

Group B Streptococcal Colonization and Intrapartum Antibiotics: Why a Vaccine is Urgently Needed

Philip Kum-Nji*

Department of Pediatrics, Children's Hospital of Richmond at Virginia, Commonwealth University School of Medicine, Richmond, Virginia, USA

ABSTRACT

The importance of global group B streptococcal (GBS) colonization during pregnancy is briefly reviewed in this short article. About 20% all pregnant women worldwide are colonized with this organism necessitating the use of intrapartum antibiotic prophylaxis (IAP) in order to prevent neonatal GBS disease. In some geographic regions rates of colonization are as high as 35%. Such a high rate of IAP is shown to be concerning because of childhood adverse effects. We briefly summarize 5 main childhood adverse outcomes from IAP which include antibiotic resistance, the development of various atopic diseases, dysbiosis, obesity, and impaired immune function. Finally, the article clearly lists 4 reasons why a GBS vaccine is specifically urgently needed in order to curb the often unnecessary if not dangerous use of IAP to prevent against the onset of neonatal GBS disease. It is hoped that such a vaccine could reduce the rate of IAP from a high of 40% to a low of 10%.

Keywords: GBS Colonization in Pregnancy; Dangers of Intrapartum Antibiotics; GBS Vaccination

INTRODUCTION

As a general academic pediatrician of more than 3 decades, I, like many other pediatricians, over the years, have been increasingly concerned about the use of antibiotics in order to prevent neonatal sepsis especially from maternal Group B Streptococcal (GBS) colonization. I recently asked a group of residents and medical student in my service in the newborn nursery in a large tertiary care hospital: "what is the rate of GBS colonization among women delivering in our hospital and throughout the nation?" The residents and students could not give a cogent answer even though the literature is quite clear on the global colonization rates of GBS during pregnancy.

More than a third of all pregnant women may be colonized with GBS [1]. Since the 2002 recommendation by the CDC that all pregnant mothers receive Intrapartum Antibiotic Prophylaxis (IAP) prior to delivery [2]. Followed in 2011 by modified recommendations from the American Academy of Pediatrics and the American College of Obstetricians and Gynecology [3,4] there has been a dramatic drop of at least 80% in the incidence of early onset GBS (EOGBS) sepsis [2]. It is easy therefore to conclude that IAP is a resounding success in reducing neonatal GBS disease but at what price?

This article will summarize the global prevalence of GBS colonization including factors associated with increased colonization rates as gleaned from the literature. We will also outline [5] important known complications associated with the potential high rate of IAP use: 1) antibiotic resistance, 2) dysbiosis, 3) atopic diseases, 4) obesity, and 5) immune function. Finally, the article will highlight some of the important reasons why a GBS vaccine is urgently

needed in order to curb the use of IAP to prevent neonatal GBS disease.

GLOBAL PREVALENCE OF GBS COLONIZATION AMONG PREGNANT WOMEN

The prevalence of GBS colonization throughout the world has been well studied [5-10]. The US, Europe, Australia and African countries south of the Sahara have the highest rates [11-13]. The lowest rates have been noted in some East Asian/Pacific Island nations [14-16]. Overall the rates of GBS colonization of 20%-30% have remained remarkably stable over the past several decades. Globally therefore, over a third of our term or near term neonates are potentially exposed to antibiotics in utero.

FACTORS ASSOCIATED WITH GBS COLONIZATION DURING PREGNANCY

It would seem that the group B streptococcus (GBS) is a normal commensal that inhabits the gastrointestinal and genitourinary tracts. Under certain conditions it may suddenly begin to multiply and become pathogenic [16-18]. Factors associated with GBS increased colonization during pregnancy have been previously explored. It is possible that the inappropriate use of systemic antibiotics may modify the gut and genital microbiome resulting in increased colonization with pathogenic bacterial including GBS [19]. In the USA and some European countries black women have been reported to have higher colonization than their non-white counterparts [6,16-18]. Other factors associated with GBS colonization are substance use [20]. Diabetes mellitus, obesity and frequency of sexual contact [21-23]. Finally, two studies so far

