

ONTARIO
MIDWIVES

EXPERTS IN NORMAL PREGNANCY, BIRTH & NEWBORN CARE



> Clinical Practice Guideline No.11



Association of Ontario Midwives

**GROUP B STREPTOCOCCUS:
PREVENTION AND MANAGEMENT IN LABOUR**

JANUARY 2010

> Clinical Practice Guideline No.11

GROUP B STREPTOCOCCUS:

PREVENTION AND MANAGEMENT IN LABOUR

Authors

Elizabeth Darling, RM MSc

Kathleen Saurette, RM

Contributors

Clinical Practice Guideline Subcommittee

Ren Barrett, RM, MEd

Cherylee Bourgeois, RM

Corinne Hare, RM

Jenni Huntly, RM

Paula Salehi, RM

Lynlee Spencer, BSc

Vicki Van Wagner, RM, PhD (c)

Rhea Wilson, RM

Insurance and Risk Management Program Steering Committee

Remi Ejiwunmi, RM, Chair

Abigail Corbin, RM

Elana Johnston, RM

Carolynn Prior van Fraassen, RM

Lisa M Weston, RM

AOM Staff

Suzannah Bennett, MHSc

Cindy Hutchinson, MSc

Tasha MacDonald, RM MHSc

Bobbi Soderstrom, RM

Acknowledgements

Megan Bobier, BA

Ontario Ministry of Health and Long-term Care

Ryerson University Midwifery Education Program

The Association of Ontario Midwives respectfully acknowledges the financial support of the Ministry of Health and Long-Term Care in the development of this guideline.

The views expressed in this guideline are strictly those of the Association of Ontario Midwives. No official endorsement by the Ministry of Health and Long-Term Care is intended or should be inferred.



Association of Ontario Midwives

365 Bloor St. E., Suite 301

Toronto, ON M4W 3L4

www.aom.on.ca

AOM CLINICAL PRACTICE GUIDELINE

GROUP B STREPTOCOCCUS: PREVENTION AND MANAGEMENT IN LABOUR

This guideline was approved by the AOM Board of Directors: January 20, 2010

Statement of Purpose

The goal of the following evidence-based Clinical Practice Guideline (CPG) is to be consistent with the midwifery philosophy of care. Midwives are encouraged to use this CPG as a tool in clinical decision-making.

Objective

The objective of this CPG is to provide a critical review of the research literature on the management of Group B Streptococcus (GBS) during labour. Evidence relating to the following will be discussed:

- The prevention of Early-onset Group B Streptococcal Disease (EOGBSD)
- Prenatal screening
- Management during the antenatal and intrapartum period

Outcomes of interest

1. Maternal outcomes: effects of exposure to intrapartum antibiotics.
2. Neonatal outcomes: perinatal mortality, perinatal morbidity, EOGBSD.

Methods:

A search of the Medline database and Cochrane library from 1994-2009 was conducted using the key words: group B streptococcus, pregnancy and management. Additional search terms were used to provide more detail on individual topics as they related to the antenatal and intrapartum management of GBS. Older studies were accessed in cases of seminal research studies, commonly cited sources for incidence rates, or significant impacts on clinical practice.

Review

This guideline was reviewed using a modified version of the AGREE instrument (1), the Values-Based Approach to CPG Development (2), as well as consensus of the CPG Subcommittee, the Insurance and Risk Management Program and the Board of Directors.

This guideline reflects information consistent with the best evidence available as of the date issued and is subject to change. The information in this guideline is not intended to dictate a course of action, but inform clinical decision-making. Local standards may cause practices to diverge from the suggestions within this guideline. If practice groups develop practice group protocols that depart from a guideline, it is advisable to document the rationale for the departure.

Midwives recognize that client expectations, preferences and interests are an essential component in clinical decision-making. Clients may choose a course of action that may differ from the recommendations in this guideline, within the context of informed choice. When clients choose a course of action that diverges from a clinical practice guideline and/or practice group protocol this should be well documented in their charts.

ABBREVIATIONS:

CI – Confidence Interval

EOGBSD - Early-onset GBS Disease

GBS - Group B Streptococcus

IAP - Intrapartum Antibiotic Prophylaxis

LOGBSD - Late-onset GBS Disease

NNT - Number Needed to Treat

OR – Odds Ratio

PROM – Prelabour Rupture of Membranes

RCT - Randomized Control Trial

RR – Relative Risk

Key to evidence statements and grading of recommendations, from the Canadian Task Force on Preventive Health Care

Evaluation of evidence criteria		Classification of recommendations criteria	
I	Evidence obtained from at least one properly randomized controlled trial	A	There is good evidence to recommend the clinical preventive action
II-1	Evidence from well-designed controlled trials without randomization	B	There is fair evidence to recommend the clinical preventive action
II-2	Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C	The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3	Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	C	The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	D	There is fair evidence to recommend against the clinical preventive action
		E	There is good evidence to recommend against the clinical preventive action
		L	There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

Reference: (3)

BACKGROUND

In the 1970s, group B streptococcus (GBS) was identified as the leading infectious cause of neonatal morbidity and mortality. GBS disease is classified according to onset of infection: early-onset GBS disease (EOGBSD) occurs within the first 7 days of life, whereas late-onset GBS disease (LOG-BSD) manifests between 1 week and 3 months of age. This guideline focuses on the prevention of EOGBSD and midwifery management during the antenatal and intrapartum period. Recommendations on neonatal follow-up for neonatal care where intrapartum antibiotic prophylaxis (IAP) has been administered fully, partially, or not at all are included in a neonatal GBS sepsis prevention guideline (forthcoming).

Prevalence of GBS

The gastrointestinal tract acts as a reservoir for GBS and is most likely the source of vaginal colonization. Approximately 10% to 35% of pregnant women are colonized with GBS in the vagina and/or rectum, with rates varying by study populations, specimen collection, or culturing techniques. (4) A recent Canadian study determined the prevalence of GBS colonization in pregnant women at 36 weeks gestation to be 19.5%. (5) When untreated, approximately 50% of infants born to GBS positive mothers become colonized and EOGBSD develops in 1% to 2% of these infants. (6) This means that in a group of 1000 untreated women, approximately 195 will be GBS positive, 98 infants will become colonized, and 1-2 will develop EOGBSD.

Incidence of EOGBSD

Incidence and mortality rates of EOGBSD vary. In the 1970s, the incidence of EOGBSD infection was initially estimated at 3/1000 live births. (7) This has dramatically declined over the past 30 years. By 1993, an American multi-state surveillance effort by the Centers for Disease Control and Prevention (CDC) found that 1.7/1000 live births resulted in EOGBSD. After the CDC promoted prevention strategies involving IAP, the EOGBSD rate was reduced by 65% to 0.7/1000 live births in 1998. (8) Since then, rates have continued to drop to 0.47/1000 live births in 1999 to 2001, and 0.34/1000 live births from 2003 to 2005. (9) While the steady de-

cline of EOGBSD has coincided with the adoption of prevention strategies, it cannot be used as definitive proof of the efficacy of these strategies.

The most recent Canadian estimations of EOGBSD incidence date prior to the introduction of current prevention guidelines. Between 1993 and 1999, the rate of EOGBSD in Alberta was 0.36/1000 total births (both live and stillbirths). (10) A population study of 2 tertiary hospitals in Toronto between 1995 and 2002, found the rate of EOGBSD to be 0.90/1000 live births. (11) However, this rate may not reflect the incidence of EOGBSD in the general population as these tertiary centres likely included referred cases.

Transmission

Transmission of GBS may occur as the fetus passes through the birth canal or as ascending infection crosses intact membranes. Fetal or neonatal GBS exposure may also occur through the spread of the bacteria into amniotic fluid, which is then aspirated. (12)

RISK FACTORS

Maternal GBS Colonization

A number of factors have been suggested to be related to the prevalence of colonization, including ethnicity, maternal age, marital status, education, smoking and multiple sexual partners. (13) However, the relationships between these factors and actual colonization rates are unclear, and research is inconsistent. (14)

Early-onset GBS Disease

Early colonization and infection of a neonate is related to maternal vaginal colonization with GBS. Several other factors increase the risk of EOGBSD. These include: preterm birth (< 37 weeks), low birth weight, prolonged rupture of membranes, intrapartum fever, chorioamnionitis and frequent (≥ 6) vaginal exams in labour. (14-18) Table 1 gives the odds ratio of EOGBSD related to these risk factors as well as to the absolute risk of developing EOGBSD when risk factors are present, when this data was available. Table 2 lists risk factors that show an increased incidence of EOGBSD. They have been

divided into 2 categories, those risk factors that appear more commonly in the population (higher prevalence) and yet have a lower attack rate of EOGBSD (10-25/1000 live births) and those factors that appear less commonly (less prevalence) but show a higher attack rate of EOGBSD (>50/1000 live births).

Two other factors associated with a high degree of risk are a previous infant with invasive EOGBSD and GBS bacteriuria in pregnancy. (12,14) The presence of GBS in a sample of clean catch urine may indicate heavy maternal colonization, thereby increasing the risk of EOGBSD. However, 2 studies have raised questions about the predictive nature of GBS bacteriuria. A study in 2002 found GBS bacteriuria in the first trimester to be only 61% predictive of a positive vaginal-perianal GBS culture at delivery. (19) This study did not include a definition of bacteriuria: whether symptomatic or asymptomatic or the number of colony-forming units (cfu/ml). It is unclear whether a set definition would have changed outcomes. Another study, with more clearly defined parameters (bacteriuria defined as >10⁴ cfu/ml), found that only 30.2% of the 53 women studied with asymptomatic GBS bacteriuria had GBS positive cultures at 35 to 37 weeks gestation. (20) These findings indicate that further research is required to determine the predictive value of asymptomatic GBS bacteriuria to heavy genital tract colonization at term and EOGBSD.

