EFFECTIVENESS OF INTRAPARTUM ANTIBIOTIC PROPHYLAXIS FOR EARLY-ONSET GBS DISEASE: AN INTEGRATIVE REVIEW

Key words: Group B *streptococcus*, pregnancy, intrapartum antibiotic prophylaxis, effectiveness, integrative review, early-onset group B *streptococcal* disease

ABSTRACT

Background: Although around 30% of women in the USA (and other high income countries who follow USA recommendations) are exposed to intrapartum antibiotic prophylaxis during childbirth for the prevention of early-onset group B *streptococcal* disease, the clinical evidence for this intervention is not robust. Intrapartum antibiotic prophylaxis aims to reduce the risk of neonatal morbidity and mortality from early-onset group B *streptococcal* disease. However, the intervention may also adversely affect non-pathogenic bacteria. Some of these bacteria are passed to the newborn during vaginal birth and are important in optimising microbial and epigenetic health. Since many women are offered intrapartum antibiotic prophylaxis, the effectiveness and implications of this intervention need to be established.

Methods An integrative review of the literature was conducted with 13 studies retrieved for critical appraisal.

Findings. No robust clinical trials supporting the effectiveness of intrapartum antibiotic prophylaxis for the prevention of early-onset group B *streptococcal* disease were identified. Less than optimal intrapartum antibiotic prophylaxis protocol adherence is common.

Discussion Current protocols have limitations and lead to many women and babies being exposed to antibiotics during labour. There is evidence linking intrapartum antibiotic prophylaxis to adverse short and long-term neonatal outcomes.

Conclusion There is no robust evidence of the effectiveness of intrapartum antibiotic prophylaxis. Most reviewed studies had significant methodological flaws. Few considered risks of the intervention and none considered longer-term consequences. Information must be available to enable women to make informed decisions around the management of group B *streptococcal* risk.

INTRODUCTION

Summary of relevance

Problem/issue:	**Early-onset group B streptococcal disease (EOGBSD) is rare. Up to a third women are given intrapartum antibiotic prophylaxis (IAP) without robust evidence of its effectiveness. The consequences and long-term health implications of prophylaxis for EOGBSD are unknown**
What is already known:	**There are no available methods to determine which babies are at greatest risk. Many women are prescribed IAP which adds to medicalisation of birth**
What this paper adds:	**This paper considers literature regarding the effectiveness of IAP for EOGBSD. Long-term health effects have not been factored into assessments of the effectiveness of this intervention**

Group B *streptococcus* (GBS), found primarily in the gastrointestinal tract, usually causes no harm to the carrier. GBS commonly colonises the vagina in pregnant women and is generally transient in nature. The bacterium can be passed to the baby just prior or during birth leading to neonatal colonisation. If unexposed to prophylaxis, neonatal GBS colonisation is common during vaginal birth. Rarely, neonatal colonisation leads to early-onset GBS disease (EOGBSD). To avoid this, intravenous intrapartum antibiotic prophylaxis (IAP) has been embraced in many high resource settings. Effectiveness is considered to be the extent to which an intervention resolves an adverse outcome. However, in addition to this definition, we suggest that effectiveness of prophylaxis should consider the risks and benefits of all health outcomes, including side effects and long-term health effects of IAP.

BACKGROUND

Incidence

In the 1970s, GBS emerged as a leading infectious cause of neonatal morbidity and mortality in many high-income countries.[1] In Europe, a large study revealed maternal GBS colonisation rates ranged from 6.5% to 36%, with a third of the studies in a highly cited systematic review reporting rates of 20% or more.[2] A more recent systematic review and meta-analysis has reported an overall global estimate of 17.9% (95% CI 16.2-19.7).[3]

Neonatal colonisation with GBS is thought to be common in babies whose mothers carry the bacteria. Most colonised babies remain healthy. However, a minority of babies will develop EOGBSD. Some

studies rate neonatal colonisation as around 50%[4] in babies not exposed to IAP, whilst more recently the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) stated a lower rate of 30%.[5] A key issue is that there are usually long term changes in infectious disease epidemiology that occur over many years due to changes in strain virulence, circulating clones and host immunity, global spread of MRSA is an example.[6] It is possible that the baseline incidence of EOGBSD, regardless of IAP usage, has changed significantly in high-income settings.

