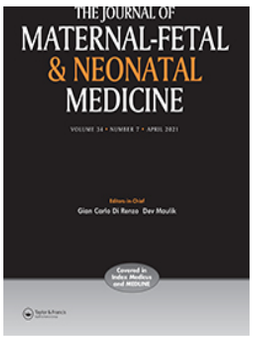

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Middle-East OBGYN Graduate Education (MOGGE) Foundation practice guidelines: prevention of group B Streptococcus infection in pregnancy and in newborn. Practice guideline no. 02-O-20

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REVIEW ARTICLE

Middle-East OBGYN Graduate Education (MOGGE) Foundation practice guidelines: prevention of group B Streptococcus infection in pregnancy and in newborn. Practice guideline no. 02-O-20

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ABSTRACT

Rectovaginal colonization with group B streptococcus (GBS) is commonly encountered in pregnancy. GBS is the most common cause of early onset neonatal sepsis, which is associated with 12% case-fatality rate. Although screening protocols and prophylactic treatment are readily available worldwide, practice in low-resource countries is challenged by lack of awareness and limited implementation of these protocols. In addition, antibiotic susceptibility pattern may vary globally owing to different regulations of antibiotic prescription or prevalence of certain bacterial serotypes. This guideline appraises current evidence on screening and management of GBS colonization in pregnancy particularly in low-resource settings.

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KEYWORDS
Low-resource setting; obstetrics; neonatal sepsis; neonatal infection; antibiotic susceptibility

1. Introduction|knowledge

1.1. Definitions

Group B streptococcus (GBS) is a gram-positive bacterium that colonizes anorectum and vagina in 18% of pregnant women [1]. Prevalence of GBS colonization varies regionally and is reported to be highest in Africa (22.4%, 18.1–26.7) [1]. Vaginal colonization with GBS during labor is associated with 50% risk of neonatal transmission [2,3]. It is most commonly transmitted into amniotic fluid through ruptured membranes. However, it may be transmitted through intact membranes or through birth canal during delivery [4]. GBS is the most common cause of early onset neonatal sepsis, which is defined as neonatal sepsis diagnosed in the first week of life [5,6], and is associated with 12% case-fatality rate [7]. Case fatality rate is even higher in developing countries, reaching 19% to 23% in some reports [8,9] Intrapartum administration of penicillin for a duration $\geq$4 h of these women is effective in preventing neonatal early-onset GBS (EOGBS) disease [10].

Because maternal GBS colonization is associated with significant neonatal complications, and is amenable to effective and available prevention, screening of women during pregnancy is recommended. However, screening protocols have been controversial. As opposed to universal screening, approximately one third of developed countries offer selective screening to pregnant women who are identified as a "high risk group" based on risk factors [11]. Either way, screening using a recto-vaginal swab and bacterial culture is universally adopted.

1.2. Regional challenges

Although the causative relation between maternal GBS and neonatal morbidity has been established since the seventies of the last century, there is still some controversies on screening tests and protocols. However,

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Supplemental data for this article can be accessed here.

practice in low-resource settings has been liable to additional challenges. Reported prevalence of maternal GBS colonization in developing countries is comparable to worldwide figures [12–14]. Nevertheless, implementation of screening protocols may be inadequate compared to other countries. We surveyed 213 obstetricians practicing in the Middle East regarding GBS screening practice in their institutes, and 77% of respondents declare no screening polices in pregnancy. Although compliance to antenatal care may seem to be a potential cause in developing countries, only 4.7% of respondents attribute limited GBS screening to patient-related causes. In fact, 91% state that the main cause is lack of hospital protocols for GBS screening. Similar results were found in a study of 200 women in Jordan, where participants attended a median of 9 prenatal visits (interquartile range: 8–12). Nevertheless, GBS screening was deficient [14].

Global inconsistency in adopting GBS screening protocols is not without cost. Incidence of early onset neonatal sepsis is 0.77 cases per 1000 live births in the United States [15], while in developing countries, incidence is as high as 23–38 per 1000 live births [16]. Although empiric universal neonatal antibiotic prophylaxis seems to reduce EOGBS disease by 68%, it was associated with 40% increase in overall mortality [17]. Empiric intrapartum treatment of term pregnant women not screened for GBS colonization has not been studied. However, unnecessary administration of treatment to all women while it is indicated in only 18% renders this approach inappropriate. Mass administration of antibiotics may be associated with maternal allergic reactions, induction of drug resistance, transmission of resistant bacteria to the baby, and increased risk of maternal and neonatal yeast infections [18]. Thus, no strategy seems to efficiently replace antepartum screening for GBS for prevention of EOGBS disease.

