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The Relationship between Preterm Premature Rupture of Membranes and Colonization of GBS – A Review

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Abstract

Purpose: Group B *Streptococcus* (GBS) is the leading cause of newborn infection. The most important risk factor for this debilitating infection in newborns is maternal colonization of the genitourinary and gastrointestinal tracts. This review investigates three main questions and what answers exist in the current literature. The first question seeks to investigate whether there is a causal relationship between GBS infection and Preterm Premature Rupture of Membranes (PPROM). The remaining questions in this review investigate the management of PPROM pertaining to the optimal time of delivery and the antibiotic treatment best suited for GBS colonized women.

Methods: A PubMed search was performed (1996-2020), using preterm rupture of membranes and GBS as the primary medical subject heading, reporting randomized clinical trials, quasi-experimental trials, and analytic studies) including retrospective and prospective cohort studies). We also searched Google for preterm rupture of membrane intervention programs and prenatal care clinics published online.

Results: We found 39 studies in our search that investigated the relationship between GBS colonization and PPROM. Of these studies, 5 were Randomized Control Trials (RCT), 8 were retrospective, and 4 were systematic reviews. Most of the studies did not show an association between GBS and PPROM. All the studies showed a benefit in antibiotic treatment however none considered specific treatment in the setting of GBS and PPROM. As for management, most of the studies did not show a benefit of expectant management or immediate delivery for these women.

Conclusion: There is no clear-cut association between PPROM and GBS. Many studies have sought out to find a significant association, but the more studies exist, the more answers exist to the question being investigated. Practices involving prophylactic antibiotic treatment at the time of PPROM and again at the time of delivery are the most beneficial management which decreases intraamniotic infection, vertical transmission, and risks of neonatal sepsis after birth. Expectant management of delivery was not found to be more effective than active management in women with PPROM and GBS colonization.

Keywords: Group B *Streptococcus*; PPROM; Rupture of membranes; Antibiotics

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Introduction

Group B streptococcus (GBS) is the leading cause of newborn infection and is the most preventable disease in newborns. Maternal colonization of the genitourinary tract is the most important risk factor for this debilitating condition in newborns [1].

Preterm Premature Rupture of Membranes (PPROM) refers to rupture of the membranes before the onset of labor in women with a pregnancy <37 weeks of gestation. It complicates 1% to 3% of all pregnancies and is responsible for approximately 30% of preterm births [2,3]. This can be detrimental in newborns since the risk of early onset neonatal sepsis in GBS-positive women is extremely high (15.2%) [3].

Whether or not GBS is an independent risk factor for PPROM is still under debate. Up until now no significant difference has been found between GBS colonized women and non-GBS colonized women who suffer from PPROM. This is a critical point of reference because neonatal sepsis is certainly a preventable disease. The more we investigate the management of PPROM, the closer we will be to attaining a prediction model for women with GBS during pregnancy.

The aim of this paper is to review the published literature on PPROM and its association with GBS, and to investigate three main questions and what answers exist in the current literature.

The first question seeks to investigate whether there is a causal relationship between GBS infection and PPROM. The remaining questions investigate the management of PPROM pertaining to the optimal time of delivery and the definitive antibiotic treatment best suited for GBS colonized women with PPROM.

Materials and Methods

A PubMed (www.pubmed.org) search was performed (1979 to 2018), using preterm rupture of membranes PPROM and GBS as the primary medical subject heading, reporting randomized clinical trials, Quasi-experimental trials, and analytic studies (including retrospective and prospective cohort studies). We also searched Google for PPROM and GBS and management protocols in hospitals published online. Criteria to select studies included a description of interventions, a defined outcome, description of the population studied, withdrawals and exclusion rates, appropriate analysis, and identification of potential bias. We excluded studies written in languages other than English and studies or prenatal care clinics with no details on the specified interventions, population, or outcomes.

We summarized the results in three sections, according to the question being investigated (Figure 1).

Results

Is there an association between GBS and PPROM?

GBS colonizes up to thirty percent of pregnant women in the vagina or rectum and is the most common cause of early-onset neonatal sepsis [4]. The question of whether GBS is an independent risk factor for preterm premature rupture of membrane has not been answered decisively [5].

Older studies report a rate of PPROM ranging from 8.1% to 26.4% among GBS carriers compared with 4% to 18% among noncarriers [6-8]. Studies differed widely in methods, validity score, and GBS prevalence. However, the range of GBS carriers with PPROM is still significant [9]. While more updated studies found no significant difference in the rate of PPROM between women with positive and negative GBS cultures [5,10-12].

Two reviews concluded no association between colonization with GBS and PPROM, or preterm delivery. The first review found no association in six of seven studies reviewed. However, women with asymptomatic bacteriuria caused by GBS had a higher rate of prematurity than did women without asymptomatic Bacteriuria [12]. In a more recent review by Valkenburg-van den Berg, no association was illustrated between maternal GBS colonization during pregnancy and preterm delivery, regardless of PPROM [9].