Women who wish to swab for GBS at 35 to 37 weeks regardless of having GBS bacteriuria in pregnancy can be informed that while GBS bacteriuria is associated with increased risk of EOGBSD, it is unclear whether GBS bacteriuria in pregnancy is better able to predict GBS colonization at delivery than an antenatal vaginal-rectal culture.

(See Table 1: Risk Factors for EOGBS Infection)

(See Table 2: Attack Rates for EOGBSD by Risk Factor)

ASSOCIATED COMPLICATIONS

Maternal Complications

GBS is a part of normal vaginal flora and most women have no symptoms related to colonization. Rarely, GBS causes urinary tract infections, amni- onitis, endometritis, sepsis and meningitis. (12)

Fetal Complications

Stillbirth is a potential outcome of fetal aspiration of GBS-infected amniotic fluid. (12)

Neonatal Complications

Most neonates with EOGBSD present with one of the following: bacteremia, pneumonia, or meningitis. CDC surveillance found that 83% of EOGBSD cases had bacteremia, 9% pneumonia and 7% meningitis. (9) In a Toronto study, similar proportions were noted: 64% bacteremia, 23% pneumonia and 12.5% meningitis. (11) The onset of EOGBSD is generally rapid: 72% of neonates with EOGBSD had positive sterile site cultures (blood or cerebral spinal fluid) within the first 24 hours and 95% were positive by 48 hours. (9)

The American case mortality rate is 6.8% (ranging from 5%-9% each year), with a threefold increase in risk for preterm neonates (RR 7.7, 95%CI 4.9-12.3). (9) The recent Canadian case fatality rates range from 6% to 9% of babies with EOGBSD with a Toronto study only noting preterm mortalities - all term infants survived. (10,11)

Studies providing current estimates of long-term morbidity from EOGBSD were not identified. Cases from the 1970s and 1980s have mainly focused on the outcomes of survivors of EOGBS meningitis and may not necessarily reflect the outcomes of infants under current standards of intensive care. According to 2 studies from the 1980s, between 50% and 70% of infants surviving EOGBS meningitis functioned normally and had no long-term sequelae. (21,22) In a prospective cohort of 20 infants with EOGBS meningitis, 15% had major sequelae, including severe cognitive delays, quadriplegia and hydrocephalus. Three infants had mild conductive deafness. (22) Another study followed 38 infants post-EOGBS meningitis and found 21% with mild or moderate deficits (borderline cognitive delay, language delay, unilateral deafness, monoparesis) and 29% with major neurological sequelae (cognitive delay, seizure, blindness, quadriparesis, micro-

Table 1: Risk Factors for EOGBS Infection (14,15)		
Risk Factor	Estimated Odds Ratio of EOGBS infection [95% CI where available]	Absolute risk of EOGBSD (%)
GBS+ culture at 28 weeks (rectovaginal)	9.64	N/A
GBS+ culture at 36 weeks (rectovaginal)	26.7	N/A
GBS+ culture at delivery (vaginal)	204 [100-419]	2.0% (N = 2443)
Low birth weight (≤ 2500 g)	7.37	0.79% (N = 3781)
Gestation <37 weeks	4.83, 10.4*	5.6% (N = 141)
Prolonged ROM >18h	7.28 [4.42-12.0], 25.8*	1.0% (N = 4889)
ROM ≤ 18 h	1.0	0.11% (N = 39 302)
Intrapartum fever > 37.5°C	4.05 [2.17-7.56], 10.0*	N/A
Vaginal exams ≥ 6	2.9	N/A
*(15)		

Table 2: Attack Rates for EOGBSD by Risk Factor (14)	
Less prevalent risk factors with higher incidence of EOGBSD (>50/1000 live births)	More prevalent risk factors with lower incidence of EOGBSD (10-25/1000 live births)
<ul style="list-style-type: none"> • Preterm premature rupture of membranes in GBS-colonized mother • Chorioamnionitis • Twin with EOGBSD • GBS bacteriuria during current pregnancy • Sibling with EOGBSD 	<ul style="list-style-type: none"> • Birth weight < 2500 g (16/1000) • Preterm < 37 weeks (10/1000) • Intrapartum fever > 37.5°C (14/1000) • Prolonged rupture of membranes > 18 hours (12/1000)

cephalus or hydrocephalus). (21)

Summary of Prevalence, Incidence and Neonatal Complications associated with GBS:

- 10% to 35% of women are colonized with GBS (4)
- 40% to 50% of babies born to colonized women are colonized when untreated (6)
- 1% to 2% of these colonized babies develop EOGBSD (6)
- 5% to 9% mortality rate in those babies who develop EOGBSD (10,11)

Using these statistics, if we take an initial group of 17 500 to 50 000 pregnant women:

- 5000 women will be GBS positive
- 2000 to 2500 babies will be colonized with GBS
- 20 to 50 babies will develop EOGBSD presenting as the following:
 - bacteremia (64% to 83%)
 - pneumonia (9% to 23%)
 - meningitis (7% to 12.5%) (9,11)
- 1 to 4.5 babies will die due to EOGBSD (from the initial group of 17 500 to 50 000 pregnant women)

PREVENTION

Several strategies to prevent GBS transmission and disease have been proposed. Early research concluded that oral antibiotics in the antenatal period were ineffective at reducing or eliminating GBS colonization. (23) An antenatal intramuscular dose of antibiotics has also been rejected as a preventative strategy. A small RCT assessed maternal GBS colonization at delivery after randomizing 53 GBS positive women to receive either antenatal intramuscular (IM) penicillin or no treatment. (24) Although the treatment reduced colonization rates (RR 0.596, 95% CI 0.472-0.869), 52% of subjects remained GBS positive at delivery. Researchers concluded that antenatal IM penicillin was insufficient as a sole therapy for GBS eradication.

Intrapartum vaginal disinfection with chlorhexidine has also been presented as method to reduce vaginal GBS colonization. A Cochrane meta-analysis of 5 studies examining chlorhexidine douching during labour showed that, when studies were combined, chlorhexidine lowered GBS colonization of neonates, with a relative risk of 0.72 (95% CI 0.56-0.91). (25) However, individually the studies that assessed vertical transmission found a range of results. Three studies assessed 3 different methods of chlorhexidine application. A RCT that compared the use of chlorhexidine gel with a placebo gel and no treatment found no difference in the colonization of newborns between treatment groups. Thirty-three of 63 neonates (52.4%) born to mothers who received chlorhexidine gel remained colonized. (26) A small study of 59 women that assessed the use of gloves lubricated with chlorhexidine found no difference in newborn colonization between treatment and control groups. (27) Only a RCT of 200 women that assessed the effect of a chlorhexidine douche versus a saline douche or compared to no treatment found a significant difference in GBS colonization between groups. The chlorhexidine arm showed a reduced vertical transmission rate of 18% compared with 35% in the saline group ($p < .0001$, 95% CI 0.12-0.22). (28) Due to the relatively small size of these trials (overall N = 2190), reviewers were not able to determine whether the use of chlorhexidine led to a significant difference in rates of EOGBSD. Reviewers noted that many of the studies included were of questionable quality and that a multicentre, double-blinded randomized trial is necessary to accurately determine the efficacy of chlorhexidine in GBS prevention. (25)

Probiotics have also been suggested as a prevention method for maternal GBS colonization. Probiotics are defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host”. (29) In vitro, they have been shown to inhibit growth and adhesion of streptococci. Therefore, they may have a role in preventing vaginal colonization by GBS. Probiotics are considered safe for use in pregnancy. (30) While there are anecdotal reports of the use of probiotics, as well as garlic suppositories and homeopathy for

GBS prevention, currently there is no large-scale published research available to either support or reject the use of alternative remedies to reduce the incidence of GBS colonization in pregnant women at term. Therefore, no recommendations on either using or not using these alternative remedies can be made due to the absence of research and subsequent lack of evidence regarding efficacy.

MANAGEMENT

Prenatal Screening for GBS

A swab taken between 35 and 37 weeks' gestation is the current "gold standard" for the prediction of GBS colonization in labouring women. Vaginal-rectal swabs collected within 5 weeks of birth are commonly cited to have a sensitivity of 87% (95% CI 83-92) and a specificity of 96% (95% CI 95-98) for detecting GBS colonization at delivery based on the findings of a cohort study involving 826 women. (31) However, a more recent prospective cohort study of 377 women found the sensitivity of a 35-week culture to be 67% (95% CI: 62-73). (19)

The specificity of the test decreases dramatically when more than 5 weeks elapse between the time of swabbing and birth. When 6 or more weeks elapse between swab and birth, the sensitivity drops to 43% and the specificity to 85%. (31) Given these findings, it is appropriate to retest for GBS colonization if the woman remains undelivered and more than 5 weeks have elapsed from the time of swab.

The CDC gives a detailed set of recommendations for collecting GBS culture specimens. A single swab is taken of the vaginal area followed by the rectal area, through the anal sphincter. This combined vaginal-rectal swab yields more GBS positive results than specimens taken from only vaginal, rectal, or other sites. The swab should be placed into transport medium that can maintain viability of the organism for up to 4 days, either at room temperature, or refrigerated. (12) In the laboratory, specimens should be cultured in a selective broth medium such as Todd-Hewitt medium supplemented with colistin and nalidixic acid for 18 to 24 hours and then sub-cultured on blood agar

plates. There has been no contradictory evidence or reason found to alter these guidelines since their publication in 2002.

