pregnancy outcome, infant, and combinations of all these search terms.

Selection process, selected studies and validity

All possibly relevant articles were selected on the basis of title and abstract by two researchers (AV, AS) and were retrieved for more detailed examination. The selected articles had to meet met the following inclusion criteria:

1. They were published in English, French, Italian, Spanish or German.
2. They reported pregnancy outcome in GBS carriers and non-GBS carriers.
3. They reported patient population did not receive antibiotics during pregnancy.

Table 1 Characteristics and results of original studies Ordered by study design and validity score

Source	Primary Location	No. of Patients	Study Design	Gestational Age at time of culture	Definition Adverse Outcome	Prevalence adverse outcome	Prevalence GBS colonization	Validity Score	OR	RR	CI	Conclusion per Study
McDonald 1992	Adelaide, Australia	786	Cohort	Between 22-28 weeks	Preterm birth <37 weeks	6.2%	10.8%	7		0.95	0.58-1.58	NR
Regan 1996	Several States, USA	10385^	Cohort	23-26 weeks	Delivery < 37 weeks	11.4%	21.1%	5		1.04	0.91-1.20	NR
Feikin@ 2001	Aarhus and Odense, Denmark	2846	Cohort	24 weeks GA	Preterm Delivery < 37 weeks GA	3.1%	8%	5		0.97	0.47-1.98	NR
Mc Kenzie 1994	Dundee, UK	1971	Cohort	1. Booking	Preterm delivery <37 weeks	6.8%	4.3%	5		0.49	0.16-1.52	NR
Minkoff 1984	Brooklyn, USA	218	Cohort	13.8 +/- 3.6 weeks	Preterm labour Contractions < 37 weeks with changes in the cervix length	16%	9.9%	4		1.84	0.86-3.94	NR
Baker 1975	Houston, USA	183*	Cohort	Second trimester (20-28 weeks GA)	Premature Onset of Labour < 37 weeks	7.1%	14.8%	2		1.73	0.51-5.89	NR
Gerards 1982	Utrecht, The Netherlands	161	Cohort	Before GA 20 weeks, selection recultured week 28 and 34	Premature Delivery >28 weeks < 37 weeks	12%	13.9%	3		0.62	0.26-1.50	NR
Hastings 1986	London, UK	1059	Cohort	Booking 28 weeks 36 weeks	Prematurity <37 weeks	6.4 %	28%	3		1.01	0.60-1.68	NR
Chua 1995	Singapore	279	Cohort	1. < 12 weeks GA 2. 13-28 weeks 3. 29-32 weeks	Preterm labour <36 weeks	8.6%	16.3% 13.5% 14.7%	2		0.54#	0.13-2.22	NR
Moller 1984	Aalborg, Denmark	2745	Cohort	Between GA 12 and 38 weeks	Delivery < 37 weeks gestation	8.4%	2%	0		2.52	1.55-4.08	R
White 1984	Liverpool, UK	8083	Cohort	Antenatally	Premature <37 weeks	4.9%	1.7%	0		1.49	0.81-2.73	NR

Source	Primary Location	No. of Patients	Study Design	Gestational Age at time of culture	Definition Adverse Outcome	Prevalence adverse outcome	Prevalence GBS colonization	Validity Score	OR	RR	CI	Conclusion per Study
Hakansson 2008	Sweden	1507	Cross sectional	Time of Delivery	Gestational age at birth < 37 weeks	6.0%	25.4%	4		0.63	0.37-1.07	NR
Dawodu 1983	Nigeria	225	Cross sectional	Labour	Premature onset of labour <37 weeks	12.4%	19.5%	2		1.12	0.48-2.60	NR
Joshi 1987	Saskatoon, Canada	3078	Cross sectional	Time of Delivery	1. Preterm Delivery <37 weeks	9.6%	2.3%	1		2.59	1.69-3.98	R
Regan 1981	New York, USA	6706	Cross sectional	Time of Delivery	Preterm Delivery <32 weeks	1.8%	13.4%	1		4.11	2.88-5.87	R
Citernesi 1996	Toscane, Italia	4672	Cross sectional	Time of Delivery	Preterm Delivery <37 weeks	5.2%	6.6%	1		1.35	0.84-2.16	NR
Lamont 1986	London, UK	98	Case Control	Time of Delivery between GA 26 and 33 weeks	Preterm labour >26 weeks <33 weeks	ND	4%	3/6	3.48		0.18-66.92	NR
Martius 1988	Seattle, USA	212	Case Control	Between AD 20-36 weeks	Premature labour contractions < 37 weeks	ND	ND	3/6	1.41		0.73-2.73	NR
Feikin@ 2001	Aarhus and Odense, Denmark	384	Case Control@	24 weeks GA	Preterm Delivery < 37 weeks GA	3.1%	8%	2/6	2.11		1.0-4.46	NR
Persson 1986	Malmö,Sweden	366¢	Case Control	Time of Delivery	Preterm Delivery < 37 weeks	ND	22%	2/6	1.24		0.5-3.06	NR

- ND= not described , NR= no relation between GBS colonization and reported outcome, R=relation between GBS colonization and reported outcome
- * Baker 1974: Only patients with second trimester cultures were analyzed in this review.
- $ Mc Kenzie 1994: Only patients with midstream urine cultures at booking were analyzed in this review
- # Chua 1995: Results in different trimester cultures were analyzed as total group in relation with preterm labour
- ^ Regan 1996: Only patients with no effective antibiotics against GBS were analyzed in this review
- @ Feikin 2001: Article presents a case control study and a cohort study, both analysed separately in this review
- ¢ Persson 1986: In total 858 women were screened for GBS. Analysis was done in all GBS positive women (183) and in 183 non-colonized women matched for age

4. It was possible to formulate a fourfold table with well defined outcome numbers.

The bibliographies of all relevant articles were searched for additional references. All the retrieved articles were screened by the two researchers to ensure that the articles described original research and met the inclusion criteria mentioned above. In case of disagreement, the articles or abstracts were re-examined and discussed until consensus was achieved. Duplicate reporting from a single institution was excluded.

A validity score was calculated according to the criteria described by the Evidence-Based Medicine Working Group.(14) To determine the validity of selected studies, each study was graded on the basis of 7 criteria for prospective studies (range 0-11) or 4 criteria for case control studies (range 0-6). The following criteria of validity were used: adequate description of study population, well defined moment of antenatal cultures, use of selective broth medium and chosen culture-site(s), completeness of follow-up and/or clear description of dropouts and adjustment for prognostic factors.

Data extraction and statistical analysis

From each report, two researchers (AV, AS) extracted information about the study location and design, study population, number of patients, inclusion and exclusion criteria, study objectives, methods for GBS screening, timing of cultures, culture-site, completeness of follow-up, frequency of GBS colonization, and frequency of preterm delivery. A selection form based on the above criteria was constructed and filled in independently by both researchers. Both filled in a fourfold prognostic table based on the available data. In cases of disagreement, articles were re-examined and discussed until consensus was achieved.

We used Review Manager (Update Software, Oxford) to calculate relative risks and 95% confidence intervals, which were graphically displayed in Forest Plots.

RESULTS

Selection of articles

After screening more than 150 citations, 60 full-text articles were retrieved. Nineteen articles describing 20 studies were included in this review. Four of the studies were case control studies(15-18) and 16 were follow-up studies (15;19-33) (see Table 1). One of the 19 articles described both a case control study and a cohort study, which we analyzed separately.(15) Follow up studies were divided into 'cohort studies,' in which cultures were taken at a well defined moment in pregnancy and reported on pregnancy outcome (n=11)(15;19-28) and 'cross-sectional studies,' in which patients were only cultured at time of delivery, preterm or term (n= 5).(29-33) Case control studies matched patients with preterm delivery with patients with the same gestational age but not in labour. From three studies, only the results of well described subgroups were included in this review.(20;22;23)

Review articles and articles which did not represent original research were excluded.(34-45) Articles were also excluded if they did not deal with our research question or did not report outcomes according to our definition(4;6;46-60), if they reported patients received antibiotics at any time during pregnancy (5;61-65), if they overlapped with another publication included in our review(66;67), if the reported outcome numbers were inconsistent(68), or if the study population was unclear.(69)

Description of selected studies

The 20 studies included 45,888 patients living in ten different countries. Results of data-extraction are listed in Table 1. The overall prevalence of GBS colonization varied from 1.7%-28% (mean 12.2%, median 10.8%). In only nine studies GBS was cultured on a selective broth medium, which is reported to be an important factor for adequate detection of GBS. In twelve studies either vaginal or rectal or cervical cultures were taken, and in four studies vaginal cultures were combined with rectal cultures. In three other studies, urine specimens were cultured, and in one study (18) samples were taken from both urine, rectum and urethra, but the study did not specify which sample was positive in patients with preterm delivery. The reported prevalence of adverse outcome varied from 1.8%-16% (mean 7.6%, median 6.8%). However, the studies did not define adverse outcome consistently. Outcome measures included so-called preterm delivery (n=7), preterm labour (n=3), premature onset of labour (n=2), delivery < 37 weeks (n=3), preterm birth (n=1), premature delivery (n=1) prematurity (n=1), premature labour (n=1) and 'premature' (n=1). The studies also do not always give a clear definition of outcome; not all studies indicate whether deliveries were spontaneous or elective, what gestational age was defined as 'term,' and whether membranes were intact or not.

Validity

Table 2A shows total validity scores for the follow-up studies (maximum validity score: 11), and Table 2A shows them for the case control studies (maximum validity score: 6). All studies were found to have methodological limitations, with a validity score from 0-7.

Table 2A Characteristics and results of original studies according to the validity in prospective studies

Source	Study population	Gest.age	Methods		Follow-up		Adjustment	Validity
	Population defined (Demografic Data Described) *Yes=1* *No=0*	*Spread of antenatal cultures* *<6 wks=2* *>6 wks=0*	*Swabs; number of sites* *Urine=0* *R/V/C=1* *RV=2*	*Used selective broth medium* *Yes=1* *No=0* *ND*	*Complete Follow-up (100%)* *Yes=2* *No=0*	*Description of follow-up* *Yes=1* *No=0*	*Adjustment for Prognostic Factors* *Yes=2* *No=0*	***Score*** ***Min 0*** ***Max 11***
Baker 1975	1	0	1	ND	ND	0	0	**2**
Regan 1981	0	0	1	ND	NA	0	0	**1**
Dawodu 1983	0	0	1	1	NA	NA	0	**2**
Gerards 1982	0	0	2	1	0	0	0	**3**
Minkoff 1984	0	2	1	0	0	1	0	**4**
Moller 1984	0	0	0	0	0	0	0	**0**
White 1984	0	0	0	0	ND	0	0	**0**
Joshi 1987	0	0	1	0	NA	NA	0	**1**
Hastings 1986	0	0	2	1	0	0	0	**3**
McDonald 1992	1	2	1	1	ND	0	2	**7**
Mc Kenzie 1994	1	2	0	0	0	0	2	**5**
Chua 1995	0	0	1	0	0	1	0	**2**
Citernesi 1996	0	0	1	0	NA	NA	0	**1**
Regan 1996	0	2	1	1	0	1	0	**5**
Feikin 2001	1	0	1	0	0	1	2	**5**
Hakansson 2008	1	0	2	1	NA	NA	0	**4**

NA= Not applicable ND= Not described

Table 2B Characteristics and results of original studies according to the validity in Case Control studies

Source	Study population	Methods		Adjustment	Validity
	Population defined (Demografic Data Described)	*Swabs; number of sites*	*Used selective broth medium*	*Adjustment for Prognostic Factors*	***Score***
	Yes=1 No=0	*Urine=0 R/V/C=1 RV=2*	*Yes=1 No=0*	*Yes=2 No=0*	***Min 0 Max 6***
Lamont 1986	*0*	*2*	*1*	*0*	***3***
Martius 1988	*1*	*1*	*1*	*0*	***3***
Feikin 2001	*1*	*1*	*0*	*0*	***2***
Persson 1986	*0*	*1**	*1*	*0*	***2***

* Persson 1986: Rectal, urethral and urine specimens were cultured, from the text it is not clear which sample was positive in women with preterm delivery

Relation between GBS colonization and preterm delivery

Relative risks for preterm delivery in women colonized with GBS are shown graphically in Forest Plots. Figure 1 presents all cohort studies and Figure 2 all cross-sectional studies. Figure 3 shows all case control studies with odds ratios.

For cohort and cross-sectional studies, the combined estimates from a random effect meta-analysis were 1.06 (95%CI 0.95-1.19) and 1.75 (95%CI 1.43-2.14), respectively. The pooled odds ratio of case control studies for colonization given preterm delivery was 1.59 (95% CI 1.03-2.44).

Pooling cross-sectional studies and case control studies revealed odds of 1.76 (95%CI 1.44- 2.15) (not shown in table).

Interpretation of results

The search strategy yielded studies with different study designs and different study periods, from countries with different prevalence of GBS colonization and preterm delivery. Preterm delivery seems positively associated with GBS colonization at the time of delivery, but colonization during pregnancy does not seem to be associated with preterm delivery.

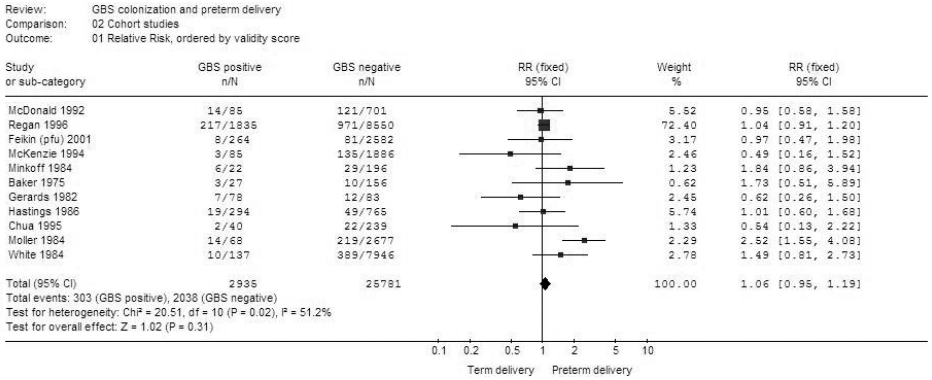

Figure 1 GBS colonization and preterm delivery in cohort studies

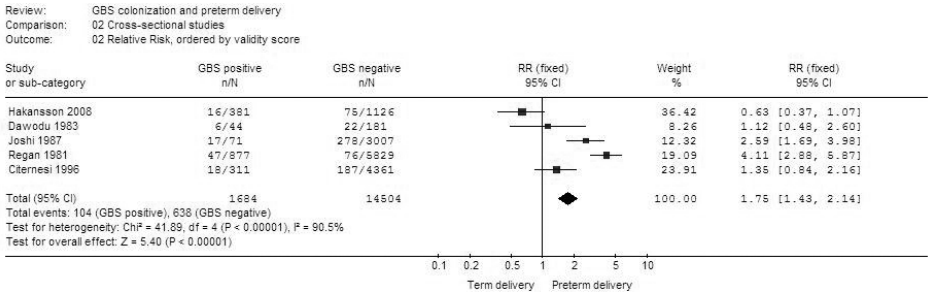

Figure 2 GBS colonization and preterm delivery in cross-sectional studies

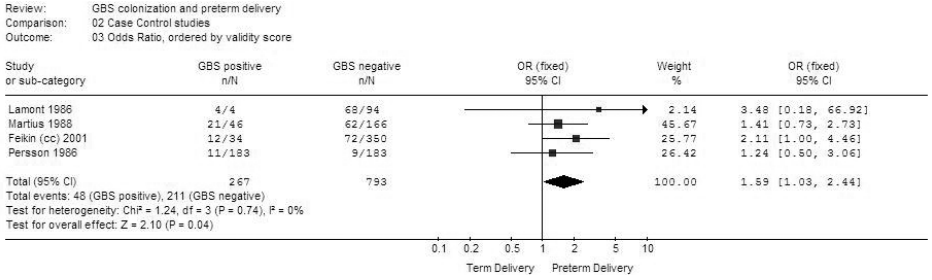

Figure 3 GBS colonization and preterm delivery in case control studies

DISCUSSION

To the best of our knowledge, this is the first systematic review on this topic containing studies from different parts of the world. This review analysed 19 publications covering 20 studies that dealt with the association between maternal GBS colonization and preterm delivery. In only one follow-up study was an association between GBS colonization during pregnancy and preterm delivery described.(27) Moller et al. found a higher risk of preterm delivery in women who had GBS in their urine, but their study had a low validity score. Cross-sectional studies during delivery and case control studies showed positive GBS cultures more frequently in patients with preterm delivery.

The results of the present study are in concordance with those of Romero et al.(39) They reviewed seven studies on genital colonization and three on asymptomatic bacteriuria with GBS in relation to preterm delivery. Genital colonization was examined in one cross-sectional study (tested at the time of admission), two case control studies, and four cohort studies. Romero et al. concluded that there was no evidence of an association between GBS colonization of the maternal genital tract and preterm delivery. The studies which examined asymptomatic GBS bacteriuria indicated that GBS bacteriuria in early pregnancy seems to be a risk factor for premature delivery. However, a major problem in literature is inconsistency of definition of asymptomatic bacteriuria.

Romero suggested that asymptomatic bacteriuria may be a marker of the most severe form of GBS genitourinary tract colonization. The incidence of GBS in quantities $>10^5$ colony forming units (cfu) /ml urine in pregnant women has been reported to be between 0.4 and 5%.(70;71) It has been shown that only 60% of bladder punctured pregnant women whose urine specimens contained $>10^5$ cfu/ml urine harboured GBS in the bladder.(18) Thus, a high quantity of GBS in urine is assumed to reflect heavy colonization of urethra, vulva and vagina. It remains unclear whether heavy GBS colonization by itself influences pregnancy outcome or whether the urinary tract infection is responsible.

Gibbs et al.(72) found no relationship between maternal genital tract GBS colonization and preterm delivery. However, in three of the four studies they described, there was a significant association between maternal genital group B streptococci colonization and premature rupture of membranes.

Recently, Colbourn and Gilbert(73) described the natural history of GBS-EOD in the UK. In a meta-analysis of eleven studies, three of which were case control studies, the pooled odds ratio for preterm delivery in mothers with GBS colonization during delivery was 1.53 (95% CI 1.14-2.05).

The vaginal microbial ecosystem in pregnant women has been shown to be an equilibrium of antagonistic and synergistic organisms.(74;75) Disruption of the normal vaginal flora, dominated by lactobacilli, may allow pathogenic bacteria to colonize and infect the

amniotic fluid, initiating preterm labour. It is generally accepted that amniotic fluid infection caused by microorganisms is associated with preterm delivery.

In a review of the association between maternal GBS colonization and preterm delivery, Kubota et al.(45) postulated that GBS was a marker of a lactobacilli-reduced vaginal environment, which would increase the risk of bacterial vaginosis. However, so far no empirical evidence of an association between GBS colonization and lactobacilli-reduced flora has been found.(76)

Intra-amniotic bacterial colonization or progression to infection depends on the effectiveness of the amniotic fluid antibacterial mechanisms and the number and pathogenicity of the colonizing bacteria. (77) It is conceivable that maternal genetic variation in response to these infections also plays a role in the risk of intra-uterine infection. Romero et al. speculated that it is not the presence of the organism itself, but the response of the host that is the critical step in this chain of events. When the host defence system is inadequate, bacterial growth may become excessive and lead to an infection ascending into the uterus. As part of its uncontrolled proliferation, the organism may penetrate the urinary tract and be detected as asymptomatic GBS bacteriuria.(39)

A review such as this one is hampered by the wide variation in the published reports, with different methods, incomplete information on follow-up, regional differences in GBS prevalence, adjustment for other risk factors, and different definitions of preterm delivery. The validity of the studies also varied widely, from 0-7 points out of 11, and the control studies in particular considered only very small groups of patients.

Approximately 6-36% of pregnant women carry GBS in the rectovaginal compartment. (9;10;78;79) The detected prevalence depends on the culture technique used, the locations tested, the culture media, the number of body sites cultured, and on the population studied. (80) Using selective broth media and sampling several culture sites (i.e., vagina and rectum) improves recovery of GBS up to 50%(81), but only seven of the studies did both. Few studies performed urine cultures to detect GBS.

Epidemiological studies on preterm delivery should adjust for known risk factors. Race, Social Economic Status (SES), age at beginning of pregnancy, duration of pregnancy, and multifetal gestation have been reported to influence GBS colonization. (9;81-84) Therefore, differences in reported prevalence of GBS can be a reflection of different risk profiles, which could also include different risk profiles for preterm delivery.

Risk factors for preterm delivery have been described, such as history of preterm delivery (RR 2,6: 95%-BI 2,0-3,4), ethnicity, age < 16 years (OR 1,7; 95%-BI 1,1-2,8)(85), cigarette smoking(86), use of cocaine(87), uterine malformation, cervical conization(88), DES exposition in utero, and multifetal gestation. Only three of the studies considered in this review described adjustments for prognostic risk factors for preterm delivery.

Finally, when we want to solve a problem, we should clearly distinguish cause and consequences. Although all the studies considered in this review described patients admitted to hospital because of contractions before 37 weeks of gestational age, most studies did not make it clear whether deliveries were spontaneous, whether membranes were intact or not, and whether preterm contractions led to preterm delivery or not. In addition, it is not known whether researchers were aware of the results of cultures. All of this might influence how follow-up studies are interpreted.

CONCLUSION

In this review we did not find a causal relationship between maternal GBS colonization and preterm delivery. However, in cases of preterm delivery, there is a significantly increased prevalence of GBS colonization. To understand the effect of GBS on pregnancy, large observational studies are needed, with clearly defined outcomes, and with prognostic risk factors for preterm delivery taken into account.