Epidemiological studies report the *likelihood* of culture-confirmed EOGBSD, as approximately 1 in 2,000 livebirths even in babies not exposed to IAP.[1] In the United Kingdom (UK), which takes a risk-based approach to screening, around 1 in 5,000 babies born to well women at term will have culture-proven EOGBSD and of these, 70% recover completely. One in 17,000 of all babies will die of the disease [5] with mortality higher in preterm babies. [7]

Diagnosis of EOGBDS

A diagnosis of culture confirmed neonatal EOGBSD is obtained from blood culture or, less commonly, cerebrospinal fluid. Definitions of EOGBSD vary. Some use a timeframe of within the first 6 days of birth.[1] Others, the first 48 or 72 hours,[7] the latter being the most internationally accepted definition.[8] The use of varying timeframes to define EOGBSD can confound estimates of disease burden in some jurisdictions. However, most researchers agree that 90% of disease is evident within 24 hours of birth, with an estimated 50% of EOGBSD presenting in utero with clear maternal and/or neonatal signs of sepsis.[9] GBS disease occurring beyond these timeframes is known as late onset GBS disease. The late onset disease has a different etiology and is beyond the scope of this paper.[7,10]

A newborn without culture-confirmed EOGBSD but with clinical symptoms may be said to have a "probable" or "possible" diagnosis but these babies are not included in culture-confirmed surveillance data leading to underestimation of the burden of disease.[7] Furthermore, detection of EOGBSD is strongly influenced by the early neonatal blood culture utilisation rate. The volume of blood sampled affects the sensitivity of the blood culture process and these parameters have never been described in published work.

As well as the varying timeframes for defining EOGBSD onset, the true incidence of EOGBSD is difficult to establish for other reasons including sampling errors, incomplete surveillance data and IAP in the newborn circulation leading to a negative blood culture and falsely low disease diagnosis.[7] GBS capsular antibody seropositivity, changing GBS serotype prevalence and virulence, might account for some of the variation in maternal GBS colonisation and EOGBSD rates.[11]

Vaccination

Maternal serotype-specific capsular antibodies are associated with protection from EOGBSD in term neonates due to the serotype in term neonates.[12] Therefore, vaccination may represent a practical alternative for women of childbearing age to subsequently protect their babies against EOGBSD. Research into GBS vaccine is ongoing[13] and a recent phase 1b/2 randomised controlled trial (RCT) completed in 2016 concluded a vaccine was well tolerated in pregnant women and led to higher GBS serotype-specific antibody concentrations in babies than a placebo, with both interventions resulting in similar safety profiles.[14]

Screening

Maternal colonisation is a prerequisite for EOGBSD. To select women whose babies may most benefit from IAP, two standard screening strategies are recommended.

The universal screening approach requires all women to be offered either a low vaginal, a low vaginal/anal or a low vaginal perianal swab late in pregnancy for GBS detection which is then cultured in laboratory conditions. Less commonly a direct polymerase chain reaction (PCR) test is used which can provide a more immediate result provided that the laboratory logistics are organised to allow for rapid testing.[15] It is currently recommended that all women found to be colonised with GBS late in pregnancy are offered IAP.

The alternative to a universal screening approach is a risk-based approach requiring women presenting with certain risk factors for GBS infection to be identified and offered IAP. Risk factors include prematurity, release of membranes for >18 hours, and maternal fever in labour.[16] Bacteruria in the index pregnancy and a previous baby diagnosed with EOGBSD are also considered risks.[7] In practice, a combination of the two screening strategies (universal and risk-based) are often used[7] thus increasing surveillance for the disease and potentially increasing the amount of women and babies exposed to IAP.

Limitations of screening

Screening for GBS and IAP will not prevent all cases of EOGBSD. Methods of screening vary in the type of sample and culture method used. Even in high-income countries, there is an inability to perform maternal serotype-specific capsular serology which would predict risk more effectively. A universal approach to screening will miss most pre-term babies and screening at the recommended 35-37 weeks of pregnancy is imprecise and leads to both false positive and false negative results.[7] In their 2007 study Angstetra and colleagues found 1191 women would need to be exposed to effective IAP

to prevent one case of EOGBSD and 5704 women needed to be screened to prevent one case of the disease. There are other limitations to this imprecise method of prophylaxis.[17]

Time constraints are an important limitation of IAP. There may be insufficient time from admission in labour to birth to administer the required amount of IAP to be effective in a woman screened positive to GBS. Similarly, if using a risk based approach, timely identification of risk and then administration of the appropriate antibiotic is often problematic.[18]

In one large multistate review of births in the USA where universal screening is recommended, lack of screening in women birthing at term accounted for 34 of the 254 cases of EOGBSD (13.4%). This result could suggest better adherence to a universal screening protocol is necessary to reduce the incidence of EOGBSD however in the same study, 61% of term infants with EOGBSD were born to women who had tested *negative* for GBS before birth highlighting the imprecise nature of the screening tool.[19]

Varying recommendations

Protocols for optimal GBS screening have changed over time despite a lack of robust evidence. Experts have been unable to decide which screening strategy is most effective.[20,21] For example, citing the same evidence for their protocols, the UK recommends a risk-based approach whereas USA recommends universal screening. Recent guidelines published by RANZCOG in Australia state "all maternity services should have an established plan for prevention of EOGBSD, whether by a universal culture or a clinical risk factor-based approach."[22]