Most of the literature reviewed suggests that there is no definite proof of a causal relationship between GBS and PPROM (Table 1).

Treatment of women with GBS and PPROM

The most common practice today is to treat women with GBS colonization with prophylactic antibiotics to minimize the risk for neonatal infection through the birth canal. The use of chemoprophylaxis of GBS to prevent Early-Onset Disease (EOD) was studied since the 1980's and is recommended by the American College of Obstetricians and Gynecologists (ACOG) since the 1990's [1,13-25].

These studies demonstrated efficacy of up to 100% when prophylaxis is given at the time of PPROM and again at the time of delivery.

GBS is susceptible to beta lactams antibiotics therefore penicillin and ampicillin are most administered. Both medications are given intravenously, however penicillin has a narrower antimicrobial activity than ampicillin. The CDC guidelines for intrapartum chemoprophylaxis states penicillin as the agent of choice with ampicillin being alternative agent [26].

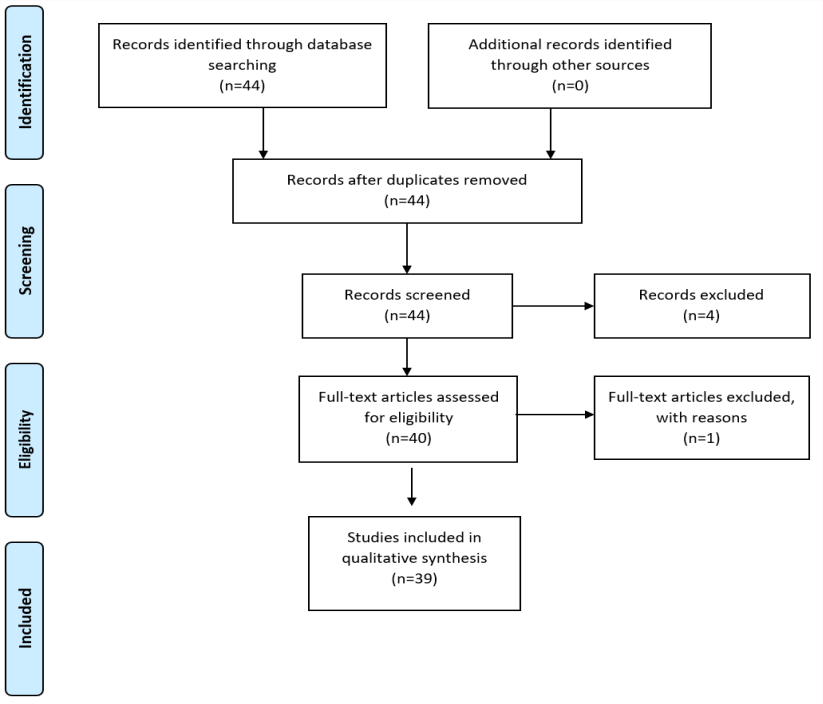

Figure 1: Results.

Table 1: Total references cited that support or do not support a relationship between GBS and PPROM (Ref = References).

Source (ref)	Year	Design	Number of subjects	Relationship between GBS and PPROM
Musilova et al. [12]	2016	**Case control**	336	No relationship found
Schaaf [4]	2010	**Cross sectional**	116	No relationship found
Nomura [13]	2005	**Case control**	203	No relationship found
Alger [11]	1988	**Case control**	45,336	No relationship found
Newton [10]	1988	**Case control**	140	No relationship found
Regan [9]	1996	**Cross sectional**	13,646	Positive relationship found

The timing of treatment serves crucial purposes: To decrease intraamniotic infection (which puts the fetus at risks for neurological damage), to prevent vertical transmission, and to decrease the risk of neonatal sepsis after birth. There are two mechanisms by which chemoprophylaxis prevent EOD. The first is by temporary decreasing the GBS colonization load in the maternal vagina and thus preventing vertical transmission, while the second approach is by reaching the fetal bloodstream and the amniotic fluid and protect the fetus from an infection [15,23].

The recommended duration of intrapartum GBS chemoprophylaxis by the CDC is at least 4 h before delivery. This recommendation is based on a study from 1998 that showed a reduced newborn GBS colonization when chemoprophylaxis was initiated at least 4 h prior to delivery. The rate of GBS transmission was 46% when antibiotic treatment was initiated 1 h prior to delivery and decreased to only 1.2% when given 4 h prior to delivery [24]. A similar study from 2007 strengthened that recommendation [27].

Although a minimal interval of 4 h is well accepted, there is still a need for more prospective studies to evaluate the optimal duration of GBS prophylaxis to prevent GBS EOD.

When PPROM occurs weeks or months before labor, the management requires a carefully balanced approach that weighs in the benefits of prolongation of pregnancy *vs.* the risk of intra-amniotic infection [28]. The different international societies offer an option of expectant management for PPROM after week 24 0/7 of gestation and until week 37 0/7 of gestation [29-33].