REFERENCE LIST

1. Nordenvall M, Sandstedt B. Chorioamnionitis in relation to gestational outcome in a Swedish population. Eur J Obstet Gynecol Reprod Biol 1990; 36(1-2.:59-67.
2. Hillier SL, Krohn MA, Kiviat NB, Watts DH, Eschenbach DA. Microbiologic causes and neonatal outcomes associated with chorioamnion infection. Am J Obstet Gynecol 1991; 165(4 Pt 1.:955-961.
3. Andrews WW, Goldenberg RL, Mercer B, Iams J, Meis P, Moawad A et al. The Preterm Prediction Study: association of second-trimester genitourinary chlamydia infection with subsequent spontaneous preterm birth. Am J Obstet Gynecol 2000; 183(3.:662-668.
4. Meis PJ, Goldenberg RL, Mercer B, Moawad A, Das A, McNellis D et al. The preterm prediction study: significance of vaginal infections. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1995; 173(4.:1231-1235.
5. McGregor JA, French JI, Richter R, Franco-Buff A, Johnson A, Hillier S et al. Antenatal microbiologic and maternal risk factors associated with prematurity. Am J Obstet Gynecol 1990; 163(5 Pt 1.:1465-1473.
6. Hillier SL, Nugent RP, Eschenbach DA, Krohn MA, Gibbs RS, Martin DH et al. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. The Vaginal Infections and Prematurity Study Group. N Engl J Med 1995; 333(26.:1737-1742.
7. Ferrieri P, Cleary PP, Seeds AE. Epidemiology of group-B streptococcal carriage in pregnant women and newborn infants. J Med Microbiol 1977; 10(1.:103-114.
8. Dillon HC, Jr., Gray E, Pass MA, Gray BM. Anorectal and vaginal carriage of group B streptococci during pregnancy. J Infect Dis 1982; 145(6.:794-799.
9. Valkenburg-van den Berg AW, Sprij AJ, Oostvogel PM, Mutsaers JA, Renes WB, Rosendaal FR et al. Prevalence of colonisation with group B Streptococci in pregnant women of a multi-ethnic population in The Netherlands. Eur J Obstet Gynecol Reprod Biol 2006; 124(2.:178-183.
10. Barcaite E, Bartusevicius A, Tameliene R, Kliucinskas M, Maleckiene L, Nadisauskiene R. Prevalence of maternal group B streptococcal colonisation in European countries. Acta Obstet Gynecol Scand 2008; 87(3.:260-271.
11. Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics 1999; 103(6.:e77.
12. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE. group. JAMA 2000; 283(15.:2008-2012.
13. Egger M, Smith G, Altman D. Systematic reviews in health care: meta-analysis in context. Sec ed. BMJ Publishing Group, 2001.
14. Laupacis A, Wells G, Richardson WS, Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. JAMA 1994; 272(3.:234-237.
15. Feikin DR, Thorsen P, Zywicki S, Arpi M, Westergaard JG, Schuchat A. Association between colonization with group B streptococci during pregnancy and preterm delivery among Danish women. Am J Obstet Gynecol 2001; 184(3.:427-433.
16. Lamont RF, Taylor-Robinson D, Newman M, Wigglesworth J, Elder MG. Spontaneous early preterm labour associated with abnormal genital bacterial colonization. Br J Obstet Gynaecol 1986; 93(8.:804-810.
17. Martius J, Krohn MA, Hillier SL, Stamm WE, Holmes KK, Eschenbach DA. Relationships of vaginal Lactobacillus species, cervical Chlamydia trachomatis, and bacterial vaginosis to preterm birth. Obstet Gynecol 1988; 71(1.:89-95.
18. Persson K, Bjerre B, Elfstrom L, Polberger S, Forsgren A. Group B streptococci at delivery: high count in urine increases risk for neonatal colonization. Scand J Infect Dis 1986; 18(6.:525-531.

19. Hoogkamp-Korstanje JA, Gerards LJ, Cats BP. Maternal carriage and neonatal acquisition of group B streptococci. J Infect Dis 1982; 145(6.:800-803.
20. Baker CJ, Barrett FF, Yow MD. The influence of advancing gestation on group B streptococcal colonization in pregnant women. Am J Obstet Gynecol 1975; 122(7.:820-823.
21. Minkoff H, Grunebaum AN, Schwarz RH, Feldman J, Cummings M, Crombleholme W et al. Risk factors for prematurity and premature rupture of membranes: a prospective study of the vaginal flora in pregnancy. Am J Obstet Gynecol 1984; 150(8.:965-972.
22. McKenzie H, Donnet ML, Howie PW, Patel NB, Benvie DT. Risk of preterm delivery in pregnant women with group B streptococcal urinary infections or urinary antibodies to group B streptococcal and E. coli antigens. Br J Obstet Gynaecol 1994; 101(2.:107-113.
23. Regan JA, Klebanoff MA, Nugent RP, Eschenbach DA, Blackwelder WC, Lou Y et al. Colonization with group B streptococci in pregnancy and adverse outcome. VIP Study Group. Am J Obstet Gynecol 1996; 174(4.:1354-1360.
24. McDonald HM, O'Loughlin JA, Jolley P, Vigneswaran R, McDonald PJ. Prenatal microbiological risk factors associated with preterm birth. Br J Obstet Gynaecol 1992; 99(3.:190-196.
25. Hastings MJ, Easmon CS, Neill J, Bloxham B, Rivers RP. Group B streptococcal colonisation and the outcome of pregnancy. J Infect 1986; 12(1.:23-29.
26. Chua S, Arulkumaran S, Chow C, Kumarasinghe G, Selamat N, Kuah BG et al. Genital Group B Streptococcus carriage in the antenatal period: its role in prom and preterm labour. Singapore Med J 1995; 36(4.:383-385.
27. Moller M, Thomsen AC, Borch K, Dinesen K, Zdravkovic M. Rupture of fetal membranes and premature delivery associated with group B streptococci in urine of pregnant women. Lancet 1984; 2(8394.:69-70.
28. White CP, Wilkins EG, Roberts C, Davidson DC. Premature delivery and group B streptococcal bacteriuria. Lancet 1984; 2(8402.:586.
29. Dawodu AH, Damole IO, Onile BA. Epidemiology of group B streptococcal carriage among pregnant women and their neonates: an African experience. Trop Geogr Med 1983; 35(2.:145-150.
30. Joshi AK, Chen CI, Turnell RW. Prevalence and significance of group B Streptococcus in a large obstetric population. CMAJ 1987; 137(3.:209-211.
31. Regan JA, Chao S, James LS. Premature rupture of membranes, preterm delivery, and group B streptococcal colonization of mothers. Am J Obstet Gynecol 1981; 141(2.:184-186.
32. Citernesi A, Formica G, Caruso S, Curiel P. [Vaginal colonization of Streptococcus B in pregnancy]. Minerva Ginecol 1996; 48(6.:227-233.
33. Hakansson S, Axemo P, Bremme K, Bryngelsson AL, Wallin MC, Ekstrom CM et al. Group B streptococcal carriage in Sweden: a national study on risk factors for mother and infant colonisation. Acta Obstet Gynecol Scand 2008; 87(1.:50-58.
34. Romero R, Espinoza J, Chaiworapongsa T, Kalache K. Infection and prematurity and the role of preventive strategies. Semin Neonatol 2002; 7(4.:259-274.
35. Gibbs RS. The relationship between infections and adverse pregnancy outcomes: an overview. Ann Periodontol 2001; 6(1.:153-163.
36. McGregor JA, French JI, Witkin S. Infection and prematurity: evidence-based approaches. Curr Opin Obstet Gynecol 1996; 8(6.:428-432.
37. Gibbs RS, Hall RT, Yow MD, McCracken GH, Jr., Nelson JD. Consensus: perinatal prophylaxis for group B streptococcal infection. Pediatr Infect Dis J 1992; 11(3.:179-183.
38. Martius J, Eschenbach DA. The role of bacterial vaginosis as a cause of amniotic fluid infection, chorioamnionitis and prematurity--a review. Arch Gynecol Obstet 1990; 247(1.:1-13.
39. Romero R, Mazor M, Oyarzun E, Sirtori M, Wu YK, Hobbins JC. Is there an association between colonization with group B Streptococcus and prematurity? J Reprod Med 1989; 34(10.:797-801.
40. Dodson MG, Fortunato SJ. Microorganisms and premature labor. J Reprod Med 1988; 33(1 Suppl.:87-96.

41. Starzyk KA, Salafia CM. A perinatal pathology view of preterm labor. Medscape Womens Health 2000; 5(6.:E1.
42. Mercer BM. Management of preterm premature rupture of the membranes. Clin Obstet Gynecol 1998; 41(4.:870-882.
43. Carey JC. Vaginal infections and prematurity. Birth 1987; 14(2.:91-93.
44. McGregor JA, French JI. Preterm Birth: The role of infection and inflammation. Medscape General Medicine 2. 1999.
45. Kubota T, Jinushi M, Sato T, Machida M. Colonization by group B streptococci and preterm birth. Contemporary Reviews in Obstetrics & Gynecology , 99-104. 1999.
46. McDonald HM, Chambers HM. Intrauterine infection and spontaneous midgestation abortion: is the spectrum of microorganisms similar to that in preterm labor? Infect Dis Obstet Gynecol 2000; 8(5-6.:220-227.
47. Begum S, Sagawa T, Fujimoto S. Screening for bacterial vaginosis and cervicitis aimed at preventing premature delivery. J Obstet Gynaecol Res 1997; 23(1.:103-110.
48. Dunlow SG, Duff P. Microbiology of the lower genital tract and amniotic fluid in asymptomatic preterm patients with intact membranes and moderate to advanced degrees of cervical effacement and dilation. Am J Perinatol 1990; 7(3.:235-238.
49. Newton ER, Clark M. Group B streptococcus and preterm rupture of membranes. Obstet Gynecol 1988; 71(2.:198-202.
50. Thomsen AC, Morup L, Hansen KB. Antibiotic elimination of group-B streptococci in urine in prevention of preterm labour. Lancet 1987; 1(8533.:591-593.
51. Bobitt JR, Damato JD, Sakakini J, Jr. Perinatal complications in group B streptococcal carriers: a longitudinal study of prenatal patients. Am J Obstet Gynecol 1985; 151(6.:711-717.
52. Holst E, Goffeng AR, Andersch B. Bacterial vaginosis and vaginal microorganisms in idiopathic premature labor and association with pregnancy outcome. J Clin Microbiol 1994; 32(1.:176-186.
53. Yim SF, Lyon DJ, Chung TK, Haines CJ. A prospective study of the microbiological environment of the genitourinary tract in Hong Kong Chinese women during pregnancy. Aust N Z J Obstet Gynaecol 1995; 35(2.:178-181.
54. Hood M, Janney A, Dameron G. Beta hemolytic streptococcus group B associated with problems of the perinatal period. Am J Obstet Gynecol 1961; 82:809-818.
55. Hay PE, Lamont RF, Taylor-Robinson D, Morgan DJ, Ison C, Pearson J. Abnormal bacterial colonisation of the genital tract and subsequent preterm delivery and late miscarriage. BMJ 1994; 308(6924.:295-298.
56. Goldenberg RL, Iams JD, Mercer BM, Meis PJ, Moawad AH, Copper RL et al. The preterm prediction study: the value of new vs standard risk factors in predicting early and all spontaneous preterm births. NICHD MFMU Network. Am J Public Health 1998; 88(2.:233-238.
57. Daugaard HO, Thomsen AC, Henriques U, Ostergaard A. Group B streptococci in the lower urogenital tract and late abortions. Am J Obstet Gynecol 1988; 158(1.:28-31.
58. Maxwell GL, Watson WJ. Preterm premature rupture of membranes: results of expectant management in patients with cervical cultures positive for group B streptococcus or Neisseria gonorrhoeae. Am J Obstet Gynecol 1992; 166(3.:945-949.
59. Murphy JF, Sykes G, Gardiner M, Hannan A, Verrier Jones ER. Group B streptococcal carrier rate in pregnant women and their newborn infants. J.Infect. 5, 165-169. 1982.
60. Goodman J, Berg R, Gribble R, Meier P, Fee SC, Mitchel P. Longitudinal Study of Group B Streptococcus Carriage in Pregnancy. Infect Dis Obstet Gynecol 1997;(5.:237-243.
61. Garland SM, Kelly N, Ugoni AM. Is antenatal group B streptococcal carriage a predictor of adverse obstetric outcome? Infect Dis Obstet Gynecol 2000; 8(3-4.:138-142.
62. Kubota T. Relationship between maternal group B streptococcal colonization and pregnancy outcome. Obstet Gynecol 1998; 92(6.:926-930.

63. Klebanoff MA, Regan JA, Rao AV, Nugent RP, Blackwelder WC, Eschenbach DA et al. Outcome of the Vaginal Infections and Prematurity Study: results of a clinical trial of erythromycin among pregnant women colonized with group B streptococci. Am J Obstet Gynecol 1995; 172(5.:1540-1545.
64. Alger LS, Lovchik JC, Hebel JR, Blackmon LR, Crenshaw MC. The association of Chlamydia trachomatis, Neisseria gonorrhoeae, and group B streptococci with preterm rupture of the membranes and pregnancy outcome. Am J Obstet Gynecol 1988; 159(2.:397-404.
65. Beltran MJ, Avila-Vergara MA, Vadillo-Ortega F, Hernandez-Guerrero C, Peraza-Garay F, Olivares-Morales S. [Cervicovaginal infection as a risk factor for premature labor]. Ginecol Obstet Mex 2002; 70:203-209.
66. McDonald H, Vigneswaran R, O'Loughlin JA. Group B streptococcal colonization and preterm labour. Aust N Z J Obstet Gynaecol 1989; 29(3 Pt 2.:291-293.
67. McDonald HM, O'Loughlin JA, Jolley P, Vigneswaran R, McDonald PJ. Vaginal infection and preterm labour. Br J Obstet Gynaecol 1991; 98(5.:427-435.
68. Hammoud MS, Thalib L, Maiyegun SO. The epidemiology of group B streptococcal colonization among obstetrical and newborn populations in Kuwait. Int J Gynaecol Obstet 2002; 76(3.:315-316.
69. Matorras R, Garcia PA, Omenaca F, Usandizaga JA, Nieto A, Herruzo R. Group B streptococcus and premature rupture of membranes and preterm delivery. Gynecol Obstet Invest 1989; 27(1.:14-18.
70. Mead PJ, Harris RE. The incidence of group B beta hemolytic streptococcus in antepartum urinary tract infections. Obstet Gynecol 1978; 51(4.:412-414.
71. McFadyen IR, Eykyn SJ, Gardner NH, Vanier TM, Bennett AE, Mayo ME et al. Bacteriuria in pregnancy. J Obstet Gynaecol Br Commonw 1973; 80(5.:385-405.
72. Gibbs RS, Romero R, Hillier SL, Eschenbach DA, Sweet RL. A review of premature birth and subclinical infection. Am J Obstet Gynecol 1992; 166(5.:1515-1528.
73. Colbourn T, Gilbert R. An overview of the natural history of early onset group B streptococcal disease in the UK. Early Hum Dev 2007; 83(3.:149-156.
74. Thorsen P, Jensen IP, Jeune B, Ebbesen N, Arpi M, Bremmelgaard A et al. Few microorganisms associated with bacterial vaginosis may constitute the pathologic core: a population-based microbiologic study among 3596 pregnant women. Am J Obstet Gynecol 1998; 178(3.:580-587.
75. Hillier SL. Diagnostic microbiology of bacterial vaginosis. Am J Obstet Gynecol 1993; 169(2 Pt 2.:455-459.
76. Genc MR, Gerber S, Nesin M, Witkin SS. Polymorphism in the interleukin-1 gene complex and spontaneous preterm delivery. Am J Obstet Gynecol 2002; 187(1.:157-163.
77. Wahbeh CJ, Hill GB, Eden RD, Gall SA. Intra-amniotic bacterial colonization in premature labor. Am J Obstet Gynecol 1984; 148(6.:739-743.
78. Ferrieri P, Cleary PP, Seeds AE. Epidemiology of group-B streptococcal carriage in pregnant women and newborn infants. J Med Microbiol 1977; 10(1.:103-114.
79. Dillon HC, Jr., Gray E, Pass MA, Gray BM. Anorectal and vaginal carriage of group B streptococci during pregnancy. J Infect Dis 1982; 145(6.:794-799.
80. Regan JA, Klebanoff MA, Nugent RP. The epidemiology of group B streptococcal colonization in pregnancy. Vaginal Infections and Prematurity Study Group. Obstet Gynecol 1991; 77(4.:604-610.
81. Schuchat A. Epidemiology of group B streptococcal disease in the United States: shifting paradigms. Clin Microbiol Rev 1998; 11(3.:497-513.
82. Regan JA, Klebanoff MA, Nugent RP. The epidemiology of group B streptococcal colonization in pregnancy. Vaginal Infections and Prematurity Study Group. Obstet Gynecol 1991; 77(4.:604-610.

83. Anthony BF, Okada DM, Hobel CJ. Epidemiology of group B Streptococcus: longitudinal observations during pregnancy. J Infect Dis 1978; 137(5.:524-530.
84. Hickman ME, Rench MA, Ferrieri P, Baker CJ. Changing epidemiology of group B streptococcal colonization. Pediatrics 1999; 104(2 Pt 1.:203-209.
85. Hediger ML, Scholl TO, Schall JI, Krueger PM. Young maternal age and preterm labor. Ann Epidemiol 1997; 7(6.:400-406.
86. Kyrklund-Blomberg NB, Granath F, Cnattingius S. Maternal smoking and causes of very preterm birth. Acta Obstet Gynecol Scand 2005; 84(6.:572-577.
87. Kliegman RM, Madura D, Kiwi R, Eisenberg I, Yamashita T. Relation of maternal cocaine use to the risks of prematurity and low birth weight. J Pediatr 1994; 124(5 Pt 1.:751-756.
88. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet 2006; 367(9509.:489-498.

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

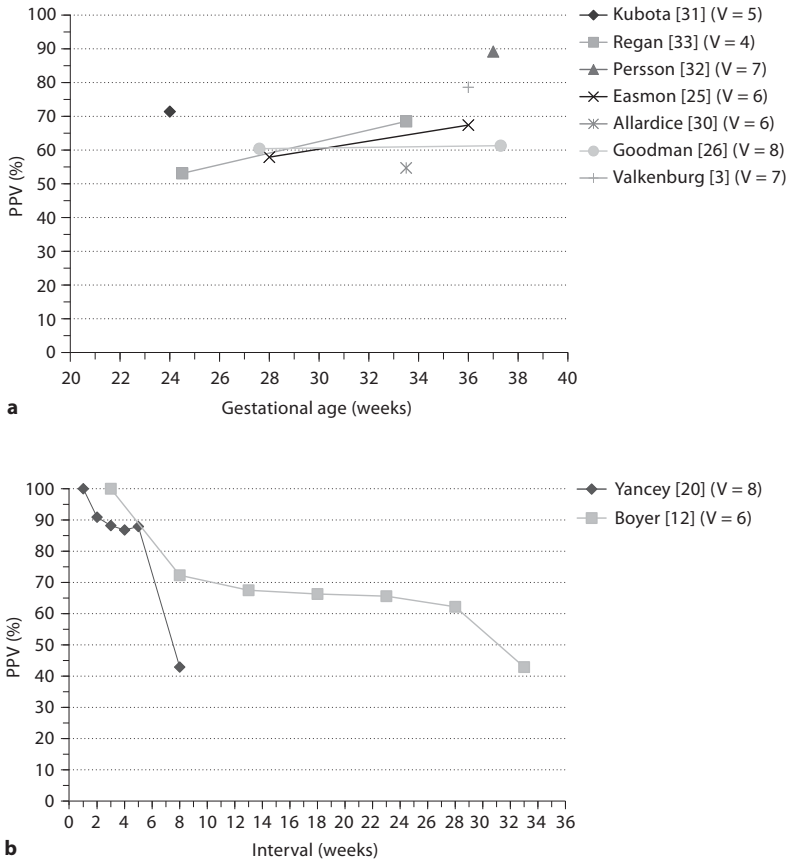

Figure 1: Positive Predictive Values in prospective (a) and retrospective (b) studies.V= validity score

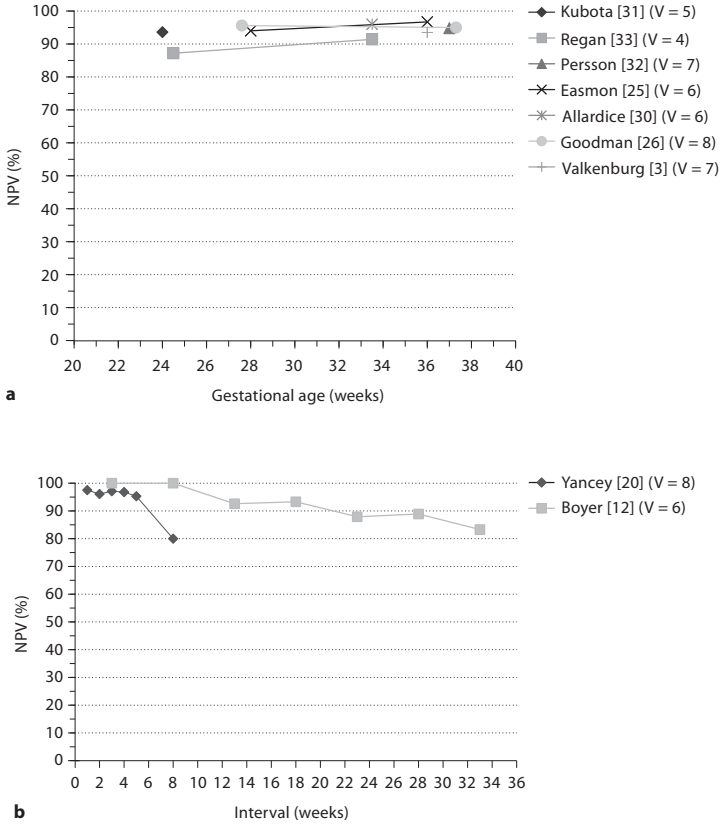

Figure 2 Negative Predictive Values in prospective (a) and retrospective (b) studies. V= validity score

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.