1.3. Resources and search approach

GBS screening and prophylaxis has been covered by several internationally recognized guidelines. We start by defining clinical questions that need to be addressed both globally and regionally. Literature search on the latest versions of accredited guidelines that represent global practice is conducted from January 2000 to January 2020. These guidelines include American College of Obstetricians and Gynecologists (ACOG) committee opinion 2002 [19], Royal Australian and New Zealand College of Obstetricians and Gynecologists (RANZCOG) 2016 [20], Royal College of Obstetricians and Gynecologists (RCOG) guidelines 2017 [21], and Society of Obstetricians and Gynecologists of Canada (SOGC) guidelines 2018 [20]. The second step involves assigning each clinical question to a panel of 2 researchers to review how a question is covered by these guidelines. The aim of this step is to verify whether the question is consistently answered, to identify variety of answers if they are inconsistent among different guidelines, and to assess the source and level of evidence supporting these answers. The third step is to apply systematic search of the literature for newly published studies related to these clinical questions, particularly recent systematic reviews, clinical trials, and large cohort studies. We also conduct a separate literature search on studies that originate primarily in the Middle East or alternatively, in other low resource countries that may share similar challenges. MEDLINE, EMBASE, SCOPUS and Cochrane library were searched for from January 2010 to April 2020. Search terms include ["Group B streptococcus" OR "GBS"] AND ["pregnancy" OR "maternal" OR "antepartum" OR "prenatal" OR "antenatal" OR "intrapartum" OR "antibiotic prophylaxis"] OR ["universal" OR "routine" OR "culture-based" OR "polymerase chain reaction" OR "PCR" OR "nucleic acid amplification test" OR "NAAT"] OR ["early-onset" OR "late-onset" AND "neonatal" AND "GBS" AND "disease" OR "sepsis"]. Search strategy and selection process are detailed in Appendix I.

The fourth step is to survey obstetricians in the Middle East to identify their needs, challenges and current practice. Respondents were obstetricians at different levels of experience, who are involved in either community based or university-based practice. The fifth and final step is to evaluate available data to adopt the highest level of evidence that is appropriate for low resource settings.

The level of evidence is determined in accordance to Oxford Center for Evidence-based Medicine – Levels of Evidence, which stratifies studies depending on their design to level 1 (A to C), level 2 (A to C), level 3 (A and B), level 4, and level 5 [22]. A KAST approach will be used to present this topic; Knowledge, Assessment, Sharing decision, and Treatment

MOGGE take home message: Knowledge	
• Prevalence of vaginal colonization with GBS in pregnant women is approximately 18%.	IIA
• Vertical transmission of GBS is associated with significant neonatal morbidity and mortality.	IIB
• Case fatality rate of early onset neonatal sepsis may be doubled in developing countries.	IV

2. Clinical evaluation and diagnosis|assessment

2.1. Screening protocol in pregnancy

2.1.1. Screening strategy

Universal screening of all pregnant women for GBS is endorsed by ACOG as the standard practice in the United States [19]. These recommendations, which have been revalidated in February 2020, are based on Center of Disease Control (CDC) guidelines, which were introduced in 2002, and revised in 2010 [23]. The rationale for CDC recommendations in 2002 was simplicity of education, conduction and reporting of universal screening compared to selective screening. Moreover, universal screening did not yield significant cost burden or higher proportion of women receiving intrapartum prophylaxis compared to other strategies [24]. A population-based study of a stratified random sample of 629,912 live births showed decline in incidence of EOGBS disease, after implementation of the new recommendations, from 0.50 per 1000 live births to 0.32 per 1000 live births (95% CI 0.26–0.38) [25]. Universal screening has been also endorsed by SOGC, last updated in 2018, based on similar evidence [20].

Reviewed in July 2019, RANZCOG guidelines state that both universal and risk-based strategies are acceptable options to screen for GBS during pregnancy (a consensus-based recommendation) [26]. RANZCOG embraced universal screening based on CDC guidelines and a recent Australian meta-analysis of 9 retrospective studies which showed superiority of universal over risk-based screening (odd ratio [OR] 0.45 (95% CI 0.37–0.53) [27]. However, RANZCOG considers risk-based screening as an option based on RCOG recommendations [26].

Most recent RCOG guideline, issued in September 2017, does not recommend universal screening for GBS [21]. These recommendations were attributed to UK national screening committee statement in March 2017. The statement is justified by possibility of spontaneous resolution of GBS carriage by time of labor, and concerns on unnecessary administration of antibiotics while long-term effect of these antibiotics to the mother and baby is unclear. On the other hand, it is not possible to predict the neonatal outcomes and development of EOGBS disease among women who test positive for GBS colonization [28].

