Chapter 8

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

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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.

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