REFERENCE LIST

1. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928-2003. Pediatrics 2005; 116(3.:595-602.
2. Schuchat A. Group B streptococcal disease: from trials and tribulations to triumph and trepidation. Clin Infect Dis 2001; 33(6.:751-756.
3. Valkenburg-van den Berg AW, Sprij AJ, Oostvogel PM, Mutsaers JA, Renes WB, Rosendaal FR, Joep DP. Prevalence of colonisation with group B Streptococci in pregnant women of a multi-ethnic population in The Netherlands. Eur J Obstet Gynecol Reprod Biol 2006; 124(2.:178-183.
4. Ferrieri P, Cleary PP, Seeds AE. Epidemiology of group-B streptococcal carriage in pregnant women and newborn infants. J Med Microbiol 1977; 10(1.:103-114.
5. Dillon HC, Jr., Gray E, Pass MA, Gray BM. Anorectal and vaginal carriage of group B streptococci during pregnancy. J Infect Dis 1982; 145(6.:794-799.
6. Bergseng H, Bevanger L, Rygg M, Bergh K. Real-time PCR targeting the sip gene for detection of group B Streptococcus colonization in pregnant women at delivery. J Med Microbiol 2007; 56(Pt 2.:223-228.
7. Gavino M, Wang E. A comparison of a new rapid real-time polymerase chain reaction system to traditional culture in determining group B streptococcus colonization. Am J Obstet Gynecol 2007; 197(4.:388-4.
8. Barcaite E, Bartusevicius A, Tameliene R, Kliucinskas M, Maleckiene L, Nadisauskiene R. Prevalence of maternal group B streptococcal colonisation in European countries. Acta Obstet Gynecol Scand 2008; 87(3.:260-271.
9. Regan JA, Klebanoff MA, Nugent RP. The epidemiology of group B streptococcal colonization in pregnancy. Vaginal Infections and Prematurity Study Group. Obstet Gynecol 1991; 77(4.:604-610.
10. Easmon CS, Tanna A, Munday P, Dawson S. Group B streptococci--gastrointestinal organisms? J Clin Pathol 1981; 34(8.:921-923.
11. Hansen SM, Uldbjerg N, Kilian M, Sorensen UB. Dynamics of Streptococcus agalactiae colonization in women during and after pregnancy and in their infants. J Clin Microbiol 2004; 42(1.:83-89.
12. Boyer KM, Gadzala CA, Kelly PD, Burd LI, Gotoff SP. Selective intrapartum chemoprophylaxis of neonatal group B streptococcal early-onset disease. II. Predictive value of prenatal cultures. J Infect Dis 1983; 148(5.:802-809.
13. Hickman ME, Rench MA, Ferrieri P, Baker CJ. Changing epidemiology of group B streptococcal colonization. Pediatrics 1999; 104(2 Pt 1.:203-209.
14. Lim DV, Morales WJ, Walsh AF, Kazanis D. Reduction of morbidity and mortality rates for neonatal group B streptococcal disease through early diagnosis and chemoprophylaxis. J Clin Microbiol 1986; 23(3.:489-492.
15. Yow MD, Mason EO, Leeds LJ, Thompson PK, Clark DJ, Gardner SE. Ampicillin prevents intrapartum transmission of group B streptococcus. JAMA 1979; 241(12.:1245-1247.
16. Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. N Engl J Med 1986; 314(26.:1665-1669.
17. Edwards RK, Clark P, Duff P. Intrapartum antibiotic prophylaxis 2: positive predictive value of antenatal group B streptococci cultures and antibiotic susceptibility of clinical isolates. Obstet Gynecol 2002; 100(3.:540-544.
18. Illuzzi JL, Bracken MB. Duration of intrapartum prophylaxis for neonatal group B streptococcal disease: a systematic review. Obstet Gynecol 2006; 108(5.:1254-1265.
19. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. MMWR Recomm Rep 2002; 51(RR-11.:1-22.
20. Yancey MK, Schuchat A, Brown LK, Ventura VL, Markenson GR. The accuracy of late antenatal screening cultures in predicting genital group B streptococcal colonization at delivery. Obstet Gynecol 1996; 88(5.:811-815.

21. Schrag SJ, Zell ER, Lynfield R, Roome A, Arnold KE, Craig AS, Harrison LH, Reingold A, Stefonek K, Smith G, Gamble M, Schuchat A. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. N Engl J Med 2002; 347(4.:233-239.
22. Hyde TB, Hilger TM, Reingold A, Farley MM, O'Brien KL, Schuchat A. Trends in incidence and antimicrobial resistance of early-onset sepsis: population-based surveillance in San Francisco and Atlanta. Pediatrics 2002; 110(4.:690-695.
23. Gilbert R. Prenatal screening for group B streptococcal infection: gaps in the evidence. Int J Epidemiol 2004; 33(1.:2-8.
24. Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. Pediatrics 2005; 115(5.:1240-1246.
25. Easmon CS, Hastings MJ, Neill J, Bloxham B, Rivers RP. Is group B streptococcal screening during pregnancy justified? Br J Obstet Gynaecol 1985; 92(3.:197-201.
26. Goodman J, Berg R, Gribble R, Meier P, Fee SC, Mitchel P. Longitudinal Study of Group B Streptococcus Carriage in Pregnancy. Infect Dis Obstet Gynecol 1997;(5.:237-243.
27. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE. group. JAMA 2000; 283(15.:2008-2012.
28. Egger M, Smith G, Altman D. Systematic reviews in health care: meta-analysis in context. Sec ed. BMJ Publishing Group, 2001.
29. Laupacis A, Wells G, Richardson WS, Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. JAMA 1994; 272(3.:234-237.
30. Allardice JG, Baskett TF, Seshia MM, Bowman N, Malazdrewicz R. Perinatal group B streptococcal colonization and infection. Am J Obstet Gynecol 1982; 142(6 Pt 1.:617-620.
31. Kubota T. Relationship between maternal group B streptococcal colonization and pregnancy outcome. Obstet Gynecol 1998; 92(6.:926-930.
32. Persson K, Bjerre B, Elfstrom L, Forsgren A. Longitudinal study of group B streptococcal carriage during late pregnancy. Scand J Infect Dis 1987; 19(3.:325-329.
33. Regan JA, Klebanoff MA, Nugent RP, Eschenbach DA, Blackwelder WC, Lou Y, Gibbs RS, Rettig PJ, Martin DH, Edelman R. Colonization with group B streptococci in pregnancy and adverse outcome. VIP Study Group. Am J Obstet Gynecol 1996; 174(4.:1354-1360.
34. Garland SM, Fliegner JR. Group B streptococcus (GBS. and neonatal infections: the case for intrapartum chemoprophylaxis. Aust N Z J Obstet Gynaecol 1991; 31(2.:119-122.
35. Gordon JS, Sbarra AJ. Incidence, technique of isolation, and treatment of group B streptococci in obstetric patients. Am J Obstet Gynecol 1976; 126(8.:1023-1026.
36. Reisner DP, Haas MJ, Zingheim RW, Williams MA, Luthy DA. Performance of a group B streptococcal prophylaxis protocol combining high-risk treatment and low-risk screening. Am J Obstet Gynecol 2000; 182(6.:1335-1343.
37. Schuchat A. Epidemiology of group B streptococcal disease in the United States: shifting paradigms. Clin Microbiol Rev 1998; 11(3.:497-513.
38. Yancey MK, Duff P. Group B streptococcal infections during pregnancy. Curr Opin Obstet Gynecol 1993; 5(4.:508-512.
39. Anthony BF. Carriage of group B streptococci during pregnancy: a puzzler. J Infect Dis 1982; 145(6.:789-793.
40. Easmon CS, Hastings MJ. GBS colonisation in mothers and babies. Antibiot Chemother 1985; 35:28-39.
41. Davis GH, MacIvor J, Freeman M. Changes in the vaginal and rectal carriage of group B streptococci during pregnancy. Aust N Z J Obstet Gynaecol 1980; 20(1.:32-34.

42. El Kersh TA, Al Nuaim LA, Kharfy TA, Al Shammary FJ, Al Saleh SS, Al Zamel FA. Detection of genital colonization of group B streptococci during late pregnancy. Saudi Med J 2002; 23(1.:56-61.
43. Jaureguy F, Carton M, Teboul J, Butel MJ, Panel P, Ghnassia JC, Doucet-Populaire F. [Risk factors and screening strategy for group B streptococcal colonization in pregnant women: results of a prospective study]. J Gynecol Obstet Biol Reprod (Paris. 2003; 32(2.:132-138.
44. Daimaru-Enoki LC, Morgan M, Nichols WS, Silverman NS. First-trimester group B Streptococcus colonization of the cervix: a risk factor for maternal colonization at term? J Reprod Med 2005; 50(7.:496-500.
45. Anthony BF, Okada DM, Hobel CJ. Epidemiology of group B Streptococcus: longitudinal observations during pregnancy. J Infect Dis 1978; 137(5.:524-530.
46. Hoogkamp-Korstanje JA, Gerards LJ, Cats BP. Maternal carriage and neonatal acquisition of group B streptococci. J Infect Dis 1982; 145(6.:800-803.
47. Anthony BF, Eisenstadt R, Carter J, Kim KS, Hobel CJ. Genital and intestinal carriage of group B streptococci during pregnancy. J Infect Dis 1981; 143(6.:761-766.
48. Bobitt JR, Damato JD, Sakakini J, Jr. Perinatal complications in group B streptococcal carriers: a longitudinal study of prenatal patients. Am J Obstet Gynecol 1985; 151(6.:711-717.
49. Iams JD, O'Shaughnessy R. Antepartum versus intrapartum selective screening for maternal group B streptococcal colonization. Am J Obstet Gynecol 1982; 143(2.:153-156.
50. Schauf V, Hlaing V. Group B streptococcal colonization in pregnancy. Obstet Gynecol 1976; 47(6.:719-721.
51. Yow MD, Leeds LJ, Thompson PK, Mason EO, Jr., Clark DJ, Beachler CW. The natural history of group B streptococcal colonization in the pregnant woman and her offspring. I. Colonization studies. Am J Obstet Gynecol 1980; 137(1.:34-38.
52. Lewin EB, Amstey MS. Natural history of group B streptococcus colonization and its therapy during pregnancy. Am J Obstet Gynecol 1981; 139(5.:512-515.
53. Badri MS, Zawaneh S, Cruz AC, Mantilla G, Baer H, Spellacy WN, Ayoub EM. Rectal colonization with group B streptococcus: relation to vaginal colonization of pregnant women. J Infect Dis 1977; 135(2.:308-312.
54. Baker CJ, Clark DJ, Barrett FF. Selective broth medium for isolation of group B streptococci. Appl Microbiol 1973; 26(6.:884-885.
55. Bergeron MG, Ke D, Menard C, Picard FJ, Gagnon M, Bernier M, Ouellette M, Roy PH, Marcoux S, Fraser WD. Rapid detection of group B streptococci in pregnant women at delivery. N Engl J Med 2000; 343(3.:175-179.
56. Straka M, Dela CW, Blackmon C, Johnson O, Stassen S, Streitman D, Golden S, Stamilio D. Rapid detection of group B streptococcus and Escherichia coli in amniotic fluid using real-time fluorescent PCR. Infect Dis Obstet Gynecol 2004; 12(3-4.:109-114.
57. Simoes JA, Aroutcheva AA, Heimler I, Faro S. Antibiotic resistance patterns of group B streptococcal clinical isolates. Infect Dis Obstet Gynecol 2004; 12(1.:1-8.
58. Trijbels-Smeulders M, Adriaanse AH, Gerards LJ, Kimpen JL. Strategy to prevent neonatal early-onset group B streptococcal (GBS. disease in the Netherlands. Reviews in Medical Microbiology 2003; 14:35-39.
59. Towers CV, Carr MH, Padilla G, Asrat T. Potential consequences of widespread antepartal use of ampicillin. Am J Obstet Gynecol 1998; 179(4.:879-883.
60. Joseph TA, Pyati SP, Jacobs N. Neonatal early-onset Escherichia coli disease. The effect of intrapartum ampicillin. Arch Pediatr Adolesc Med 1998; 152(1.:35-40.
61. Terrone DA, Rinehart BK, Einstein MH, Britt LB, Martin JN, Jr., Perry KG. Neonatal sepsis and death caused by resistant Escherichia coli: possible consequences of extended maternal ampicillin administration. Am J Obstet Gynecol 1999; 180(6 Pt 1.:1345-1348.
62. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, Lemons JA, Donovan EF, Stark AR, Tyson JE, Oh W, Bauer CR, Korones SB, Shankaran S, Laptook AR, Stevenson DK, Papile

LA, Poole WK. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. N Engl J Med 2002; 347(4.:240-247.
63. Erffmeyer JE. Adverse reactions to penicillin. Part I. Ann Allergy 1981; 47(4.:288-293.
64. Erffmeyer JE. Adverse reactions to penicillin. Part II. Ann Allergy 1981; 47(4.:294-300.
65. Idsoe O, Guthe T, Willcox RR, de Weck AL. Nature and extent of penicillin side-reactions, with particular reference to fatalities from anaphylactic shock. Bull World Health Organ 1968; 38(2.:159-188.
66. Surtees SJ, Stockton MG, Gietzen TW. Allergy to penicillin: fable or fact? BMJ 1991; 302(6784.:1051-1052.
67. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn: Guidelines for prevention of group B streptococcal (GBS. infection by chemoprophylaxis. Pediatrics 1992; 90(5.:775-778.
68. Gibbs RS, Schrag S, Schuchat A. Perinatal infections due to group B streptococci. Obstet Gynecol 2004; 104(5 Pt 1.:1062-1076.

Chapter 7

Opportunities for improvement of prevention of GBS-EOD

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Submitted

ABSTRACT

Despite considerable efforts and economic resources spent on prevention of early-onset group B streptococcal disease (GBS-EOD), it is still an important cause of neonatal infection and early neonatal mortality within the first seven days of life.

In this article, we identify potential areas for improvement of prevention of GBS-EOD. Opportunities for improvement can be found in development and implementation of local prevention protocols as well as in optimal timing of screening, the correct choice of sampling sites, the best conditions of transport of swabs and culture procedures and the best choice of antibiotics. Knowledge about the route to disease and the possible preventive measures as well as training in recognizing GBS-EOD is important. Caregivers should be aware that there are a lot of little steps in the chain of prevention where improvement of prevention of GBS-EOD can be made.

INTRODUCTION

Invasive Group B streptococcal disease emerged in the 1970's as a leading infectious cause of perinatal morbidity and mortality.(1) Vertical transmission of GBS from mother to child occurs during labor. The gastrointestinal tract of the mother has been recognized as the source of vaginal GBS colonization. The frequency of GBS colonization ranges from 10% to 35% in women of reproductive age.(2;3) Studies on vertical GBS transmission in colonized mothers during labor report incidences of colonization of the infant between 16 and 69%.(4-9) Early-onset group B streptococcal disease (GBS-EOD) occurs in approximately 1% of newborns who are colonized with GBS and typically presents with sepsis, pneumonia or meningitis.(10) Risk factors for acquiring GBS-EOD are prolonged rupture of membranes, preterm labor, intrapartum fever, GBS bacteriuria during pregnancy or a previous child with GBS.(11)

Because infants with early onset group B streptococcal disease (GBS-EOD) are infected during labor, the opportunity for timely prevention is limited. Prevention of disease rather than treatment is the focus of attempts to reduce neonatal GBS infections and the burden of the disease.

Intrapartum antibiotic prophylaxis (IAP) given to women at risk of transmitting GBS to their baby can prevent GBS-EOD.(9;12) 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 labor with one of the established risk factors for GBS-EOD.

Today, after implementation of prevention strategies, the overall incidence of GBS-EOD in many countries has declined progressively.(2-5) However, current strategies for prevention of GBS-EOD are still subject of controversy. Despite considerable efforts and economic resources spent on prevention of GBS-EOD, it is still an important cause of neonatal infection and mortality within the first seven days of life.(1-3;6-14)

Factors contributing to ongoing disease

Nowadays, as shown in several recent studies, in countries where culture based screening is performed, GBS-EOD mainly occurs in term infants born to mothers screened negative for GBS colonization and in preterm infants born to mothers who were not screened and did not receive IAP.(3;14;15) Missed opportunities for prevention of GBS-EOD in case of a screening based strategy were identified in a recent study by Stoll et al(13) and revealed failure to screen all women during pregnancy, failure to provide antibiotics to all colonized women or to those who delivered preterm with unknown colonization status, and false negative GBS screens among some women who deliver infants with GBS infection.

Negative GBS screens among women who deliver infants with GBS-EOD are particularly troubling and may be attributable to insufficient sampling, delay in processing, suboptimal laboratory techniques, recent antibiotic use or colonization after screening was performed,

ie wrong timing of antenatal cultures. This, together with several other aspects of antenatal and perinatal clinical practice, including lack of guidelines, lack of communication, improper implementation of IAP and microbiological factors including antibiotic resistance, may all contribute to ongoing disease.

Opportunities for improvement of prevention of GBS-EOD

With regard to the remaining burden of disease it is important to identify potential areas for improvement in the total process from antenatal care to discharge of a healthy women with a healthy baby.

Prevention Strategy

Among all opportunities for improvement, one of the most important factors in decreasing GBS-EOD is that there is at least a nationwide guideline for preventing GBS-EOD, ideally translated into protocols for each region or each hospital.

The best prevention strategy maximizes treatment in women who need it, and refrains from treatment in women who do not need it. Wilson and Jugner defined in 1968 criteria for appraising validity of a screening programme, which still upheld today as classics; the gold standard of screening. (Table 1)(14)

However, several adaptations have been made to the classic criteria of Wilson and Jungner, and several new criteria have also emerged. Emerging criteria reflect broader trends that have shaped both Western medicine and society more generally over the past generation (e.g. increased consumerism, the shift away from paternalism towards informed choice, a focus on evidence-based health care, and the rise of managed care models that emphasize cost-effectiveness, quality assurance, and accountability of decision-makers.(15) All these

Table 1 The Wilson-Jungner criteria for appraising the validity of a screening program.(14)

1.	The condition being screened for should be an important health problem
2.	The natural history of the condition should be well understood
3.	There should be a detectable early stage
4.	Treatment at an early stage should be of more benefit than at a later stage
5.	A suitable test should be devised for the early stage
6.	The test should be acceptable
7.	Intervals for repeating the test should be determined
8.	Adequate health service provision should be made for the extra clinical workload resulting from screening
9.	The risks, both physical and psychological, should be less than the benefits
10.	The costs should be balanced against the benefits

criteria should be taken into account when a nationwide guideline or local protocol is established.

Management strategy to prevent GBS-EOD depends on local factors, including the percentage of GBS carriers and the percentage of pregnant women with perinatal risk factors within the population, the organization of perinatal care and the availability of laboratory facilities. The choice for a prevention strategy is based on rationality, cost-effectiveness, current knowledge and implementation and should be in line with criteria for screening.

In this article, we will not particularly describe pros and cons of different prevention strategies of GBS-EOD, but focus on identifying GBS carriage, different aspects of IAP and identifying GBS-EOD in newborns.

Improvement of prenatal screening

Accuracy of GBS prenatal screening can be improved. The aim of GBS screening is to predict vaginal GBS colonization at time of delivery. Methods that maximize the likelihood of GBS recovery are required, and specific culture media are needed. Critical factors that influence the accuracy of detecting GBS maternal colonization include anatomic sites of samplng the GBS bacteria, timing sampling in pregnancy, transport conditions of swabs and culture procedures. In addition, failure to culture GBS may be caused by maternal factors, such as use of oral antibiotics before specimen collection.

Sampling sites

The recommended method of collection of GBS is based on a 1977 study in which was shown that the gastrointestinal tract was the primary site of GBS colonization. In 17.9% of rectal cultures from pregnant women GBS was found, compared to 10.2% of vaginal cultures.(16) Results from later studies showed that swabs taken from both the anorectum and the vaginal introitus increase the likelihood of GBS isolation by 5-27% over vaginal culture alone.(19-21) In recent cohort studies similar detection rates were found when the vaginal-rectal collection method was compared with the vaginal-perianal collection method.(22-24) Patients indicated less pain and discomfort with the vaginal-perianal collection method. Therefore, vaginal-perianal cultures may be reasonable, patient-preferred alternatives for the recommended vaginal-rectal cultures for detection of GBS during pregnancy.(17)

Transport

For shipment from outpatient clinics to a microbiology laboratory it is important to know how long Group B streptococci in swabs will survive at room temperatures.

The CDC guidelines state specifically that the viability of GBS can be maintained for up to 4 days in appropriate transport media, i.e. Amies transport medium.(3) There are few data, which support this statement. One study showed that there will be a loss of positive culture

results if the GBS colony density is low or if the room ambient temperature is relatively high (> 30^0C).(18) Even when appropriate transport media are used, the sensitivity of culture is best when the specimen is stored at 4 ^{0}C before culture and processed within 24 hours of collection.(19) Further research is needed to know more about best transport and storage conditions.

Culture Procedures

The use of selective broth media (i.e. broths containing antimicrobial agents to inhibit competing organisms) is essential. In these media, the yield of screening cultures increases by as much as 50%.(28;29) Appropriate selective broth media, either SBM broth or Lim broth, are commercially available. Of course, it is important that the person who sends the swab to the laboratory clearly indicates that a GBS screening is requested, so that the appropriate media are used.

