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CLINICAL STUDY

Opportunities to reduce overuse of antibiotics for perinatal group B streptococcal disease prevention and management of preterm premature rupture of membranes

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Abstract

Objective: To identify opportunities to reduce overuse of antibiotics for prevention of perinatal group B streptococcal (GBS) disease and management of preterm premature rupture of membranes (pPROM).

Methods: An anonymous written questionnaire was sent to each of 1031 Fellows of the American College of Obstetricians and Gynecologists, and the responses were subjected to statistical analysis.

Results: Among those of the 404 respondents who saw obstetric patients in 2001, most (84%) screened for GBS colonization, and 22% of these prescribed prenatal antibiotics to try to eradicate GBS colonization. Of the 382 respondents (95%) who prescribed antibiotics for pPROM, 36% continued antibiotics for more than 7 days despite negative results from GBS cultures collected before initiation of treatment. Having more years of clinical experience (adjusted odds ratio (OR) 3.0, 95% confidence interval (CI) 1.5 to 6.2), working in a non-academic setting (adjusted OR 2.7, 95% CI 1.0 to 6.9), and prescribing antibiotics prenatally for GBS colonization (adjusted OR 2.0, 95% CI 1.1 to 3.4) were associated with prescribing prolonged antibiotics for pPROM.

Conclusion: Prenatal antibiotic treatment for GBS colonization and prolonged antibiotic treatment for pPROM contribute to overuse of antibiotics in obstetrics.

Keywords: *pPROM, group B streptococcus, antibiotic prophylaxis, perinatal sepsis, prematurity*

Introduction

Prophylactic use of antimicrobials can play an important role in improving pregnancy outcomes. For example, widespread use of intrapartum antimicrobial prophylaxis for prevention of perinatal group B streptococcal (GBS) disease in the USA led to a 70% decline in a leading infectious cause of neonatal mortality [1, 2]. Prophylactic antibiotics may also promote beneficial outcomes among women with preterm premature rupture of the fetal membranes (pPROM), either by prolonging the latency of the pregnancy [3–9] or by preventing adverse neonatal and maternal outcomes due to infectious causes [7, 10].

However, use of prophylactic antibiotics is not always appropriate. Prenatal prophylaxis to eradicate GBS colonization before the intrapartum period has never been recommended, because early studies demonstrated that eradication was rarely achieved or maintained [11, 12]. Provider practices regarding prenatal prophylaxis, however, have not been characterized. Because current prevention guidelines recommend late antenatal culture-based screening for all pregnant women, prenatal prophylaxis for colonized women could lead to substantial overuse of

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antibiotics during pregnancy if it were a common obstetric practice [2, 13, 14].

For the case of preterm delivery, prophylactic antibiotic recommendations are more complex. From the narrow perspective of GBS prevention, guidelines are most clear. Because preterm delivery is associated with an increased risk of neonatal GBS disease, all women with unknown or positive GBS status who present in preterm labor should receive GBS intrapartum prophylaxis. To avoid overuse of antibiotics, women of unknown GBS colonization status should be tested for GBS before initiating prophylaxis; GBS prophylaxis should be stopped for women who are subsequently found to have negative culture results [2].

From the broader perspective of preventing adverse outcomes of pPROM, however, antibiotic prophylaxis is supported in some cases even in women known to be GBS-negative. ACOG's practice guidelines for the clinical management of pPROM from 1998 recommend antibiotic use with expectant management [15]. Antimicrobial regimens are primarily 7-day courses and include agents such as ampicillin and erythromycin or co-amoxiclav (amoxicillin/clavulanic acid) [15]. These guidelines, based on the best evidence available at the time, were motivated in part by an influential randomized controlled multicenter trial [16] of women with pPROM that found multiple benefits of antibiotic treatment, including fewer cases of neonatal respiratory distress and necrotizing enterocolitis. However, this trial only enrolled women with pPROM remote from term (24 to 32 weeks' gestation) and did not allow the use of corticosteroids, factors which both influence the effect of antibiotics on improving pPROM outcomes. A recent large prospective randomized controlled trial that enrolled women of any gestational age < 37 weeks, and treated more than 75% of subjects with steroids, did not fully support earlier results [17]. Use of erythromycin was associated with limited maternal and neonatal benefits, including prolonged latency and reduced neonatal morbidity. Use of co-amoxiclav, however, was associated with increased risks of necrotizing enterocolitis and therefore not recommended despite prolonging latency slightly [17].

In the light of these newer concerns about adverse consequences of antibiotics, as well as growing concerns about emerging antimicrobial resistance among pathogens affecting preterm infants [18], an ACOG Practice Bulletin on intrapartum prophylaxis [19] recommends that providers consider antibiotic prophylaxis for pPROM on an individual patient basis and stresses that antibiotics are most beneficial for cases of extreme prematurity where prolongation of latency is the primary objective. This statement, which came out after our survey was completed, does not replace the 1998 pPROM guidelines; it also does not define extreme prematurity or provide detailed management guidance.