In 2020, Hasperhoven et al. presents a meta-analysis of 15 observational studies including 11 studies that directly compare screening-based versus risk-based protocols. Pooled analysis reveals that universal screening was associated with lower risk of EOGBS disease compared with risk-based screening (relative risk [RR] 0.43, 95% confidence interval [CI] 0.32–0.56). In addition, risk-based screening was not superior to "no policy" (RR 0.86, 95% CI 0.61–1.20) [29]. In absence of large clinical trials, available evidence supports superiority of universal screening. In addition, universal screening is less complex, easy to apply, and is not influenced by inadequate documentation, which is commonly encountered in low resource settings.

As stated above, 77% of respondents to our survey endorse no screening for their patients in pregnancy. In response to a question regarding constrains to implementation of GBS culture in their practice, approximately 50% of obstetricians endorse unavailability of data on accredited labs that would perform the test, 25% endorse high cost of testing, and 24% endorse no constrains. Only 0.04% of respondents attribute constrains to patient refusal after proper counseling. In response to these results, "PREV-GBS," a campaign sponsored by MOGGE foundation, is currently under construction. The aim of this campaign is to create an electronic database of GBS-validated labs, sorted regionally, and to establish feasible mechanisms to connect obstetricians to these labs and provide readily service and resources for sample collection. In addition, this campaign aims at raising awareness about GBS risk among obstetricians and pregnant women [30].

2.1.2. Timing of screening

Timing of screening has been highly consistent in the literature. ACOG recommends GBS screening between 36 and 37 + 6 weeks of gestation [19], while RCOG, SOGC and RANZCOG recommended screening between 35 and 37 weeks of pregnancy [20,21,26]. Because test results are generally valid for 5 weeks, the late window adopted by ACOG is intended to cover deliveries occurring at 41 weeks, which are greater than those occurring between 35 and 37 weeks of gestation in the United States (6.7 vs. 1.9%, respectively) [31]. It is generally advised that women at higher risk of spontaneous or iatrogenic preterm labor should be offered 35 weeks before anticipated labor.

A systematic review compared early antenatal GBS culture (before 35 weeks) to late culture (after 35 weeks in term pregnancies) using culture at delivery as a reference. The study included 7 prospective studies and showed that mean positive and negative predictive values of late culture were higher compared to early culture (70.2 vs. 58.8%, and 95.2 vs. 93.0%, respectively) [32]. Culture results may be available

within 24 to 48 h. However, culture results are not conclusive and 17–25% of GBS-positive results in late pregnancy becomes negative by time of delivery. Similarly, 5–7% of GBS-negative swabs turn positive at delivery [21].

2.1.3. GBS validity

ACOG committee opinion recommends that GBS test validity be limited to 5 weeks. Afterwards, repeating a negative GBS test may be reasonable [19]. These recommendations come from a single study, which correlates test-to-delivery interval with test performance [33]. The study reports decline in positive and negative predictive values if test-delivery interval increases from 5 weeks to 6 or more weeks (88–43%, 95–80%, respectively). However, these results were based on swabs from 7 patients and 25 patients who were screened 6 weeks or more before delivery, and tested positive and negative, respectively. Nevertheless, these results are consistent with the meta-analysis that we reported earlier, which emphasizes superiority of screening after 35 weeks compared to earlier screening [32].

2.1.4. Screening method

A vaginal and rectal swab obtained by a single swab is universally adopted by RCOG, ACOG, RANZCOG, and SOGC [19–21,26]. The swab is obtained from lower vagina (near the introitus) first and then from the rectum (through the anal sphincter). The swab is obtained blindly without using a speculum or examiners' fingers, and this should be clearly explained to pregnant women. Obtaining 2 separate swabs is also acceptable [21,26]. According to CDC recommendations, GBS isolates can survive in room temperature using a non-nutrient transport media. However, delay in processing for 1-4 days increases false negative results and samples should be refrigerated. Isolates should be cultured in an enriched medium [23].

Accuracy of culture of self-collected swabs, compared to provider collection, was evaluated by 4 crossover clinical trials [34–37]. Studying 251 women, Mercer et al. found that testing of self-collected swabs was more sensitive than nurse-collected swabs (91.7 vs 70.8%, respectively; $p < 0.05$) [35]. In 2 trials recruiting a total of 570 women, sensitivity of self-collection was comparable to provider-collection (79 vs. 83% and 88 vs. 97%, respectively) [34,36]. However, a recent study by Seto et al. on 672 women reports significantly lower sensitivity of swabs obtained by the patients versus those obtained by health care providers (61.4 vs. 97.6%, respectively; $p < 0.05$) [37]. In this study, non-Chinese women and women who use vaginal pessaries were less likely to experience discordance in culture results. The results may reflect impact of patient education, and convenience to do the test on sensitivity of self-collected swabs. Preference of self-collection has been generally high in these reports.