Timing

In countries were a screening regimen is followed, GBS-EOD mainly occurs in term infants born to mothers screened negative for GBS colonization and in preterm infants born to mothers who were not screened.(20-22) As GBS carriage is highly variable, antenatal GBS cultures are not always good predictors of maternal GBS carriage during delivery. Whether these negative cultures were false negative or the mothers acquired GBS in the interval between the screening culture and the time of delivery is unknown. Negative GBS screens may provide a false sense of reassurance both to the patient and her caregivers. In addition, women with GBS may not be colonized at the time of labor and thus receive IAP unnecessarily.

After a systematic review we confirmed recommendations to screen all pregnant women for colonization of GBS at 35-37 weeks gestation. However, one should be aware of the limitations of screening. Positive predictive values for antenatal GBS-cultures at gestation of 35-37 weeks ranged from 43-100% (mean 69%) and negative predictive values from 80-100% (mean 94%). GBS-cultures collected in late pregnancy correspond with high positive predictive values for colonization during delivery. The negative predictive value is high and relatively constant with regard to gestational age, but still 6% of GBS carriers during delivery remains undetected.(23)

Several studies have confirmed the benefit of using a reliable, highly sensitive, easy to perform, rapid test. To allow a timely and targeted IAP to GBS-positive women screened during labor, turnaround time of such tests should be short. These tests should be available 24 hours a day, 7 days a week. An accurate rapid test for GBS colonization proved difficult to develop. Despite the development of antigenic and hybridization-based tests in the last

two decades, a rapid and accurate culture method for GBS colonization is still unavailable. Although these tests have good specificities, they have disappointing performance with low sensitivities, which only increase with heavy colonization.

Communication and Implementation

In a recent prospective surveillance study from the USA all cases of GBS-EOD during 4 years in a cohort of 400 000 live births were reported. Despite CDC recommendations for universal antenatal screening for GBS, only 58% of mothers who delivered infants with GBS-EOD were screened. (in 63% of term deliveries and in 44% of preterm deliveries) Only 76% of mothers with GBS bacteriuria, 76% with a positive GBS screen and 66% with unknown GBS colonization status and a risk factor (gestation < 37 weeks, ROM more than 18 hours before delivery, maternal temperature > 38.0^0C) received intrapartum antibiotics.(13)

Guidelines are adressed to obstetric and neonatal-care practitioners, laboratories and labor-and delivery facilities. For ideal implementation of guidelines, good collaboration and communication is extremly important. Each hospital should have a protocol for prevention of GBS-EOD which is known to all professionals involved in the care of pregnant women. This protocol should document the way of selection of mothers to whom administration of IAP is advised, complete with documentation of risk factors (in case of risk factor based strategy), procedures for collecting specimens for culture of GBS at 35-37 weeks of gestation (in case of a screening strategy), transport and laboratory procedures, mode of administering IAP, dosage and duration and way of secondary prevention of GBS-EOD among newborn infants (i.e. observation vs treatment).

Results should be easily available for clinical workers on the floor, who ideally have been trained in the protocol and exactly know what to do in patients with risk factors for GBS-EOD or positive screening results. Health-care providers should inform women about recommended interventions.

Good implementation of guidelines requires knowledge of and adherence to the protocol for both the patient and caregivers.

Choice of antibiotics

Penicillin is the preferred antibiotic for IAP to prevent GBS-EOD. It is the first choice before ampicillin or amoxicillin, because of its narrower spectrum of antimicrobial activity, its decreased potential for selection of resistant organisms and its likely minor effect on enteric bacterial species. The efficiacy of all three agents administered intravenously for the prevention of GBS-EOD has been reported in clinical studies.(12)

Dosage

Proper dosing of antibiotics is essential to prevent the fetus from infection. In various countries with different prevention protocols, several dosing regimen recommendations exist and

are currently used. The rationale behind these regimens is not always clear nor evidence based. There is strikingly little information available on the pharmacokinetics of antibiotics in pregnancy in general and in the peripartal period in particular. Future studies should focus on research on pharmacokinetics of antibiotics during pregnancy and childbirth.

The CDC recommends penicillin G in a dosing regimen of 5 million units iv, followed by 2.5-3.0 million units iv every 4 hours. The range of 2.5-3.0 million units after the first 5 million units is recommended to achieve adequate drug levels in the fetal circulation and amniotic fluid while avoiding neurotoxicity. In order to reduce the need for pharmacies to specially prepare doses, the choice of dose should be guided by which formulations of penicillin G are readily available.(5)

As an alternative but equally recommended is Ampicillin in a 2 gram initial dose, followed by 1 gram every 4 hours until delivery. (Figure 1)

Outside the USA, intravenous amoxicillin is sometimes used in the prevention of neontal GBS disease.

Amoxicillin dosing regimens have been derived from studies using ampicillin, a beta-lactam antibiotic closely related to amoxicillin. Since the consequences of changes in

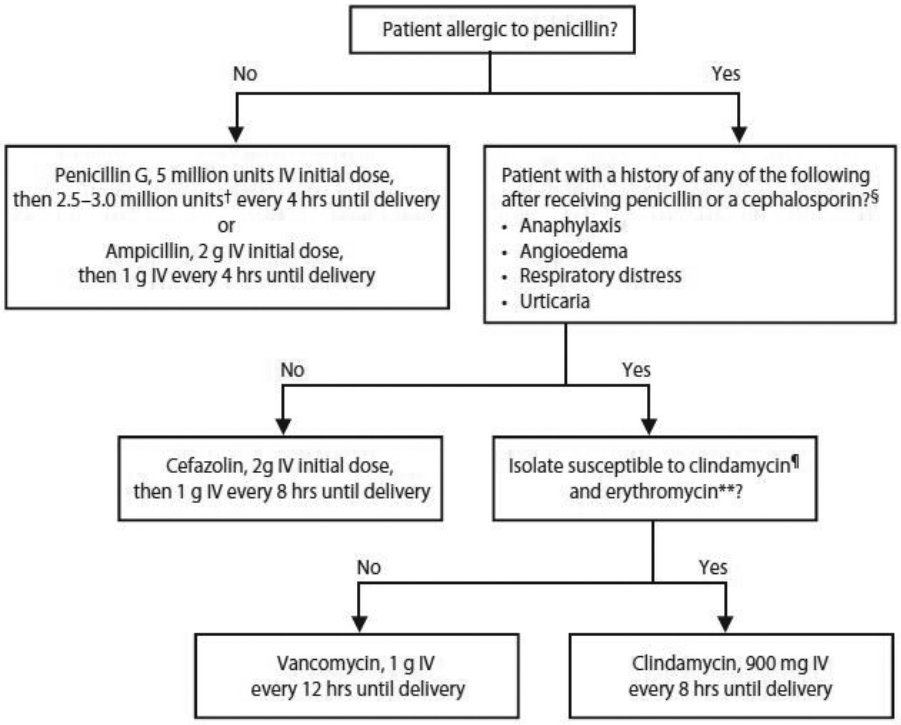

Figure 1 Algorithm for intrapartum antibiotic prophylaxis for prevention of GBS-EOD(5)

antibiotic dosing are unknown, it is not possible to study different regimens in pregnant women. Computer-simulations using data of the prescribed regimens are an accepted alternative, particularly when detailed information on the pharmacokinetics and the inherent inter-individual variation are avilable.

Muller et al. described in a simulation model in women with preterm prelabor rupture of membranes that a dosing regimen of bolus injections of 1 gram amoxicillin every 6 hours was predicted to be adequate for the prevention of GBS infection in pregnant patients.(24) This regimen was described as the usual regimen in a former review of the Cochrane Library.(25) After revision, the Library doesn't provide recommendations for antibiotic dosing regimens anymore. A 2 gram loading dose does not seem to be beneficial and the 1 gram doses can safely be administered by bolus injection increasing the comfort of the patient and facilitating prophylaxis.(31) The remaining difference between the CDC regimen and the former Cochrane regimen is the dosing interval of 4 hours versus 6 hours. Muller advises a 4-hour dosing regimen instead of a 6-hour dosing interval, since the common urgency of care in delivery rooms can easily result in inaccuracies in the administration. Using a 4-hour dosing interval results in a higher probability of target attainment, even when doses are accidentally skipped.

Dutch guidelines advise benzylpenicillin, in an initial dose of 2 million Units and subsequent doses of 1 million Units every four hours. As an alternative guidelines mention an initial dose of 2 gram amoxicillin or ampicillin, followed by 1 gram every four hours until delivery.(26)

Alternatives in penicillin-allergic patients

Considering a prevalence of GBS colonization of 20% and a prevalence of penicillin allergy of 10%, it is estimated that 2% of the pregnant women is both GBS colonized and penicillin allergic.

Penicillin skin testing can be performed in pregnant women, so that penicillin can be administered safely if the result is negative.(27)

To select the antibiotic prophylaxis for penicillin allergic women at high risk of anaphylaxis properly , antimicrobial susceptibility testing of GBS isolates is essential and should be documented. An antibiotic that is frequently prescribed in women with penicillin allergy is clindamycine. However, there is increasing resistance among GBS isolates. Resistance of GBS isolates to erythromycin and clindamycin has been reported many times.(28-31)

Resistance to erythromycin and clindamycin in a multicultural population of pregnant women in The Hague in the Netherlands was found in 8% and 7%, respectively. (30)

Nevertheless, susceptibility testing to macrolides is rarely performed (< 1% of colonized women who are allergic to penicillin) and clindamycin is administered to 70% of women allergic to penicillin.(21)

CDC guidelines recommend that penicillin-allergic women at high risk for anaphylaxis (i.e. a history of anaphylaxis, angioedema, respiratory distress or urticaria following administration of a penicillin or a cephalosporin) should receive clindamycine if their GBS isolate is susceptible to clindamycine and erythromycin, as determined by antimicrobial susceptibilitytesting; if the isolate is sensitive to clindamycin but resistant to erythromycin, clindamycine may be used if testing for inducible clindamycin resistance is negative.

However, data on the pharmacokinetics of clindamycine in pregnant women and non pregnant individuals are scarce.(39-41) Data suggest that in pregnant women the current dosing regimen of 900 mg every 8 hours reach adequate concentrations, but the concentration-time profiles in the fetus might be inadequate. More pharmacokinetic studies including data of both the mother and the neonate are needed to investigate whether the currently advised regimen is adequate to prevent GBS-EOD.

Penicillin-allergic women at high risk for anaphylaxis should receive vancomycine if their isolate is intrinsically resistant to clindamycin as determined by antimicrobial susceptibility-testing, if the isolate demonstrates inducible resistance to clindamycin or if susceptibility to both agents is unknown. (Figure 1)

Duration of administration of antibiotics

The Centre for Disease Control and Prevention (CDC) issued recommendations for the prevention of GBS-EOD specifying that profylaxis is considered adequate only if antibiotic administration is started at least 4 hours prior to delivery. Because of various delivery circumstances, as many as 50% of GBS carriers women may not get IAP 4 hours before delivery.(42) As a consequence, soon after birth healthy-appearing infants born to mothers who received inadequate IAP routinely undergo invasive testing (including white blood cell count and blood culture) to exclude infection. Only a few studies have evaluated the influence of timing of profylaxis on neonatal colonization and the reported rates of transmission are quite heterogeneous. In a systematic review a rationale for the 4 hour threshold of the CDC guidelines was not found.(32) A recent prospective cohortstudy described colonization rates of infants born to mothers who received inadequate or no profhylaxis. Among 137 infants born to mothers who received inadequate prophylaxis, 3.6% were colonized. Eighty-two women received prophylaxis < 2 hours before delivery and two of their infants (2.4%) were colonized. Of 30 infants who were not exposed to prophylaxis, 60% were colonized. Colonization was significantly more frequent among infants born to untreated mothers compared with infants born to women who received inadequate profylaxis. This suggests that inadequate prophylaxis may effectively interrupt GBS transmission. IAP should therefore

always been given to women with higher risk of neonatal GBS-EOD, even if delivery is expected to be within a few hours.(44)

To conclude, research on the pharmacokinetics of various antibiotics should be continued for optimization of the GBS disease prophylaxis.

Secondary prevention of GBS-EOD among newborn infants

Prevention strategies will never prevent all cases of GBS-EOD. Rapid detection of neonatal infections and initiation of appropriate treatment is needed to minimize morbidity and mortality. The detection of GBS-EOD poses certain clinical challenges, because neonatal care providers must take into account the clinical appearance of the infant, the presence of maternal risk factors for GBS-EOD and infant exposure to intrapartum antibiotics. Figure 2 describes the algorithm for managing infants with signs of sepsis, infants born to women with chorioamnionitis and well-appearing infants exposed to inadequate intrapartum antibiotics.(5)

Detection of disease after IAP

As use of IAP to prevent GBS-EOD increased, concern was expressed that signs of sepsis in the newborn could be delayed or masked, impairing the ability of clinicians to detect GBS-EOD. (45;46) However, several studies conducted since 1996 did not find significant difference in the clinical presentation of GBS-EOD between infants exposed to IAP and those not exposed.(22;33-36) Approximately 90% of cases of GBS-EOD continue to manifest within the first 24 hours of life.

Neonatal infection is diagnosed by laboratory tests, i.e. CRP (routinely) or procalcitonin (PCT) concentrations (sporadically). The concentrations of both proteins are increased in cord blood in response to infection. Measurements of CRP and PCT levels in cord blood plasma contribute to the diagnosis EOD.(37-40) There are significant differences between infected and uninfected neonates in levels of CRP and PCT levels in cord blood, also when prenatal antibiotic therapy was administered.

Knowledge, training and awareness

Training in recognizing GBS-EOD and knowledge about the route to disease and the possible preventive measures deserve continued attention of all workers in obstetric care, either in hospitals or at home. Parents need to be informed about the disease so that they can recognize alarm symptoms when they are alone with their baby.

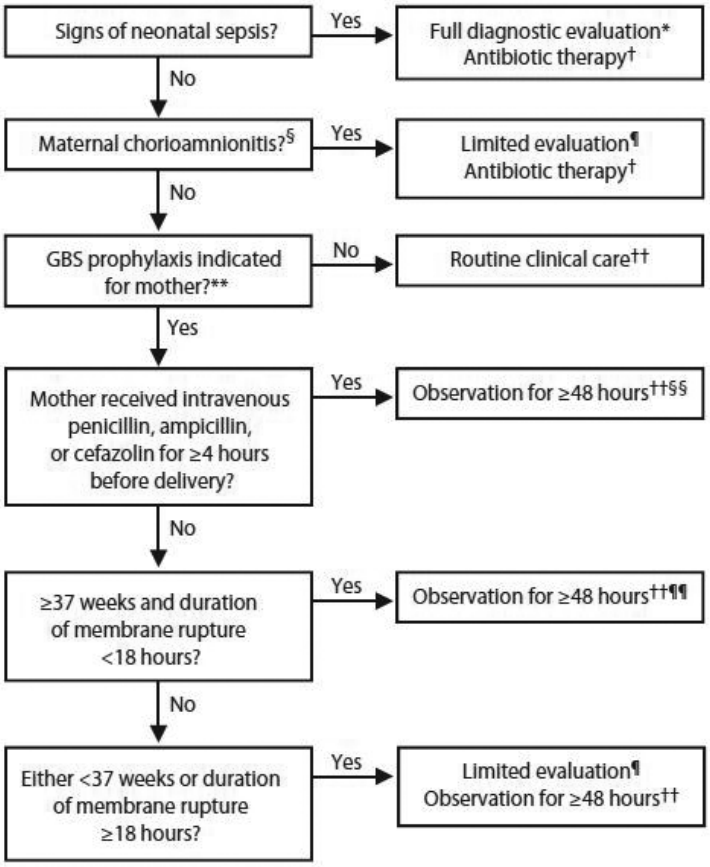

Figure 2 Algorithm for secondary prevention of early-onset group B streptococcal (GBS) disease among newborns(5)

* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

¶ Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).

†† If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

§§ If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

¶ ¶ Some experts recommend a CBC with differential and platelets at age 6–12 hours.

CONCLUSION

To identify potential areas for improvement of prevention of GBS-EOD, training in recognizing GBS-EOD is important. Opportunities for improvement can be found in development and implementation of local prevention protocols as well as in optimal timing of screening, a correct choice of sampling sites, the best conditions of transport of swabs and culture procedures and the best choice of antibiotics. Knowledge about the route to disease and the possible preventive measures deserve continued attention of all workers in obstetric care, either in hospitals or at home. Caregivers need to be aware that there are a lot of little steps in the chain of prevention where improvement can be made.

REFERENCE LIST

1. Schuchat A. Epidemiology of group B streptococcal disease in the United States: shifting paradigms. Clin Microbiol Rev 1998 Jul;11(3.:497-513.
2. Barcaite E, Bartusevicius A, Tameliene R, Kliucinskas M, Maleckiene L, Nadisauskiene R. Prevalence of maternal group B streptococcal colonisation in European countries. Acta Obstet Gynecol Scand 2008;87(3.:260-71.
3. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. MMWR Recomm Rep 2002 Aug 16;51(RR-11.:1-22.
4. Pylipow M, Gaddis M, Kinney JS. Selective intrapartum prophylaxis for group B streptococcus colonization: management and outcome of newborns. Pediatrics 1994 Apr;93(4.:631-5.
5. de Cueto M, Sanchez MJ, Molto L, Miranda JA, Herruzo AJ, Ruiz-Bravo A, et al. Efficacy of a universal screening program for the prevention of neonatal group B streptococcal disease. Eur J Clin Microbiol Infect Dis 1995 Sep;14(9.:810-2.
6. Hickman ME, Rench MA, Ferrieri P, Baker CJ. Changing epidemiology of group B streptococcal colonization. Pediatrics 1999 Aug;104(2 Pt 1.:203-9.
7. Lim DV, Morales WJ, Walsh AF, Kazanis D. Reduction of morbidity and mortality rates for neonatal group B streptococcal disease through early diagnosis and chemoprophylaxis. J Clin Microbiol 1986 Mar;23(3.:489-92.
8. Adriaanse AH, Kollee LA, Muytjens HL, Nijhuis JG, de Haan AF, Eskes TK. Randomized study of vaginal chlorhexidine disinfection during labor to prevent vertical transmission of group B streptococci. Eur J Obstet Gynecol Reprod Biol 1995 Aug;61(2.:135-41.
9. Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. Cochrane Database Syst Rev 2009;(3.:CD007467.
10. Itakura A, Kurauchi O, Morikawa S, Matsuzawa K, Mizutani S, Tomoda Y. A prospective study on the relationship between intrapartum maternal group-B streptococcal concentration and signs of infection in neonates. J Obstet Gynaecol Res 1996 Apr;22(2.:101-5.
11. Oddie S, Embleton ND. Risk factors for early onset neonatal group B streptococcal sepsis: case-control study. BMJ 2002 Aug 10;325(7359.:308.
12. Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. N Engl J Med 1986 Jun 26;314(26.:1665-9.
13. Stoll BJ, Hansen NI, Sanchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics 2011 May;127(5.:817-26.
14. Wilson JM, Jungner YG. [Principles and practice of mass screening for disease]. Bol Oficina Sanit Panam 1968 Oct;65(4.:281-393.
15. Petros M. Revisiting the Wilson-Jungner criteria: how can supplemental criteria guide public health in the era of genetic screening? Genet Med 2012 Jan;14(1.:129-34.
16. Badri MS, Zawaneh S, Cruz AC, Mantilla G, Baer H, Spellacy WN, et al. Rectal colonization with group B streptococcus: relation to vaginal colonization of pregnant women. J Infect Dis 1977 Feb;135(2.:308-12.
17. Trappe KL, Shaffer LE, Stempel LE. Vaginal-perianal compared with vaginal-rectal cultures for detecting group B streptococci during pregnancy. Obstet Gynecol 2011 Aug;118(2 Pt 1.:313-7.
18. Stoner KA, Rabe LK, Hillier SL. Effect of transport time, temperature, and concentration on the survival of group B streptococci in amies transport medium. J Clin Microbiol 2004 Nov;42(11.:5385-7.
19. Ostroff RM, Steaffens JW. Effect of specimen storage, antibiotics, and feminine hygiene products on the detection of group B Streptococcus by culture and the STREP B OIA test. Diagn Microbiol Infect Dis 1995 Jul;22(3.:253-9.
20. Poyart C, Reglier-Poupet H, Tazi A, Billoet A, Dmytruk N, Bidet P, et al. Invasive group B streptococcal infections in infants, France. Emerg Infect Dis 2008 Oct;14(10.:1647-9.