Intravenous Antibiotic Prophylaxis

When first introduced in the 1980s, IAP was viewed by some as an interim EOGBSD prevention strategy, partly because of concerns for the potential emergence of resistance and partly because of concerns by some that intrapartum antibiotic exposure may increase the risk of sepsis due to non-GBS pathogens, an issue that was not evident in a recently published large epidemiological report from the USA.[23] However, the use of IAP has doubled in the last 30 years from 12% to 30% and remains the mainstay of prophylaxis against EOGBSD in most high-income settings.[23]

Women thought to be at risk of transmitting the GBS bacteria to their baby may be required to change their model of care late in pregnancy due to a positive GBS culture. The woman is then asked to attend the birth unit early in labour to have an intravenous cannula sited and an intravenous antibiotic

given, at least 4 hours before birth. Once the first dose has been given, most protocols require intravenous antibiotics, commonly penicillin, to be administered every four hours during active labour until the birth of the baby. Following a diagnosed of risk of EOGBSD with or without the administration of IAP, many protocols require women and babies to remain in hospital for neonatal observation for signs of sepsis.

Recommended doses of penicillin or ampicillin vary. The aim of IAP is to rapidly achieve adequate levels in the fetal circulation and amniotic fluid while avoiding potentially neurotoxic serum levels in the mother or fetus. None of the antibiotics recommended for GBS prevention in women with penicillin-allergy (cefazolin, clindamycin, erythromycin, vancomycin) have been evaluated in controlled trials.[24] These medications were chosen based on available pharmacokinetic and pharmacodynamics data and expert opinion regarding safe intravenous agents appropriate for pregnant women.[24]

Risks of Intrapartum antibiotic prophylaxis

The widespread use of antibiotics in the past 80 years has saved millions of lives. However, administration of antibiotics to women in labour is not without risks. These include increases in drug resistant organisms, adverse maternal reactions ranging from mild allergic responses to life threatening anaphylaxis, and medicalisation of birth.[5] Research indicates a correlation between maturation of a baby's immune system and perinatal transfer of maternal commensal bacteria.[25] As antibiotics are not selective in killing only pathogenic bacteria,[26] the microbiota of both mother and baby may be adversely affected by giving IAP. Although maternal and neonatal health are inextricably linked, this paper will concentrate on the effects of IAP on neonatal health.

Effectiveness of IAP

Declines in EOGBSD in the USA coincided with increased prevention activities in the 1990s. The decline in neonatal disease has been attributed to widespread use of IAP. In the last thirty years, incidence of culture-confirmed and reported EOGBSD decreased from 1.8 cases/1000 livebirths in the early 1990s to 0.26 cases/1000 livebirths, an 86% reduction by 2010.[10,24].These data appear to support the effectiveness of IAP; however**,** association is not causation. The initial implementation of IAP in the USA was not a coordinated process and cannot be closely fixed in time. Surveillance data in many jurisdictions is reported voluntarily and therefore will not represent all cases of EOGBSD. Furthermore, passive surveillance data for EOGBSD is likely to be unreliable owing to differing culture utilisation standards and the difficulty in capturing data from a large number of pathology services across jurisdictions.

Since 2002, reported rates of EOGBSD have not substantially changed in the USA.[24] Data from the

UK suggest there has been a small increase in EOGBSD cases between 2003-2010. Whether changes in USA and UK data and others worldwide reflect variations in reporting of cases, natural fluctuation in disease events, a true change in EOGBSD or less than optimal implementation of IAP is difficult to assess. Furthermore, diagnosis, and therefore rates of EOGBSD cases, apply to livebirths only, stillbirths and miscarriage where GBS is present are not included in surveillance data.[7]

With the absence of reliable data reflecting the true incidence of EOGBSD and dearth of evidence to support the safety of IAP, effectiveness of this prophylaxis and consideration of the benefits and risks, needs to be further understood. We undertook an integrative literature review to study the wider evidence of the effectiveness of IAP.

METHOD

An integrative literature review provides a broad understanding of a research question as it allows the inclusion of studies with diverse methodologies. Our integrative review aimed to provide insight for discussion of the literature surrounding the effectiveness of IAP. To achieve this, the review utilised an integrative methodology framework by Whittemore and Knafl [27] The framework includes problem identification (as outlined above), a comprehensive literature search and a findings and discussion section. This framework enables a high-quality review which may influence evidence-based practice initiatives and changes in maternity care.

Literature search

A high-quality literature review should demonstrate how relevant studies have been located in the wider body of research.[28] To achieve this, the search strategy incorporated electronic searches in the Cochrane Database of Systematic Reviews, Medline, Embase and Science Direct was undertaken in 2015. Alerts were placed on databases to capture new research into this topic.