2.2. Screening tests

Culture-based testing has been recognized as the standard test for GBS carriage among pregnant women. Real time polymerase chain reaction (RT-PCR) has been proposed as an alternative to culture. The rationale for using RT-PCR test is to provide quick results, which would allow testing of women with unknown GBS carriage status particularly when they present in labor. Results are obtained after 30–45 min with the new PCR, 100 min with conventional PCR, while culture results are usually available after 36 h [38].

Feuerschuette et al. performed a meta-analysis of 15 prospective studies (6368 women) that assessed diagnostic performance of RT-PCR in laboring women [39]. Pooled sensitivity and specificity of the test for the diagnosis of GBS colonization were 93.7% (CI 92.1–95.3) and 97.6% (CI 96.9–98.0), respectively. According to CDC, an intrapartum point-of-care test is considered clinically beneficial if both sensitivity and specificity are equal to or greater than 90% [23].

Although diagnostic performance of RT-PCR seems satisfactory and eligible to intrapartum screening, the test is currently opposed by several limitations. Unlike bacterial culture, RT-PCR does not permit antibiotic susceptibility testing. Therefore, the value of his test would be limited in women with penicillin allergy, or in certain regions where penicillin resistance may be reported as discussed later. Furthermore, molecular diagnostic testing is not universally available. Implementation of RT-PCR as an intrapartum screening test for GBS would require 24-h readily availability of a laboratory facility with validated RT-PCR results. Furthermore, failure rate of the test was reported in approximately 10% of cases [40].

A cost analysis of intrapartum GBS PCR screening compared to antenatal universal culture-based screening was conducted in France between 2009 and 2010. El Helali et. al. concludes that PCR is cost-neutral compared to culture-based screening [41]. Similar conclusions were presented by Picchiassi et al., who endorsed limited cost burden of implantation of intrapartum PCR [42]. However, cost analysis may vary

significantly among countries, and this is attributed to the variation in costs of medications and services. In the above study, El Helali et al. calculates costs of a unit of penicillin G, culture test, and PCR test as $1.5, $4.8, and $48.5, respectively. Thereby, the cost of culture is approximately 3.2 times the cost of a unit of penicillin G, cost of PCR test is 32 times the cost of penicillin G, and cost of PCR is 10.1 times the cost of culture [41]. In Egypt, an example of a low-resource country, cost of PCR is roughly 180 times the cost of penicillin G, cost of culture is 14 times the cost of penicillin G and cost of PCR is 12.9 times the cost of culture. This example highlights that cost of PCR may be relatively higher in low resource countries compared to other services. In addition, availability of validated PCR labs may be significantly limited.

Therefore, current recommendations may be related to logistics of implementing RT-PCR rather than diagnostic performance of the test. SOGC recommends that RT-PCR may be reserved for hospitals attached to labs that have the capacity to provide validate RT-PCR testing and quality control. ACOG endorses limitations of the test and therefore, it does not recommend using PCR as an alternative to universal culture-base screening [19]. Similarly, RCOG does not support the use of RT-PCR in labor setting. Because it adopts risk-based screening, RCOG states that it is not clear whether implementation of this technology would reduce the need for antibiotic prophylaxis in women with risk factors [21]. Although RANZCOG agrees to the high diagnostic performance of PCR, they do not recommend this test for screening because it requires advanced laboratory technology and higher cost burden compared to culture-based screening [26]. European consensus conference endorses universal intrapartum screening using rapid real time testing with subsequent antibiotic prophylaxis according to test results [43].

2.3. Clinical diagnosis of GBS

GBS is a normal inhabitant of the vagina and rectum. Therefore, it is unlikely to present with symptoms that warrant testing and is diagnosed via universal screening. However, urinary tract infection (UTI) is not uncommon in pregnancy; the incidence varies between 2 and 13% [44]. Approximately 1–5% cases of UTI are caused by GBS colonization [45].

It is important to emphasize the importance of bacterial culture and antibiotic susceptibility testing to secure prompt and efficient treatment of UTIs in pregnancy. Pregnant women are at higher risk of developing pyelonephritis (up to 40%), which is associated with maternal morbidity and obstetric complications e.g. preterm labor and low birth weight [46–48]. Providers should be aware of the causative bacterium and this may require communication with the lab specially when the report is morphology-based and not conclusive (e.g. reporting gram positive cocci). If UTI is caused by GBS, the patient should be notified, screening is omitted, and intrapartum treatment should be administered.