Although antibiotic prophylaxis in the obstetric setting can greatly reduce morbidity and mortality, unnecessary use of antibiotics has the potential to harm both the mother and newborn, and in some circumstances may also adversely affect the community by increasing risk of antimicrobial resistance. We conducted a national survey of obstetrician-gynecologists to characterize antibiotic prescription practices related to perinatal GBS disease prevention and management of pPROM, to evaluate compliance with current recommendations, and to identify opportunities to reduce overuse of prophylactic antibiotics.

Methods

In June 2002, an anonymous questionnaire was sent to 1031 ACOG Fellows, comprising 409 Fellows in the Collaborative Ambulatory Research Network (CARN: a group of volunteers established in 1990 which helps ACOG monitor provider practices by participating in roughly four surveys per year), and 622 randomly selected non-CARN Fellows. Those who did not respond received a second mailing approximately 6 weeks later. The study protocol was considered by an Institutional Review Board at the Centers for Disease Control and Prevention and designated exempt from the need for formal human subjects review.

The survey, which aimed to assess antibiotic prescribing practices of obstetrician-gynecologists both in perinatal care and for upper respiratory tract infections (URTIs), included predominantly multiple choice questions about respondents' demographics, practice settings and patient populations. Questions related to antibiotic use for GBS disease prevention and pPROM were primarily in a scale format (always/sometimes/never) and included:

(1) Do you screen your obstetric patients for vaginorectal group B streptococcal (GBS) colonization?
(2) If you find GBS vaginorectal colonization in an obstetric patient, how often do you prescribe **prenatal** antibiotics to attempt to eradicate colonization (not bacteriuria)?
(3) (3a) In a woman with preterm rupture of membranes but **no** fever, uterine tenderness or signs of imminent delivery, how often do you prescribe antibiotics?
(4) (3b) If the GBS culture is negative in the situation described above, how often do you continue antibiotics **beyond one week** after the onset of preterm rupture of membranes?

(5) (3c) In the above described situation in which you continue antibiotics with a negative GBS culture (or no culture), what is the usual reason for continuing antibiotics?
(6) (3d) Which agent(s) do you commonly prescribe for preterm rupture of membranes (orally or IV or both) in the above situation?

These last two questions (3c and 3d) asked respondents to check all answers that applied. The rest of the survey, which consisted of questions about antibiotic prescribing practices for URTIs, was analyzed separately [20].

To assess the current practices of providers we excluded individuals enrolled in training programs or who saw no obstetric patients in 2001. Survey responses were double-entered. Statistical analysis was performed using SAS version 9.0 (SAS Institute, Cary, NC, USA). Continuous variables (clinical experience and proportion of pregnant patients seen) were categorized by quartiles. Answers to questions using an always/sometimes/never format were condensed to the categories ever/never for analysis purposes. Univariate associations were evaluated using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables; significance was assessed using Mantel–Haenszel–Cochran summary odds ratios (ORs) and 95% confidence intervals (CIs). Independent variables that were evaluated included gender, CARN status, years of clinical experience, location and type of practice, proportion of pregnant patients seen, and prescription of antibiotics for the common cold. CARN status, gender, years of clinical experience and all variables significant at $p < 0.15$ in univariate analysis were evaluated in multivariable models using stepwise logistic regression. Because the CARN group differed from the non-CARN group in response rate and demographics (see below), all multivariable models controlled for CARN status. The final multivariable model contained all main effects significant at $p < 0.05$. All two-way interactions of main effects were evaluated.

Results

Of 1031 mailed surveys, 519 were returned for an overall response rate of 50%; the response rate for the CARN group was higher than for non-CARN Fellows (65% versus 41%, $p < 0.001$). Of these 519 respondents, 97 were excluded because they did not see obstetric patients, and 18 were excluded for other reasons; 404 (215 CARN and 189 non-CARN) were eligible for inclusion in the analysis. The CARN and non-CARN groups did not differ significantly for a majority of characteristics. Respondents had a median of 15 years of clinical experience, and 56% were men. The CARN group had more years of clinical experience than the non-CARN group (median years experience 16 versus 10, $p < 0.001$).

A high proportion of respondents (84%) screened obstetric patients for GBS colonization. In our study, the proportion of respondents that performed prenatal GBS screening was significantly higher among both groups than in 1999, when an earlier survey of ACOG members was conducted [21]. In this earlier 1999 survey, 70% of the CARN group screened for GBS in obstetric patients (versus 86% in 2001, $p < 0.001$), and 70% of the non-CARN group screened (versus 84% in 2001, $p < 0.001$). Providers who screened in 2001 did not differ significantly from those who did not by demographic characteristics, practice type or practice location. However, those whose practice served more than 25% obstetric patients were more likely to screen for GBS colonization (adjusted OR 2.5, 95% CI 1.4 to 5).