Inclusion criteria

Peer reviewed articles, written in (or translated to) English; primary research including randomised and non-randomised studies, reviews of primary research and commentaries were retrieved. Search terms included Intrapartum AND group B strep* AND antibiotic. Key words to limit search included antibiotic prophylaxis, infant, newborn, labour OR labor.

Reference lists of the included studies were scrutinised to identify additional, relevant articles. Due to the long-term use of IAP, publications were considered from 1980 onwards. Articles focused on outcomes and effectiveness of screening strategies and IAP protocols on early-onset sepsis (EOS) and EOGBSD were included.

The search located 189 potentially relevant articles. Figure 1 reveals the process of reducing the number of articles from 189 to 13 for critical appraisal.

Place Fig 1 here (inclusion flow chart)

Evaluation of study quality

Extraction of methodological features is recommended to assist in the evaluation of quality in included studies. This may be achieved by assigning quality scores to articles and is conducive to reviews in which the sampling frame is narrow and studies are similar in age and design. Evaluation of studies becomes more complex when, as in our review, diverse methodologies are included.

Critical appraisal tools assist the reader to reach judgements about the quality of a study. The Critical Appraisal Skills Programme (CASP) tool was chosen to evaluate data for our review. This tool allows for the assessment of methodological quality by using checklists that are intended specifically for various study designs.[29] The CASP tool approaches research by asking three main questions: Is the study valid? What are the results? Are the results useful? Articles are then further analysed and scored using a checklist relevant for the type of study evaluated. In our review, CASP scores ≥10 equated to high quality, 5-9 to medium quality and ≤ 4 to low quality studies. Results of CASP scoring are available in Tables 1-3.

Analysis of the data

While 'effectiveness' in the retrieved studies does not distinguish between efficacy and effectiveness, a distinction is made in this paper. Traditionally, efficacy of an intervention has been determined in clinical trials which, in order to reduce bias, are highly regulated, have internal validity with results that are generalisable, provided the characteristics of the population studied is similar to the population in which the trial was done. Efficacy asks of an intervention: 'can it work under ideal/controlled conditions?' Effectiveness asks: 'does it work in the real world?' Observational studies may therefore present a more realistic appreciation of effectiveness as these seek to explore the external validity of an intervention in day to day maternity care. We acknowledge that there is value in both study designs. In the studies retrieved in our search however, the term effectiveness was used in clinical trials as well as observational studies. In this paper, clinical trials and observational studies are assessed for effectiveness separately. A summary of each study-type appears in Tables 1-3.

FINDINGS

The 13 studies included in our integrative review consist of one systematic review and two narrative reviews located in Table 1, four randomised controlled trials (RCT) located in Table 2

and six observational studies located in Table 3. The tables provide details of study designs and outcomes and the CASP score for each study.

In the following section, we present our integrative review starting with an analysis of the research included in the recent Cochrane Systematic review and Meta-analysis. This includes analysis of four RCTs we retrieved (three of these were also included in the Cochrane review) and two narrative reviews. A summary of the limitations and biases of the included studies is provided in the appended Table 1 and Table 2. Finally, we discuss the six observational studies retrieved in our search summarised in Table 3.

Effectiveness in a controlled context (systematic review of RCTs and RCTs)

The highest level of evidence of effectiveness is a robust systematic review of high quality randomised controlled trials. In our search, we located only one systematic review by Ohlsson and Shah[30] (Table 1). This 2014 Cochrane review found four studies that met inclusion criteria; Boyer & Gotoff (1986), Tuppurainen and Hallman (1989), Matorras, et al., (1991) and Edwards et al (2002). Whilst included in the review, the study by Edwards et al [31] compared penicillin with ampicillin rather than a placebo and therefore did not meet the criteria for inclusion in the Cochrane meta-analysis. Our review retrieved the same three RCTs identified in the Cochrane review; Boyer and Gotoff [4], Tuppurainen and Hallman [32] and Matorras and colleagues., [33] plus a more contemporary Egyptian clinical trial by Nabhan and colleagues.[34]

We explore the three studies[4,32,33]included in both our review and in the Cochrane meta-analysis. Each study compared IAP with a placebo and concluded that IAP was an effective prophylaxis against EOGBSD. When the three studies were combined for Cochrane's meta-analysis[30], there was a statistically significant reduction in the risk of EOGBSD (RR 0.17, 95% CI 0.04-0.74). However, we assigned CASP scores of ≤ 4 for each of these three studies since significant methodological flaws affected the internal validity of each study, which undermined their rigour and therefore their results.[30] This assessment is in agreement with Ohlsson and Shah who considered the quality of all RCTs included in their systematic review to be so low that even though a statistically significant reduction in EOGBSD was found in meta-analysis, the review could not provide robust evidence of effectiveness of IAP to reduce EOGBSD. Serious biases included inadequate reporting of sample size, [4,32,33] inappropriate allocation of randomisation [4,32,33] and selective reporting. [4,32] None of the RCTs complied with the Consolidated Standards of reporting Trials (CONSORT) as these guidelines were not introduced until 1996.[35] Biases and limitations of the RCTs are discussed further in the following sections.

