Prevention of neonatal group B streptococcal disease

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ABSTRACT

Group B streptococcal (GBS) disease and its early onset continues to pose major economic and perinatal implications regarding maternal and neonatal morbidity and mortality rates and methods of treatment. Universal GBS screening via rectovaginal culture is now recommended between 36 and 37 weeks and 6 days of gestation for all pregnant women. Timely identification of groups of women suitable for intravenous intrapartum antibiotic prophylaxis of GBS early onset infection has also proven to be effective, although less so than the universal screening approach.

Keywords: group B Streptococcus, antibiotics, prophylaxis, pregnancy, universal screening

INTRODUCTION

Streptococcus agalactiae, or group B streptococcus (GBS), is an encapsulated Gram-positive diplococcus, an otherwise opportunistic pathogen frequently associated with gastrointestinal and rectovaginal colonization in healthy adult women of childbearing age (11-35%) [1-6].

MATERIAL AND METHODS

We identified data in published literature such as systematic literature reviews, meta-analyses, randomized control trials/controlled clinical trials, observational studies, through searches of PubMed, Medline, WHOLIS and SCOPUS, as well as online surveys of policies from medical societies, clinical practice guideline collections and national and international medical specialty societies from 1980-2020, using keywords such as group B streptococcus, intrapartum antibiotic prophylaxis, neonatal GBS infection.

PREVALENCE OF MATERNAL GBS COLONIZATION

According to a review conducted by Russell et al., it is estimated that around 18% of women are GBS carriers. GBS maternal colonization is more prevalent in the Caribbean (35%), compared to Southern and Eastern Asia (13% and 11%, respectively) [4] and is best studied in high income countries, less so in middle or low-income ones [7-15]. Bacterial serotypes I-V were the most frequently identified colonizing GBS isolates, of which serotype III, associated with invasive disease, was noted in one fourth of the cases studied [4].

Maternal colonization with group B streptococcus has been reported to cause a multitude of conditions ranging from asymptomatic bacteriuria and urinary tract infection to chorioamnionitis, post-
partum endometritis or bacteremia, leading to stillbirth, preterm delivery or puerperal sepsis [16-18].

PREVALENCE OF NEONATAL GBS INFECTION

Up to 50% of infants born to GBS colonized women will develop early onset disease, most commonly within the first 7 days after birth of (about 0.25 cases in 1000 live-born babies [19]), via vertical transmission. A third of the total number of invasive infections will manifest within 7-90 days after birth (about 0.27 cases in 1000 live-born babies [18]) Around to 2-3% of neonatal GBS disease result in either fetal and neonatal mortality, neonatal infection, or loss of pregnancy [19]. Early onset GBS infection frequently manifests as sepsis, pneumonia or, less frequently, meningitis. Late-onset GBS infection may involve severe neurological neonatal consequences, including cognitive delay, cerebral palsy, blindness, hearing loss [20-24], bacteremia, meningitis or, less frequent, organ or soft tissue infection [16-18]. Late onset GBS disease (LOGBSD) transmission remains poorly understood. Possible risk factors for LOGBSD include: maternal GBS colonization, premature delivery [25,26], nosocomial outbreaks [25,27] and breast milk [28-30].

A systematic review in 2012 [15] reported an overall rate of invasive GBS disease among infants of 0.53 in 1000 live-born babies with the highest incidence in Africa (1.21 per 1000 live births) and the lowest incidence in Southeast Asia (0.016 in 1000 live-born babies). The global mortality rate is estimated to be at about 8.4% [8]. Higher mortality rates have been reported in cases of premature newborns with diagnosed GBS early onset infection than in infected infants delivered at term (19.2%, as opposed to 2.1%) [31].

RISK FACTORS FOR GBS COLONIZATION AND GBS EOD

Maternal GBS colonization is favored by the presence of one or more of the following: African-American race, young maternal age (under 20 years), older age or older age at first pregnancy, smoking, obesity, socioeconomic disadvantage, low maternal levels of anti-capsular antigen, multiple pregnancy, meconium-stained amniotic fluid [32-35].