While isolates of GBS remain highly sensitive to penicillin, ampicillin, cefazolin and vancomycin, some strains appear to exhibit resistance to erythromycin and clindamycin. Several studies have documented the resistance rates of isolates against clindamycin and erythromycin. (5,19,32,33) Recent CDC surveillance found 32% of GBS isolates to be resistant to erythromycin and 15% resistant to clindamycin, with 99% of the isolates that showed resistance to clindamycin being also resistant to erythromycin. (9) Sensitivity tests should be requested for the specimens of women with a penicillin allergy in order to ensure the appropriate selection of effective alternative antibiotics for these clients.

Self-collected swabs appear to be as accurate as swabs collected by health professionals. (34-36) Two out of 3 studies found that women reported a preference for collecting their own specimens. (34,35) Thus, women should be offered the choice to self-swab or to have their midwife collect the swab. It is important that women be given proper instructions for self-swabbing, in plain language. Ensuring that the client understands the technique by describing the instructions for self-swabbing back to the care provider is particularly important in cases where the client may have difficulty understanding, such as when there is a language barrier.

While prenatal vaginal/rectal cultures are the current gold standard for predicting intrapartum colonization, a reliable rapid test with the ability to diagnose GBS colonization in labour would be ideal. Presently, rapid screening tests have not been found to exhibit adequate sensitivity and specificity to justify their use. (37)

The development of a more reliable rapid test could prevent the treatment of women who might have tested positive on prenatal cultures but became GBS negative in the time between testing and delivery. Moreover, it would also facilitate treatment for GBS carriers who previously tested negative or those with an unknown GBS status. However, the

prospect of a rapid test also assumes access to a 24-hour laboratory and might only be accessible for births based in hospital. As new diagnostic technologies become available, the health system should ensure that clients have the same access to testing during a hospital or home birth. There is no research available that assesses the predictive value of multiple prenatal cultures. There is no research to guide practice if a woman has more than one swab within 5 weeks of delivery indicating two different results.

Recommendations

- 1. Offer all women screening for group B streptococcus at 35 to 37 weeks' gestation with a culture done from one swab first to the vagina then to the rectal area (through the anal sphincter). It is appropriate to offer women instructions on how to swab themselves for self-collection. [II-2-A]**
- 2. Offer re-screening to all women if > 5 weeks has elapsed from initial swab and the woman remains undelivered. [II-2-A]**
- 3. Request sensitivity testing for the GBS swab if the woman has reported a penicillin allergy. [II-2-A]**

Intrapartum Antibiotic Prophylaxis (IAP)

Clinical trials in the late 1980s that evaluated various treatment methods for reducing EOGBSD (38-40) found that IAP was the most effective method of interrupting transmission of the bacteria from GBS carriers to their newborns, thereby preventing EOGBSD.

In 1986, the efficacy of IAP in preventing GBS transmission was assessed in a small RCT. For this study, from 1979-1984, vaginal and rectal GBS swabs were taken from 13 381 pregnant women in private obstetrical offices in Chicago. No information related to the timing of these swabs was given. Of the 3087 women who swabbed positive, those who presented to the hospital in labour who were preterm (<37 weeks) or who had ruptured membranes for more than 12 hours were asked to participate in the study. One hundred eighty GBS carriers, who were also preterm or had ruptured membranes >12 hours were randomized to re-

ceive either IAP or no treatment and all newborns were assessed for GBS colonization. Women who received IAP were significantly less likely to deliver a colonized neonate ($p < .001$). This study has been critiqued for excluding women who developed intrapartum fever from the analysis, which may have altered results. As well, researchers had no control over the gestational age at which cultures were taken. (38) A second RCT with 199 participants found a significant difference in the incidence of EOGBSD between GBS carriers who received IAP and those who did not ($p < .01$). Rather than relying on prenatal cultures, this study determined GBS status through the use of a rapid latex agglutination test at hospital admission. (39) This study has been criticized for its unbalanced intervention and control groups (44% intervention group, 56% control) possibly indicating some bias at play. (41) Finally, the effect of IAP was assessed in another RCT that randomized 121 GBS colonized women to IAP treatment or no treatment. Again, researchers found a significant difference in colonization ($p < .001$) and clinically infected newborns ($p < .05$) between groups, however there was no significant difference in the rate of sepsis cases between the groups. (40) More recent RCTs on the efficacy of IAP do not exist and are unlikely to be developed, as IAP has now become a standard of care in the prevention of EOGBSD.

Two meta-analyses have also attempted to assess the efficacy of IAP. In 1996, a Cochrane review included 5 randomized controlled trials, concluding that IAP reduced both infant colonization with GBS (OR 0.10, 95% CI 0.07-0.14), and incidence of EOGBS infection (OR 0.17, 95% CI 0.07-0.39). The review found no significant difference in rates of neonatal mortality, but this was attributed to the small sample sizes of the included studies. (42) The most recent Cochrane review (2009) examined 3 trials, excluding 2 trials assessed by the previous meta-analysis. Again, IAP was found to reduce EOGBS infection as compared to no treatment (RR 0.17, 95% CI 0.04-0.74). Reviewers concluded that IAP had no significant effect on mortality rates from either GBS infection or other causes of infection. IAP also had no apparent effect on late-onset GBS disease rates or maternal infection rates. The

reviewed trials' design were strongly critiqued, citing high levels of potential bias where attack rates reported in control groups were between 47/1000-57/1000, which is unusually high. This review concluded that there is a "lack of evidence from well-designed trials to recommend IAP for [EOGBSD] prevention." (41) Despite the poor quality of these early studies, IAP has been widely accepted as the best means of preventing EOGBSD.

RISKS OF INTRAPARTUM ANTIBIOTIC PROPHYLAXIS

Though neonatal complications of EOGBSD are potentially very serious, they are relatively rare outcomes and must be weighed against the also rare but important harmful effects associated with IAP such as severe "maternal allergic reactions, increase in drug-resistant organisms and exposure of newborn infants to resistant bacteria," as well as the relatively common side-effects of postnatal maternal and neonatal yeast infections. (41)

Anaphylaxis

One of the main concerns of widespread use of IAP is the danger, albeit rare, of anaphylaxis. Anaphylactic reactions to penicillin are estimated to range from 4 to 40/100 000. In addition, as many as 10% of adults have less severe allergic reactions to penicillin, such as rash. (12)

Antibiotic Resistance

Prior to the use of IAP to prevent EOGBSD, the parturient population was not significantly exposed to antimicrobial agents. Some unintended consequences related to the widespread use of intrapartum antibiotics could include increased rates of neonatal sepsis by bacteria other than GBS, the emergence of resistant pathogens (GBS and others) and the development of antibiotic resistant infections in the mother or her infant, as well as changes in patterns of antibiotic resistance. (43)

Researchers have raised concerns that the increase in IAP use may result in the emergence of strains of GBS that will no longer respond to traditional antibiotic therapy. This is a valid concern as studies have shown a growing resistance of some

GBS isolates to clindamycin and erythromycin (9,19,32,33,44). For example, in one prospective study, vaginal and anorectal cultures were evaluated for GBS colonization and antibiotic susceptibility profiles. In this study, 25% of isolates were resistant to erythromycin and 21% were resistant to clindamycin, which represents a 400% increase from a similar study conducted at the same institution seven years prior. No GBS strains were resistant to ampicillin or penicillin. (45)

Two studies from the late 1990s demonstrated that, in vitro, some GBS clinical isolates exhibited intermediate or decreased sensitivity to penicillins. (46,47) Ongoing surveillance of GBS antibiotic resistance is recommended throughout the literature.

Increased Rates of Sepsis Due to Other Organisms

There is also a concern that widespread IAP use may be responsible for a rise in neonatal non-GBS early-onset disease. However, current available evidence is conflicting. Surveillance of 19 Connecticut hospitals between 1996 and 1999, found no significant increase in the incidence of non-GBS early onset cases. The rate of EOGBSD dropped from 0.61/1000 to 0.23/1000 live births and non-GBS EOD rates remained steady at an incidence of 0.67/1000 live births overall. (48) Between 1996 and 1998, researchers noted a rise in the proportion of E. Coli infections that were ampicillin resistant, however this proportion decreased in the final year of the study period. Researchers hypothesized that this may have been a result of natural fluctuations of bacterial populations.