MOGGE take home message: Assessment	
• All pregnant women should be screened for rectovaginal GBS colonization. Universal culture-based screening is superior to risk-based screening and is simpler, and less influenced by inadequate documentation and recall bias.	IIA
• GBS screening is recommended between 36 and 37 weeks of gestation.	IIA
• GBS culture results may be valid for 5 weeks. Afterwards, a negative GBS culture may need to be repeated	IIB
• A single swab is obtained from lower vagina (near the introitus) first and then from the rectum (through the anal sphincter).	V
• Self-collection is reasonable if preferred by the pregnant woman and it may increase acceptance to screening. However, sample collection should be clearly communicated to her before a sample is collected.	IB
• Pregnant women with symptomatic bacteriuria should be adequately treated and the causative organism should be documented.	IIB

3. Decision making and patient counseling | sharing decision

3.1. Nature of GBS colonization

Patient counseling regarding GBS testing is crucial to ensure compliance to screening protocol. As a part of counseling process, providers should explain that GBS colonization of the vagina and rectum is normal and approximately 1:5 women test positive. Primary focus of GBS is the gastrointestinal tract, from which it may be transmitted to genito-urinary tract [20]. It is important to elucidate the meaning of a "normal inhabitant" and confirm that GBS is not a *sexually transmitted infection* and does not transmit an infection to the partner. The stigma and implications of diagnosis of a sexually transmitted disease may disrupt compliance even if the question is not asked by the patient.

3.2. Risks associated with GBS colonization

Obstetricians and mid-wives should explain to their patients the importance of GBS testing and intrapartum antibiotics if indicated. GBS is the most common cause of EOGBS disease [5,6]. Maternal colonization with GBS at birth may be transmitted to 50% of

newborn babies, and approximately 1–2% may develop EOGBS disease if intrapartum antibiotic prophylaxis (IAP) is not administered [49,50]. EOGBS is more common among term neonates, who account for 70% of cases. However, neonatal mortality is significantly higher among preterm babies (19 vs. 2% in term babies) [51]. In 95% of cases, EOGBS disease manifests *within the first 48 h after birth*, where the baby may present with clinical features of bacteremia (83%), meningitis (9.5%), pneumonia (6%), sepsis and septic shock (1%) [51]. Case fatality rate is developing countries reaches 19–23% in some reports [8,9].

Patient counseling should also cover peripartum maternal complications associated with GBS colonization including intra-amniotic infection, endometritis, and wound infection [52]. Risk of bacteremia following GBS postpartum infection is 31–35%, and of these cases, 5–25% may progress to sepsis [53,54].

Because neither screening nor prophylaxis is completely preventive, it is reasonable to review warning symptoms with parents prior to discharge, which include abnormal behavior, floppiness, difficulty with feeding, abnormally high or low temperature (lower than 36 °C or higher than 38 °C), rapid or abnormal breathing, or change in skin color [21]. This information should be provided both verbally and through printed material. Parents should be aware that although most cases of EOGBS develop within 48 h, approximately 5% may develop between 2 and 7 days. In addition, they should be aware of the risk of late onset GBS disease, which may present between 7 and 89 days, and is not prevented by IAP [55].

MOGGE take home message: Sharing decision	
• Patient education on maternal and neonatal risks of GBS colonization is crucial. Education should be provided both verbally and through printed material.	V
• Pregnant women should be counseled that GBS is not a sexually transmitted infection and is a normal inhabitant of the gastrointestinal and genital tract.	V
• After delivery and prior to discharge, parents should be educated on warning symptoms of EOGBS disease.	V

4. Act: management of GBS colonization|treat

4.1. Treatment of GBS in pregnancy

Screening for asymptomatic bacteriuria during pregnancy is recognized as a part of routine antenatal care by several internationally recognized committees including ACOG, RCOG and SOGC [19–21]. A recent meta-analysis included 15 clinical trials, which assess outcomes of antibiotic treatment in pregnant women with asymptomatic bacteriuria (presence of 100,000 colony forming units or more per mL of urine in absence of symptoms). Data from over 2000 women, shows that treatment of asymptomatic bacteriuria reduces risks of pyelonephritis (RR 0.24; 95% CI 0.13–0.41), low birth weight (RR 0.64, 95% CI 0.45–0.93), and preterm delivery (RR 0.34; 95% CI 0.13–0.88) [56].