21. Van Dyke MK, Phares CR, Lynfield R, Thomas AR, Arnold KE, Craig AS, et al. Evaluation of universal antenatal screening for group B streptococcus. N Engl J Med 2009 Jun 18;360(25.:2626-36.
22. Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. Pediatrics 2005 May;115(5.:1240-6.
23. Valkenburg-van den Berg AW, Houtman-Roelofsen RL, Oostvogel PM, Dekker FW, Dorr PJ, Sprij AJ. Timing of group B streptococcus screening in pregnancy: a systematic review. Gynecol Obstet Invest 2010;69(3.:174-83.
24. Muller AE, DeJongh J, Oostvogel PM, Voskuyl RA, Dorr PJ, Danhof M, et al. Amoxicillin pharmacokinetics in pregnant women with preterm premature rupture of the membranes. Am J Obstet Gynecol 2008 Jan;198(1.:108-6.
25. Smaill F. Intrapartum antibiotics for group B streptococcal colonisation. Cochrane Database Syst Rev 2000;(2.:CD000115.
26. Trijbels-Smeulders M, Adriaanse AH, Gerards LJ, Kimpen JL. Strategy to prevent neonatal early-onset group B streptococcal (GBS. disease in the Netherlands. Reviews in Medical Microbiology 2003;14:35-9.
27. Macy E. Penicillin skin testing in pregnant women with a history of penicillin allergy and group B streptococcus colonization. Ann Allergy Asthma Immunol 2006 Aug;97(2.:164-8.
28. Blaschke AJ, Pulver LS, Korgenski EK, Savitz LA, Daly JA, Byington CL. Clindamycin-resistant group B Streptococcus and failure of intrapartum prophylaxis to prevent early-onset disease. J Pediatr 2010 Mar;156(3.:501-3.
29. Phares CR, Lynfield R, Farley MM, Mohle-Boetani J, Harrison LH, Petit S, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. JAMA 2008 May 7;299(17.:2056-65.
30. Muller AE, Valkenburg-van den Berg AW, Kreft D, Oostvogel PM, Sprij AJ, van Belkum A. Low rate of carriage of macrolide-resistant group B streptococci in pregnant women in The Netherlands. Eur J Obstet Gynecol Reprod Biol 2008 Mar;137(1.:17-20.
31. Castor ML, Whitney CG, Como-Sabetti K, Facklam RR, Ferrieri P, Bartkus JM, et al. Antibiotic resistance patterns in invasive group B streptococcal isolates. Infect Dis Obstet Gynecol 2008;2008:727505.
32. Illuzzi JL, Bracken MB. Duration of intrapartum prophylaxis for neonatal group B streptococcal disease: a systematic review. Obstet Gynecol 2006 Nov;108(5.:1254-65.
33. Bromberger P, Lawrence JM, Braun D, Saunders B, Contreras R, Petitti DB. The influence of intrapartum antibiotics on the clinical spectrum of early-onset group B streptococcal infection in term infants. Pediatrics 2000 Aug;106(2 Pt 1.:244-50.
34. Escobar GJ, Li DK, Armstrong MA, Gardner MN, Folck BF, Verdi JE, et al. Neonatal sepsis workups in infants >/=2000 grams at birth: A population-based study. Pediatrics 2000 Aug;106(2 Pt 1.:256-63.
35. Pinto NM, Soskolne EI, Pearlman MD, Faix RG. Neonatal early-onset group B streptococcal disease in the era of intrapartum chemoprophylaxis: residual problems. J Perinatol 2003 Jun;23(4.:265-71.
36. Pulver LS, Hopfenbeck MM, Young PC, Stoddard GJ, Korgenski K, Daly J, et al. Continued early onset group B streptococcal infections in the era of intrapartum prophylaxis. J Perinatol 2009 Jan;29(1.:20-5.
37. Janota J, Stranak Z, Belohlavkova S. [Interleukin-6, procalcitonin, C-reactive protein and the immature to total neutrophil ratio (I/T. in the diagnosis of early-onset sepsis in low birth weight neonates]. Ceska Gynekol 2000 Dec;65 Suppl 1:29-33.
38. Joram N, Boscher C, Denizot S, Loubersac V, Winer N, Roze JC, et al. Umbilical cord blood procalcitonin and C reactive protein concentrations as markers for early diagnosis of very early onset neonatal infection. Arch Dis Child Fetal Neonatal Ed 2006 Jan;91(1.:F65-F66.
39. Kocabas E, Sarikcioglu A, Aksaray N, Seydaoglu G, Seyhun Y, Yaman A. Role of procalcitonin, C-reactive protein, interleukin-6, interleukin-8 and tumor necrosis factor-alpha in the diagnosis of neonatal sepsis. Turk J Pediatr 2007 Jan;49(1.:7-20.
40. Kordek A, Giedrys-Kalemba S, Pawlus B, Podraza W, Czajka R. Umbilical cord blood serum procalcitonin concentration in the diagnosis of early neonatal infection. J Perinatol 2003 Mar;23(2.:148-53.

Chapter 8

The strategy for prevention of GBS-EOD in the Netherlands; plea for the combination strategy

8

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Submitted

ABSTRACT

Introduction of the Dutch modified risk factor based strategy on prevention of Group B streptococcal disease in 1998 resulted in a slight reduction in the incidence of early-onset group B streptococcal disease (GBS-EOD), but not in a decrease in severe morbidity and case fatality rate. The current Dutch guideline is not effective and a new strategy to prevent GBS-EOD is justified.

We describe several alternative prevention strategies for the Dutch modified risk factor based strategy and we hypothesize about the best strategy for the Netherlands.

The combination strategy seems applicable for the Dutch situation and organisation of obstetrical care. In this strategy, screening of all pregnant women is combined with IAP only for carriers with risk factors for GBS-EOD during labor. This strategy is cost-effective with a low number of women that get antibiotics during delivery. Advantage of the combination strategy is that GBS status of the mother is always known, which allows caregivers and parents to observe babies from GBS positive mothers who did not receive IAP. The combination strategy will not interfere with the Dutch obstetrical system and will not lead to extra hospital referrals.

Therefore, we plea for the combination strategy as the new Dutch strategy in prevention of 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. Transmission 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)

The Dutch Society of Obstetrics and Gynaecology (NVOG) and the Dutch Society of Paediatrics (NvK) approved modified risk factor based guidelines for prevention of early-onset Group B streptococcal disease (GBS-EOD) in 1998. These guidelines on prevention of GBS-EOD recommend intrapartum maternal administration of antibiotics in women with intrapartum temperature > 38ºC, in women with GBS bacteriuria during current pregnancy and in women who previously delivered an infant with early-onset GBS disease, irrespective to their GBS status.(33) In women presenting with any of the other risk factors associated with early onset GBS disease, i.e. delivery at <37 weeks' gestation or rupture of membranes for more than 24 hrs, screening for GBS carriage is performed first, followed by intrapartum antibiotic prophylaxis (IAP) when the culture is positive. In case the delivery occurs before the result is available, the obstetrician should decide about antibiotic prophylaxis, based on the severity of the risk factor. The choice for this modified risk factor based strategy was made in 1998, with the intention to reduce the number of cases of GBS-EOD while few women receive antibiotics during delivery. The disadvantages of this strategy are, that 30%-40% of GBS-EOD may occur in the absence of factors and that in most cases of preterm delivery and /or prolonged rupture of membranes delivery occurs before culture results are available.(33)

There has been a disappointing limited decrease in the incidence of proven GBS-EOD in the Netherlands. In proven sepsis, streptococci are isolated from blood and/or from

cerebrospinal fluid combined with physical signs of infection in the neonate. In probable sepsis GBS is detected in serious ill children at various sites, but not in blood and/or cerebrospinal fluid. Incidence of proven sepsis declined from 0.54 per 1000 live births to 0.36 per 1000 live births.(34) There was no decrease in the incidence of probable early-onset GBS sepsis, meningitis or case fatality rate. According to the Netherlands Perinatal Registry, which doesn't distinguish between incidences of proven and probable GBS-EOD, 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). Between 2000 and 2009 a case fatality rate for GBS-EOD of 6.3% was found.

Revision of current Dutch guidelines

Since the overall effect of the Dutch guideline on the incidence of GBS-EOD is disappointing, revision of the Dutch guidelines was considered in 2006. Because of the presumed lack of evidence to change towards an alternative strategy, the Dutch prevention strategy remained as it was. However, given the on-going burden of GBS-EOD, adaptation of the Dutch guidelines should be reconsidered, particularly concerning perinatal mortality in the Netherlands, which is high compared to other European countries.(35)

In the USA, guidelines for prevention of GBS-EOD recommend the screening based strategy. Extrapolation of prevention strategies from the USA to the Netherlands may be inappropriate, since there are differences in for example the organization of perinatal care.

It is important to know that most women colonized with GBS are asymptomatic, so screening is needed if these women are to be identified. However, of the women in labor who are GBS positive, very few (1%) will give birth to babies who are infected with GBS. Hence, giving intravenous antibiotics to all women in labor who are GBS positive will put a large number of women and babies at risk of adverse effects unnecessarily.

Alternative strategies

There are several alternatives in prevention strategies for the Dutch modified risk factor based strategy.

Risk factor based strategy

The risk factor based strategy was based on multiple studies indicating that certain clinical risk factors were overly represented in mothers of infants who went on to develop GBS-EOD. With this strategy prenatal screening cultures are not obtained and IAP is directed to any women with prolonged rupture of the membranes, gestation < 37 weeks or intrapartum fever. Additionally, IAP is given to women with antenatal GBS bacteriuria (a presumed marker of heavy colonization and a risk factor for GBS-EOD) and to those who had experienced a previous delivery of a newborn with GBS disease.

Screening based strategy

In the screening based strategy, cultures are obtained at 35-37 weeks 'gestation. After onset of labor or rupture of membranes, IAP is then given to women who are identified as GBS carriers. In case of unscreened women or if the culture result is not available, IAP is given as well. As with the risk factor based strategy, IAP is also given to women with intrapartum fever, to women with antenatal GBS bacteriuria and to those who have experienced a previous delivery of a newborn with GBS-EOD. This strategy is recommended by the CDC in the USA since 2002.(6;32)

Combined screening/risk factor based strategy

The combined screening/risk factor based strategy (Combinationstrategy) that originates from the Canadian Task Force on Preventive Health Care, consists of a culture taken at 35-37 weeks of gestation and IAP only for GBS colonized women with risk factors and not for those without risk factors. In addition, in this strategy, IAP is given in all cases of preterm labor if screening results are not available, in women with intrapartum temperature > 38ºC, in women with GBS bacteriuria during current pregnancy and in women who previously gave birth to an infant with early-onset GBS disease, irrespective to their GBS status.

Disadvantages of screening

Disadvantages of IAP are the medical interference in normal labor and in the neonatal period as well as increased demand for prenatal counselling and increased maternal anxiety. In the Dutch organization of obstetrical care, a screening based strategy during pregnancy will need adjustment and dedication and therefore will take some time until full implementation.

The potential for causing maternal psychological stress by testing in pregnancy has always been a concern for clinicians concerned with maternal welfare. A study among 183 pregnant Taiwanese women reported significantly greater psychological distress on state-anxiety scores among women with GBS colonization, but after delivery, anxiety scores did not differ between GBS positive and GBS negative women. Among all women screened for GBS, those with positive and negative results alike, there was great approval for the test and the desire to have screening for their next pregnancy.(36) Clinician concerns about maternal anxiety should therefore not be an impediment to test for GBS.

Unintended consequences after adoption of a prevention strategy

Although implementation of intrapartum prophylaxis strategies in the USA has been associated with a substantial decrease in newborn illness and death from GBS, there are concerns regarding unintended consequences of the increased use of antimicrobials among pregnant women and newborns.

If a culture based screening would be introduced In the Netherlands, obstetrical inhospital care in the Netherlands will increase and many otherwise healthy pregnant women get

IAP. In an era of increased patient autonomy, IAP may be rejected when offered to healthy pregnant women. This strategy is at odds with home delivery, because it is unlikely that IAP is to be administered at home.

On the other hand, the fact that nowadays more patients are well informed about possibilities for screening and prevention of GBS-EOD, may also lead to specific requests and outrage when testing for GBS carriage is not routinely performed during pregnancy.(37)

Resistance

The widespread use of antibiotics is known to contribute to the development of resistant organisms. This is a particular risk when broad-spectrum antibiotics such as ampicillin and amoxicillin are used.(3;38;39)

Anaphylaxis

Wider use of antibiotics will also lead to an increase in adverse antibiotic events, potentially including anaphylaxis and death. Estimates of these events for anaphylaxis are 1: 10.000 and for death 1:100.000 treated patients, although the evidence base for these much quoted figures is limited.(40)

Anaphylaxis-related mortality is likely to be a rare event because the majority of women receiving intrapartum antibiotics will be in hospital settings were rapid intervention is readily available. Allergic reactions occur in an estimated 0.7%-4.0% of all treatment courses with penicillin, the most common of which is a maculopapular rash. Maternal anaphylaxis associated with GBS prophylaxis was reported in 1990s (41) ; since the release of the 1996 guidelines, four reports of nonfatal cases of anaphylaxis associated with GBS IAP in the USA have been published.(42-45)

Fetal effects of severe anaphylaxis have not been reported. There might be fetal distress and injury due to maternal hypoxia and hypotension.

Effects on children on short and long term

One study reported an association between the use of intrapartum antibiotics for prevention of GBS-EOD and late-onset (7-90 days) serious bacterial infections (LOD) caused by several micro-organisms.(46) The incidence of postnatal yeast infections may increase with the use of intrapartum antibiotics.(47) Possibly acquired abnormalities in early-life bacterial colonization may affect the development of the immune system and change the pattern of initial colonization of the gut in the first days of life. This may be linked to later development of allergic disease.(46;48;49)

Changing patterns of sepsis

Major concerns about IAP comes from reports of clusters or increases in gram-negative infections among newborns in association with declines in GBS infections in the context

of increasing IAP use.(50-52) A review on this issue suggested no consistent trend toward increased incidence of gram-negative or drug-resistant early onset neonatal sepsis.(38) One large report of infants with very low birth weight documented a shift from gram-positive to gram-negative early onset infections in the context of increased GBS prevention, with increases in E. Coli infections.(53) This phenomenon did not extend to the general population.(54;55) A recent analysis of babies with E. coli sepsis in the first week of life compared with the birth cohort has revealed no increased risk of neonatal sepsis from E. coli associated with intrapartum antimicrobials.(56) This remains an important issue and emphasizes the importance of ongoing neonatal infection surveillance.

Comparison of strategies

There are no randomized controlled trials comparing different screening protocols.

Estimates of the efficacy of the screening strategies are based on observational studies.

A decision model used to predict outcomes for two strategies in the United States revealed that a screening based strategy would result in 31% of pregnant women being offered IAP compared with 17% of women with a risk factor based strategy. Screening was predicted to prevent 75% of GBS-EOD, whilst the risk factor strategy would prevent 54%.(57;58)

The CDC conducted a retrospective cohort study in eight states of the USA among a birth cohort of more than 600.000 and including 312 cases of GBS-EOD, to assess the relative effectiveness of the screening based strategy and the risk factor based strategy. Adjusting for confounders, women of the cohort of the screening based strategy had a > 50 % lower risk of delivering a baby with GBS disease than did those exposed to the risk factor based strategy. (RR for GBS-EOD following screening based versus risk factor based IAP 0.46, CI 0.36-0.60)(59)

Two features seemed to account for the superior effectiveness of screening based strategy. First, the screening based strategy prevented disease among women who had no obstetric risk factors, who in the pre-prevention era had represented up to 45% of early onset cases.(60) Secondly, adherence to the protocol as well as eligibility of women for IAP were more frequently performed in deliveries in the screening cohort than in the cohort of the risk factor based strategy.

Theoretic model for the Netherlands

Table 1 shows a comparison of different strategies with respect to percentage of screening of pregnant women, percentage of women who receive IAP, percentage of unprotected deliveries (i.e. no IAP to prevent GBS-EOD) and percentage of infants who acquire GBS-EOD.

To compare the different strategies in this theoretic model, some assumptions have been made;

Table 1 Comparison of strategies for prevention of GBS-EOD; a theoretic model

Strategy	Screening	IAP for	Screened women	IAP	Unprotected - GBS-EOD	NNT
No strategy	No	Nobody	0%	0%	100% / 0.15%	
Risk factor based	No	Women with RF	0%	20%	40% / 0.06%	222
Screening based	Yes	Women with GBS+	100%	21%	0% / 0%	140
Combination	Yes	Women with GBS+ **and** RF	100%	4.2%	40% / 0.06%	47

IAP = Intrapartum antibiotic prophylaxis
RF= Risk factor
NNT= Number needed to treat

The incidence of GBS-EOD without any prevention strategy is 0.15%; in the Netherlands, prevalence of GBS carriage among pregnant women is 21%; in 20% of pregnant women there is one or more risk factor for GBS-EOD present during labor; 40% of GBS-EOD occurs in the absence of risk factors; positive and negative predictive values for antepartum cultures are 100% and IAP is always effective in preventing GBS-EOD.

The best preventive strategy maximizes treatment in women who need it, and minimizes treatment in women who do not need it. As shown in the table, the combination of the screening/risk factor based (combination) strategy has the lowest number needed to treat, i.e. only 47 pregnant women need to receive IAP to prevent one case of GBS-EOD. There is an equal percentage of unprotected infants in comparison to the risk factor based strategy. However, the great advantage of the combinationstrategy is that GBS status is always known, which allows caregivers to observe babies from GBS positive mothers who did not receive IAP because there is no risk factor. Parents of these babies can be informed to watch for signs of GBS-EOD as well.

In the Dutch obstetrical system, a distinction is made between low and high risk pregnancies and deliveries. Low risk pregnancies and deliveries are attended by a “primary caregiver” (midwife or general practitioner) and deliveries may take place at home, in a freestanding birth clinic or in a hospital. High risk pregnancies and deliveries, defined as the presence of conditions that place women and/or newborns at risk during pregnancy and delivery, are attended by a secondary care caregiver (obstetrician) and deliveries take place in a hospital. Preterm labor, prolonged prelabor rupture of membranes and intrapartum fever are indicators for high risk delivery. Women with one of the five risk factors, as described in the guidelines, will always be referred to a hospital. Therefore both the risk factor based and the combination strategy will not interfere with the Dutch obstetrical system and will not lead to extra hospital referrals.

Cost effectiveness

In a 2005 study a cost-effectiveness analysis based on different decision models for the Dutch situation was performed. The screening strategy, the risk factor based strategy, the combined screening/risk factor based strategy and the current Dutch strategy (modified risk factor based strategy) were compared with respect to costs and effects.

This study showed that the screening based strategy showed the highest reduction in GBS-EOD, but for the highest costs, resulting in a high cost-effectiveness ratio. The risk factor based strategy (as recommended by the CDC in 1996) and a combined screening/risk factor based strategy are more cost-effective.(61) However, in this study several assumptions have been made, which have been criticized later.(62) The higher amount of estimated costs of the screening based strategy could partly be explained by the costs of 48 hours clinical observation of healthy infants of GBS culture positive mothers. The costs of this neonatal observation period contribute to more than half of the total costs in the screening approach. Neonatal observation is not necessary in the risk factor based strategy. Although 48 hours clinical observation is recommended in current Dutch guidelines and in the CDC guidelines, the necessity for this procedure in the Netherlands may be questioned. In the Netherlands an effective postnatal home care system exists, supervised by midwives and specially trained maternity nurses, which could replace the need for clinical observation. Omitting the clinical observation of clinically healthy infants reduces the costs calculated for the screening based strategy.

CONCLUSION

Introduction of the Dutch modified risk factor based strategy on prevention of GBS-EOD resulted in a slight reduction in the incidence of proven GBS-EOD, but not in a decrease in severe morbidity and mortality. Latest information even shows increase in cases of GBS sepsis per year. Therefore, it is obvious that the current Dutch guideline is not effective and a new strategy to prevent GBS-EOD is justified. The combination strategy seems applicable for the Dutch situation and organisation of obstetrical care. In this strategy, screening of all pregnant women is combined with IAP only for carriers with risk factors for GBS-EOD during labor. This strategy is comparable cost-effective with the risk based strategy, but the number of women that get IAP much lower. This is of great advantage, since particularly in case of preventive interventions, attention should be paid to risks and unintended consequences of widespread use of antibiotics. Another great advantage of the combination strategy is that GBS status is always known, which allows caregivers and parents to observe babies from GBS positive mothers who did not receive IAP. The combination strategy will not interfere with the Dutch obstetrical system and will not lead to extra hospital referrals. Future studies should focus on implementation of this strategy in the Dutch system of obstetric care with the ultimate goal to decrease the burden of GBS-EOD in the Netherlands.

REFERENCE LIST

1. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. Pediatr Infect Dis J 2011 Nov;30(11.:937-41.
2. Schuchat A. Epidemiology of group B streptococcal disease in the United States: shifting paradigms. Clin Microbiol Rev 1998 Jul;11(3.:497-513.
3. Stoll BJ, Hansen NI, Sanchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics 2011 May;127(5.:817-26.
4. Edmond KM, Kortsalioudaki C, Scott S, Schrag SJ, Zaidi AK, Cousens S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. Lancet 2012 Feb 11;379(9815.:547-56.
5. Barcaite E, Bartusevicius A, Tameliene R, Kliucinskas M, Maleckiene L, Nadisauskiene R. Prevalence of maternal group B streptococcal colonisation in European countries. Acta Obstet Gynecol Scand 2008;87(3.:260-71.
6. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. MMWR Recomm Rep 2002 Aug 16;51(RR-11.:1-22.
7. Lewin EB, Amstey MS. Natural history of group B streptococcus colonization and its therapy during pregnancy. Am J Obstet Gynecol 1981 Mar 1;139(5.:512-5.
8. Hoogkamp-Korstanje JA, Gerards LJ, Cats BP. Maternal carriage and neonatal acquisition of group B streptococci. J Infect Dis 1982 Jun;145(6.:800-3.
9. Hansen SM, Uldbjerg N, Kilian M, Sorensen UB. Dynamics of Streptococcus agalactiae colonization in women during and after pregnancy and in their infants. J Clin Microbiol 2004 Jan;42(1.:83-9.
10. Yancey MK, Schuchat A, Brown LK, Ventura VL, Markenson GR. The accuracy of late antenatal screening cultures in predicting genital group B streptococcal colonization at delivery. Obstet Gynecol 1996 Nov;88(5.:811-5.
11. Valkenburg-van den Berg AW, Houtman-Roelofsen RL, Oostvogel PM, Dekker FW, Dorr PJ, Sprij AJ. Timing of group B streptococcus screening in pregnancy: a systematic review. Gynecol Obstet Invest 2010;69(3.:174-83.
12. Quirante J, Ceballos R, Cassady G. Group B beta-hemolytic streptococcal infection in the newborn. I. Early onset infection. Am J Dis Child 1974 Nov;128(5.:659-65.
13. Tseng PI, Kandall SR. Group B streptococcal disease. In neonates and infants. N Y State J Med 1974 Nov;74(12.:2169-73.
14. Yagupsky P, Menegus MA, Powell KR. The changing spectrum of group B streptococcal disease in infants: an eleven-year experience in a tertiary care hospital. Pediatr Infect Dis J 1991 Nov;10(11.:801-8.
15. Garland SM. Early onset neonatal group B streptococcus (GBS. infection: associated obstetric risk factors. Aust N Z J Obstet Gynaecol 1991 May;31(2.:117-8.
16. Adair CE, Kowalsky L, Quon H, Ma D, Stoffman J, McGeer A, et al. Risk factors for early-onset group B streptococcal disease in neonates: a population-based case-control study. CMAJ 2003 Aug 5;169(3.:198-203.
17. Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics 1999 Jun;103(6.:e77.
18. Oddie S, Embleton ND. Risk factors for early onset neonatal group B streptococcal sepsis: case-control study. BMJ 2002 Aug 10;325(7359.:308.
19. Spaans WA, Knox AJ, Koya HB, Mantell CD. Risk factors for neonatal infection. Aust N Z J Obstet Gynaecol 1990 Nov;30(4.:327-30.