A recent case-control study found no evidence to suggest that the incidence of non-GBS early-onset sepsis changed between 1997 and 2001. It also concluded that exposure to IAP did not increase the odds of a neonate having non-GBS infection. (49) A review of studies that investigated the trends of all-cause sepsis and non-GBS early-onset disease concluded that there was no evidence to suggest an increase in all-cause early-onset disease and little evidence of a rise in non-GBS early-onset disease, other than in preterm and very low birth weight infants. (50) Conversely, a study using

data from the Infection Control Surveillance Database of 20 981 live births looked at the incidence of EOGBSD and gram-negative neonatal sepsis (e.g. E. Coli, Enterobacter) in the years 1992-1996 compared to 1997, which was the first full year following the publication of CDC GBS guidelines recommending universal screening and IAP for GBS positive women. (51) Increased use of IAP for GBS was observed following the publication of the new guidelines along with a decrease in EOGBSD from the years 1992-1996 compared to 1997 (1.7/1000 vs. 0/3 730, $p = .02$). The authors also noted an increased rate of gram-negative neonatal sepsis in the same study periods (0.29/1000 from 1992-1996 vs. 1.3/1000 in 1997, $p = .02$). The mortality rate of gram-negative neonatal sepsis for the cases in this study was 60%, tenfold higher than the EOGBSD mortality rate (6.7%). (51) A retrospective chart review at Yale-New Haven hospital from 1979-2006 compared rates of infants with E. Coli sepsis in relation to changes in the use of IAP for GBS, as well as patterns of ampicillin resistance. After IAP use became widespread, there was an increase of early-onset E. Coli sepsis in very low birth weight infants (2.83/1000 vs. 10.22/1000), and ampicillin-resistant strains of E. Coli. Intrapartum ampicillin exposure was determined to be an independent risk factor for ampicillin-resistant E. Coli early-onset sepsis. A significant increase in late-onset E. Coli sepsis was also observed for both pre-term and term infants. (43)

In summary, it is unclear whether or not the widespread use of prophylactic antibiotics to prevent EOGBSD may be associated with an increase in illness due to other organisms. Further surveillance of these outcomes is warranted. In the meantime, limiting exposure to IAP to those infants at highest risk of developing EOGBSD may be the best approach to alleviating these concerns.

Yeast

One study has investigated the relationship between women who received IAP and rates of neonatal thrush and maternal breast candidiasis in the first month postpartum. (52) Mothers who received IAP were more likely to be diagnosed with breast candidiasis with an OR of 2.10 (95% CI

1.08-4.08), however neonatal rates of thrush were not statistically significant. As a dyad, mother/neonate pairs exposed to IAP were more likely to develop yeast infections versus the unexposed pairs, with an OR of 2.14 (95% CI 1.15-3.97). This was a small study of 435 women that based cases of infection on women's reports of diagnosis by a physician, but these reports were not confirmed by examination by the study team. These findings suggest that yeast infections may be a complication of the use of IAP and given the potential for such infections to interfere with successful breastfeeding, this topic warrants further study.

Asthma and Allergies in Children

There is controversy in the literature about whether or not early exposure to antibiotics increases the risk of asthma and allergies in children. A systematic review of both retrospective and prospective observational studies identified 8 relevant studies examining the relationship between early antibiotic exposure and asthma. (53) The reviewers concluded that exposure to at least one dose of antibiotics during the first year of life is a risk factor for childhood asthma and calculated a pooled OR of 2.05 (95% CI 1.41 to 2.99). The authors acknowledged methodological limitations with the included studies, which may limit the reliability of the results. Criticisms of the purported relationship between antibiotic exposure and asthma suggest that the absence of an association between antibiotic exposure and other types of atopic disease, and the lack of significant association between antibiotic exposure and asthma in prospective studies that adjusted for confounding variables, make "reverse causation" a more plausible explanation for the findings. Reverse causation refers to the tendency of children with asthma to be more likely to be exposed to antibiotics, as a result of confounding with respiratory infections. (54,55)

However, 3 large Canadian studies published subsequent to the 2006 systematic review (56-58) all found associations between early ("early" is not consistently defined in the literature) antibiotic exposure and childhood asthma after adjusting for confounding variables including respiratory infections. Only one of these studies included exposure

to antibiotics in pregnancy as a variable (57) and none of the studies specifically examined the use of intrapartum antibiotics. The observational nature of these studies makes it impossible to conclude that a causal relationship exists, but the observed association supports a cautious approach to unnecessary antibiotic use in early childhood.

APPROACHES TO SELECTIVE INTRAPARTUM ANTIBIOTIC PROPHYLAXIS

As there is no reliable method for detecting which specific newborns will fall ill with EOGBSD, and because of the rare but real risks of IAP, there have been ongoing debates over which labouring women should receive IAP. In 1996, 2 approaches to IAP were recommended by the CDC and subsequently adopted by the Society of Obstetricians and Gynecologists of Canada (SOGC) in 1997. The first of these approaches, the “risk-factor” approach, involves giving IAP to labouring women with one or more of the following risk factors: gestation < 37 weeks, ROM ≥ 18h, intrapartum fever ≥ 38°C, GBS bacteriuria in pregnancy or a prior infant with GBS disease. The second approach, the “screening” approach, involves collecting a vaginal-rectal culture from all women between 35 and 37 weeks’ gestation and treating all GBS carriers with IAP. Women with GBS bacteriuria in pregnancy or a prior child with GBS disease are not swabbed and automatically receive IAP. (59) There are clear drawbacks to each approach. The risk factor approach is unable to detect the significant proportion of EOGBSD cases that do not present risk factors at labour, while pregnancies at highest risk may be missed with 35-37 weeks’ gestation screening alone. (17,60)

In 1996, either approach was considered suitable, as there was no existing research comparing the 2 strategies. Theoretical model calculations predicted that 13.5% to 18% of women would receive IAP vs. 16.5% to 27% with a screening strategy. (61,62) There are no RCTs that compare the 2 strategies against each other.

Risk Factor Strategy

Several non-RCT studies indicate that the risk factor approach lowered rates of EOGBSD, as compared to no treatment. A retrospective study in a single American hospital measured the incidence of EOGBSD for the 3 years after the implementation of a risk-factor protocol and found a continuous decrease in EOGBSD and a concurrent increase in IAP use. (63) While the authors postulate that these 2 factors are associated, this study design is not able to prove a cause and effect relationship. A study in 4 American hospitals also showed a decline in EOGBSD incidence between pre- and post- risk factor protocol periods, but it was not found to be statistically significant. (64) Researchers hypothesized that 68% of cases of EOGBSD in the pre-protocol period had maternal risk factors, arguing that these infections may have been prevented with a risk factor approach. An 11-site case-control study compared infants with EOGBSD born to mothers with at least one risk factor with babies who did not develop EOGBSD but were also born to mothers with one or more risk factors. IAP was associated with a lower risk of EOGBSD and the effectiveness of IAP was estimated to be 86%. Assuming that 70% of EOGBSD cases have maternal risk factors and that IAP is 86% effective, the authors calculated that a risk-based approach would prevent 60% of cases of EOGBSD. (65)

Universal Screening Strategy

In 2002, the CDC issued new guidelines recommending a policy of universal screening. This recommendation was put forth after a large retrospective cohort study determined that rates of EOGBSD were significantly lower in women who were screened (RR 0.46, 95% CI: 0.36-0.60) versus women treated based on risk factors alone. (66) Women with prenatal GBS cultures taken more than 2 days before delivery were considered part of the “culture based” group, while those who did not have a recorded prenatal culture were assigned to the “risk factor” group. Women with risk factors who did not receive IAP, despite adequate time in hospital were excluded from the study. The screening approach was calculated to be greater than 50% more effective at preventing EOGBSD than a risk factor based approach (adjusted RR 0.46, 95%

CI 0.36-0.60). Based on their results, researchers predicted that a strategy of universal screening could decrease rates of EOGBSD to 0.32/1000 live births. (66) Of interest was the finding that antibiotic use in either strategy group would have been nearly equal (31% versus 29%), contrary to earlier predictions that suggested screening-based strategies would dramatically increase the numbers of women given IAP. Declining rates of EOGBSD following the implementation of screening strategies has further supported the efficacy of a screening approach. (67-70)

It should be noted that no approach will be 100% effective. Recent studies assessing the efficacy of screening protocols have found that despite declining rates of EOGBSD, the majority of cases (61%-82%) were in infants of women who had screened GBS negative. (70,71) This indicates that rates of EOGBSD have declined in women targeted for IAP (GBS carriers), but that the predictive value of the screening culture needs further improvement to avoid false negatives.

One study reported that the number of cases of full-term infants with EOGBSD occurring among mothers who had GBS negative results, could not simply be due to the predicted number of false negatives associated with the test. Some factors identified that may contribute to false negative GBS results include: the transience of GBS colonization, screening more than 5 weeks before delivery, incorrect collection of specimens or processing of cultures as well as inaccurate recording or reporting the GBS results. (70) When recording the results of the GBS swab on the antenatal record, writing in the date that the swab was taken may help remind midwives to re-swab if the GBS results have lapsed beyond 5 weeks.

Screening with Risk Factors Strategy

Finally, a third approach involves screening all women but only administering IAP to GBS carriers who also possess risk factors. This screening with risk factors approach was evaluated by the Canadian Task Force on Preventative Health Care in 2003. They estimated that with universal screening and IAP given only with the presence of additional risk factors, that only 3.4% of women would be offered

antibiotic prophylaxis, reducing the incidence of EOGBSD by 51%. (72) Less research has focused on this approach. This strategy would reduce the number of women and babies who are exposed to the potential adverse effects associated with IAP while still reducing the incidence of EOGBSD.

While earlier studies assessed treatment for GBS positive women with risk factors, none of these studies consistently tested for colonization at 35-37 weeks or used a standardized set of risk factors. (38) In 1994, a prospective cohort study observed the outcomes of a protocol of IAP aimed at GBS positive women who had at least 1 risk factor (fever $\geq 37.5^{\circ}\text{C}$, premature labour, prolonged ROM). (73) Initially, prolonged ROM was defined as > 6 hours, but in the last 6 months of the study the definition was changed to > 12 hours. Of 332 GBS carriers, 122 (37%) of these women also had a risk factor; however only 70 of these women received IAP, due to logistical reasons or a failure to adhere to protocol. Researchers found that GBS carriers with one or more risk factors who received IAP showed significantly lower rates of EOGBSD than women who did not receive IAP ($p < .05$).

