INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

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REVIEW ARTICLE

PRE-VAGINAL DELIVERY ANTIBIOTIC PROPHYLAXIS: COMMON PRACTICE AND CONTROVERSY

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ARTICLE INFO

Article History:

Received 19th September, 2016
Received in revised form 8th October, 2016
Accepted 4th November, 2016
Published online 28th December, 2016

Key words:

Group B *Streptococcus*, intrapartum antibiotic prophylaxis, vaginal delivery, current practice, controversy

ABSTRACT

Group B *Streptococcus* GBS sporadically colonizes the vagina and rectum of approximately one-quarter of pregnant women. It is the most common cause of neonatal sepsis, with an incidence of 0.29-0.39 cases per 1000 live births. There is a lack of consensus regarding screening and management of GBS among professional societies. Certain societies such as the American College of Obstetrics and Gynecology advocate mandatory screening as well as intrapartum antibiotic prophylaxis, while other societies such as the Royal College of Obstetricians and Gynaecologists deemed screening futile and costly as colonization is intermittent by nature. This review examines the current practice and controversy surrounding GBS screening and management as well as the benefits and harms of intrapartum antibiotic prophylaxis prior to vaginal delivery.

INTRODUCTION

Background

In the 1970s Group B *Streptococcus* (GBS) emerged as a significant cause of perinatal morbidity and mortality and remains the leading cause of neonatal sepsis. Although GBS was first isolated in the 1930s, the link between GBS and neonatal sepsis was not elucidated until 1964 by Dr. Eickhoff[1]. Group B *Streptococcus* or *Streptococcus agalactiae* is a Gram-positive commensal bacterium that colonizes the vagina and rectum of approximately one-quarter of pregnant women, worldwide[2-4]. Usually, Group B *Streptococcus* is a commensal microorganism, however may become an opportunistic pathogen, resulting not only in neonatal morbidity and mortality, but also in maternal morbidity including postpartum endometritis, urinary tract infection and puerperal sepsis[5].

The incidence of GBS varies between 0.29 and 0.39 cases per 1000 live births, with an average of 0.35 and 0.41 cases per 1000 live births in the United States and United Kingdom, respectively[5, 6].

Group B *Streptococcal* infection in newborns before the seventh day of life is defined as early-onset disease (EOD), which manifests as sepsis and pneumonia, while late-onset disease (LOD) appears between the eight day and third month of life, presenting as meningitis[7, 8]. Early-onset disease is preventable with the administration of intrapartum antibiotic prophlylaxis (IAP)[9,10]within 4 hours of delivery, however, there are no preventive strategies available for LOD[11].

The GBS-specific obstetric risk factors include GBS bacteriuria and positive vaginal swab for GBS in the current pregnancy, intrapartum maternal pyrexia > 38°C, history of invasive GBS infection in previous pregnancy and suspected or confirmed chorioamnionitis[5].

A pregnant woman who tests positive for GBS and receives IAP has a 1 in 4,000 chance of delivering a baby who will develop GBS disease, compared to a 1 in 200 chance without IAP[10]. There is a lack of global consensus regarding the need of antepartum screening, the selection of candidates for a screening programme, which antibiotics should be administered and when, and whether intrapartum antibiotic administration is truly effective.

Since GBS is a commensal microorganism of the vaginal and rectal flora, which instead of being present persistently, appears intermittently, a woman who initially tested negative, may, in fact, become positive by the time of delivery[12]. This pattern would necessitate not only repetitive screening, which

would be cumbersome for pregnant women, but would also result in excessive costs for the healthcare system.

This review aims to examine the current practice and controversy in GBS screening and management as well as the benefits and harms of IAP prior to vaginal delivery.

Current Practice

Current practice regarding screening and intrapartum prophylaxis of perinatal GBS infection varies widely across the globe. For instance, the Royal College of Obstetricians and Gynaecologists (RCOG) in the United Kingdom opted for risk-based management instead of universal screening[13]. Intrapartum antibiotic prophylaxis is offered in a timely manner to all women whose babies are at a higher risk of EOD with aforementioned obstetric risk factors listed in the background section.