As with other bacteria, asymptomatic bacteriuria may be caused by GBS. Again, it is important to recognize and report the causative organism if asymptomatic bacteriuria is diagnosed. Similar to symptomatic urinary tract infection, asymptomatic bacteriuria should be treated to reduce the risk of obstetric complications [56]. In additions, treatment of antepartum GBS bacteriuria may be associated with reduced risk of chorioamnionitis during labor [57]. However, asymptomatic GBS bacteriuria may indicate heavy colonization and 43% of GBS-treated women present with persistent GBS colonization in labor [58]. Therefore, GBS asymptomatic bacteriuria precludes GBS screening, and IAP should be administered regardless of antenatal treatment. Oral probiotics was not found to be effective in reducing the incidence of GBS colonization during pregnancy [59].

4.2. IAP for GBS colonization

4.2.1. Indications of IAP

Pregnant women who are screened positive for GBS should receive IAP. A meta-analysis of 14 studies, including 13 clinical trials, shows that IAP of GBS-colonized women was associated with reduced risk of GBS colonization (RR 0.10, 95% CI 0.06–0.16), EOGBS disease (RR 0.24, 95% CI 0.13–0.45), and non-GBS infections (RR 0.34, 95% CI 0.20–0.59) [60]. Because risk of persistent GBS colonization is high among women with symptomatic or asymptomatic GBS bacteriuria, screening is not necessary and IAP should be administered to these women [58]. Similarly, a meta-analysis of 3 retrospective studies shows that women with history of GBS colonization in a prior pregnancy are at increased risk of GBS colonization in current pregnancy (50.2 vs. 14.1%, odds ratio [OR] 6.05; 95% CI 4.84–7.55) [61], making GBS colonization in the first pregnancy one of the most determinant risks of GBS colonization in subsequent pregnancies [62]. Although these women can be reliably screened for GBS in current pregnancy, they should receive IAP if screening is not performed or if results are not available [19].

According to CDC recommendations in 2010, if GBS colonization status is unknown, preterm labor, defined as labor prior to 37 weeks' gestation, is an indication

for IAP due to incased risk of neonatal morbidity among preterm babies infected with GBS [23]. Women at or beyond 37 weeks may receive IAP only if additional intrapartum risk factors develop including membrane rupture for 18 or more hours or intrapartum temperature at or above 38.0 °C [23]. Women with a previous infant diagnosed with GBS disease should also receive IAP [23]. Because lack of documentation and communication may present a barrier to define this indication in low resource countries, women should be specifically asked about history of neonatal hospital admissions, morbidity or mortality, particularly in the first week of life. Obstetricians should keep a low threshold of considering these situations as "potential" EOGBS disease, particularly if no other cause is clearly revealed, and may consider IAP.

4.2.2. Timing of IAP

Adequate IAP is defined by CDC as intravenous (IV) administration of penicillin, ampicillin, or cefazolin $\geq$4 h before delivery [23]. This recommendation is based on a clinical trial (4525 women) that established an inverse relationship between duration of IAP of GBS-colonized mothers and incidence of neonatal GBS colonization; administration of IAP for $<$1 h, 1–2 h, 2–4 h, and $>$4 h was associated with neonatal colonization in 46, 29, 2.9, and, 1.2% of neonates, respectively [63]. However, this study did not determine incidence of EOGBS disease in relation to treatment duration. Lin et al. conducted a case-control study including 109 GBS-colonized women and 207 controls, and found that IAP administration for more than 2 h was effectively preventive of EOGBS disease compared to treatment for shorter durations (89 vs. 71%, respectively) [64]. Administration of IAP $>$4 h is recommended by both ACOG and RCOG [19,21].

Illuzzi and Bracken debate the 4-h cutoff as a definition of adequate treatment; a systematic review of 4 observational studies disclosed that IAP duration $\geq$2 h and $\geq$1 h were found adequate by 2 studies and 1 study, respectively. One study was indecisive. [65]. Although number and quality of included studies may limit validity of this argument, these conclusions were pharmacologically supported. A prospective study of 98 GBS-positive women, who received IAP, was conducted and umbilical cord blood samples were collected at delivery. Interestingly, penicillin G concentration was significantly higher in fetuses exposed to IAP for $<$4 h compared to those exposed to IAP for a longer duration. Penicillin G concentration increased linearly in the first hour of administration, then dropped significantly thereafter. These results highlight that short administration of IAP was sufficient to achieve minimal inhibitory concentration for GBS. Therefore, considering IAP for $<$4 h inadequate may be inaccurate [66].

However, studies that clinically support these pharmacologic findings are still lacking. In addition, because of risk of discharging neonates at risk particularly in low resource countries, where neonatal care may not be readily accessible, a "4-h" cutoff should be still used to define adequate treatment. However, administration of IAP should not be omitted when labor is imminent on admission because administration of IAP, even for a short duration, may provide some benefit to neonates. To ensure adequate treatment is achieved, IAP may start with rupture of membranes or when patient is in active labor. Earlier administration may be considered in multiparous women if rapid labor is clinically anticipated.