Unfortunately, specific antibiotic treatment for women who are GBS carriers with PPROM does not exist in the literature. No trial or study has been carried out to find the optimal antibiotic treatment for this group of women. Additionally, the length of antibiotic treatment in the presence of GBS and PPROM is of uncertainty.

Time of delivery of GBS & PPROM

One of the commonly debated subjects linked to management of PPROM affected by GBS colonization is time of delivery. To plan optimal management, the physician must be aware that the length of latency period can detrimentally affect neonatal outcome.

A group of retrospective studies demonstrated no difference in latency period in women with PPROM and GBS compared to women with PPROM without GBS. Ganor-Paz et al. demonstrated no difference in length of latency period (time of PPROM until delivery) in GBS and non-GBS carriers in 182 women with PPROM between 24 to 35 weeks. These results are consistent with other studies [5,34-36].

A Cochrane review from 2017 supports expectant management in women with PPROM [37]. Although this review did not investigate women with PPROM and GBS colonization, it respectively consists of 12 studies (3,617 women) and concludes that there is no significant difference in neonatal sepsis between early birth and expectant management in women with PPROM less than 37 weeks (RR 0.93, 95% CI 0.66-1.30), or proven neonatal infection (RR: 1.24, 95% CI 0.70-2.21). Moreover, this review illustrates that active management increases the incidence of Respiratory Distress Syndrome (RDS) (RR: 1.26, 95% CI 1.05) compared to expectant management [38].

Contrarily, another trial illustrated that PPROM between 34 and 37 weeks with positive GBS may benefit from immediate delivery due to neonatal risks of intra-amniotic infection [2]. The risk of neonatal sepsis in GBS carriers was much higher when women were managed expectantly compared to immediate delivery (15.2% *vs.* 1.8%, odds-ratio 0.1; 95% CI: 0.01-0.84). This study concluded that in GBS colonized women, longer time to delivery was associated with a higher risk of neonatal sepsis, whereas there was no such association in the GBS-negative women (P<0.095) [2]. Newton et al. [10], presented similar results in their study. Women with GBS had earlier ruptured of membranes (30.7 *vs.* 31.6 weeks) and shorter latent periods (76.8 *vs.* 138.5 h). GBS women were found to have a higher risk for intra-amniotic infection (6/16 *vs.* 26/120) and endometritis (4/10 *vs.* 3/94). This study concluded that GBS is detrimental for the mother and the neonate and thus active management should be carried out to prevent complications [7].

There are few studies which consider GBS colonization in the setting of PPROM and whether expectant management is appropriate. The PPROMT trial, perhaps the largest study regarding the management of PPROM, did not consider GBS status but did conclude recommendations about expectant management *vs.* immediate delivery: Expectant management resulted in less neonatal morbidity and mortality. Even the different international societies do not refer to PPROM in the setting of GBS colonization, and do not determine the optimal time of delivery in PPROM and GBS colonization [29-33].

Overall, there is no consensus for management of latency period. No gold standard exists. A large enough and updated protocol has yet to be advised to accomplish optimal management standards.

Discussion

A universal prenatal screening test for GBS and intrapartum antibiotic management is essential in decreasing the amount of perinatal morbidity and mortality today. It seems that neonatal sepsis is still encountered in places where it could be nearly eradicated. Although intrapartum antibiotic prophylaxis has been effectively safe, research that evaluates the strategy and timing for treatment continues to be important for prevention of GBS early-onset neonatal sepsis.

The first question this original review sought to answer is if there is an association between PPROM and GBS. The literature was

challenging due to opposing studies however most of them concluded that there is no clear-cut association between PPROM and GBS [4,10-13]. Most of the literature that exists concerns GBS and preterm delivery. A very narrow niche applies to GBS and PPROM, and even in that niche there are contradicting conclusions.

The next query this article raised was the optimal management and treatment for women with PPROM and GBS. When evaluating the management of women who are GBS positive and experience PPROM, obstetricians are facing a dilemma. There are no guidelines or recommendations by the various national and international societies regarding a specific type of antibiotic, duration of that treatment or any other follow-up for those women. There is a need to explore if antibiotic type should be rendered specifically to GBS and PPROM. No study has shed light on whether this group of women deserves a definitive type of antibiotic regimen. The only guidelines that exist today are for the treatment of PPROM, regardless of GBS colonization.

The question of immediate delivery or expectant management after PPROM was investigated. A handful of retrospective studies demonstrated no difference in neonatal outcomes between length of latency period in women with PPROM and GBS compared to women with PPROM without GBS [2,5,7,10,34-36].

The obstetrician caring for women with positive GBS cultures should be able to predict and prevent complications. The goal of this review was to eventually create a digital prediction model which will aid physicians in managing women with PPROM and GBS based on variables and literature findings. There is a dire need for larger multi-center studies to achieve this goal.

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