Selective reporting bias

Selective reporting bias can be defined as the selective revealing or suppression of information. The Cochrane review found evidence of selective reporting bias in RCTs by Tuppuranien and Hallman[32] and Boyer and Gotoff [4]. For example, the approach by Boyer and Gotoff [4] was criticised by Ohlsson and Shah as indicating a high degree of selective reporting bias and provision of incomplete outcome data. Boyer and Gotoff reported on results after different numbers of women had been enrolled in their study conducted between 1979 and 1984. In their 1985 paper, Boyer and Gotoff reported on outcomes for 79 women and in their 1986 paper, reporting on the same study, there were 160 women. Ohlsson and Shah identified these authors waited for an additional neonatal outcome in the control group before publishing their 1986 statistically significant findings.[30] Further, intention to treat did not guide their analysis since maternal and neonatal outcomes were not reported in 11% of women randomised. Curiously, women who developed a fever and their babies were excluded from analysis.

While the 2014 Cochrane Review[30] rejected the results of the included RCTs based on identified biases, not all researchers have reached this conclusion. A 2013 narrative review by Schrag and Verani, with a CASP score of 4, was at odds with the Cochrane review's findings[10] (Table 1). Reporting on the experience of IAP in the USA, this review claimed that the trials conducted by Boyer and Gotoff [4] and Tuppurainen and Hallman [32] demonstrated that IAP *was highly effective*, with no mention of their flawed methodology.[10] The selective reporting bias in the Boyer and Gotoff [4] trial was not cited as a methodological problem, instead the review stated that, in relation to Boyer and Gotoff [4] "…one trial with ampicillin was stopped early due to overwhelming efficacy."[10] Clearly authors were reaching different conclusions based on interpretation of the same data.

The RCT by Matorras and colleagues[33] took a novel approach to the definition of EOGBSD and included babies with possible EOGBSD based on symptoms as well as culture confirmed disease. These authors concluded that IAP was effective in reducing the rate of neonatal GBS colonisation but this reduction did not translate into a significant decrease in culture-proven EOGBSD. Matorras and colleagues then re-analysed their data including "clinically infected" newborns, defined as babies born to mothers with culture-confirmed GBS, showing symptoms of EOGBSD, but without diagnosis confirmed by culture. The authors considered it appropriate to include babies with clinical symptoms of EOGBSD, also referred to as "possible" or "probable" EOGBSD, since they considered microbiological confirmation of EOGBSD in neonates was problematic in the 1990s.[33] Following a non-significant finding of IAP on culture-proven cases of EOGBSD, the authors went on to include the group of babies with a clinically suspected infection and found a significant impact of IAP. The inclusion of possible EOGBSD leaves the trial open to bias as clinical judgement is subjective by nature. Therefore, the possible lack of objectivity in this trial may have undermined its validity. Whether the inclusion of clinically infected babies was appropriate or not is debatable.

Measurement bias in un-blinded studies

Lack of objectively is also evidenced by the absence of double blinding in a clinical trial. The absence of double blinding was a criticism of all three studies.[4,32,33] Participating women and clinicians were aware of the mother's GBS status and receipt or not of IAP. Objectivity when assessing newborns for disease in a clinical trial cannot be achieved if women and clinicians are aware of group allocation. For example, while the inclusion by Matorras and colleagues of clinically infected neonates reflects the difficulties of assessing the true incidence of EOGBSD, the lack of blinding in this trial may have exposed the study to assessment bias as diagnosing clinicians were aware of the mother's GBS status.[30]

Variation in screening techniques

Presence of maternal GBS was ascertained by vaginal/rectal swab in only two of the included studies.[4,33] Methods of collection, processing and reporting were unclear which may decrease the accuracy of the screening test. Cultures were also performed at various gestations, thus further limiting accuracy due to the transient nature of GBS colonisation.[4,32,33]

Other risk factors for Group B Streptococcus

All of the RCTs [4,32,33] included women with mixed or unknown risk status but this was poorly reported by the trial authors. It is not clear whether women with other risk factors, such as GBS colonisation plus pre-labour spontaneous release of membranes (pSROM) or premature labour, were evenly distributed between intervention and control groups. Randomisation was not stratified by other risk factors in any of the included studies.