4.2.3. Antimicrobial agents

IV penicillin G is the standard antibiotic used for GBS prophylaxis worldwide. Penicillin G is a cheap and available antibiotic, and it has a narrow spectrum targeting gram-positive bacteria. Therefore, it is less likely to induce drug resistance. IV ampicillin is used as an alternative [23]. CDC recommended regimen, adopted by ACOG and SOGC, is 5 million units followed by 2.5–3.0 million units every 4 h. Similarly, ampicillin initial dose is 2 grams, followed by 1 gram every 4 h. IAP should continue till delivery [19,20,23].

Penicillin/ampicillin is given to all GBS-positive women with no known allergy to penicillin. In these women, risk of anaphylaxis is extremely low (4:10,000 – 4:100,000)[67]. To date, GBS seems to be highly susceptible to penicillin and prevalence of resistant isolates was 0% in many reports [68–73]. Therefore, antibiotic susceptibility is not currently recommended as a routine in women with no known allergy to penicillin.

However, a recent study of 39 GBS isolates, conducted in the United States, showed resistance to penicillin in 15.4% of these isolates [74]. Concerning reports have arisen from low-resource countries; penicillin and ampicillin resistance were reported in 45 and 9% of GBS-positive women in Ethiopia [75]. Gizachew et al. studied antibiotic resistance among 385 Ethiopian women, and prevalence of penicillin resistance was approximately 10% [76]. A recent study on 292 Kenyan women reported penicillin and ampicillin resistance in 71 and 55% of cases, respectively [77]. Nevertheless, some reports from these countries still report complete susceptibility of GBS isolates to

penicillin in the same time frame [13,78]. Nevertheless, a conclusion made by a recent meta-analysis of 35 studies conducted in Africa emphasizes this concern, and polled penicillin resistance was estimated to be 33.6% [79].

Global discrepancy in prevalence of penicillin resistance may be contributed to racial variations, bacterial serotypes, or more seriously, to antibiotic misuse. In many low resource countries, antibiotics are available over the counter and self-administration is not uncommon. Although most studies support susceptibility to penicillin, initial susceptibility screening may be recommended, especially when GBS prophylaxis protocol is recently implemented, to determine local pattern of bacterial resistance before local recommendations are adopted.

In women allergic to penicillin, administration of a different antibiotic should be considered. Unlike penicillin, alternative antibiotics are associated with known high prevalence of bacterial resistance [80]. Therefore, culture-based GBS screening in women with known penicillin allergy should routinely include antibiotic susceptibility testing. An exception is cephalosporins including cefuroxime, a second-generation cephalosporin, which has a similar antibiotic susceptibility to penicillin [80,81]. Therefore, cephalosporins (cefuroxime) should be considered the first alternative whenever possible. Accordingly, medication allergy should be investigated at booking visit. In women with known or suspected penicillin allergy, it is important to determine whether a woman is truly allergic to penicillin and to assess severity of allergic reaction. True penicillin allergy, which is an IgE-mediated adverse effect, is rare (1–5 per 10,000) [82]. Limited side effects, such as vomiting, should not preclude administration of penicillin in labor [21]. Women who report non-severe allergic reactions (i.e. no anaphylaxis, angioedema, respiratory distress or urticaria) can safely receive cefuroxime. The concept of "10% cross reactivity" between penicillin and cephalosporins has been recently verified; current evidence supports that similarity of side chains, rather than ß-lactam structure, determine cross reactivity between these groups of antibiotics. Therefore, cephalosporins with different side-chain determinants, including cefuroxime and cefazolin, are unlikely to cross react with penicillin [83]. This crucial fact is commonly overlooked; Briody et al. reported that approximately 56% of women with no history of penicillin anaphylaxis received antibiotics other than penicillin or cefazolin [84]. IV Cefuroxime is given as 1.5-gram loading dose followed by 750 mg every 8 h. In women with severe allergy to beta-lactam and if antibiotic susceptibility is not available, vancomycin, in a dose of 1 gram every 12 h, is given [21]. Clindamycin should be only used in women with severe allergy to penicillin if GBS isolates are sensitive [23]. In these women, if vancomycin and antibiotic susceptibility reports are not available, providers should be aware that bacterial resistance to clindamycin varies between 14 and 52.4% [73,80, 85] and neonates should be treated as at risk if clindamycin is administered without antibiotic susceptibility report. Because of increased resistance to erythromycin and limited placental crossing, it is no longer considered an option for IAP [23]. It is worthy-mentioning that there is limited data on definition of adequate treatment of non-β-lactam antibiotics, and they are not subjected to the 4-h rule.