Among respondents who performed antenatal GBS screening, nearly one in four (22%) prescribed prenatal antibiotics sometimes (9%) or always (13%), in an attempt to eradicate GBS colonization. Factors associated with prescribing prenatal antibiotics for GBS colonization are shown in Table I. In multivariable analysis, prolonged use of antibiotics for pPROM (adjusted OR 2.4, 95% CI 1.3 to 4.5) and prescribing antibiotics for the common cold (adjusted OR 2.0, 95% CI 1.1 to 3.8) were significantly associated with prescribing prenatal antibiotics in an attempt to eradicate GBS colonization.

Almost all respondents (95%) prescribed antibiotics for women with pPROM; 75% of the prescribers reported always prescribing antibiotics in this situation. Those who never prescribed antibiotics were more likely to work in small practices (adjusted OR 2.7, 95% CI 1.1 to 6.8). Among the 369 respondents who reported screening for GBS and prescribing antibiotics for pPROM, 134 (36%) reported continuing antibiotics for more than 7 days for GBS-negative women with pPROM and no signs of clinical infection. Of these, common reasons for prolonged antibiotic use included empiric treatment of chorioamnionitis (30%), prolongation of the pregnancy (7%), or both (39%). Mistrust of GBS culture was never the sole reason for continuing therapy beyond 7 days, but was reported by 24% as one of the reasons for continued therapy. A majority of respondents (55%) prescribed multiple agents for prolonged courses. The most common agents included ampicillin (84% or 113 of 134) and erythromycin (29% or 39 of 134); 7 % (10 of 134) used amoxicillin clavulanate.

Providers who continued antibiotics for more than 7 days for GBS-negative women with pPROM were more likely to be men, to have more years of clinical

Table I. Factors associated with obstetrician-gynecologists who attempt to eradicate group B streptococcal colonization by prenatal antibiotic therapy

Factor	Offer antibiotics, % ($n = 74$)*	Never offer antibiotics, % ($n = 260$)*	OR (95% CI)	OR† (95% CI)
CARN member	55	55	1.0 (0.6, 1.7)	1.2 (0.7, 2.3)
Male	61	52	1.5 (0.9, 2.5)	
Clinical experience in years§				
0–7	20	29		
8–14	23	25	1.3 (0.6, 2.8)	
15–21	23	26	1.3 (0.6, 2.7)	
22 +	35	20	2.5 (1.2, 5.1)	
Solo or 2-clinician practice setting	40	27	1.8 (1.0, 3.0)	
Urban practice setting	39	28	1.7 (1.0, 2.8)	
Prolonged antibiotics for GBS-ve pPROM	49	33	2.0 (1.2, 3.5)	2.4 (1.3, 4.5)
Antibiotics for coryza	58	44	1.8 (1.0, 3.1)	2.0 (1.1, 3.8)

All independent variables were examined. CARN status, sex, clinical experience and results with $p < 0.15$ were included. *This denominator is constant throughout the table, except with prolonged use of antibiotics for pPROM where $n = 311$ (69; 242) and prescription of antibiotics for the common cold, where $n = 267$ (60; 207). †Adjusted odds ratios are given for all variables included in the final model. §The overall effect of this variable had a p value of 0.07 in univariate analysis.

Table II. Factors associated with obstetrician-gynecologists who continue antibiotics for more than 7 days for women with pPROM and negative GBS cultures

Factor	$\leqslant$ 7 days % ($n = 134$)*	$>$ 7 days % ($n = 235$)*	OR (95% CI)	OR† (95% CI)
CARN member	49	54	0.8 (0.5, 1.2)	0.59 (0.4, 1.0)
Male	66	49	2.1 (1.3, 3.2)	
Clinical experience in years§				
0–7	19	30		
8–14	24	29	1.2 (0.6, 2.2)	1.0 (0.5, 2.1)
15–21	26	25	1.6 (0.9, 3.1)	1.3 (0.6, 2.6)
22 +	34	17	3.1 (1.6, 5.8)	3.0 (1.5, 6.2)
Non-academic practice setting	93	86	2.3 (1.1, 4.9)	2.7 (1.0, 6.9)
Anti-GBS prenatal antibiotics	30	18	2.0 (1.2, 3.5)	1.9 (1.1, 3.4)
Patient population $\leqslant$ 75% obstetric	93	89	1.8 (0.3, 1.2)	

All independent variables were examined. Results with $p < 0.15$ were included in this table. *This denominator is constant throughout the table, except with the prescription of prenatal antibiotics for colonization where $n = 311$ (113;198). †Adjusted odds ratios, for all variables included in the final model. §The overall effect of this variable had a p value of 0.002 in univariate analysis and 0.005 in multivariable analysis.

experience, to practice outside a university setting and, to prescribe prenatal antibiotics in an attempt to eradicate GBS colonization (Table II). In multivariable analysis, predictors of prolonged antibiotic therapy included being a non-CARN member, having more clinical experience, working in a non-academic setting, and prescribing antibiotics prenatally to eradicate GBS colonization.

