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Chapter 9

Summary, General Discussion and Future Perspectives

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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 than 24 hrs does not predict GBS colonization. Occurrence of this risk factor in itself is therefore not helpful in identifying mothers at higher 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 optimal 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.

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