GBS early onset disease (GBS EOD), which presents within 0 to 6 days after birth is caused by vertical transmission from the colonized mother, by either fetal aspiration during labor or neonatal aspiration during birth, or both. Among the risk factors for GBS EOD are included: prior delivery of an infant with GBS disease, diagnosed maternal GBS asymptomatic bacteriuria during the current pregnancy, premature rupture of the membranes, prolonged rupture of the membranes for 12 or more hours before delivery, presence of chorioamnionitis/intra-amniotic infection, intrapartum pyrexia, premature delivery (under 37 weeks of gestation), very low birth weight [7,36-38], presence of another twin with current early-onset GBS infection [6,16,38].

GBD SCREENING METHODS FOR INTRAPARTUM ANTIBIOTIC PROPHYLAXIS

Prevention of GBS EOD can be commonly achieved using two methods: 1) antenatal universal culture-based screening for GBS, best performed from 36 to 37 weeks and 6 days of gestation, using vaginal and rectal cultures in all cases of pregnant women [16] (with the following exceptions: maternal GBS identified in urine during current pregnancy or prior birth of baby with invasive GBS disease [38-41]), or 2) assessing possible risk factors and offering intravenous intrapartum antibiotic prophylaxis to all women with one or more risk factors present.

The universal culture-screening strategy has been proven to be superior in preventing GBS EOD, with a > 50% success rate compared to chemoprophylaxis administered based upon identification of maternal risk factors [7,11,16,42]. Cultures must not be performed earlier than 5 weeks from the estimated date of delivery because in many cases there is transient or intermittent colonization and GBS infection status in early pregnancy may not be relevant in late pregnancy. If, however, more than 5 weeks have passed since the last swab and pregnancy is overdue, additional GBS cultures must be collected, otherwise their predictive value decreases from 94% to around 87%, as reported by Vircrannie et al. [43].

Among the most frequent disadvantages of the risk-based approach, one must note the numerous reports of GBS EOD that occurred in infants of women with no identifiable risk factors. Almost 20% of GBS-positive women did not present GBS EOD risk factors and thus would not have been eligible for intrapartum antibiotic prophylaxis. Therefore, American College of Obstetricians and Gynecologists (ACOG) recommended universal culture-screening method rather than risk-based screening for GBS [39-41]. A meta-analysis published in 2020 comparing intrapartum antibiotic prophylaxis according to GBS screening methods reported that [44]: 1) universal screening reduced the risk for early onset GBS of the newborn; 2) risk assessment did not significantly reduce early-onset GBS of the newborn when compared with no strategy; 3) when reporting on the use of antibiotics, universal screening was not associated with higher antibiotic ad-
ministration rates when compared to risk-assessment strategy (31 versus 29%).

Recently, identification of GBS in cases of women presenting in labor or with unknown GBS status can be achieved using microbiological methods such as nucleic acid amplification testing methods (NAATs) or real-time polymerase chain reaction (PCR) tests. Both methods have higher reported sensitivity and specificity rates compared to generic cultures (90.9%-100% NAATs sensitivity, 93.7% sensitivity [45] and 97.6% specificity in cases of RT-PCR GBS testing [46]).

**INTRAPARTUM ANTIBiotic PROPHylAXIS (IAP)**

Sixty-three percent of the ninety-five countries listed on the International Federation of Gynecology and Obstetrics (FIGO) website [47] have a national IAP policy, the majority of which (58%) employ both risk factor and microbiological screening methods, whilst 42% only use the risk factor-based approach [48].

IAP policies have been reported in all developed region countries. In upper-middle-income countries, the most used GBS screening methods reported are the microbiological and the risk-based approach, respectively. Microbiological testing is, however, prevalent in high-income countries (54%) as opposed to risk-based screening methods. The majority of low and lower-middle-income countries (76%) reported no IAP policy. A quarter of countries reporting any IAP policy were from lower-middle-income countries (risk-based screening policies). Twenty-five countries reported IAP based on clinical risk factors as specifically previous birth of an infant with GBS EOD (in which case all countries are using the risk-based approach administered IAP). Twenty-three of the twenty-five countries also recommended use of IAP in cases of premature or prolonged rupture of membranes (more than 18 hours) or in cases of antenatal GBS bacteriuria. Thirty-five countries have reported using microbiological GBS testing performed at 35-37 weeks' gestation. Additional microbiological screening was reported in Japan and Bulgaria (at 20 weeks' gestation) and in Poland, Bangladesh, Iran, Thailand and Trinidad and Tobago, where use of RT-PCR testing was noted in cases of patients presenting in labor [49].