The retrieved narrative review by Money and Allen (2013), focused on the need for intervention if women had confirmed GBS colonisation and/or another risk factor for GBS. This narrative review (Table 1) with a CASP score of 6, was undertaken to update Canada's GBS guidelines.[36] The guideline recommended that women with pSROM and an antenatal GBS positive culture would benefit from immediate induction of labour plus IAP, based largely on the TermPROM trial. TermPROM had concluded that, for women who were GBS positive with pSROM, immediate induction of labour may be the preferred option to prevent neonatal infection. In TermPROM, IAP was given at the discretion of the clinician, however it was recommended that IAP was administered for known maternal GBS carriage and for GBS risk factors.[37]

While Money and Allen [36] identified a reduction in all cause neonatal infections when IAP plus induction of labour was undertaken for women at term with pSROM and a positive GBS culture, their narrative review was unable to find any robust evidence for the continuation of IAP without pSROM and level II evidence only from their retrieved observational studies.[24]

Generalisability

Notwithstanding the methodological limitations of the studies discussed, are we able to translate findings into maternity practice today? We conclude that it is important to consider that maternity and neonatal care have changed considerably in the three decades since the included studies occurred. Three RCTs, although undertaken in high-income countries, are more than 20 years old (1986-1991).[4,32,33] Generalising findings into contemporary practice from decades-old care environments to modern day maternity and neonatal care is problematic and may not lead to valid conclusions. Rather contemporary studies of higher quality are required to be able to reliably guide current practice.

No contemporary studies were located for the 2014 update of previous Cochrane Reviews.[38 39] This may be due to the widespread use of IAP since the 1980s and hence a lack of equipoise to undertake further RCTs. An exception is the most recent RCT retrieved in our search[34] (Table 2). This study was not retrieved in the Cochrane review. The trial, undertaken in Egypt (CASP score 10) provided a single dose of ampicillin to all women randomised to the treatment arm of the trial regardless of GBS status and assessed all-cause maternal and early-onset neonatal sepsis.[34] Although results conflicted with other RCTs, finding a single dose of IAP did not provide any maternal or neonatal benefits, maternity practices in Egypt contrasted with those in high-income settings elsewhere so we did not consider these findings generalisable.[34]

In summary, the methodological limitations of the RCTs we retrieved prevent us from concluding that IAP is effective. This finding is in agreement with the conclusion of the 2014 Cochrane review.[30] By contrast, the two narrative reviews by Money and Allen [36] and Schrag and Verani [10] (Table 1) that reviewed a combination of RCTs and observational studies, concluded that IAP is effective against EOGBSD but has limitations. Money and Allen [36] however did not identify robust evidence to endorse the practice of IAP for women whose babies were at risk of EOGBSD, unless the women presented with pSROM.

In their narrative review, Schrag and Verani [10]suggested that in order to determine effectiveness the interpretation and application of IAP protocols must be considered. The authors concluded that, although they reported IAP to be effective, GBS screening and adherence to IAP protocols remained sub-optimal and further reduction of EOGBSD may be achieved only with improved protocol compliance. Despite CDC guideline revisions in 2002[40] aiming to clarify protocols GBS for screening

and administration of IAP, less than optimal adherence to screening protocols continued to be reported.

Observational studies

Our literature review retrieved six observational studies undertaken between 2001 and 2013 (Table 3). These studies assessed the practical effectiveness of IAP in the maternity care setting. Unlike the RCTs which mainly scored poorly in CASP assessment, the quality of observational studies was assessed as medium to high (CASP scores 7-10). Overall the six observational studies retrieved[18,41-45] identified a positive association between IAP and reductions in EOGBSD.

At the same time the studies showed that protocol adherence was far from optimal and suggested better compliance with protocols for both screening and IAP were needed to ensure maximum effectiveness to further reduce the already low reported incidence of EOGBSD. Authors were concerned about the continued reduced protocol compliance, which they referred to as 'missed opportunities' or 'protocol failure. The American Centers for disease control and prevention (CDC) agreed with the notion of suboptimal compliance and their most recent iteration repeated the need for better protocol compliance. [24]

Reasons for missed opportunities

Reasons for missed opportunities were described as multifactorial and included inherent limitations of screening strategies, the less than optimal positive and negative predictive values of a universal screening approach [18] or clinicians' inability to recognise and act upon risk factors.[43]

Pinto and colleagues identified that 68 (70%) newborns with EOGBSD among a cohort of 92, did not receive any IAP due to some form of reduced protocol compliance.[43] The limitations of universal screening was confirmed by a later observational studys involving 4,696 women of ≥32 weeks, identified as GBS positive or negative by universal screening.[18] The study found 8.3% (n=292) of 3524 women with a negative GBS screen in pregnancy were positive during labour and missed IAP, while 50.5% (n=592) of 1172 women with a positive screen in pregnancy were negative during labour and received IAP unnecessarily (Table 3).[18]