20. Yancey MK, Duff P, Kubilis P, Clark P, Frentzen BH. Risk factors for neonatal sepsis. Obstet Gynecol 1996 Feb;87(2.:188-94.
21. Boyer KM, Gadzala CA, Kelly PD, Burd LI, Gotoff SP. Selective intrapartum chemoprophylaxis of neonatal group B streptococcal early-onset disease. II. Predictive value of prenatal cultures. J Infect Dis 1983 Nov;148(5.:802-9.
22. Stewardson-Krieger PB, Gotoff SP. Risk factors in early-onset neonatal group b streptococcal infections. Infection 1978;6(2.:50-3.
23. Schuchat A, Wenger JD. Epidemiology of group B streptococcal disease. Risk factors, prevention strategies, and vaccine development. Epidemiol Rev 1994;16(2.:374-402.
24. Schuchat A, Zywicki SS, Dinsmoor MJ, Mercer B, Romaguera J, O'Sullivan MJ, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case-control study. Pediatrics 2000 Jan;105(1 Pt 1.:21-6.
25. Wood EG, Dillon HC, Jr. A prospective study of group B streptococcal bacteriuria in pregnancy. Am J Obstet Gynecol 1981 Jul 1;140(5.:515-20.
26. Persson K, Christensen KK, Christensen P, Forsgren A, Jorgensen C, Persson PH. Asymptomatic bacteriuria during pregnancy with special reference to group B streptococci. Scand J Infect Dis 1985;17(2.:195-9.
27. Carstensen H, Christensen KK, Grennert L, Persson K, Polberger S. Early-onset neonatal group B streptococcal septicaemia in siblings. J Infect 1988 Nov;17(3.:201-4.
28. Faxelius G, Bremme K, Kvist-Christensen K, Christensen P, Ringertz S. Neonatal septicemia due to group B streptococci--perinatal risk factors and outcome of subsequent pregnancies. J Perinat Med 1988;16(5-6.:423-30.
29. Philipson EH, Herson VC. Intrapartum chemoprophylaxis for group B streptococcus infection to prevent neonatal disease: who should be treated? Am J Perinatol 1996 Nov;13(8.:487-90.
30. Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. N Engl J Med 1986 Jun 26;314(26.:1665-9.
31. Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. Cochrane Database Syst Rev 2009;(3.:CD007467.
32. Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep 2010 Nov 19;59(RR-10.:1-36.
33. Trijbels-Smeulders M, Adriaanse AH, Gerards LJ, Kimpen JL. Strategy to prevent neonatal early-onset group B streptococcal (GBS. disease in the Netherlands. Reviews in Medical Microbiology 2003;14:35-9.
34. Trijbels-Smeulders M, de Jonge GA, Pasker-de Jong PC, Gerards LJ, Adriaanse AH, van Lingen RA, et al. Epidemiology of neonatal group B streptococcal disease in the Netherlands before and after introduction of guidelines for prevention. Arch Dis Child Fetal Neonatal Ed 2007 Jul;92(4.:F271-F276.
35. Mohangoo AD, Buitendijk SE, Hukkelhoven CW, Ravelli AC, Rijninks-van Driel GC, Tamminga P, et al. [Higher perinatal mortality in The Netherlands than in other European countries: the Peristat-II study]. Ned Tijdschr Geneeskd 2008 Dec 13;152(50.:2718-27.
36. Cheng PJ, Shaw SW, Lin PY, Huang SY, Soong YK. Maternal anxiety about prenatal screening for group B streptococcus disease and impact of positive colonization results. Eur J Obstet Gynecol Reprod Biol 2006 Sep;128(1-2.:29-33.
37. McCartney M. Streptococcus B in pregnancy: to screen or not to screen? BMJ 2012;344:e2803.
38. Moore MR, Schrag SJ, Schuchat A. Effects of intrapartum antimicrobial prophylaxis for prevention of group-B-streptococcal disease on the incidence and ecology of early-onset neonatal sepsis. Lancet Infect Dis 2003 Apr;3(4.:201-13.
39. Stoll BJ, Hansen NI, Higgins RD, Fanaroff AA, Duara S, Goldberg R, et al. Very low birth weight preterm infants with early onset neonatal sepsis: the predominance of gram-negative infections

continues in the National Institute of Child Health and Human Development Neonatal Research Network, 2002-2003. Pediatr Infect Dis J 2005 Jul;24(7.:635-9.
40. Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy 1988 Nov;18(6.:515-40.
41. Pylipow M, Gaddis M, Kinney JS. Selective intrapartum prophylaxis for group B streptococcus colonization: management and outcome of newborns. Pediatrics 1994 Apr;93(4.:631-5.
42. Dunn AB, Blomquist J, Khouzami V. Anaphylaxis in labor secondary to prophylaxis against group B Streptococcus. A case report. J Reprod Med 1999 Apr;44(4.:381-4.
43. Gei AF, Pacheco LD, Vanhook JW, Hankins GD. The use of a continuous infusion of epinephrine for anaphylactic shock during labor. Obstet Gynecol 2003 Dec;102(6.:1332-5.
44. Sheikh J. Intrapartum anaphylaxis to penicillin in a woman with rheumatoid arthritis who had no prior penicillin allergy. Ann Allergy Asthma Immunol 2007 Sep;99(3.:287-9.
45. Chaudhuri K, Gonzales J, Jesurun CA, Ambat MT, Mandal-Chaudhuri S. Anaphylactic shock in pregnancy: a case study and review of the literature. Int J Obstet Anesth 2008 Oct;17(4.:350-7.
46. Glasgow TS, Young PC, Wallin J, Kwok C, Stoddard G, Firth S, et al. Association of intrapartum antibiotic exposure and late-onset serious bacterial infections in infants. Pediatrics 2005 Sep;116(3.:696-702.
47. Dinsmoor MJ, Viloria R, Lief L, Elder S. Use of intrapartum antibiotics and the incidence of postnatal maternal and neonatal yeast infections. Obstet Gynecol 2005 Jul;106(1.:19-22.
48. Bedford-Russell AR. New modalities for treating neonatal infection. Eur J Pediatr 1996 Aug;155 Suppl 2:S21-S24.
49. Murch SH. Toll of allergy reduced by probiotics. Lancet 2001 Apr 7;357(9262.:1057-9.
50. Terrone DA, Rinehart BK, Einstein MH, Britt LB, Martin JN, Jr., Perry KG. Neonatal sepsis and death caused by resistant Escherichia coli: possible consequences of extended maternal ampicillin administration. Am J Obstet Gynecol 1999 Jun;180(6 Pt 1.:1345-8.
51. Towers CV, Carr MH, Padilla G, Asrat T. Potential consequences of widespread antepartal use of ampicillin. Am J Obstet Gynecol 1998 Oct;179(4.:879-83.
52. Joseph TA, Pyati SP, Jacobs N. Neonatal early-onset Escherichia coli disease. The effect of intrapartum ampicillin. Arch Pediatr Adolesc Med 1998 Jan;152(1.:35-40.
53. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. N Engl J Med 2002 Jul 25;347(4.:240-7.
54. Baltimore RS, Huie SM, Meek JI, Schuchat A, O'Brien KL. Early-onset neonatal sepsis in the era of group B streptococcal prevention. Pediatrics 2001 Nov;108(5.:1094-8.
55. Hyde TB, Hilger TM, Reingold A, Farley MM, O'Brien KL, Schuchat A. Trends in incidence and antimicrobial resistance of early-onset sepsis: population-based surveillance in San Francisco and Atlanta. Pediatrics 2002 Oct;110(4.:690-5.
56. Schrag SJ, Hadler JL, Arnold KE, Martell-Cleary P, Reingold A, Schuchat A. Risk factors for invasive, early-onset Escherichia coli infections in the era of widespread intrapartum antibiotic use. Pediatrics 2006 Aug;118(2.:570-6.
57. Benitz WE, Gould JB, Druzin ML. Preventing early-onset group B streptococcal sepsis: strategy development using decision analysis. Pediatrics 1999 Jun;103(6.:e76.
58. Benitz WE, Gould JB, Druzin ML. Antimicrobial prevention of early-onset group B streptococcal sepsis: estimates of risk reduction based on a critical literature review. Pediatrics 1999 Jun;103(6.:e78.
59. Schrag SJ, Zell ER, Lynfield R, Roome A, Arnold KE, Craig AS, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. N Engl J Med 2002 Jul 25;347(4.:233-9.

60. Rosenstein NE, Schuchat A. Opportunities for prevention of perinatal group B streptococcal disease: a multistate surveillance analysis. The Neonatal Group B Streptococcal Disease Study Group. Obstet Gynecol 1997 Dec;90(6.:901-6.
61. Akker-van Marle ME, Rijnders ME, Dommelen P, Fekkes M, Wouwe JP, Amelink-Verburg MP, et al. Cost-effectiveness of different treatment strategies with intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal disease. BJOG 2005 Jun;112(6.:820-6.
62. Wolf H, Wouters MG, Trijbels-Smeulders M. Re: Cost-effectiveness of different treatment strategies with intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal disease. BJOG 2006 Mar;113(3.:357-9.

Chapter 9

Summary, General Discussion and Future Perspectives

9

Group B Streptococcus (GBS, Streptococcus agalactiae) has been recognized as an important cause of perinatal morbidity and mortality.(1-3) The frequency of GBS colonization ranges from 10% to 35% in women of reproductive age.(4;5) GBS colonization can be transient, intermittent or persistent.(6-8) Vertical transmission of GBS from mother to child occurs during labor. Studies on vertical GBS transmission in colonized mothers during labor report incidences of colonization of the infant between 16 and 69%.(9-14) Early-onset group B streptococcal disease (GBS-EOD) occurs in approximately 1% of newborns who are colonized with GBS.(15)

Established risk factors for acquiring GBS-EOD are prolonged rupture of membranes, preterm labor, intrapartum fever, GBS bacteriuria during pregnancy or a previous child with GBS-EOD.(16) Intrapartum antibiotic prophylaxis (IAP) given to women at risk of transmitting GBS to their baby may prevent GBS-EOD.(14;17) Identification of mothers at risk may be performed by screening (taking a culture during pregnancy to detect maternal colonization) and/ or by identifying pregnancies with one or more 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.(18) 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 recommended worldwide in both screening based and risk factor based strategies. In women with preterm labor (< 37 weeks) or prolonged rupture of membranes (>18 hours), a culture is taken, followed by IAP when the culture is GBS-positive. Culture results are available after 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) or by symptoms of infection.

After implementation of prevention strategies, the overall incidence of GBS-EOD in many countries over the world has declined progressively.(18-21) However, current strategies for prevention of GBS-EOD are still subject of controversy. Despite considerable efforts and economic resources spent on prevention of GBS-EOD, it is still an important cause of neonatal infection and early neonatal mortality within the first seven days of life.(2;18;20;22;23)

In the Netherlands, there has been a limited decrease in the incidence of GBS-EOD.(24) 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.(25) 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. Other

factors contributing to ongoing disease could be insufficient sampling, delay in processing, suboptimal laboratory techniques, recent antibiotic use or colonization after screening was performed, ie wrong timing of antenatal cultures. These factors, together with several other aspects of antenatal and perinatal clinical practice including lack of guidelines, lack of communication, improper implementation of IAP and microbiological factors such as antibiotic resistance, may all cause that opportunities in the prevention and further decline of GBS-EOD are missed. Since the overall effect of the Dutch guideline on the incidence of GBS-EOD is disappointing, adaptation of the Dutch guidelines should be reconsidered. The aim of this thesis is to contribute to the information needed for the establishment of an optimal preventive strategy for GBS-EOD.

This thesis

The best prevention strategy maximizes treatment in women who need it, and minimizes treatment in women who do not need it. To be able to optimize the Dutch strategy it is essential to start with knowledge about the prevalence of GBS colonization of pregnant women in the Netherlands, which may have changed due to recent changes in demographics, in particular with regard to ethnic background of women living in major cities. In our study described in **chapter 2,** we show that in the multicultural, urban population of pregnant women in The Hague, the Netherlands, the prevalence of GBS colonization is 21%. We found differences between 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 show that it is not possible to identify a subgroup of pregnant women that is at higher risk for GBS colonization. Positive predictive value of GBS carriage at 35-37 weeks gestation for carriage at time of parturition was 79% and negative predictive value was 93%.

A secondary analysis of our cohort of pregnant women was performed to evaluate whether labor before 37 weeks of gestation or prolonged rupture of membranes can predict prenatal GBS status. If women with these risk factors are at higher risk to carry GBS, Dutch guidelines could be improved by advising direct administration of antibiotics to women with these risk factors instead of waiting for culture results before start IAP. We found that occurrence of the risk factors preterm birth and/or rupture of membranes for more then 24 hrs does not predict GBS colonization. Occurrence of this risk factor in itself is therefore not helpful in identifying mothers at higer risk for a baby with GBS-EOD.(**Chapter 3**)

In the Dutch modified risk factor based guideline on prevention of GBS-EOD, intrapartum maternal administration of benzylpenicillin is advised in women eligible for IAP. In case of a history of penicillin allergy, clindamycin or erythromycin is recommended as alternative. Previous reports have documented universal susceptibility to benzylpenicillin and cephalosporins, but resistance of GBS to erythromycin and clindamycin has increased during the

last decade in several countries, with some geographical variations.(26-29) Especially for antibiotics used in widespread prophylactic treatment regimens, continuous surveillance for resistance and clonal spread of resistant microorganisms is needed. In **chapter 4** we describe the prevalence of phenotypic and genotypic macrolide-resistance among group B streptococci isolated in the Dutch prevalence study as described in Chapter 2 and we explore the possibility of clonal spread of resistant GBS isolates in a multicultural population. Antimicrobial resistance patterns of 107 GBS isolates were determined using Etests. Macrolide resistance genes *mef*(A), *erm*(TR) and *erm*(B) were determined with PCR and a subset of 39 isolates, including the 8 isolates harbouring macrolide resistance genes, was subjected to RAPD analysis to detect clonal spreading. Resistance to erythromycin and clindamycin was found in 8% and 7%, respectively. Macrolide resistance genes *mef*(A), *erm*(TR) and *erm*(B) were found in 1, 2 and 5 isolates, respectively; only five of these eight isolates exhibited both genotypic as well as phenotypic resistance. One genotype occurred in 36% of the subset. Earlier reports on prevalence of phenotypic resistance were confirmed. Among the susceptible isolates one clonal type of GBS was clearly predominant; one of the resistant isolates shared its genotype. When such clonal types acquire resistance traits in the future, GBS disease may become harder to control.

Preterm delivery in GBS colonized mothers is a recognized risk factor for early-onset neonatal GBS disease (GBS-EOD)(30), but whether maternal GBS genital colonization is related to preterm labor is unclear. In the search for opportunities for timely interventions in the prevention of GBS-EOD, we critically reviewed the literature to find any association between maternal GBS colonization and preterm delivery. In **chapter 5** results of this systematic review are described. The search strategy yielded studies with different study designs and different study periods, from countries with different prevalence of GBS colonization and preterm labor. Preterm labor seems positively associated with GBS colonization at the time of delivery, but colonization during pregnancy is not associated with occurrence of preterm delivery. A positive relationship between colonization and risk of preterm birth would provide opportunities for further research regarding antibiotic interventions in the prevention of preterm labor caused by GBS.

In **chapter 6** we describe a meta-analysis 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. GBS colonization can be transient, intermittent or persistent. International studies report that the majority of remaining GBS-EOD nowadays occurs in infants whose mothers screened negative for GBS colonization.(31) 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.(32;33) Improving the effectiveness of GBS screening and awareness of its limitations might help to further decrease the prevalence of GBS-EOD.

We found that the positive predictive values (PPVs) correlate positively with increasing gestational age at time of GBS culture. 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. Our systematic review confirms the recommendations to screen pregnant women for colonization of GBS at 35-37 weeks gestation. However, since 6% of GBS carriers during delivery remain undetected in antenatal cultures one should be aware of the limitations of screening. There are two options for preventing GBS-EOD in preterm infants whose mothers are not yet screened: either giving IAP in all premature deliveries or screening of all pregnant women early in pregnancy and culturing again later in pregnancy.

With regard to the remaining burden of disease it is important to identify potential areas for improvement in the total process from antenatal care to discharge of a healthy women with a healthy baby. In **chapter 7** we indicate opportunities for improvement of prevention of GBS-EOD. Training in recognizing GBS-EOD is important. Knowledge about the route to disease and the possible preventive measures deserve continued attention of all workers in obstetric care, either in hospitals or at home. Caregivers need to be aware that there are a lot of small steps in the chain of prevention where improvement can be made. These include establishment of national and local prevention guidelines, accuracy of GBS prenatal screening, good implementation and communication, correct procedures for laboratory techniques, proper dosage and duration of IAP and clear appointments about secondary prevention of GBS-EOD among newborn infants. In **chapter 8,** we describe several strategies for prevention of GBS-EOD as alternatives for the current Dutch modified risk factor based guideline. As mentioned before, the best preventive strategy maximizes treatment in women who need it, and minimizes treatment in women who do not need it. We suggest that changing the current guideline into a guideline which advocates the combinationstrategy will result in a optimimal prevention of GBS-EOD in the Netherlands. In theory, the combination of the screening based strategy and risk factor based strategy (combinationstrategy) has the lowest number needed to treat, i.e. only 47 pregnant women need to get IAP to prevent one case of GBS-EOD. There is an equal percentage of unprotected infants in comparison to the risk factor based strategy. However, the great advantage of the combinationstrategy is that GBS status is always known, which allows caregivers to be extra alert on babies from GBS positive mothers who do not receive IAP because there is no risk factor. Parents of these newborns can be informed as well to watch for signs of GBS-EOD. This combination strategy will not interfere with the Dutch obstetrical system and will not lead to extra hospital referrals.

Future Perspectives and directions of research

This thesis contributes to the information needed for the establishment of an optimal preventive strategy for GBS-EOD. Although much progress has been made in the prevention of

GBS-EOD, important challenges remain. Early-onset disease has declined among all racial and ethnic groups, yet disparities persist. Research aimed at better understanding racial or ethnic differences in GBS disease might lead to opportunities for more effective prevention efforts. Continued monitoring and analysis of cases of GBS-EOD is needed in order to get tools for future prevention. The evidence is incomplete for several areas related to GBS prevention, including strategies to prevent GBS-EOD among preterm infants, the role of bacteriuria as a risk factor in the era of universal screening and effectiveness of recommended antibiotics other than penicillin for penicillin allergic women at high risk for anaphylaxis. 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, therefore permitting practitioners to draw more dependable conclusions from culture results. By identification of most virulent GBS strains, IAP can targeted been given in carriers of these specific GBS strains, thereby decreasing the total proportion of women treated with antibiotics unnecessarily . The development of a rapid laboratory test to identify GBS will bring us closer to the possibility of an intrapartum test for GBS screening. This screening test for GBS should consist of a simple bedside kit that enables delivery staff to perform a test, have a turn-around time of less than 1 hour and have a sensitivity and specificity of > 90%. Ideally, a rapid test for intrapartum use also would give information about resistance to clindamycin and/or erythromycin in order to guide antibiotic choice for penicillin-allergic women. Alternative strategies continue to merit evaluation. These include use of the vaginal disinfectant chlorhexidine applied topically during labor, as well as newborn washes with chlorhexidine formulation.

In recognition of the shortcomings of IAP-based prevention strategies, vaccination has the most potential for eradicating invasive GBS disease of the neonate and the young infant, as well as of the mother. Several other advantages might be anticipated; vaccination would avoid antibiotics, screening and labor intrusions and could protect against both early and late onset disease. Development of GBS vaccines is scientifically feasible(34) and multiple phase II studies, including among pregnant women, have already been conducted. Practical, legal and business concerns have thus far hindered the achievements of licensure of GBS vaccines targeted for use in pregnancy. To ensure effective vaccine development, it will be important to monitor the distribution pattern of the prevalent serotypes and sequence types in all regions of the world continuously, thereby ensuring the inclusion of the most relevant components in a global GBS vaccine.(35) However, a vaccination program is effective only if the entire target audience is reached, and this will be a continuous challenge for anyone involved in the area of prevention of disease. The introduction in 1998 of a Dutch national guideline on prevention of GBS-EOD resulted in a slight reduction in the incidence of proven GBS-EOD, but not in a decrease in severe morbidity and mortality. Latest

information even shows increase in cases of GBS sepsis per year. It is therefore clear that the current Dutch guideline is not effective enough and a new strategy to prevent GBS-EOD is justified, in particular with regard to the fact that perinatal mortality in the Netherlands is high compared to other European countries.(25) Until a safe and efficacious vaccine is licensed and implemented, areas of research in the Netherlands should include studies on cost-effectiveness of several prevention strategies, including trials on vaginal chlorhexidine flushing compared to intravenous antibiotics in GBS carriers during term delivery. Cases of GBS-EOD in the Netherlands should be monitored and analyzed in order to improve future prevention. By evaluating and debating existing guidelines and giving priority to find the best prevention strategy for GBS-EOD, it should be possible to further decrease the burden of this disease in the Netherlands.