Correspondence to: Philip Kum-Nji, Department of Pediatrics, Children's Hospital of Richmond at Virginia, Commonwealth University School of Medicine, Richmond, Virginia, USA; E-mail: pkumnji@vcu.edu

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clearly show that young mothers less than 20 years have higher colonization rates than their older counterparts [6,16]. One recent study showed that tobacco smoking during pregnancy increased GBS colonization by a factor of 2 even after controlling for various potential confounders [6]. Interestingly, this inverse relationship between tobacco smoking and GBS was only noted among the non-smokers. The mechanism whereby tobacco smoke could lead to increased colonization of pathogenic organism in the respiratory, GI and genitourinary tracts is not quite clear.

Again as stated above, it would seem that GBS is simply part of the stable microbiome of everybody [19]. Numerous studies show that the development of the microbiome is influenced by factors such as type of delivery (vaginal *vs.* c/section), type of feeding (formula *vs.* breastfeeding), type of adult diet (vegetarian *vs.* other) and antibiotic use during the prenatal and neonatal periods [24,25]. What is not quite clear is how this microbiome changes from birth to adulthood. It is also possible, indeed probable, that this microbiome development can be disrupted by certain environmental factors leading to either an increase or a decrease in pathologic microorganisms already colonizing the body. Thus it is necessary to understand what factors disrupt the microbiome during pregnancy leading to increased GBS colonization resulting in neonatal GBS disease.

DANGERS OF IAP

Development of resistance

In some countries including the United States, more than one third of all term or near term neonates have mothers with documented exposure to intrapartum antibiotics [26,27]. However, IAP has been associated with the development of resistance. The spread of antibiotic resistance is in part due to the overuse and misuse of antibiotics for the prevention and/or treatment of various infections in the neonate, especially GBS. Little is written on antibiotic stewardship in perinatal care. Ledger et al [28]. Recently suggested that we are using too many antibiotics during pregnancy. He opined that up to 40% of all pregnant women in the United States use antibiotics during pregnancy to prevent or treat infections in both mother and the fetus.

In preterm neonates intrapartum antibiotics can result in preventing or reducing neonatal infections and chorioamnionitis [29-31], but can also result in adverse outcomes such as Necrotizing Enterocolitis (NEC) [32,33]. The most worrisome outcome is, of course, drug resistance. Among infants without culture-proven sepsis or without NEC, higher antibiotic utilization rates were associated with adverse neonatal outcomes such as increased rates of retinitis of prematurity, various neurodevelopmental disorders, and mortality [32,33].

Dysbiosis in children

The early use of antibiotics has been shown in numerous studies to result in gut dysbiosis. Gut dysbiosis is defined as an imbalance of gut microflora or microbiota. Stated simplistically, gut dysbiosis occurs when the commensals (good bacteria) are decreased and the pathogens (bad bacteria) increase than is normally the case. Gut dysbiosis often manifests as gassiness, colicky abdominal pain, bloating, diarrhea and /or constipation, food intolerance or food sensitivity. Increased use of IAP is now known to result in the increasing occurrence of gut dysbiosis in the pediatric population [34-37]. Thus we can conclude that since the perinatal use of antibiotics in infants is over 40% [28]. This must surely contribute

to gut dysbiosis.

Atopic diseases

Atopic illnesses such as Atopic Dermatitis (AD), asthma, and Allergic Rhinitis (AR) are diseases that are now being increasingly linked to overuse or inappropriate use of antibiotics. Asthma has been linked to antibiotic use to treat infections during the perinatal period [38-41]. In the late eighties Strachan opined that repeated infections (both respiratory and bacterial) decrease the likelihood of allergic diseases [42]. Thus was born the hygiene hypothesis. It has subsequently been shown that frequent infection results in stimulation of the T1 helper (TH1) cells and less of the TH2 (T2 helper) cells [43]. In a too clean environment, there are very few infections so the TH2 cells are preferentially stimulated and the body's immune defenses are skewed toward developing allergic diseases.