However, the current practice in the United States entails screening all pregnant women between gestational weeks 35 and 37 for GBS by vaginal and rectal swabs[14]. Antibiotic prophylaxis is strongly supported in the United States due to the dramatic reduction in EOD rates from 1.7 to 0.3 cases per 1000 births[9,11]. The American College of Obstetricians and Gynecologists (ACOG) recommends an initial dose of 5 million units of penicillin G intravenously (IV) and then another 2.5 million units IV every 4 hours until delivery. A widely-adopted alternative is an initial dose of 2 grams (g) of ampicillin, then 1 g IV every 4 hours until delivery. In patients with a penicillin allergy, IV clindamycin is used as an alternative antibiotic regimen[15].

In view of obtaining insight into the attitudes and practice patterns of obstetricians practicing in the United States, the ACOG mailed a survey to 546 society members in 2015. A response rate of 60% was obtained, revealing that 97% of obstetricians collect screening samples for GBS at 35-37 weeks gestation. Sixty-two percent of obstetricians disclosed that they collect samples from the distal vagina and rectum, while 26% of obstetricians harvest samples solely from the distal vagina[16].

Table 1 serves to depict the discrepancies between current practice in countries across the globe.

that antibiotics are efficient at preventing early as well as late-onset *streptococcal* disease. In the United Kingdom, only pregnant women manifesting the following features receive antibiotic prophylaxis: GBS bacteriuria or GBS positive vaginal swab in current pregnancy, intrapartum maternal pyrexia > 38°C, history of invasive GBS infection in previous pregnancy and suspected or confirmed chorioamnionitis[5].

Isolation rates vary according to the microbiological method used. The sites from which cultures may be obtained include the posterior vaginal fornices, periurethral mucosa, distal rectum, external anal sphincter, and perianal skin[19.] Approximately 99% of GBS display β-hemolysis when cultured on blood agar media[7]. The principal drawback of using a culture medium to isolate GBS is the required duration of 36 hours, which is not suitable for labouring women, as the result will be obtained postpartum[20]. Quilan *et al*. undertook a study examining whether combined rectovaginal swabs would influence the management of GBS in comparison to only vaginal swabs. Cultures were collected from 220 pregnant women between 35 and 37 weeks gestation, of whom 54 (24.3%) tested positive. Of these women, 37 (68.5%) had both positive vaginal and anorectal cultures, 7 (13%) had only positive vaginal cultures, while 10 (18.5%) had only positive anorectal cultures, concluding that anorectal cultures should not be omitted from the screening process, despite the possibility of patient apprehension. In terms of screening, combined vaginal and rectal swabs obtained between 35 and 37 weeks gestation are preferred as they appear to have the best predictive value[21].

The two current methods available for isolating GBS are culture and Polymerase Chain Reaction (PCR). The PCR amplifies the CFB gene in addition to detecting the GBS antigen. Group B *Streptococci* grow on blood agar as well as on selective enriched media such as Todd-Hewitt broth with gentamicin and nalidixic acid. Bidgani *et al*. conducted a study evaluating the efficacy of GBS detection using culture-based methods compared to PCR. The primary outcome of this study was that the frequency of GBS isolated on culture was higher from rectal samples than from vaginal samples, while the detection rate of GBS from vaginal samples by PCR was superior to rectal samples.

Table 1 Discrepancies Regarding the Management of GBS Worldwide

Country	Screening	Type of screening	Timing of screening (weeks)	Site of sample collection	IAP	Drug of choice (IV)	Dosage
U.K.	No	Selective	N/A	N/A	N/A	N/A	N/A
U.S.A.	Yes	Universal	35-37	Vagina, rectum	Yes	Penicillin G	L:5 million U M: 2.5 million U
Italy	Yes	Universal	35-37	Vagina, rectum	Yes	Ampicillin	L: 2 g M: 1 g
Romania	Yes	Universal	34-36	Vagina	Yes	Ampicillin	L: 2 g M: 1 g
Japan	Yes	Universal	33-37	Vagina, perianal skin	Yes	Sulbactam/ampicillin	L: 1.5 g M: continuous infusion
Uruguay	Yes	Universal	35-37	Vagina, rectum	Yes	Penicillin G	L:5 million U M: 2.5 million U
Taiwan	No	Selective	N/A	N/A	N/A	N/A	N/A

N/A: non-applicable, L: loading, M: maintenance, U: units

Current Controversy

There are a number of controversial matters pertaining to the management of GBS. These include the need for antenatal screening, the selection of candidates for screening, the site(s) of sample collection, the method of sample processing, and antibiotic administration concerning the type and timing of IAP. Moreover, not all professional medical societies consider

The sensitivity and specificity of PCR were 92.8% and 81.1%, respectively, compared to 81.6% and 70.7% for culture. Thus, PCR provides rapid and accurate detection of asymptomatic GBS carriage: 3 hours compared to the 36 hours of classic culture. In addition to being lengthy, the growth of GBS on culture media is largely influenced by the presence of other bacteria from the vaginal microbiome that may inhibit the

growth of GBS[22]. The PCR has a high specificity and sensitivity in addition to yielding rapid results, although is costly.