4.2.4. Intrapartum management of GBS positive women

4.2.4.1 Vaginal delivery. Membrane sweeping is a widely utilized procedure to expedite onset of labor. In GBS-positive women anticipated to deliver vaginally, membrane sweeping does not seem to adversely affect maternal or neonatal outcomes, and GBS status should not be considered a contraindication to this procedure [86]. Data on mechanical cervical ripening in GBS-positive women is limited [87]. Although there is no evidence that artificial rupture of membranes may increase risk of EOGBS disease, it may reduce duration of IAP exposure by expediting labor. Therefore, it is reasonable to postpone amniotomy, especially in multiparous women, until IAP is adequately administered [19]. Vaginal cleansing with chlorhexidine does not reduce risk of EOGBS disease in GBS-positive women [88]. A recent prospective study of 163 women assessed the use of vaginal antiseptics to reduce risk of intrapartum GBS colonization. Women were tested for GBS colonization shortly before delivery, treated with dequalinium chloride 10 mg vaginal tablet, and then retested for GBS colonization. The study concluded that vaginal antiseptics may reduce GBS colonization by approximately 57% [89].

4.2.4.2 Cesarean delivery. GBS IAP is not indicated in women undergoing planned cesarean delivery who are not in labor and who present with intact membranes. In these situations, the risk EOGBS disease is extremely low (3:1,000,000) [51]. GBS-positive women, scheduled for cesarean delivery, who present in labor or with rupture of membrane should receive cefazolin, which serves as an IAP and a perioperative antibiotic as well [87].

MOGGE take home message: Treat	
• Screening and treatment of asymptomatic bacteriuria should be routinely performed in pregnancy.	IA
• IAP is indicated in women with GBS bacteriuria, whether symptomatic or asymptomatic, in current pregnancy.	IB
• IAP is indicated in women who test positive for GBS colonization in current pregnancy.	IIA
• IAP should be administered to all women with positive or unknown GBS status who deliver prior to 37 weeks of gestation.	IIA
• Women who deliver at or beyond 37 weeks with unknown GBS status should receive IAP if they have history of GBS colonization in a prior pregnancy, if membrane rupture occurs for 18 or more hours, or if intrapartum temperature is $\geq$ 38.0 °C.	IIB
• Women with a previous infant diagnosed with GBS disease should also receive IAP. Because lack of documentation, women should be specifically asked about history of neonatal hospital admissions, neonatal morbidity and mortality, particularly in the first week of life. Obstetricians should consider keeping a low threshold of considering these situations a "potential" EOGBS disease and may consider IAP.	IV
• IAP is considered adequate if penicillin, ampicillin, or cefazolin are administered for at least 4 hours. Therefore, IAP may start with rupture of membranes or when patient is in active labor. Earlier administration may be considered in multiparous women if rapid labor is clinically anticipated. Data on adequacy of other antibiotics is limited	IB
• Administration of IAP should not be omitted when labor is imminent on admission because administration of IAP, even for a short duration, may provide some benefit to neonates.	IIB
• In absence of history of penicillin allergy, IV penicillin G (5 million units followed by 2.5-3.0 million units every 4 hours) is the standard antibiotic. IV ampicillin may be used as an alternative.	IIB
• Because resistance to penicillin is globally inconsistent, antibiotic susceptibility may be tested at time of GBS culture particularly when screening is newly implemented and national data on antibiotic susceptibility of GBS is not available.	IV
• Limited side effects to penicillin, such as vomiting, should not be considered an allergic reaction and should not preclude administration of penicillin in labor.	IV
• Women who report non-severe allergic reactions to penicillin (i.e. no anaphylaxis, angioedema, respiratory distress or urticaria) should receive cefuroxime/cefaclor as an alternative.	IIB
• In women with severe allergy to beta-lactam and if antibiotic susceptibility is not available, vancomycin, in a dose of 1 gram every 12 hours, should be given.	IIB
• Clindamycin should be only used in women with severe allergy to penicillin if antibiotic susceptibility shows GBS isolates are sensitive to clindamycin.	IIB
• Erythromycin should not be used for IAP.	IIB
• Maternal GBS colonization is not a contraindication to membrane sweeping.	IIB
• During labor, artificial rupture of membranes, especially in multiparous women, may be postponed until IAP is adequately administered.	IV
• Vaginal cleansing with chlorhexidine does not reduce risk of EOGBS disease in GBS-positive women.	IA
• GBS IAP is not indicated in women undergoing planned cesarean delivery who are not in labor and who present with intact membranes.	IIC
• GBS-positive women, scheduled for cesarean delivery, who present in labor or with rupture of membrane should receive preoperative cefazolin.	V

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