A study undertaken in the same year found that of 79 cases of culture proven EOGBSD, 84% (n=67) of the newborns were born to women who received no IAP. Women in this study were identified for IAP by a risk-based approach. This study noted that clinicians commonly miss risk factors, but where women received the correct medication, correct dosages of that medication and timely administration of IAP, incidences of EOGBSD were unlikely.[44]

Timing of IAP in relation to birth

Regardless of screening strategy, timing of prophylaxis relative to birth is a key element in the effectiveness of IAP and has been reported as a major reason for sub-optimal protocol compliance. An early study by Lin and colleagues (2001) suggested that for IAP to have maximum effectiveness it should be given at least 2 hours prior to birth.[41] This recommendation has been challenged by a larger and more contemporary study by [45] which was included in the Schrag and Verani narrative review. The authors noted that IAP is most effective when provided more than four hours prior to birth. Effectiveness dropped markedly when IAP was given less than 4 hours before birth as it was thought that there was insufficient time for an anti-bacterial therapeutic effect.[45] The four hour timeframe is endorsed by Schrag and Verani [10] and the Centers for disease control and prevention [24] and many IAP protocols worldwide, including Australia use to this timeframe.

Depending on local colonisation rates and screening protocols, a study by Coco (2002) suggested around one fifth of women admitted for birth in advanced labour would be GBS positive and would give birth before the required 4 hours. Therefore the effectiveness of IAP may be limited by the inability to correctly administer at least one of the recommended doses before the birth.[42] This small study (Table 3) considered that timing constraints were more pronounced where a universal screening approach was adopted conflicting with others such as Pinto and colleagues who suggested a risk-based approach caused more protocol failures due to time constraints. Both these studies agreed however, that timing of antibiotic administration was the most common reason for women not receiving adequate IAP. It is important to note that none of the retrieved reviews, RCTs or observational studies critiqued considered the potential for long-term health effects of IAP.

DISCUSSION

The state of the evidence explored in this integrative review is far from reassuring. If, as we hypothesise, reduced protocol compliance is widely reflected across maternity settings, the global claim that the reduction in EOGBSD is solely due to IAP is questionable.

It is remarkable that in the USA and other high-income countries the common practice of administering IAP to women with a positive GBS culture has been so poorly studied. Only three randomised controlled trials, conducted more than 20 years ago, and enrolling 488 women and one contemporary study which is not able to be generalised have been published.

If enough women are given IAP that kills GBS, then it is likely that the reported incidence, at least of culture proven EOGBSD will reduce. It is unlikely that this simple equation reveals the whole story.

What the observational evidence described here does reveal is that for IAP to prevent EOGBSD all women at risk of transmitting the bacteria must be accurately identified and IAP given in a timely manner. Our literature review reveals this is not happening, in fact due to inherent limitations in screening and administering, IAP will never prevent all cases of EOGBSD.

Furthermore, all located observational studies considered a traditional view of effectiveness i.e. the extent to which an intervention resolves an adverse outcome. None of the retrieved studies considered the risks versus the benefits of IAP, including side effects and long-term health issues.

Effectiveness is considered to be the extent to which an intervention resolves an adverse outcome. While the Cochrane meta-analysis of the three small, dated studies,[4,32,33] found there was a significant decrease in incidence of EOGBSD when IAP was used, the reviewers were unable to recommend the continuing use of IAP due to the lack of evidence from robust trials.

While RCTs are considered the gold standard in evaluating healthcare interventions, they can yield biased results if lacking methodological rigor.[46] Ohlsson and Shah [30] reported studies included in their Cochrane review had a high risk of both performance and selection bias.[4,32,33]We agree that these studies had serious flaws and should not be relied upon as robust evidence for the effectiveness of IAP.

Observational studies, which provide level II evidence[24] associate IAP administered 2-4 hours before birth, with a lower incidence of culture-confirmed EOGBSD. However, at what cost? Risks versus benefits and the long-term consequences of IAP were not taken into consideration in any of the retrieved studies.

Although all observational studies agreed on the short-term effectiveness of IAP, they noted that both standard methods of screening for IAP are imprecise and capture many women that, although presenting with an antenatal diagnosis of GBS colonisation or other risk factors, would not have a baby with EOGBSD. As there is no practical method to determine which mothers are at the greatest risk of having an infant affected by EOGBSD, many well women and babies are prescribed IAP unnecessarily. Observational studies showed protocol failures for IAP administration were common and therefore undermined the short-term effectiveness of IAP. A recent retrospective observational study[47] retrieved after our literature search found that, in a cohort of 488 women who were GBS positive there was a 40% protocol failure. However almost 80% of these failures (n=157) were deemed unavoidable. The authors considered that the protocol failures would have occurred even with optimal protocol adherence.