More recently, a Swiss retrospective study assessed a “screening with risk factors” protocol in a cohort of 9385 live births at a single hospital. Under their protocol, women were screened for GBS at 35 to 37 weeks’ gestation and IAP was given to GBS positive or GBS-unknown women with the following risk factors: ROM $> 12\text{h}$, preterm labour, maternal signs of infection (fever $> 38^{\circ}\text{C}$, leukocytosis, C-reactive protein > 20 mg/L, persistent fetal tachycardia), previous neonate with EOGBS sepsis. This protocol reduced the rate of EOGBS sepsis from a pre-protocol rate of 1/1000 to 0.53/1000, but this was not found to be statistically significant (RR 0.54, 95% CI 0.2-1.47). (74) A “screening with risk factors” strategy merits further investigation as it may be a more targeted approach to EOGBSD prevention and result in lower rates of IAP use. A screening with risk factors strategy is consistent with safe care, supports normal birth and low rates of intervention as well as supporting successful breastfeeding. Well-designed research is needed to compare the relative efficacy of this approach to

Table 3: Summary of IAP Strategies

Prevention Strategy	Percentage of women receiving IAP	Theoretical reduction in EOGBSD	NNT with IAP to prevent one case of EOGBSD
Risk-factor only	29% (66)	39%-53% (75)	1087 (62)
Universal screening only	31% (66)	65%-86% (76)	1029 (62), 16-2059 (72)
Combined screening + risk-factor	3.4%-6% (66,72,73)	51%-75% (38,77)	6 (72)

the screening strategy.

Current research suggests that a screening only strategy for IAP is effective at reducing rates of EOGBSD, despite the lack of RCTs comparing this approach versus other strategies. Research evidence on prevention strategies for GBS currently favours the screening strategies over the risk factor strategy. Until further evidence is available, either of the EOGBSD prevention strategies involving antenatal GBS screening may be offered to women through an informed choice discussion. For women who refuse GBS screening or for women who commence labour prior to the results of the GBS screen being available, a risk-factor strategy should be offered for the prevention of EOGBSD.

(See Table 3: Summary of IAP Strategies)

Recommendations

4. The following EOGBSD prevention strategies should be offered to women as part of their informed choice discussion regarding GBS:

a) Universal screening strategy

Offer intrapartum antibiotic GBS prophylaxis to:

- i) Any women positive by GBS culture screening done at 35 to 37 weeks;
- ii) Any women with an infant previously infected with GBS, regardless of GBS status in current pregnancy;
- iii) Any women with documented GBS bacteriuria (regardless of level of colony-forming units per mL) in this pregnancy;
- iv) Any GBS unknown women with the following risk factors: preterm labour (< 37 weeks' gestation); prolonged rupture of

membranes (> 18 h); maternal fever (temperature $\geq 38^{\circ}\text{C}$).

Women should be informed that this is the current strategy endorsed by the SOGC and the CDC. [II-2-B]

b) Screening with risk factors strategy:

Offer intrapartum antibiotic GBS prophylaxis to:

- i) All women positive by GBS culture screening done at 35 to 37 weeks *and* who also develop one or more of the following risk factors:
 - Preterm labour (< 37 weeks' gestation)
 - Prolonged rupture of membranes (≥ 18 h)
 - Maternal fever (temperature $\geq 38^{\circ}\text{C}$)
- ii) Any women with an infant previously infected with GBS, regardless of GBS status in current pregnancy;
- iii) Any women with documented GBS bacteriuria (regardless of level of cfu/mL) in this pregnancy.

Women should be informed that there is limited research upon which to compare the relative efficacy of this approach to a screening strategy, nor are there well-designed RCTs that compare this approach against no treatment. [II-3-C]

5. Women who decline antenatal GBS cultures are considered GBS unknown and those who develop risk factors intrapartum should be offered IAP [II-2-B].

Women may find it helpful to know the statistics

included in Tables 1, 2 and 3 and *Summary of Prevalence, Incidence and Neonatal Complications associated with GBS* to guide their decision-making regarding the prevention of EOGBSD.

PRACTICAL ASPECTS OF MANAGEMENT: ADEQUATE IAP

Most recommendations for IAP suggest initiating IAP at the beginning of active labour. No research was found that assessed the administration of IAP in early labour.

While the CDC recommends administering penicillin every 4 hours, very little research has focused on the actual pharmacokinetics of IAP. Evidence is slowly mounting that IAP may be effective much more rapidly than the 4-hour guideline. A study in 1998 compared the colonization of newborns with the timing of IAP and found dramatic decreases in the rates of colonization after only 2 hours from IAP administration. Between 2 to 4 hours, only 2.8% of newborns were colonized (78) versus 47% of newborns that did not receive IAP. There were no cases of EOGBSD in the study. Similarly, a study which measured vaginal GBS colony counts in labouring women receiving IAP found that counts dropped fivefold within the first 2 hours, then twentyfold by 4 hours. (79)

Finally several studies have investigated the time for cord blood to contain bactericidal levels of antibiotics. In 2 studies that sampled cord blood from women undergoing elective caesarean sections, bactericidal levels of ampicillin were reached between 5 and 30 minutes. (80,81) Another study that sampled cord blood of labouring women found that penicillin G peaked at approximately one hour after administration of IAP. All cord blood samples taken post-IAP showed levels of penicillin that would be considered bactericidal for GBS. (82) If a woman chooses IAP, antibiotics should be administered whenever possible, even in rapidly progressing labours.

The issue of whether or not IAP has been administered fully, partially or not at all is an issue for the management of neonates, but will be more thoroughly discussed in the clinical practice guideline on the postpartum management of GBS (forth-

coming).

Treatment Recommendations for GBS Intrapartum Antibiotic Prophylaxis

The recommended antibiotic regime for IAP as recommended by the CDC:

- I. Penicillin G 5 million units IV initial dose, followed by 2.5 million units IV every 4 hours until delivery.
- II. If penicillin G is not available, ampicillin 2 g IV initial dose, followed by 1 g IV every 4 hours until delivery, is an acceptable alternative.
- III. If woman is penicillin allergic but not at risk of anaphylaxis, then cefazolin 2 g IV initial dose, followed by 1 g every 8 hours until delivery.
- IV. If woman is penicillin allergic and at risk of anaphylaxis, then clindamycin 900 mg IV every 8 hours until delivery or erythromycin 500 mg IV every 6 hours until delivery.
- V. If GBS has demonstrated resistance to clindamycin or erythromycin or if susceptibility unknown, then vancomycin 1 g IV every 12 hours until delivery. (59)

Vancomycin Hydrochloride

Vancomycin will very rarely be administered in the prevention of EOGBSD.

Vancomycin hydrochloride is indicated for GBS IAP in the rare event that a woman has a penicillin allergy and is at risk of anaphylaxis and also tests positive for a GBS strain that is resistant to both clindamycin and erythromycin.

Women for whom vancomycin is the only IAP option should be aware of the following:

Vancomycin must be administered intravenously in a dilute solution by intermittent infusion over a period of not less than 60 minutes (at a rate of no more than 10 mg/min), by IV pump. Exaggerated hypotension, including shock, and rarely cardiac arrest may result from rapid bolus administration of vancomycin.

Vancomycin is irritating to tissue and causes drug fever, pain and possibly necrosis if injected intra-

muscularly. (83)

Due to the controlled conditions under which vancomycin is administered, home birth is not a feasible option for GBS positive women choosing IAP, whose only choice of antibiotic is vancomycin.

PRACTICAL ASPECTS OF MANAGEMENT: HOME BIRTH

IAP is routinely offered and administered by midwives to women who are planning home births or who prefer to labour at home for as long as possible. No research was found regarding the provision of IAP in an out-of-hospital setting. In 2010, the Designated Drugs Regulation O.Reg. 884/93 was amended under the Midwifery Act, 1991, providing midwives the authority to prescribe and administer antibiotics for GBS IAP. (84) As such, prescription and administration of antibiotics at home should be discussed with clients as part of an informed choice discussion regarding the risks and benefits of IAP administration, potential significant side-effects (such as anaphylaxis) and emergency measures including the administration of epinephrine. Until better evidence emerges, the antenatal and intrapartum management of GBS should not differ whether in home or hospital. In the rare event that vancomycin is the only antibiotic option available, it should only be administered in a hospital setting.

PRACTICAL ASPECTS OF MANAGEMENT: PRELABOUR RUPTURE OF MEMBRANES

Being GBS positive when prelabour rupture of membranes presents raises 2 significant questions for care providers:

- When is the ideal time to start IAP?
- When is the ideal time to induce labour?

There are no prospective studies that have been designed to examine either of these questions. The most relevant published evidence comes from secondary analyses of data collected as part of the Term PROM trial. This large, multicentre RCT ran-

domized women with PROM at term to induction (with oxytocin or PGE2 gel) or expectant management for a period of up to 4 days. (85) Of the 5041 participants, 4834 women were cultured for GBS at delivery. Researchers found a non-significant trend suggesting that GBS carriers were at lower risk of EOGBSD if induced with oxytocin than if they were managed expectantly (OR 0.29, 95% CI 0.08-1.05, $p = .06$). This study has led to SOGC recommendations that women with term PROM be offered induction immediately. (86)

Though the Hannah study notes a correlation between GBS status and neonatal infection, it is important to note that this RCT predates the implementation of the IAP screening and treatment strategy. The GBS status of many women in this study was not known until after delivery. Additionally, despite the study's protocol to give IAP to women known to be GBS positive at entry to the trial, IAP was administered in a minority of patients, which may have contributed to higher neonatal infection rates. The Term PROM study does not provide sufficient evidence to compare the strategy of immediate induction with induction after a moderate waiting period, or with ongoing expectant management within a context of universal prenatal screening and IAP for all GBS positive women. Further research on the timing of induction of labour for GBS positive women with PROM is warranted.