The choice and timing of IAP varies according to national and institutional protocols. In a survey undertaken by the ACOG, in which 546 physicians took part; 71% use penicillin as the first-line treatment, while 27% use ampicillin and only 2% choose cefazolin[16]. Baecher *et al*. conducted a double-blind randomized control trial evaluating intrapartum oral amoxicillin versus placebo in 32 pregnant women in which the primary endpoint was GBS colonization at the time of labour. Of the patients who received amoxicillin and a repeat culture, 43% tested positive for GBS. However, treatment with amoxicillin did not have a significant impact on colonization at the time of delivery. Thus, Baecher *et al*. concluded that oral amoxicillin is inefficient at reducing GBS colonization[23].

Fairlie *et al*. sought to evaluate the efficacy of IV pencillin or ampicillin compared to IV clindamycin by conducting a database study comprising 7,691 births in 10 U.S. States over the course of a year. Of the 7,691 live births, 254 (3.3%) neonates developed EOD. Thirteen percent of women had one or more risk factors for GBS. Thirty one percent of the women received IAP according to the following regimen: combined penicillin and ampicillin in 75% of cases, clindamycin in 9% and cefazolin in 8%. The timing of antibiotic administration was dichotomized into between 2 and 4 hours prior to labour. The effectiveness achieved with penicillin and ampicillin was 91% compared to only 22% for clindamycin. Regarding the timing of administration, surprisingly, effectiveness was greater in the group that received antibiotics 4 hours antepartum (83.7%) compared to the 2-4 hour group (37%)[24]. The limited efficacy of clindamycin is attributed to its poor penetration into fetal circulation[25-27].

Berardi *et al*. evaluated the effect of penicillin prophylaxis administered within 4 hours of delivery in 167 neonates born to 167 GBS culture-positive women. Among the 167 neonates, only 137 neonates (82%) received adequate IAP with IV penicillin within 4 hours of delivery. Of the 137 neonates born to GBS culture-positive women, 5 (3.6%) were colonized at the time of delivery, proven by samples collected from the pharynx, ear and rectum. Of these 3 sites, the neonatal rectum was the most heavily colonized, hence yielding a positive GBS culture in 72.2% of neonates. Regarding the timing of IAP, 4 timeframes were employed based on time to delivery: within 60 minutes, within 60-120 minutes, 120-180 minutes and 181-240 minutes. Evidence of colonization was found only in neonates born to mothers who received IAP in an interval of more than 2 hours prior to delivery[8].

Benefits of Antibiotic Prophylaxis

The benefit of IAP refers to the prevention of vertical transmission of GBS and subsequent EOD, carrying a staggering mortality rate as high as 50%[28]. Guidelines and protocols established in the 1990s concerning screening and IAP have decreased the burden of GBS sepsis from 1.7 to 0.4 cases per 1000 live births, worldwide, although the incidence of LOD remained unchanged[2,4,9,29,30]. Scasso *et al*. assessed the colonization status and pharmacokinetic profile of penicillin G in the umbilical cord and amniotic fluid during 4 hours of IAP in 60 GBS carriers in active labour with a singleton pregnancy of 37 weeks gestation or more. Intravenous penicillin G was administered as per regimen of an initial 5,000 units loading dose followed by 2,500 units every hour until delivery, for a maximum of 4 hours. Rectovaginal samples were collected prior to the initiation of IAP and then at 2 and 4 hour intervals after the initial dose. Fifty-three women had negative cultures after 2 hours of IAP, while 12 women (12%) remained positive for GBS after 4 hours of IAP[17].

The ORACLE trial conducted by Gilbert *et al*. compared the intrapartum prophylactic use of oral amoxicillin with clavulanic acid and erythromycin to no antibiotics in preterm premature rupture of membranes (P-PROM), regardless of GBS status. The risk of acquiring vertically-transmitted GBS in the placebo group was 1.55% compared to 0.55% in the treatment group. This trial confirmed a significant reduction in neonatal GBS colonization, infection and mortality in pregnant women with P-PROM who received IAP[31].