REFERENCE LIST

1. Schuchat A. Epidemiology of group B streptococcal disease in the United States: shifting paradigms. Clin Microbiol Rev 1998 Jul;11(3.:497-513.
2. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. Pediatr Infect Dis J 2011 Nov;30(11.:937-41.
3. Edmond KM, Kortsalioudaki C, Scott S, Schrag SJ, Zaidi AK, Cousens S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. Lancet 2012 Feb 11;379(9815.:547-56.
4. Barcaite E, Bartusevicius A, Tameliene R, Kliucinskas M, Maleckiene L, Nadisauskiene R. Prevalence of maternal group B streptococcal colonisation in European countries. Acta Obstet Gynecol Scand 2008;87(3.:260-71.
5. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. MMWR Recomm Rep 2002 Aug 16;51(RR-11.:1-22.
6. Lewin EB, Amstey MS. Natural history of group B streptococcus colonization and its therapy during pregnancy. Am J Obstet Gynecol 1981 Mar 1;139(5.:512-5.
7. Hoogkamp-Korstanje JA, Gerards LJ, Cats BP. Maternal carriage and neonatal acquisition of group B streptococci. J Infect Dis 1982 Jun;145(6.:800-3.
8. Hansen SM, Uldbjerg N, Kilian M, Sorensen UB. Dynamics of Streptococcus agalactiae colonization in women during and after pregnancy and in their infants. J Clin Microbiol 2004 Jan;42(1.:83-9.
9. Pylipow M, Gaddis M, Kinney JS. Selective intrapartum prophylaxis for group B streptococcus colonization: management and outcome of newborns. Pediatrics 1994 Apr;93(4.:631-5.
10. de Cueto M, Sanchez MJ, Molto L, Miranda JA, Herruzo AJ, Ruiz-Bravo A, et al. Efficacy of a universal screening program for the prevention of neonatal group B streptococcal disease. Eur J Clin Microbiol Infect Dis 1995 Sep;14(9.:810-2.
11. Hickman ME, Rench MA, Ferrieri P, Baker CJ. Changing epidemiology of group B streptococcal colonization. Pediatrics 1999 Aug;104(2 Pt 1.:203-9.
12. Lim DV, Morales WJ, Walsh AF, Kazanis D. Reduction of morbidity and mortality rates for neonatal group B streptococcal disease through early diagnosis and chemoprophylaxis. J Clin Microbiol 1986 Mar;23(3.:489-92.
13. Adriaanse AH, Kollee LA, Muytjens HL, Nijhuis JG, de Haan AF, Eskes TK. Randomized study of vaginal chlorhexidine disinfection during labor to prevent vertical transmission of group B streptococci. Eur J Obstet Gynecol Reprod Biol 1995 Aug;61(2.:135-41.
14. Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. Cochrane Database Syst Rev 2009;(3.:CD007467.
15. Itakura A, Kurauchi O, Morikawa S, Matsuzawa K, Mizutani S, Tomoda Y. A prospective study on the relationship between intrapartum maternal group-B streptococcal concentration and signs of infection in neonates. J Obstet Gynaecol Res 1996 Apr;22(2.:101-5.
16. Oddie S, Embleton ND. Risk factors for early onset neonatal group B streptococcal sepsis: case-control study. BMJ 2002 Aug 10;325(7359.:308.
17. Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. N Engl J Med 1986 Jun 26;314(26.:1665-9.
18. Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep 2010 Nov 19;59(RR-10.:1-36.
19. Schuchat A. Group B streptococcus. Lancet 1999 Jan 2;353(9146.:51-6.
20. Van Dyke MK, Phares CR, Lynfield R, Thomas AR, Arnold KE, Craig AS, et al. Evaluation of universal antenatal screening for group B streptococcus. N Engl J Med 2009 Jun 18;360(25.:2626-36.

21. Verani JR, Schrag SJ. Group B streptococcal disease in infants: progress in prevention and continued challenges. Clin Perinatol 2010 Jun;37(2.:375-92.
22. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn: Guidelines for prevention of group B streptococcal (GBS. infection by chemoprophylaxis. Pediatrics 1992 Nov;90(5.:775-8.
23. Stoll BJ, Hansen NI, Sanchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics 2011 May;127(5.:817-26.
24. Trijbels-Smeulders M, de Jonge GA, Pasker-de Jong PC, Gerards LJ, Adriaanse AH, van Lingen RA, et al. Epidemiology of neonatal group B streptococcal disease in the Netherlands before and after introduction of guidelines for prevention. Arch Dis Child Fetal Neonatal Ed 2007 Jul;92(4.:F271-F276.
25. Mohangoo AD, Buitendijk SE, Hukkelhoven CW, Ravelli AC, Rijninks-van Driel GC, Tamminga P, et al. [Higher perinatal mortality in The Netherlands than in other European countries: the Peristat-II study]. Ned Tijdschr Geneeskd 2008 Dec 13;152(50.:2718-27.
26. Blaschke AJ, Pulver LS, Korgenski EK, Savitz LA, Daly JA, Byington CL. Clindamycin-resistant group B Streptococcus and failure of intrapartum prophylaxis to prevent early-onset disease. J Pediatr 2010 Mar;156(3.:501-3.
27. Phares CR, Lynfield R, Farley MM, Mohle-Boetani J, Harrison LH, Petit S, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. JAMA 2008 May 7;299(17.:2056-65.
28. Muller AE, Valkenburg-van den Berg AW, Kreft D, Oostvogel PM, Sprij AJ, van Belkum A. Low rate of carriage of macrolide-resistant group B streptococci in pregnant women in The Netherlands. Eur J Obstet Gynecol Reprod Biol 2008 Mar;137(1.:17-20.
29. Castor ML, Whitney CG, Como-Sabetti K, Facklam RR, Ferrieri P, Bartkus JM, et al. Antibiotic resistance patterns in invasive group B streptococcal isolates. Infect Dis Obstet Gynecol 2008;2008:727505.
30. Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics 1999 Jun;103(6.:e77.
31. Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. Pediatrics 2005 May;115(5.:1240-6.
32. Easmon CS, Hastings MJ, Neill J, Bloxham B, Rivers RP. Is group B streptococcal screening during pregnancy justified? Br J Obstet Gynaecol 1985 Mar;92(3.:197-201.
33. Goodman J, Berg R, Gribble R, Meier P, Fee SC, Mitchel P. Longitudinal Study of Group B Streptococcus Carriage in Pregnancy. Infect Dis Obstet Gynecol 1997;(5.:237-43.
34. Heath PT, Feldman RG. Vaccination against group B streptococcus. Expert Rev Vaccines 2005 Apr;4(2.:207-18.
35. Johri AK, Paoletti LC, Glaser P, Dua M, Sharma PK, Grandi G, et al. Group B Streptococcus: global incidence and vaccine development. Nat Rev Microbiol 2006 Dec;4(12.:932-42.

Chapter 10

Nederlandse Samenvatting

10

Groep B Streptokokken (*Streptococcus Agalactiae*, GBS) zijn in de westerse wereld belangrijke verwekkers van vroege en soms zeer ernstig verlopende infecties bij pasgeborenen.(1-3) Besmetting met GBS vindt plaats van moeder naar kind tijdens de baring (verticale transmissie). Er is sprake van GBS-dragerschap bij 10% tot 35% van de vrouwen in de fertiele levensfase.(4;5) GBS-dragerschap kan van voorbijgaande aard zijn, maar ook intermitterend of continue.(6-8) Studies naar verticale transmissie bij vrouwen die GBS-drager zijn, rapporteren kolonisatie van het kind in 16 tot 69% van de gevallen.(9-14) Neonatale groep B streptokokken ziekte (GBS-early onset disease, GBS-EOD) komt voor bij ongeveer 1% van de pasgeborenen die zijn gekoloniseerd met GBS.(15)

Van een aantal factoren is bekend of wordt aangenomen dat zij, indien GBS in het baringskanaal aanwezig is, de kans op een infectie vroeg in de neonatale periode aanzienlijk vergroten. Deze risicofactoren zijn 1.vroeggeboorte, 2.langdurig gebroken vliezen, 3.koorts van de moeder tijdens de baring, 4.GBS-bacteriurie en 5.GBS-ziekte bij een eerder kind.(16)

Het is effectief gebleken om -aan vrouwen die risico lopen om een kind met GBS-ziekte te krijgen- tijdens de bevalling antibioticaprofylaxe toe te dienen om GBS-ziekte bij de pasgeborene te voorkomen.(14;17) Het opsporen van deze zwangeren met een verhoogd risico op verticale transmissie, kan door middel van screening (een kweek afnemen tijdens de zwangerschap om GBS-kolonisatie op te sporen) (screeningstrategie) en/of door het identificeren van zwangerschappen met één of meer van de risicofactoren voor GBS-EOD (risicofactorstrategie).

In de wereld bestaat geen eenduidig beleid voor de preventie van GBS-EOD. In de Verenigde Staten bijvoorbeeld, wordt door de 'Centers for Disease Control en Prevention' (CDC) aanbevolen alle zwangere vrouwen bij een zwangerschapsduur van 35-37 weken te screenen op dragerschap en preventief antibiotica tijdens de bevalling te geven aan alle GBS-dragers.(18)

De huidige Nederlandse richtlijn voor preventie van perinatale groep B streptokokken-ziekte, geformuleerd door de Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG) en de Nederlandse Vereniging voor Kindergeneeskunde (NvK), gaat uit van de risicofactorstrategie. In de richtlijn wordt geadviseerd tijdens de bevalling intraveneus antibiotica te geven aan vrouwen met koorts (> 38°C), zwangeren met GBS-bacteriurie of vrouwen die een eerder kind hadden met GBS-infectie. Bij vrouwen met vroegtijdige weeën (<37 weken) of langdurig gebroken vliezen (> 18 uur), wordt in de Nederlandse richtlijn geadviseerd een rectovaginale kweek af te nemen, gevolgd door intraveneuze antibioticaprofylaxe als de kweekuitslag positief is. Meestal is de kweekuitslag bekend na 24 tot 48 uur. Wanneer de bevalling plaatsvindt vóórdat de uitslag van de kweek beschikbaar is, moet de gynaecoloog beslissen over het al dan niet intraveneus toedienen van antibiotica tijdens de bevalling. De beslissing is meestal gebaseerd op de ernst van de risicofactor(en) of op symptomen van infectie.

Sinds de implementatie van preventiestrategieën is de totale incidentie van GBS-EOD in vele landen over de hele wereld geleidelijk afgenomen,(18-21) maar de huidige strategieën voor preventie van GBS-EOD zijn nog steeds onderwerp van discussie. Ondanks aanzienlijke inspanning en investeringen in geld besteed aan de preventie van GBS-EOD, blijft het een belangrijke oorzaak van neonatale infectie en neonatale sterfte binnen de eerste zeven dagen van het leven.(2;18;20;22;23)

In Nederland is er sinds de invoering van de huidige richtlijn ter preventie van perinatale groep B streptokokkenziekte sprake van een beperkte daling van de incidentie van GBS-EOD.(24) Dit geeft aanleiding tot discussie over verbetering of verandering van de richtlijn. Deze discussie is actueel naar aanleiding van cijfers over de perinatale sterfte in Nederland, die hoog is in vergelijking met andere Europese landen.(25)

De beperkte effectiviteit van de huidige richtlijn zou kunnen worden verklaard door het feit dat in geval van het optreden van vroeggeboorte of langdurig gebroken vliezen, mogelijkheden tot preventie kunnen worden gemist als gevolg van vertraging bij het verkrijgen van kweekresultaten. Andere factoren die bijdragen aan het voortbestaan van GBS-ziekte zijn onjuiste kweekafname, vertraging in de verwerking van kweken, suboptimale laboratoriumtechnieken, recent gebruik van antibiotica of optreden van kolonisatie nadat de screeningskweek werd uitgevoerd, onder andere door een verkeerde timing van de afname van de kweek. Ook factoren zoals het ontbreken van (lokale) richtlijnen, gebrek aan communicatie van alle betrokkenen bij pre-en perinatale zorg of onjuiste uitvoering van de richtlijn en microbiologische factoren zoals resistentie tegen antibiotica, kunnen leiden tot het missen van mogelijkheden tot preventie en daarmee tot het uitblijven van een verdere daling van GBS-EOD.

Omdat het totale effect van de Nederlandse richtlijn op de incidentie van GBS-EOD teleurstellend is, dient aanpassing van de Nederlandse richtlijn plaats te vinden. Het doel van dit proefschrift is een bijdrage te leveren aan de informatie die nodig is voor het opstellen van een optimale preventie strategie voor GBS-EOD.

Dit proefschrift

De beste preventiestrategie maximaliseert de behandeling bij vrouwen die het nodig hebben, en minimaliseert de behandeling bij vrouwen die het niet nodig hebben. Alvorens de Nederlandse strategie te kunnen optimaliseren, is het essentieel om kennis over de prevalentie van GBS-kolonisatie van zwangere vrouwen in Nederland te verkrijgen. Prevalentie van dragerschap zou veranderd kunnen zijn als gevolg van recente demografische veranderingen, in het bijzonder met betrekking tot de etnische achtergrond van vrouwen die in grote steden wonen. In onze studie beschreven in **hoofdstuk 2** tonen we aan dat onder de multiculturele, randstedelijke bevolking van de zwangere vrouwen in Den Haag, Nederland, de prevalentie van GBS-kolonisatie 21% is. We vonden ethnische verschillen tussen gekoloniseerde en niet-gekoloniseerde vrouwen, maar we konden geen verschillen

aantonen tussen gekoloniseerde en niet-gekoloniseerde vrouwen met betrekking tot leeftijd, pariteit of sociaal-economische achtergrond. De resultaten van deze studie laten zien dat het niet mogelijk is een subgroep van zwangere vrouwen die een hoger risico op GBS-kolonisatie hebben, te identificeren. De positief voorspellende waarde van GBS-dragerschap bij 35-37 weken zwangerschap voor dragerschap op het moment van de bevalling was 79% en de negatief voorspellende waarde was 93%.

Een secundaire analyse van ons cohort van zwangere vrouwen werd uitgevoerd om na te gaan of het optreden van vroeggeboorte vóór 37 weken zwangerschapsduur of het optreden van langdurig gebroken vliezen kan voorspellen wat de prenatale GBS-status is. Als vrouwen met deze risicofactoren een hoger risico lopen om GBS-drager te zijn, kan de Nederlandse richtlijn worden verbeterd door het adviseren van directe toediening van antibiotica aan vrouwen met deze risicofactoren, in plaats van te wachten tot kweekresultaten bekend zijn voordat antibioticaprofylaxe wordt gestart. We vonden dat het optreden van de risicofactoren vroeggeboorte en/of gebroken vliezen langer dan 24 uur niet voorspellend is voor GBS-kolonisatie. Het optreden van deze risicofactor op zich is dus niet te gebruiken bij het identificeren van moeders met een hoger risico op een baby met GBS-EOD. (**Hoofdstuk 3**)

In de Nederlandse richtlijn voor preventie van perinatale GBS-ziekte wordt aangeraden intraveneus benzylpenicilline te geven aan vrouwen die in aanmerking komen voor profylactisch antibiotica tijdens de bevalling. Indien er sprake is van penicilline-allergie, wordt clindamycine of erytromycine aanbevolen als alternatief. Diverse studies rapporteren universele gevoeligheid voor benzylpenicilline en cefalosporines, maar de resistentie van GBS voor erytromycine en clindamycine is in de loop van de laatste tien jaar in verschillende landen toegenomen.(26-29)

Wanneer antibiotica op grote schaal gebruikt wordt ter preventie van ziekte, is waakzaamheid geboden met betrekking tot de ontwikkeling van antibiotica-ongevoeligheid en klonale verspreiding van resistente micro-organismen.

In **hoofdstuk 4** beschrijven we de prevalentie van fenotypische en genotypische resistentie tegen macroliden bij groep B streptokokken die werden geïsoleerd in de Nederlandse prevalentiestudie, zoals beschreven in hoofdstuk 2. Wij onderzochten de mogelijkheid van klonale verspreiding van resistente GBS isolaten in een multiculturele populatie. De antimicrobiële resistentie patronen van 107 GBS isolaten werden bepaald met behulp van Etests. Door middel van PCR-onderzoek werd aanwezigheid van macrolide resistentiegenen *mef* (A), *erm* (TR) en *erm* (B) bepaald. Een subgroep van 39 isolaten, waaronder de 8 isolaten met macrolide resistentiegenen, werd onderworpen aan RAPD-analyse om klonale verspreiding te detecteren. Resistentie tegen erytromycine en clindamycine werd gevonden in respectievelijk 8% en 7%. De macrolide resistentiegenen *mef* (A), *erm* (TR)

en *erm* (B) werden gevonden in respectievelijk 1, 2 en 5 isolaten; slechts vijf van deze acht isolaten vertoonden zowel genotypische als fenotypische resistentie. Van de geanalyseerde subgroep behoorde 36% tot eenzelfde genotype. Eerdere berichten over de prevalentie van fenotypische resistentie werden bevestigd. Onder de gevoelige isolaten was duidelijk één GBS-kloon overheersend en één van de resistente isolaten had eenzelfde genotype als deze GBS-kloon. Wanneer dergelijke klonen in de toekomst resistentie verwerven, kan GBS-ziekte moeilijker te controleren worden.

Vroeggeboorte bij moeders die GBS-drager zijn is een erkende risicofactor voor GBS-ziekte(30), maar of maternaal GBS-dragerschap is gerelateerd aan vroeggeboorte is onduidelijk. Een positieve relatie tussen GBS-kolonisatie en optreden van vroegtijdige geboorte zou mogelijkheden bieden voor verder onderzoek met betrekking tot antibiotische interventies bij de preventie van vroeggeboorte als gevolg van GBS.

In de zoektocht naar mogelijkheden voor tijdige interventie in de preventie van GBS-EOD, werd een literatuurstudie verricht om een samenhang tussen GBS-dragerschap en vroeggeboorte te vinden. In **hoofdstuk 5** worden de resultaten van deze systematische review beschreven. De zoekstrategie leverde studies op met uiteenlopende studieopzet in verschillende studieperiodes, uit landen met verschillende prevalentie van GBS-dragerschap en vroeggeboorte. Vroeggeboorte lijkt positief geassocieerd met GBS-kolonisatie op het moment van bevalling, maar dragerschap tijdens de zwangerschap is niet geassocieerd met het optreden van vroeggeboorte.

In **hoofdstuk 6** worden de uitkomsten van een meta-analyse naar het optimale tijdstip van GBS-screening in de zwangerschap beschreven. GBS-kolonisatie kan van voorbijgaande aard zijn, maar ook intermitterend of continue aanwezig zijn. Onderzoeksresultaten van meerdere landen laten zien dat het merendeel van de GBS-ziekte tegenwoordig voorkomt bij zuigelingen van wie de moeder bij screening GBS negatief was.(31) De voorspellende waarde van GBS-kweken afgenomen bij een zwangerschapsduur van 35-37 weken is in geen enkele studie 100% gebleken. Bovendien, door screening rondom deze amenorroeduur zal geen informatie worden verkregen over GBS-dragerschap in de preterme periode, terwijl GBS-ziekte juist bij preterm geboren kinderen het meest gevaarlijk is.(32;33) Verbetering van de effectiviteit van GBS-screening en het bewustzijn van de beperkingen zou kunnen helpen bij het verder verminderen van de incidentie van GBS-EOD. Uit analyse blijkt dat de positief voorspellende waarde (PPV) positief correleert met toenemende zwangerschapsduur ten tijde van de GBS-kweek. De PPV neemt af wanneer het interval tussen de prenataal afgenomen kweek en de kweek afgenomen bij de bevalling toeneemt, vooral wanneer het interval meer is dan zes weken. De negatief voorspellende waarde blijft constant en staat daarom los van de zwangerschapsduur waarbij de kweek is uitgevoerd. Onze systematische review bevestigt de internationale aanbevelingen om GBS-screening tijdens

de zwangerschap te verrichten rond 35-37 weken zwangerschapsduur. Omdat 6% van de vrouwen die GBS-drager is tijdens de bevalling, onopgemerkt blijft tijdens de antenatale kweken moet men zich bewust zijn van de beperkingen van de screening. Er zijn twee opties voor het voorkomen van GBS-EOD bij premature zuigelingen van wie de moeder nog niet gescreend is: ofwel antibiotica geven aan alle vrouwen met een vroeggeboorte, of screening van alle zwangere vrouwen in het begin van de zwangerschap en het herhalen van de kweken later in de zwangerschap.