One 1999 publication re-analyzed previously published data to establish odds ratios for factors associated with increased risk for EOGBSD in neonates. This re-analysis calculated the OR of EOGBSD at stratified time periods from the data of 3 studies (31,87,88) (see Table 4), revealing increasing risk of EOGBSD with increasing length of rupture of membranes. (14) It is important to note that these figures relate to time of rupture of amniotic membranes and not specifically to PROM, nor are they reflective of current practices for administering IAP. Because this was a secondary analysis of data collected prior to the introduction of universal screening and IAP, it is difficult to determine whether or not the calculated risks are valid today.

(See Table 4: ORs for EOGBS stratified by Duration

Table 4: ORs for EOGBS Stratified by Duration of Rupture of the Amniotic Membranes* (From (14) citing (31,87,88))				
Duration of ROM (h)	OR (95% CI)	P All groups	P Groups ≤18 hours	References
0-6	1.0	0.24	0.76	(31)
6-12	1.33 (0.28-6.30)			
12-18	2.05 (0.42-9.73)			
>18	7.32 (2.24-23.8)			
0-6	1.0	< 0.001	0.089	(87)
7-12	2.43 (1.12-5.32)			
13-18	2.00 (0.76-5.30)			
19-24	7.48 (3.48-16.0)			
25-48	11.4 (5.32-24.4)			
> 48	14.3 (6.39-32.1)			
0-9	1.0	< 0.001	0.71	(88)
10-19	1.60 (0.25-10.1)			
20-29	26.5 (8.95-78.2)			
30+	28.8 (10.1-82.1)			
Pooled data for patients with ROM ≤ or > 18 h or < or ≥ 20 h from above studies				
≤ 18	1.0	= 0.0025		(31)
> 18	5.92 (2.1-16.1)			
≤ 18	1.0	< 0.001		(87)
> 18	7.23 (4.42-12.0)			
< 20	1.0	< 0.001		(88)
≥ 20	26.2 (10.7-63.9)			
* Regardless of whether rupture of membranes was during labour or prior to labour				

of Rupture of the Amniotic Membranes* (From (14) citing (31,87,88))

Studies related to administering antibiotics prior to active labour for GBS positive women with term PROM during a period of expectant management were not found. In the absence of research on this topic, midwives are currently using a variety of approaches to ensuring adequate administration of IAP for these women. Further research is necessary.

Please see the AOM CPG titled “Management of Prelabour Rupture of Membranes at Term” for a full discussion related to management of PROM.

Summary Statement - GBS Positive Women with

PROM

Most recommendations for IAP suggest initiating IAP at the beginning of active labour. No research appears to have assessed the administration of IAP in early labour.

The Term PROM study does not provide sufficient evidence to compare the strategy of immediate induction with induction after moderate waiting period, or with ongoing expectant management within a context of IAP for all GBS positive women.

The odds ratio of EOGBSD increases with increasing length of rupture of membranes (see Table 4).

IAP may be effective more rapidly than the 4-hour guideline. There is evidence from cord blood sam-

ples of labouring women that penicillin G concentration peaks at approximately one hour after administration of IAP.

An expectant management approach for a period up to 18 hours is appropriate only in the absence of any signs of fetal or maternal compromise/distress (e.g. meconium in the amniotic fluid, maternal fever or evidence of infection, decreased fetal movement). Teaching regarding practices that may minimize risk of infection, as well as when to page the midwife if complications develop is recommended. For a full discussion related to PROM management, please see the AOM CPG on management of PROM at Term.

Recommendations

6. Women should be informed of the research gaps regarding the most effective approach to preventing EOGBSD in infants born to GBS carriers who experience term PROM.
7. Offer a choice between expectant management and immediate induction of labour with oxytocin to women with a positive GBS swab result at term who experience PROM for < 18 hours, and have no other risk factors [III-B].
8. Recommend induction of labour with oxytocin to women who are GBS positive with PROM \geq 18 hours [III-B]. IAP should be offered upon commencement of induction of labour.
9. Offer GBS positive women with PROM choosing expectant management a range of options for prophylactic antibiotic administration [III-B]:
 - a. IAP in active labour [II-2-B]
 - b. IAP in the latent phase [III-C]
 - c. IAP upon the initiation of induction of labour [III-B]

Please note: recommendations 6 to 9 differ from those of the SOGC and ACOG. Rigorous information sharing with women to assist them in making decisions is essential.

RISK MANAGEMENT

Practice groups may wish to create a written pro-

ocol specific to the practice group that documents which of the recommendations within the Clinical Practice Guideline they are adopting and how they are putting into practice those recommendations, including what would be included in an informed choice discussion with each client. Midwives are advised to document clearly that an informed choice discussion has taken place. If the practice group has a written protocol about what should be discussed with each client, that discussion should be followed. Any deviation from that discussion should also be documented in the woman's chart. If there is no protocol about what information is provided then documentation in the woman's chart should provide details of that discussion. If, based on the client's health or risk status, the midwife makes recommendations for surveillance or intervention that the client declines, the midwife should document that her recommendation was declined.

ACKNOWLEDGEMENTS

The Association of Ontario Midwives acknowledges the support of the Ontario Ministry of Health and Long-Term Care and Ryerson University in providing resources for the development of this guideline.

SUMMARY OF RECOMMENDATIONS

1. Offer all women screening for group B streptococcus at 35 to 37 weeks' gestation with a culture done from one swab first to the vagina then to the rectal area (through the anal sphincter). It is appropriate to offer women instructions on how to swab and have them do it themselves. [II-2-A]
2. Offer rescreening to all women if > 5 weeks has elapsed from initial swab and they remain undelivered. [II-2-A]
3. Request sensitivity testing for the GBS swab for women who report penicillin allergies. [II-2-A]
4. Either of the following EOGBSD prevention

strategies may be offered to women as part of their informed choice discussion regarding GBS:

a. Universal screening strategy

Offer intrapartum antibiotic GBS prophylaxis to:

- i. Any women positive by GBS culture screening done at 35 to 37 weeks;
- ii. Any women with an infant previously infected with GBS;
- iii. Any women with documented GBS bacteriuria (regardless of level of cfu/mL) in this pregnancy;
- iv. Any GBS unknown women with the following risk factors: preterm labour (< 37 weeks' gestation); prolonged rupture of membranes (> 18 hours); maternal fever (temperature $\geq 38^{\circ}\text{C}$). Women should be informed that this is the current strategy endorsed by the SOGC and the CDC. [II-2-B]

b. Screening with risk factors strategy:

Offer intrapartum antibiotic GBS prophylaxis to:

- i. All women positive by GBS culture screening done at 35 to 37 weeks and who also develop 1 or more of the following risk factors:
 - Preterm labour (< 37 weeks' gestation)
 - Prolonged rupture of membranes (≥ 18 hours)
 - Maternal fever (temperature $\geq 38^{\circ}\text{C}$)
- ii. Any women with documented GBS bacteriuria (regardless of level of cfu/mL) in this pregnancy
- iii. Any women with an infant previously infected with GBS, regardless of GBS status in current pregnancy.

Women should be informed that there is limited research upon which to compare the relative efficacy of this approach to a screening strategy, nor are there well-designed RCTs that compare this approach against no treatment. [II-3-C]

5. Women who decline antenatal GBS cultures are considered GBS unknown and those who develop risk factors intrapartum should be offered IAP [II-2-B].
6. Women should be informed of the research gaps regarding the most effective approach to preventing EOGBSD in infants born to GBS carriers who experience term PROM.

7. Offer a choice between expectant management and immediate induction of labour with oxytocin to women with a positive GBS swab result at term who experience PROM for < 18 hours, and have no other risk factors [III-B].
8. Recommend induction of labour with oxytocin to women who are GBS positive with PROM ≥ 18 hours [III-B]. IAP should be offered upon commencement of induction of labour.
9. Offer GBS positive women with PROM choosing expectant management a range of options for prophylactic antibiotic administration [III-B]:
 - a. IAP in active labour [II-2-B]
 - b. IAP in the latent phase [III-C]
 - c. IAP upon the initiation of induction of labour [III-B]

Please note: recommendations 6 to 9 differ from those of the SOGC and ACOG. Rigorous information sharing with women to assist them in making decisions is essential.