**ANTIBiotics RECOMMENDED FOR THE TREATMENT GBS COLONIZATION**

Intravenous penicillin-based antibiotics remain the main IAP recommendation (83%), with penicillin as the main choice (76%) and ampicillin (24%) as an alternative [49].

In cases of patients with allergic reactions to penicillin, risk for anaphylaxis must be evaluated. If the patient falls into “low risk” category for anaphylaxis based on previous history (isolated maculopapular rash without itching, headache, gastrointestinal distress), cefazolin must be administered, 2 g intravenously as first dose, then 1 g every 8 hours until delivery. If the patient falls into “high risk” category for anaphylaxis based on previous history (previous episode of anaphylaxis, hypotension, angioedema, respiratory distress syndrome, urticaria, pruritic rash occurring within 30 minutes after drug being administrated), susceptibility testing for clindamycin and erythromycin should be performed and administered in case of no adverse reactions [50,51]. Use of these types of medication must be done with care since resistance rates to clindamycin and erythromycin have increased in the last years to 26-43% and 50-55% in the US, respectively [31,52]. Erythromycin is no longer offered for prophylaxis in the US. In case of resistance to erythromycin and susceptibility to clindamycin, 900 mg of clindamycin will be administered intravenously every 8 hours until delivery [39-41]. In the UK, clindamycin is no longer recommended as intrapartum prophylaxis [53]. In case of resistance to clindamycin vancomycin will be administered 2 g intravenously first dose and then 1 g every 12 hours until delivery, with the maximum dosing in adults with normal renal function of 4 g per 24 hours [39-41]. For IAP to be beneficial, at least 4 hours of antibiotic therapy must be performed. Newborns exposed to IAP, especially within 30 minutes to 2 hours before delivery, have an expected serum antibiotic concentration that far exceeds the minimum inhibitory concentration against GBS [54].

There are possible neonatal adverse reactions secondary to IAP exposure, leading to dysbiosis of the infant’s founding microbiome, with potential harmful effects in later life [55-59].

**GBS BACTERIURIA**

High levels of GBS bacteriuria are a direct result of important rectovaginal GBS colonization. In case of maternal GBS bacteriuria diagnosed in the current pregnancy, intrapartum antibiotic prophylaxis is offered routinely, even if future urine cultures are negative or if treatment is received. Treatment of GBS bacteriuria does not cause long-term eradication of the colonization, therefore, culture-based screening at the recommended gestational age is not routinely recommended [60].

**PLANNED CESAREAN DELIVERY**

Regardless of the GBS infection status or the gestational age, intrapartum GBS prophylaxis is not recommended in cases of patients with intact amni-
otic membranes who are undergoing a planned cesarean birth and who do not present in labor [16].

VACCINATION AGAINST GBS

Recently, research has been done regarding the possibility of prevention of early and late-onset GBS infection via vaccination in both infants and pregnant women. GBS vaccination, although still under development, is effective in cases where: antibiotic prophylaxis is not suitable or was not administered intrapartum for the required minimum of 4 hours; women present with GBS isolates with antibiotic resistance; or in areas without proper access to antibiotics [61].

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CONCLUSIONS

Intrapartum antibiotic prophylaxis has improved neonatal outcome and has helped prevent early onset group B streptococcal disease, although there is emerging research concerning the potential harmful antibiotic effects on infant microbiota and overall resistance to drugs. Screening policies for intrapartum chemoprophylaxis have yet to be implemented worldwide, especially in low-income countries. Further research must still be done into the development of a potential vaccination against GBS.
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