Om de mortaliteit en morbiditeit ten gevolge van GBS-ziekte verder terug te kunnen dringen, is het van belang aanknopingspunten voor verbetering te identificeren. Hierbij dienen mogelijkheden voor verbetering te worden onderzocht in het totale proces van prenatale zorg voor de zwangere tot en met ontslag van een gezonde moeder met een gezonde baby. In **hoofdstuk 7** worden mogelijkheden voor verbetering van de preventie van GBS-EOD beschreven. Training in het herkennen van GBS-ziekte is belangrijk. Kennis over de pathologie van het ziektebeeld en de mogelijke preventieve maatregelen verdienen blijvende aandacht van alle zorgverleners in de keten. Zorgverleners moeten zich ervan bewust zijn dat er in de keten van preventie vele kleine stappen zijn waar verbetering kan worden bewerkstelligd. Hierbij valt te denken aan het opstellen van nationale en lokale preventie-richtlijnen, juiste timing en techniek van afname van GBS-kweken, een goede implementatie en communicatie, de juiste procedures voor laboratorium technieken, de juiste dosering en duur van antibioticaprofylaxe en duidelijke afspraken over de secundaire preventie van GBS-ziekte bij pasgeboren baby's. In **hoofdstuk 8** zijn verschillende strategieën voor de preventie van GBS-EOD genoemd als alternatieven voor de huidige Nederlandse richtlijn die op de risicofactorstrategie is gebaseerd. Zoals eerder vermeld, is de beste preventieve strategie een strategie die behandeling geeft aan vrouwen die het nodig hebben, en geen behandeling aan vrouwen die het niet nodig hebben. We adviseren aanpassing van de huidige richtlijn en pleiten voor de combinatiestrategie als optimale preventiestrategie ter preventie van perinatale GBS-ziekte in Nederland.

In theorie heeft deze combinatie van zowel op screening als op risicofactoren gebaseerde strategie (de combinatiestrategie) het laagste 'number needed to treat', dat wil zeggen slechts 47 zwangere vrouwen moeten tijdens de bevalling intraveneus antibiotica krijgen om één geval van GBS-ziekte te voorkomen. Er is een gelijk percentage onbeschermde zuigelingen in vergelijking met de risicofactor strategie. Echter, het grote voordeel van de combinatiestrategie is dat de GBS-status altijd bekend is. Dit maakt het mogelijk dat zorgverleners extra alert zijn bij baby's van GBS-positieve moeders die geen antibiotica kregen tijdens de bevalling omdat er geen risicofactor was. Ouders van deze pasgeborenen kunnen extra worden geïnformeerd en instructies krijgen om op tekenen van GBS-EOD te letten. Deze combinatie strategie zal niet interfereren met het huidige Nederlandse verloskundige systeem en zal niet leiden tot extra ziekenhuisverwijzingen.

Toekomstperspectieven en richtingen van onderzoek

Dit proefschrift draagt bij aan de informatie die nodig is voor het opstellen van een optimale preventiestrategie voor GBS-EOD.

Hoewel er veel vooruitgang is geboekt in de preventie van GBS-EOD, blijven er grote en belangrijke uitdagingen bestaan. De incidentie van GBS-ziekte is afgenomen onder alle rassen en etnische groepen, maar verschillen blijven bestaan. Onderzoek gericht op een beter begrip van etnische verschillen in het optreden van GBS-infectie kan leiden tot mogelijkheden voor meer doeltreffende inspanningen met betrekking tot preventie. Voortdurend toezicht op en analyse van kinderen met GBS-EOD is nodig om handvatten te krijgen voor preventie in de toekomst. Er is nog onvoldoende onderzoek gedaan op verschillende terreinen die verband houden met GBS-preventie, zoals studies naar strategieën om GBS-EOD te voorkomen bij te vroeg geboren baby's, de rol van bacteriurie als risicofactor en de effectiviteit van de aanbevolen antibiotica bij vrouwen met penicillineallergie en hoog risico op anafylaxie. Er dienen nieuwe, goed ontworpen en goed uitgevoerde studies te worden verricht om de beste timing van prenatale kweken voor GBS te bepalen. Daartoe behoren onder meer longitudinale prospectieve cohortstudies waarbij kweken worden afgenomen tijdens verschillende momenten in de zwangerschap. Dit levert meer betrouwbare gegevens op om individuele verschillen in GBS-kolonisatie te vergelijken en meer betrouwbare conclusies te trekken uit kweekresultaten.

Door identificatie van de meest virulente GBS-stammen, kan gericht antibiotica worden gegeven aan dragers van deze specifieke GBS-stammen, waardoor het totale aantal vrouwen dat onnodig wordt behandeld tijdens de bevalling kan afnemen. De ontwikkeling van een snelle laboratoriumtest om GBS te identificeren zal mogelijk maken dat pas op het moment van de bevalling zelf getest wordt op GBS-dragerschap. Deze screeningstest voor GBS dient te bestaan uit een eenvoudige "bedside kit" die binnen een uur betrouwbaar uitsluitsel geeft over GBS-dragerschap.

Alternatieve strategieën voor preventie van GBS-ziekte dienen te blijven worden onderzocht. Hierbij kan bijvoorbeeld gedacht worden aan het gebruik van het vaginale ontsmettingsmiddel chloorhexidine tijdens de bevalling.

Met het besef van de tekortkomingen van alle strategieën waarbij antibiotica worden gebruikt ter preventie van GBS-ziekte, heeft als alternatief waarschijnlijk vooral vaccinatie het grootste potentieel voor de bestrijding van invasieve GBS-infectie van de pasgeborene en het jonge kind. Er zijn hierbij verschillende voordelen; vaccinatie maakt antibioticagebruik onnodig, voorkomt de noodzaak van screening en biedt bescherming tegen zowel de vroege als de latere ontstane GBS-ziekte. De ontwikkeling van GBS-vaccins is wetenschappelijk haalbaar(34) en meerdere fase II studies, ook onder zwangere vrouwen, zijn al uitgevoerd.

Praktische, juridische en zakelijke bezwaren hebben tot nu toe het verwerven van licentie voor GBS-vaccins voor gebruik tijdens de zwangerschap verhinderd. Om een effectief vaccin te kunnen ontwikkelen, is het belangrijk om het verspreidingspatroon van de voorkomende serotypen in alle delen van de wereld te volgen, zodat gezorgd kan worden dat een globaal GBS-vaccin de meest relevante componenten bevat.(35) Een vaccinatieprogramma is alleen effectief als de gehele doelgroep wordt bereikt en dit zal een voortdurende uitdaging zijn voor iedereen die betrokken is bij de preventie van ziekten.

De introductie van een Nederlandse landelijke richtlijn voor de preventie van GBS-EOD in 1998 resulteerde in een lichte daling van de incidentie van bewezen GBS-EOD, maar niet in een daling van ernstige morbiditeit en mortaliteit. Recente informatie toont zelfs toename van het aantal gevallen van GBS-sepsis per jaar. Het is dus duidelijk dat de huidige Nederlandse richtlijn niet effectief genoeg is en dat de ontwikkeling van een nieuwe strategie om GBS-EOD te voorkomen gerechtvaardigd is, in het bijzonder met betrekking tot het feit dat de perinatale sterfte in Nederland hoog is in vergelijking met andere Europese landen.(25) Tot een veilig en werkzaam vaccin is ontwikkeld en kan worden gebruikt, moet onderzoek in Nederland zich richten op kosteneffectiviteit van verschillende preventiestrategieën, waaronder het gebruik van vaginale chloorhexidine spoeling in vergelijking met intraveneuze antibiotica voor GBS-dragers tijdens de bevalling. Kinderen met GBS-EOD in Nederland moeten worden geanalyseerd om toekomstige preventie te verbeteren. Door de evaluatie van en discussie over bestaande richtlijnen en het geven van hoge prioriteit aan de zoektocht naar de beste preventiestrategie voor GBS-EOD, moet het mogelijk zijn om verdere daling van groep B streptokokkenziekte in Nederland te bewerkstelligen.

REFERENCE LIST

1. Schuchat A. Epidemiology of group B streptococcal disease in the United States: shifting paradigms. Clin Microbiol Rev 1998 Jul;11(3.:497-513.
2. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. Pediatr Infect Dis J 2011 Nov;30(11.:937-41.
3. Edmond KM, Kortsalioudaki C, Scott S, Schrag SJ, Zaidi AK, Cousens S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. Lancet 2012 Feb 11;379(9815.:547-56.
4. Barcaite E, Bartusevicius A, Tameliene R, Kliucinskas M, Maleckiene L, Nadisauskiene R. Prevalence of maternal group B streptococcal colonisation in European countries. Acta Obstet Gynecol Scand 2008;87(3.:260-71.
5. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. MMWR Recomm Rep 2002 Aug 16;51(RR-11.:1-22.
6. Lewin EB, Amstey MS. Natural history of group B streptococcus colonization and its therapy during pregnancy. Am J Obstet Gynecol 1981 Mar 1;139(5.:512-5.
7. Hoogkamp-Korstanje JA, Gerards LJ, Cats BP. Maternal carriage and neonatal acquisition of group B streptococci. J Infect Dis 1982 Jun;145(6.:800-3.
8. Hansen SM, Uldbjerg N, Kilian M, Sorensen UB. Dynamics of Streptococcus agalactiae colonization in women during and after pregnancy and in their infants. J Clin Microbiol 2004 Jan;42(1.:83-9.
9. Pylipow M, Gaddis M, Kinney JS. Selective intrapartum prophylaxis for group B streptococcus colonization: management and outcome of newborns. Pediatrics 1994 Apr;93(4.:631-5.
10. de Cueto M, Sanchez MJ, Molto L, Miranda JA, Herruzo AJ, Ruiz-Bravo A, et al. Efficacy of a universal screening program for the prevention of neonatal group B streptococcal disease. Eur J Clin Microbiol Infect Dis 1995 Sep;14(9.:810-2.
11. Hickman ME, Rench MA, Ferrieri P, Baker CJ. Changing epidemiology of group B streptococcal colonization. Pediatrics 1999 Aug;104(2 Pt 1.:203-9.
12. Lim DV, Morales WJ, Walsh AF, Kazanis D. Reduction of morbidity and mortality rates for neonatal group B streptococcal disease through early diagnosis and chemoprophylaxis. J Clin Microbiol 1986 Mar;23(3.:489-92.
13. Adriaanse AH, Kollee LA, Muytjens HL, Nijhuis JG, de Haan AF, Eskes TK. Randomized study of vaginal chlorhexidine disinfection during labor to prevent vertical transmission of group B streptococci. Eur J Obstet Gynecol Reprod Biol 1995 Aug;61(2.:135-41.
14. Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. Cochrane Database Syst Rev 2009;(3.:CD007467.
15. Itakura A, Kurauchi O, Morikawa S, Matsuzawa K, Mizutani S, Tomoda Y. A prospective study on the relationship between intrapartum maternal group-B streptococcal concentration and signs of infection in neonates. J Obstet Gynaecol Res 1996 Apr;22(2.:101-5.
16. Oddie S, Embleton ND. Risk factors for early onset neonatal group B streptococcal sepsis: case-control study. BMJ 2002 Aug 10;325(7359.:308.
17. Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. N Engl J Med 1986 Jun 26;314(26.:1665-9.
18. Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep 2010 Nov 19;59(RR-10.:1-36.
19. Schuchat A. Group B streptococcus. Lancet 1999 Jan 2;353(9146.:51-6.
20. Van Dyke MK, Phares CR, Lynfield R, Thomas AR, Arnold KE, Craig AS, et al. Evaluation of universal antenatal screening for group B streptococcus. N Engl J Med 2009 Jun 18;360(25.:2626-36.

21. Verani JR, Schrag SJ. Group B streptococcal disease in infants: progress in prevention and continued challenges. Clin Perinatol 2010 Jun;37(2.:375-92.
22. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn: Guidelines for prevention of group B streptococcal (GBS. infection by chemoprophylaxis. Pediatrics 1992 Nov;90(5.:775-8.
23. Stoll BJ, Hansen NI, Sanchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics 2011 May;127(5.:817-26.
24. Trijbels-Smeulders M, de Jonge GA, Pasker-de Jong PC, Gerards LJ, Adriaanse AH, van Lingen RA, et al. Epidemiology of neonatal group B streptococcal disease in the Netherlands before and after introduction of guidelines for prevention. Arch Dis Child Fetal Neonatal Ed 2007 Jul;92(4.:F271-F276.
25. Mohangoo AD, Buitendijk SE, Hukkelhoven CW, Ravelli AC, Rijninks-van Driel GC, Tamminga P, et al. [Higher perinatal mortality in The Netherlands than in other European countries: the Peristat-II study]. Ned Tijdschr Geneeskd 2008 Dec 13;152(50.:2718-27.
26. Blaschke AJ, Pulver LS, Korgenski EK, Savitz LA, Daly JA, Byington CL. Clindamycin-resistant group B Streptococcus and failure of intrapartum prophylaxis to prevent early-onset disease. J Pediatr 2010 Mar;156(3.:501-3.
27. Phares CR, Lynfield R, Farley MM, Mohle-Boetani J, Harrison LH, Petit S, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. JAMA 2008 May 7;299(17.:2056-65.
28. Muller AE, Valkenburg-van den Berg AW, Kreft D, Oostvogel PM, Sprij AJ, van Belkum A. Low rate of carriage of macrolide-resistant group B streptococci in pregnant women in The Netherlands. Eur J Obstet Gynecol Reprod Biol 2008 Mar;137(1.:17-20.
29. Castor ML, Whitney CG, Como-Sabetti K, Facklam RR, Ferrieri P, Bartkus JM, et al. Antibiotic resistance patterns in invasive group B streptococcal isolates. Infect Dis Obstet Gynecol 2008;2008:727505.
30. Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics 1999 Jun;103(6.:e77.
31. Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. Pediatrics 2005 May;115(5.:1240-6.
32. Easmon CS, Hastings MJ, Neill J, Bloxham B, Rivers RP. Is group B streptococcal screening during pregnancy justified? Br J Obstet Gynaecol 1985 Mar;92(3.:197-201.
33. Goodman J, Berg R, Gribble R, Meier P, Fee SC, Mitchel P. Longitudinal Study of Group B Streptococcus Carriage in Pregnancy. Infect Dis Obstet Gynecol 1997;(5.:237-43.
34. Heath PT, Feldman RG. Vaccination against group B streptococcus. Expert Rev Vaccines 2005 Apr;4(2.:207-18.
35. Johri AK, Paoletti LC, Glaser P, Dua M, Sharma PK, Grandi G, et al. Group B Streptococcus: global incidence and vaccine development. Nat Rev Microbiol 2006 Dec;4(12.:932-42.

Appendices

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PUBLICATIONS

A.W. Valkenburg-vd Berg, P.M. Oostvogel, P.J. Dörr, W.B. Renes, A.J. Sprij, H.H.H. Kanhai
Uit het veld: Prevalentiestudie naar GBS-dragerschap onder zwangere vrouwen in Den Haag. Infectieziektenbulletin (RIVM) 13 (02) 69-70 Januari 2002

A.W. Valkenburg-van den Berg
Refereeravond in Den Haag: Nieuw preventieprotocol gepresenteerd.
Nieuwsbrief Stichting Ouders Groep B Streptokokkenpatienten. 4 (1) juli 2003

Arijaan W. Valkenburg-van den Berg, Arwen J. Sprij, Paul M. Oostvogel, Johan A.E.M. Mutsaers, Wouter B. Renes, Frits R. Rosendaal, P. Joep Dörr
Prevalence of colonization with Group B Streptococci in pregnant women of a multi-ethnic population in the Netherlands. European Journal of Obstetrics & Gynecology and Reproductive Biology 2006 Feb 1;124(2): 178-83

Anouk E. Muller, **Arijaan W. Valkenburg-van den Berg**, Deborah Kreft, Paul M. Oostvogel, P. Joep Dörr, Johan A.E.M. Mutsaers, Casper L. Jansen, Arwen J. Sprij, Alex van Belkum
Carriage of benzylpenicillin-intermediate and macrolide-resistant group B streptococci in pregnant women in The Netherlands. Eur J Obstet Gynecol Reprod Biol. 2008 Mar;137(1):17-20

Valkenburg-van den Berg AW, Sprij AJ, Dekker FW, Dörr PJ, Kanhai HH
Association between colonization with Group B Streptococcus and preterm delivery: a systematic review. Acta Obstet Gynecol Scand. 2009;88(9):958-67

Arijaan W. Valkenburg-van den Berg, Rebecca L. Houtman-Roelofsen, Paul M. Oostvogel, Friedo W. Dekker , P. Joep Dörr, Arwen J. Sprij
Timing of GBS screening in pregnancy: A systematic review. Gynecol Obstet Invest. 2009 Dec 17;69(3):174-183

Arijaan Valkenburg-vd Berg, Christianne de Groot, Corla Vredevoogd, Jan Lind
Reactie op "Het Memoblokje" van de Stichting HELLP-syndroom. INZICHT, Nieuwsbulletin Stichting HELLP-syndroom. September 210

Arijaan W. Valkenburg-van den Berg, Friedo W. Dekker, P. Joep Dörr, Humphrey H.H. Kanhai, Arwen J. Sprij
Preterm labor and/or prolonged rupture of membranes is not associated with antenatal carriage of Group B Streptococcus (GBS) (submitted)

Arijaan W. Valkenburg-van den Berg, Arwen J. Sprij, Humphrey H.H. Kanhai, P. Joep Dörr
Opportunities for improvement of prevention of GBS-EOD (submitted)

Arijaan W. Valkenburg-van den Berg, Arwen J. Sprij, Humphrey H.H. Kanhai, P. Joep Dörr
The strategy for prevention of GBS-EOD in the Netherlands; plea for the combination strategy (submitted)

CURRICULUM VITAE

Foto Jos Poeder, Delft

De schrijfster van dit proefschrift werd op 27 september 1974 geboren in Delft. Na het behalen van haar VWO-diploma met klassieke talen (1992) aan het Christelijk Lyceum te Delft volgde zij het Basisjaar aan de Evangelische Hogeschool te Amersfoort.

In 1993 begon zij aan haar studie Geneeskunde aan de Erasmus Universiteit van Rotterdam. Keuzeonderzoek werd verricht op de afdeling Neonatologie van het Sophia Kinderziekenhuis te Rotterdam. Hier werkte zij mee aan een vroegtijdig interventieprogramma ter preventie van groei- en ontwikkelingsstoornissen bij prematuur geboren kinderen met een laag geboortegewicht. In 1997 vertrok ze naar Afrika, voor een klinische stage van enkele maanden in het Presbyterian Church of East Africa Kikuyu Hospital te Kikuyu in Kenia. Daarna was zij tijdens haar afstudeeronderzoek betrokken bij de ontwikkeling van een meetinstrument voor het meten van de kwaliteit van leven van ouders van een kind met een aangeboren aandoening. Dit onderzoek vond plaats op de afdelingen Medische Psychologie en Kinderchirurgie van het Sophia Kinderziekenhuis te Rotterdam.

Na haar doctoraalexamen in 1998 begon zij aan haar co-schappen. Zij maakte kennis met de Verloskunde en Gynaecologie tijdens haar co-schap in het Westeinde Ziekenhuis te Den Haag. Hier werd definitief de liefde voor dit vak geboren. Tijdens het keuze-coschap Verloskunde en Gynaecologie participeerde zij in de follow-up van een prospectieve studie naar onder andere de prevalentie van Humaan Papilloma Virus bij geringe cytologische afwijking in het uitstrijkje van de cervix.

Na het behalen van het artsexamen (najaar 2000) werkte zij als AGNIO (assistent geneeskundige niet in opleiding) op de afdeling Verloskunde en Gynaecologie van het Westeinde Ziekenhuis te Den Haag. In 2002 begon zij als AGIKO (assistent geneeskundige in opleiding tot klinisch onderzoeker) aan het in dit proefschrift beschreven onderzoek in het Westeinde Ziekenhuis te Den Haag. In 2004 startte zij in dit ziekenhuis, inmiddels Medisch Centrum Haaglanden, met de opleiding tot gynaecoloog (opleiders prof. dr. P.J. Dörr en mw. dr. M.J. Kagie), gevolgd door het academisch deel van de opleiding in het Leids Universitair Medisch Centrum te Leiden (opleiders prof. dr. H.H.H. Kanhai, mw. prof. dr. G.G. Kenter en prof. dr. J.M.M. van Lith). In augustus 2011 begon ze als gynaecoloog aan het fellowship Perinatologie in het VU Medisch Centrum te Amsterdam, waar zij tot heden met veel plezier werkzaam is.

Als laatste genoemd, maar ten diepste de belangrijkste mijlpalen uit schrijfsters levensloop tot nog toe: in 1998 trouwde zij met Arco Valkenburg en werden in hun gezin Job (2002), Sara (2004), Mees (2007) en Noortje (2010) geboren.

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Er werd onderweg hard gewerkt, gezongen, gelachen, gehuild, gebaard, gezucht, gerend, gestruikeld, bij de pakken neergezeten, gejuicht en gehaast. Steeds waren daar toeschouwers, aanmoedigers, helpers en dragers, toevallige passanten, meelopers, aanjagers, verzorgers, trainers en belangstellenden. Hele stukken van de weg werden afgelegd in zonneschijn, maar soms regende het of kwam de mist op, zodat de weg alleen maar hobbelig leek en moeilijk begaanbaar. Steeds bleef het verlangen naar het eindpunt en het uitzicht, maar ook onderweg werd regelmatig op het pad stilgestaan om van de omgeving en onverwachte vergezichten te genieten. Het was goed om steeds te kunnen vertrouwen op de bagage die mij ooit werd meegegeven en bovendien voor alles terug te kunnen vallen op hen waarmee ik arm in arm liep.

En zo kwam ik samen met velen daar waar ik nu ben. De afgelegde afstand zorgt voor vreugde en trots, maar vooral ook voor dankbaarheid. Ere Wie ere toekomt!

Lieve mama en daddy, jullie stonden aan het begin, hielpen mij op weg en zijn altijd blijven aanmoedigen. Allerliefste Ar, bij jou is het steeds weer goed thuiskomen. Ik hoop dat we samen met Job, Saar, Mees en Noor nog vele mooie wegen zullen gaan!

Lieverds, het boekje is klaar. Op weg naar morgen!