Harms of Antibiotic Prophylaxis

The administration of IAP has shown to be associated with several risks concerning both mother and fetus. The harms of IAP encompass emergence and exacerbation of antibiotic resistance, dysregulation of the fetal microbiome, maternal anaphylaxis and an association with the childhood onset of asthma, allergies, type 1 diabetes mellitus, obesity, and autism[32-35].Morales *et al*. observed a significant increase in the proportion of GBS samples resistant to erythromycin and clindamycin between 1988-1997 compared to 1980-1983[36]. In 2002, the percentage of erythromycin-resistant GBS in the United States varied between 7% and 25% and from 3% to 15% for clindamycin[15, 37-40].Apart from the increase in antibiotic resistance, unnecessary antibiotic prophylaxis results in the proliferation of other opportunistic pathogens such as *Clostridium difficile* and yeasts[35].

Anaphylaxis is a potential scenario that may ensue in pregnant women who are unaware of being allergic to an antibiotic in the GBS IAP regimen. The estimated incidence of anaphylaxis due to penicillin is 1 in 10,000 patients treated. The RCOG estimates that universal GBS screening where 30% of women receive intrapartum penicillin would result in an average of 2 deaths per year[41].

The early neonatal period is the most important period for microbiota-induced homeostasis[42]. Perinatal antibiotic administration exerts a profound effect on the development of the fetal and neonatal intestinal microbiome[43]. Disruption of the neonatal intestinal microbiome has compelling consequences on childhood health[44]. A less dense microbial flora is associated with higher rates of neonatal sepsis due to a weakened host response[45].

Although pre-delivery antibiotics are administered short-term, they are given at a crucial time, when neonatal acquisition of gut bacteria is just beginning[46]. Perinatal antibiotic administration was found to be associated with childhood obesity. The mechanism of obesity lies within the loss of *Helicobacter pylori* which is responsible for the regulation of the gastric cytokines ghrelin and leptin. The removal of *H. pylori* from the neonatal gut results in an increase of postprandial ghrelin levels, at a time when long-term adiposity is being programmed[47]. Cho *et al*. demonstrated a link between mutations in genes involved in carbohydrate metabolism resulting in obesity and the administration of antibiotics[48].The disappearance of *H. pylori* from the gastric microbial flora in rats resulted in a decrease of the gastric T-cell population,

providing a basis for skin allergies, allergic rhinitis and asthma[32, 49].

Microbial dysbiosis, occurring as a result of the effect of antibiotics on the gut microbiota, is associated with type 2 diabetes mellitus. Pregnant women receiving antibiotics are therefore more prone to deliver newborns that will develop type 2 diabetes mellitus during adulthood. The bacterium *Akkermansia muciniphilia* exerts an antidiabetogenic role, which when depleted by the administration of antibiotics, predisposes to type 2 diabetes mellitus[50].

Recommendations

Despite being the leading cause of neonatal sepsis worldwide, GBS only affects a minute proportion of neonates[6,15, 51-54]. Group B *Streptococcal* sepsis has a high number needed to treat (NNT): 100. As such, in order to protect 1 neonate from GBS sepsis, over 100 mothers would need to be exposed unnecessarily to antibiotics[55]. Furthermore, the survival rates without IAP are very high at 98% in neonates born at 37 weeks gestation and above, 90% in preterm a neonates born between 34 and 36 weeks gestation and 70% in neonates born at 33 weeks and below[9]. These figures highlight that only premature neonates would benefit from GBS prophylaxis.

Moreover, IAP is inadequate at preventing LOD 2,4,9,11,29,30. Screening is costly and inefficient due to the fact that GBS colonizes the female genital tract intermittently[12]. Certain authors suggested introducing a vaccine for all pregnant women with hopes of abolishing GBS colonization[11, 46, 56], however due to its low prevalence and high survival rate without treatment, the drawbacks seem to outweigh the benefits. Our recommendation is to carry out selective screening and to subsequently treat high-risk pregnant women, presenting one or more of the following obstetric risk factors: GBS bacteriuria and positive vaginal swab for GBS in current pregnancy, intrapartum maternal pyrexia > 38°C, history of invasive GBS infection in previous pregnancy and suspected or confirmed chorioamnionitis.

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