REFERENCES

- (1) The AGREE Collaboration. Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument. 2001.
- (2) Association of Ontario Midwives. Collated Response: A Values Based Approach to CPG Development. 2006.
- (3) Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. *CMAJ* 2003 Aug 5;169(3):207-208.
- (4) Schuchat A. Epidemiology of group B streptococcal disease in the United States: shifting paradigms. *Clin.Microbiol.Rev.* 1998 Jul;11(3):497-513.
- (5) Spaetgens R, DeBella K, Ma D, Robertson S, Mucenski M, Davies HD. Perinatal antibiotic usage and changes in colonization and resistance rates of group B streptococcus and other pathogens. *Obstet.Gynecol.* 2002 Sep;100(3):525-533.
- (6) Baker C, Edwards M. Group B streptococcal infections. In: Remington J, Klein JO, editors. *Infectious diseases of the fetus and newborn infant*. 3rd ed. Philadelphia: WB Saunders; 1995. p. 980.
- (7) Franciosi RA, Knostman JD, Zimmerman RA. Group B streptococcal neonatal and infant infections. *J.Pediatr.* 1973 Apr;82(4):707-718.
- (8) Schrag SJ, Zywicki S, Farley MM, Reingold AL, Harrison LH, Lefkowitz LB, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. *N.Engl.J.Med.* 2000 Jan 6;342(1):15-20.
- (9) Phares CR, Lynfield R, Farley MM, Mohle-Boetani J, Harrison LH, Petit S, Craig AS, Schaffner W, Zansky SM, Gershman K, Stefonek KR, Albanese BA, Zell ER, Schuchat A, Schrag SJ. Active Bacterial Core surveillance/ Emerging Infections Program Network. *JAMA* 2008 May 7;299(17):2056-2065.
- (10) Davies HD, Raj S, Adair C, Robinson J, McGeer A, Alberta GBS Study Group. Population-based active surveillance for neonatal group B streptococcal infections in Alberta, Canada: implications for vaccine formulation. *Pediatr.Infect.Dis.J.* 2001 Sep;20(9):879-884.
- (11) Hamada S, Vearncombe M, McGeer A, Shah PS. Neonatal group B streptococcal disease: incidence, presentation, and mortality. *J.Matern.Fetal.Neonatal Med.* 2008 Jan;21(1):53-57.
- (12) Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. *MMWR Recomm Rep.* 2002 Aug 16;51(RR-11):1-22.
- (13) REGAN JAM, KLEBANOFF, MARK A. MD, MPH, NUGENT RPP, FOR THE VAGINAL INFECTIONS AND PREMATURITY STUDY GROUP. The Epidemiology of Group B Streptococcal Colonization in Pr... : *Obstetrics & Gynecology*. *Obstetrics & Gynecology* 1991;77(4):604.
- (14) Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review.[see comment]. *Pediatrics* 1999 Jun;103(6):e77.
- (15) Schuchat A, Zywicki SS, Dinsmoor MJ, Mercer B, Romaguera J, O'Sullivan MJ, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multi-center case-control study. *Pediatrics* 2000 Jan;105(1 Pt 1):21-26.
- (16) Dillon HC,Jr, Khare S, Gray BM. Group B streptococcal carriage and disease: a 6-year prospective study. *J.Pediatr.* 1987 Jan;110(1):31-36.
- (17) Oddie S, Embleton ND. Risk factors for early onset neonatal group B streptococcal sepsis: case-control study. *BMJ* 2002 Aug 10;325(7359):308.
- (18) McLaren RA, Chauhan SP, Gross TL. Intrapartum factors in early-onset group B streptococcal sepsis in term neonates: a case-control study. *Am.J.Obstet.Gynecol.* 1996 discussion 1937-40; Jun;174(6):1934-1937.
- (19) Edwards RK, Clark PD, Patrick. Intrapartum Antibiotic Prophylaxis 2: Positive Predictive Value of Antenatal Group B Streptococci Cultures and Antibiotic Susceptibility of Clinical Isolates. *Obstetrics & Gynecology* 2002 September;100(3):540-544.
- (20) McKenna DS, Matson S, Northern I. Maternal group B streptococcal (GBS) genital tract colonization at term in women who have asymptomatic GBS bacteriuria. *Infect.Dis.Obstet.Gynecol.* 2003;11(4):203-207.
- (21) Edwards MS, Rench MA, Haffar AA, Murphy MA, Desmond MM, Baker CJ. Long-term sequelae of group B streptococcal meningitis in infants. *J.Pediatr.* 1985 May;106(5):717-722.
- (22) Chin KC, Fitzhardinge PM. Sequelae of early-onset group B hemolytic streptococcal neonatal meningitis. *J.Pediatr.* 1985 May;106(5):819-822.
- (23) Benitz WE, Gould JB, Druzin ML. Antimicrobial prevention of early-onset group B streptococcal sepsis: estimates of risk reduction based on a critical literature review.[see comment]. *Pediatrics* 1999 Jun;103(6):e78.
- (24) Pinette MG, Thayer K, Wax JR, Blackstone J, Cartin A. Efficacy of intramuscular penicillin in the eradication of group B streptococcal colonization at delivery. *J.Matern.Fetal.Neonatal Med.* 2005 May;17(5):333-335.
- (25) Stade BC, Shah VS, Ohlsson A. Vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection. *Cochrane Database of Systematic Reviews* 2008;4.
- (26) Adriaanse AH, Kollee LA, Muyltjens HL, Nijhuis JG, de Haan AF, Eskes TK. Randomized study of vaginal chlorhexidine disinfection during labor to prevent vertical transmission of group B streptococci. *Eur.J.Obstet.Gynecol.Reprod.Biol.* 1995 Aug;61(2):135-141.
- (27) Hennequin Y, Tecco L, Vokaer A. Use of chlorhexidine during labor: how effective against neonatal group B streptococci colonization? *Acta Obstet.Gynecol.Scand.* 1995 Feb;74(2):168.
- (28) Stray-Pedersen B, Bergan T, Hafstad A, Normann E, Groggaard J, Vangdal M. Vaginal disinfection with chlorhexidine during childbirth. *Int.J.Antimicrob.Agents* 1999 Aug;12(3):245-251.
- (29) Food and Agriculture Organization of the United Nations, World Health Organization. Report of a Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria. 2001.
- (30) Reid G, Pirkka K. Taking probiotics during pregnancy: Are they useful therapy for mothers and newborns? *Can.Fam.Physician* 2005;51(11):1477.
- (31) Yancey MK, Schuchat A, Brown LK, Ventura VL, Markenson GR. The accuracy of late antenatal screening cultures in predicting genital group B streptococcal colonization at delivery. *Obstet.Gynecol.* 1996 Nov;88(5):811-815.
- (32) Pearlman MD, Pierson CL, Faix RG. Frequent resistance of clinical group B streptococci isolates to clindamycin and erythromycin. *Obstet.Gynecol.* 1998 Aug;92(2):258-261.
- (33) Morales WJ, Dickey SS, Bornick P, Lim DV. Change in antibiotic resistance of group B streptococcus: impact on intrapartum management. *Am.J.Obstet.Gynecol.* 1999 Aug;181(2):310-314.
- (34) Mercer BM, Taylor MC, Fricke JL, Baselski VS, Sibai BM. The accuracy and patient preference for self-collected group B Streptococcus cultures. *Am.J.Obstet.Gynecol.* 1995 Oct;173(4):1325-1328.
- (35) Molnar P, Biringer A, McGeer A, McIsaac W. Can pregnant women obtain their own specimens for group B streptococcus? A comparison of maternal versus physician screening. *The Mount Sinai GBS Screening Group. Fam.Pract.* 1997 Oct;14(5):403-406.
- (36) Arya A, Cryan B, O'Sullivan K, Greene RA, Higgins JR. Self-collected versus health professional-collected genital swabs to identify the prevalence of group B streptococcus: a comparison of patient preference and efficacy. *European Journal of Obstetrics, Gynecology, & Reproductive Biology* 2008 Jul;139(1):43-45.
- (37) Honest H, Sharma S, Khan KS. Rapid tests for group B Streptococcus colonization in laboring women: a systematic review. *Pediatrics* 2006 Apr;117(4):1055-1066.
- (38) Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal

- disease with selective intrapartum chemoprophylaxis. *N.Engl.J.Med.* 1986 Jun 26;314(26):1665-1669.
- (39) TUPPURAINEN, NINA MD, Dr Med Sci, HALLMAN, MIKKO MD, Dr Med Sci. Prevention of Neonatal Group B Streptococcal Disease: Intrap... : *Obstetrics & Gynecology. Obstet. Gynecol.* 1989;73(4):583.
- (40) Matorras R, Garcia-Perea A, Omenaca F, Diez-Enciso M, Madero R, Usandizaga JA. Intrapartum chemoprophylaxis of early-onset group B streptococcal disease. *Eur.J.Obstet. Gynecol.Reprod.Biol.* 1991 Jun 5;40(1):57-62.
- (41) Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. *Cochrane Database Syst.Rev.* 2009 Jul 8;(3)(3):CD007467.
- (42) Smaill F. Intrapartum antibiotics for group B streptococcal colonisation. *Cochrane Database Syst.Rev.* 2000(2):000115.
- (43) Bizzarro MJ, Dembry LM, Baltimore RS, Gallagher PG. Changing patterns in neonatal *Escherichia coli* sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis *Pediatrics* 2008 Apr;121(4):689-696.
- (44) Bland ML, Vermillion ST, Soper DE, Austin M. Antibiotic resistance patterns of group B streptococci in late third-trimester rectovaginal cultures. *Am.J.Obstet.Gynecol.* 2001 May;184(6):1125-1126.
- (45) Panda B, Iruretagoyena I, Stiller R, Panda A. Antibiotic resistance and penicillin tolerance in ano-vaginal group B streptococci. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians* 2009 February;22(2).
- (46) Rouse DJ, Andrews WW, Lin FC, Mott CW, Ware JC, Philips JB. Antibiotic susceptibility profile of group B Streptococcus acquired vertically. *Obstet Gynecol* 1998;92.
- (47) Fernandez M, Hickman ME, Baker CJ. Antimicrobial susceptibilities of group B streptococci isolated between 1992 and 1996 from patients with bacteremia or meningitis. *Antimicrob Agents Chemother* 1998;42.
- (48) Baltimore RS, Huie SM, Meek JI, Schuchat A, , et al. Early-Onset Neonatal Sepsis in the Era of Group B Streptococcal Prevention. *Pediatrics* 2001 November;108(5):1094-1098.
- (49) Schrag SJ, Hadler JL, Arnold KE, Martell-Cleary P, Reingold A, Schuchat A. Risk factors for invasive, early-onset *Escherichia coli* infections in the era of widespread intrapartum antibiotic use. *Paediatrics* 2006;118(2):570-576.
- (50) Moore MR, Schrag SJ, Schuchat A. Effects of intrapartum antimicrobial prophylaxis for prevention of group-B-streptococcal disease on the incidence and ecology of early-onset neonatal sepsis. *Lancet Infect.Dis.* 2003 Apr;3(4):201-213.
- (51) Levine EM, Ghai V, Barton JJ, Strom CM. Intrapartum antibiotic prophylaxis increases the incidence of gram-negative neonatal sepsis. *Infect.Dis.Obstet.Gynecol.* 1999;7.
- (52) Dinsmoor MJ, Vilorio R, Lief L, Elder S. Use of intrapartum antibiotics and the incidence of postnatal maternal and neonatal yeast infections. *Obstet.Gynecol.* 2005 Jul;106(1):19-22.
- (53) Marra F, Lynd L, Coombes M, Richardson K, Legal M, Fitzgerald JM, et al. Does antibiotic exposure during infancy lead to development of asthma?: a systematic review and metaanalysis. *Chest* 2006 Mar;129(3):610-618.
- (54) Celedon JC. Antibiotic use during the first year of life and asthma. *Chest* 2006 Nov;130(5):1624; author reply 1624-5.
- (55) Wickens K, Ingham T, Epton M, Pattemore P, Town I, Fishwick D, et al. The association of early life exposure to antibiotics and the development of asthma, eczema and atopy in a birth cohort: confounding or causality? *Clin.Exp.Allergy* 2008 Aug;38(8):1318-1324.
- (56) Marra F, Marra CA, Richardson K, Lynd LD, Kozyrskyj A, Patrick DM, et al. Antibiotic use in children is associated with increased risk of asthma. *Pediatrics* 2009 Mar;123(3):1003-1010.
- (57) Martel MJ, Rey E, Malo JL, Perreault S, Beauchesne MF, Forget A, et al. Determinants of the incidence of childhood asthma: a two-stage case-control study. *Am.J.Epidemiol.* 2009 Jan 15;169(2):195-205.
- (58) Kozyrskyj AL, Ernst P, Becker AB. Increased risk of childhood asthma from antibiotic use in early life. *Chest* 2007 Jun;131(6):1753-1759.
- (59) Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease: a public health perspective. *Centers for Disease Control and Prevention. MMWR Recomm Rep.* 1996 May 31;45(RR-7):1-24.
- (60) Daniels J, Gray J, Pattison H, Roberts T, Edwards E, Milner P, et al. Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness. *Health Technol.Assess.* 2009 Sep;13(42):1-154, iii-iv.
- (61) Rouse DJ, Goldenberg RL, Cliver SP, Cutter GR, Mennemeyer ST, Fargason CA, Jr. Strategies for the prevention of early-onset neonatal group B streptococcal sepsis: a decision analysis. *Obstet.Gynecol.* 1994 Apr;83(4):483-494.
- (62) Stan CM, Boulvain M, Bovier PA, Auckenthaler R, Berner M, Irion O. Choosing a strategy to prevent neonatal early-onset group B streptococcal sepsis: economic evaluation. *BJOG* 2001 Aug;108(8):840-847.
- (63) Factor SH, Levine OS, Nassar A, Potter J, Fajardo A, O'Sullivan MJ, et al. Impact of a risk-based prevention policy on neonatal group B streptococcal disease. *Am.J.Obstet. Gynecol.* 1998 Dec;179(6 Pt 1):1568-1571.
- (64) Lieu TA, Mohle-Boetani JC, Ray GT, Ackerson LM, Walton DL. Neonatal group B streptococcal infection in a managed care population. *Perinatal Group B Streptococcal Infection Study Group. Obstet.Gynecol.* 1998 Jul;92(1):21-27.
- (65) Lin FY, Brenner RA, Johnson YR, Azimi PH, Philips JB, 3rd, Regan JA, et al. The effectiveness of risk-based intrapartum chemoprophylaxis for the prevention of early-onset neonatal group B streptococcal disease. *Am.J.Obstet.Gynecol.* 2001 May;184(6):1204-1210.
- (66) Schrag SJ, Zell ER, Lynfield R, Roome A, Arnold KE, Craig AS, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. *N.Engl.J.Med.* 2002 Jul 25;347(4):233-239.
- (67) Main EK, Slagle T. Prevention of early-onset invasive neonatal group B streptococcal disease in a private hospital setting: the superiority of culture-based protocols. *Am.J.Obstet.Gynecol.* 2000 Jun;182(6):1344-1354.
- (68) Jeffery HE, Moses Lahra M. Eight-year outcome of universal screening and intrapartum antibiotics for maternal group B streptococcal carriers. *Pediatrics* 1998 Jan;101(1):E2.
- (69) Hafner E, Sterniste W, Rosen A, Schuchter K, Plattner M, Asboth F, et al. Group B streptococci during pregnancy: a comparison of two screening and treatment protocols. *Am.J.Obstet.Gynecol.* 1998 Sep;179(3 Pt 1):677-681.
- (70) Van Dyke MK, Phares CR, Lynfield R, Thomas AR, Arnold KE, Craig AS, et al. Evaluation of universal antenatal screening for group B streptococcus. *N.Engl.J.Med.* 2009 Jun 18;360(25):2626-2636.
- (71) Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. *Pediatrics* 2005 May;115(5):1240-1246.
- (72) Canadian Task Force on Preventive Health Care. Prevention of group B streptococcal infection in newborns. Recommendation statement from the Canadian Task Force on Preventive Health Care. *Can.Fam.Physician* 2002 944-6; May;48:934-935.
- (73) Pylipow M, Gaddis M, Kinney JS. Selective intrapartum prophylaxis for group B streptococcus colonization: management and outcome of newborns. *Pediatrics* 1994 Apr;93(4):631-635.
- (74) Renner RM, Renner A, Schmid S, Hoesli I, Nars P, Holzgreve W, et al. Efficacy of a strategy to prevent neonatal early-onset group B streptococcal (GBS) sepsis. *J.Perinat.Med.* 2006;34(1):32-38.
- (75) Rosenstein NE SA. Opportunities for prevention of perinatal group B streptococcal

- disease: a multistate surveillance analysis. *Obstet Gynecol* 1997;90.
- (76) Koenig JM KW. Group B streptococcus and early-onset sepsis in the era of maternal prophylaxis. [Review] [117 refs]. *Pediatric Clinics of North America* 2009 June 2009;56(3).
- (77) Revised guidelines for prevention of early-onset group B streptococcal (GBS) infection. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. *Pediatrics* 1997 Mar;99(3):489-496.
- (78) de Cueto M, Sanchez MJ, Sampedro A, Miranda JA, Herruzo AJ, Rosa-Fraile M. Timing of intrapartum ampicillin and prevention of vertical transmission of group B streptococcus. *Obstet.Gynecol.* 1998 Jan;91(1):112-114.
- (79) McNanley AR, Glantz JC, Hardy DJ, Vicino D. The effect of intrapartum penicillin on vaginal group B streptococcus colony counts. *American Journal of Obstetrics & Gynecology* 2007 December;197(6):583e1-583e4.
- (80) Colombo DFa, Lew JLa, Pedersen CAB, Johnson JRa, FanHavard P. Optimal timing of ampicillin administration to pregnant women for establishing bactericidal levels in the prophylaxis of Group B Streptococcus. *American Journal of Obstetrics & Gynecology* 2006 February;194(2):466-470.
- (81) Bloom SL, Cox SM, Bawdon RE, Gilstrap LC. Ampicillin for neonatal group B streptococcal prophylaxis: how rapidly can bactericidal concentrations be achieved?. *Am.J.Obstet. Gynecol.* 1996 Oct;175(4 Pt 1):974-976.
- (82) Illuzzi JL, Bracken MB. Duration of intrapartum prophylaxis for neonatal group B streptococcal disease: a systematic review. *Obstet.Gynecol.* 2006 Nov;108(5):1254-1265.
- (83) Carol Repchinsky B editor. *CPS :Compendium of Pharmaceuticals & Specialties 2009* (English). 44th ed.: CANADIAN PHARMACISTS ASSOC.; 2009.
- (84) O. Reg. 13/10, s. 2. Midwifery Act, 1991 / Loi de 1991 sur les sages-femmes. ONTARIO REGULATION 884/93. DESIGNATED DRUGS.
- (85) Hannah ME, Ohlsson A, Wang EE, Matlow A, Foster GA, Willan AR, et al. Maternal colonization with group B Streptococcus and prelabor rupture of membranes at term: the role of induction of labor. Term PROM Study Group. *Am.J.Obstet.Gynecol.* 1997 Oct;177(4):780-785.
- (86) Money DM, Dobson S. The Prevention of Early-Onset Neonatal Group B Streptococcal Disease. SOGC Clinical Practice Guideline No. 149, September 2004. *J Obstet Gynaecol Can* 2004 September 2004;29(9):826-32).
- (87) Boyer KM, Gadzala CA, Burd LI, Fisher DE, Paton JB, Gotoff SP. Selective intrapartum chemoprophylaxis of neonatal group B streptococcal early-onset disease. I. Epidemiologic rationale *J.Infect.Dis.* 1983 Nov;148(5):795-801.
- (88) Romero R, Mazor M. Infection and preterm labor *Clin.Obstet.Gynecol.* 1988 Sep;31(3):553-584.