Discussion

Our finding that nearly a quarter of all respondents who screened for GBS colonization prescribed antibiotics prenatally in an attempt to eradicate GBS colonization documents an important overuse of antibiotics that is of even more concern now that universal GBS screening is recommended. Since the release of the first consensus guidelines in 1996, this potential source of inappropriate antibiotic use has not been evaluated. Whereas treatment for prenatal urinary tract infection involving GBS is appropriate, prevention guidelines have consistently advised against prenatal antibiotics to eradicate GBS colonization, on the basis of studies showing the failure of such regimens to lead to successful eradication at the time of delivery [11,12]. Growing evidence of adverse neonatal outcomes associated with beta-lactam regimens given late in pregnancy provides further reason to avoid this practice [4, 6, 17]. Targeted education of obstetrician-gynecologists

highlighting the importance of limiting use of GBS chemoprophylaxis to the intrapartum period could lead to reductions in prenatal antibiotic prescription, particularly as universal prenatal screening for GBS becomes widespread. Since providers who prescribed prenatal antibiotics for GBS colonization were also more likely to prescribe antibiotics for the common cold, such providers appear to have a tendency to overuse antibiotics and may need targeted messages to address these practices.

Because data on the benefits of antibiotics for pPROM are less clear, ACOG's guidelines are more permissive, although a recent practice bulletin published after our survey suggests restricting antibiotics for pPROM to cases of extreme prematurity, in order to minimize adverse consequences of antibiotics [19]. Almost all survey respondents initiated short courses of antibiotics for pPROM and discontinued therapy within 7 days for GBS-negative women with no signs of intrapartum infection. Termination of therapy for GBS-negative women is consistent with GBS prevention recommendations. Initiation of antibiotics for women with pPROM close to term may not always be indicated, however, and particularly not for women where the GBS status is known to be negative at the time of arrival.

Approximately a third of obstetrician-gynecologists continued antibiotics for more than 7 days for women with negative GBS cultures without clinical signs of infection. This extended duration of therapy does not have empiric support and represents overuse of antibiotics except in exceptional circumstances. Additionally, many included beta-lactam agents in pPROM regimens although beta-lactams, and particularly those closely related to co-amoxiclav, should be used with caution for GBS-negative women with pPROM in view of growing evidence for an association between co-amoxiclav and an increased risk of necrotizing enterocolitis [17].

Providers prescribing prolonged regimens were more likely to have extensive years of clinical practice, suggesting that older providers may have been more influenced by earlier studies highlighting the benefits of antibiotics, particularly before use of corticosteroids and tocolytics was routine. They also tended to work in non-academic settings. As pPROM management recommendations evolve, outreach to these groups in particular might be important. Until recommendations can clearly delineate the circumstances where antibiotics are beneficial for pPROM, decision-making theory suggests that providers choosing prolonged therapy for GBS-negative women are likely to continue current patterns of use [22].

Mistrust of GBS culture results was never the sole reason for prolonged therapy, although almost a quarter of respondents listed it as a contributing factor. As universal GBS screening is implemented, monitoring of laboratory compliance with specimen processing recommendations will be important to maintain clinician confidence in GBS culture results.

This evaluation shares many of the limitations of survey investigations. The response rate (50%) was somewhat lower than rates achieved in other surveys of ACOG Fellows (60 to 70%), although it was higher than that achieved in a survey of maternal-fetal medicine specialists on a similar topic [23]. As is often the case with self-administered surveys, we may have elicited a biased response due to self-reporting of practices. In particular, respondents may have given answers they thought the investigators wanted, therefore underestimating overuse of antibiotics.

Nonetheless, our survey identified some important opportunities to reduce overuse of antibiotics in the obstetric setting. For perinatal GBS disease prevention, careful adherence to the current prevention guidelines, which are consistent among the major professional organizations, will help limit inappropriate antibiotic use. For pPROM, prevention strategies have not yet been identified and interventions to minimize the neonatal morbidity associated with pPROM require more research. In the meantime, unnecessary antibiotic use can be avoided by encouraging physicians to weigh the risks involved in each case, to administer antibiotics preferentially in cases of extreme prematurity, and to limit duration of therapy.

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