It is likely that early antibiotic use may not only destroy pathogenic bacteria but may also destroy useful commensal phyla such as the Bacteroidetes and the Firmicutes which are mainly responsible for producing the body's short chain fatty acids (SCFAs). SCFAs are very important in regulating the body's immune system and may actually directly or indirectly modulate the differentiation or proliferation of T cells [41]. It is therefore logical to conclude that because antibiotics can destroy these important commensals, there could be decreased production of these important immune modulators.

Obesity

The association between antibiotic exposure and growth first emerged from animal studies several decades ago when farmers noted that small doses of antibiotics made their animals grow bigger and faster [44,45]. Emerging data now show that early antibiotic use may also be linked to obesity. In studies in which children received intrapartum antibiotics in the 2nd or 3rd trimester of pregnancy, they were more likely to be obese at 7 years than their untreated counterparts [46,47].

Exposure to antibiotics any time after delivery has also been demonstrated to predict obesity later in life. Thus antibiotic use during the first 6 months of life was associated with increased BMI [48]. The type of antibiotic exposure is also important with broad spectrum antibiotics use causing higher obesity rates than narrow-spectrum ones [49]. Antibiotics used for treating pathogenic bacteria inadvertently may also destroy useful commensals such as the Firmicutes and Bacteroidetes species. The destruction of these important commensals causes a shift or change in the gut microbiota resulting in decreased production of SCFAs subsequently results in increased glucose utilization [50].

Immune function

It is now well documented that SCFAs (mainly acetate, butyrate, and propionate), produced from fermentation of dietary fibers by the Bacteriodes and Firmicutes, are actively involved in both the innate and cellular immune response. Thus SCFAs enhance the epithelial barrier of the gut through induction of genes encoding tight-junctions components [51-53]. SCFAs, through a complex mechanism, exert their activity directly or indirectly on antigen-presenting cells, epithelial cells, and T cells to influence inflammatory response to various infections [41,54,55]. Therefore, antibiotic-treated subjects would partly eliminate the Firmicutes and Bacteriodes thus reducing their ability to produce SCFAs with the resultant impairment of the overall immune function.

WHY GBS VACCINE IS URGENTLY NEEDED

GBS vaccine is urgently needed for at least 4 reasons:

1) The unchanging high prevalence of GBS colonization among pregnant women: The prevalence of GBS colonization is high and does not seem to have changed over the past several decades. Studies show that GBS colonization occurs in about 20%-30% of women of term or near term newborns in the United States [5-9]. In most other countries of the world [1,9-12]. Thus a high proportion of IAP antibiotics will always be needed to curb neonatal GBS disease.

2) Lack of screening of most pregnant women: Universal screening of all pregnant women prior to delivery is highly desirable so that they can be appropriately treated prior to delivery. However, this is practically impossible for various reasons including preterm delivery. Indeed only 50% of preterm neonates are screened for GBS colonization prior to delivery [56]. Furthermore, 20% of EOGBS disease and almost 50% of LOD occur in preterm neonates less than 35 weeks [57].

3) The transient nature of GBS colonization throughout pregnancy: It has been shown that at most 40% of women initially +ve for GBS are still +ve at delivery [58]. Thus a high proportion of women may be receiving unnecessary IAP and women who may have benefitted from IAP may not be treated because they initially screened negative.

4) The unchanging prevalence of late onset GBS disease: Recent studies show that while early onset GBS disease in neonates has dramatically declined by almost 40%, the late onset disease has remained surprisingly stable in the era of intrapartum antibiotics [57].

It is therefore hoped that an effective vaccine would reduce the use of intrapartum antibiotics from a current high rate of about 40%+ to less than 10% of all births

CONCLUSION

Despite the advancement in the diagnosis, prevention, and treatment of GBS disease, this pathogen continues to cause significant disease in young infants and children globally. Thus a GBS vaccine is urgently needed and would greatly reduce the unnecessary use of intrapartum antibiotics thus avoiding many of the complications enumerated above.

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