We consider that the inherent limitations of current CDC recommendations of universal screening and IAP, together with a lack of evidence of the long-term health effects of IAP, does not justify the widespread use of this intervention. Limitations include the inability to calculate the true rate of EOGBSD itself plus the inability to calculate the true reduction in EOGBSD in the presence of IAP, due to incomplete surveillance data.

A major limitation with studies retrieved for our review is a lack of discussion around the theory that rates of EOGBSD may have been reducing for reasons other than widespread IAP. As well as the difficulty of assessing true rates of EOGBSD in the community, broad changes in population (herd) immunity, diverse changes in living circumstances and processes of care or unexplained waxing and waning of bacterial clones (serotypes in the case of GBS) may have caused variations in rates that were not considered any of the studies.

A long-term health effect of considerable concern is the impact of IAP on the baby's microbiome. The human microbiome encompasses an ecosystem of approximately 90 trillion microbes that impact on host physiology and are known to protect the host from pathogens.[48] During vaginal birth, and maybe even in utero, the baby begins the process of seeding a founding microbiome.[49] It appears that this founding group of commensal microbiomes together with exclusive breastfeeding is important in optimising newborn immune and epigenetic health. Both in adults and children, microbial diversity can be disrupted by the administration of antibiotics causing dysbiosis of the host microbiome. Dysbiosis of the neonatal microbiome may occur indirectly by the administration of IAP to the mother in labour.[50] New technologies have enabled studies linking a reduction in the diversity of the human microbiota to diseases such as obesity, inflammatory bowel disease, autoimmune disease and, more recently, neurological disease.[51] Interactions between a newborn and her/his microbiome appear crucial for normal development, but how host–microbe symbiosis is established and maintained remains underexplored. We noted a lack of consideration given to effects of antibiotics on the health of the newborn in all retrieved studies, and in particular the effect on the newborn's immature immune system and developing microbiome.

Given this emerging research and the fact that around a third of birthing women are exposed to IAP that 30 years ago, was supposed to be a stop gap until better methods to reduce the risk of EOGBSD could be offered and, since 1191 women must to be exposed to IAP and 5704 to have screening to prevent one case of EOGBSD,[17] it would seem likely that we are unnecessarily exposing newborns to an intervention whose long-term adverse effects may outweigh short-term effectiveness.

As IAP is a flawed approach and was never intended to be a long-term solution for the reduction of EOGBSD, it may be time to consider a completely different strategy. These may include education

and discussion around optimising vaginal and intestinal health, which may assist a reduction in maternal GBS colonisation and pre-labour SROM in the first instance. Furthermore, a serological screening option for women to assess whether a protective antibody against specific GBS serotypes is present may be a solution and finally, the possibility of a vaccine is now well underway with a 1b/2 phase RCT completed in 2016 that demonstrated immunogenicity of a vaccine.

CONCLUSION

Although our integrative review found evidence of a positive association between IAP and EOGBSD, there is a lack of robust evidence supporting the widespread administration of antibiotics during birth and an emerging body of evidence suggesting a potential for long-term harm.

Some babies will benefit from IAP and, in the near future, there will be a place in maternity care for IAP for the management of EOGBSD risk but clinicians and policy makers must consider the cost to the majority of mothers and babies who receive no benefit and possibly incur harm. In light of this, clinicians and policy makers must question the use of widespread screening and IAP and document a realistic assessment of the evidence in our policies, guidelines and information for consumers. We do not have a simple means of quantifying and communicating this relative risk to women. However, women should be given access to current knowledge so that they can decide what risk they are prepared to embrace.

Investigation into potentially harmful long-term effects of intrapartum antibiotics needs to be undertaken and further investigation of alternatives is warranted. We must urgently question the widespread use of IAP as a public health imperative.

REFERENCES

1. Edmond K, Kortsalioudaki C, Scott S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. *Lancet* 2012; **379**(9815): 547-56.
2. Barcaite E, Bartusevicius A, Tameliene R, Kliucinskas M, Maleckiene L, Nadisauskiene R. Prevalence of maternal group B streptococcal colonisation in European countries. *Acta Obstetricia et Gynecologica Scandinavica* 2008; **87**: 260-71.
3. Kwatra G, Cunnington M, Merrall E, et al. Prevelance of maternal colonisation with group B streptococcus: a systematic review and meta-analysis. *Lancet Infect Dis* 2016.
4. Boyer K, Gotoff S. Prevention of group B streptococcal disease with selective chemoprophylaxis. *The New England Journal of Medicine* 1986; **314**(26): 1665-9.
5. Royal College of Obstetricians and Gyneacologists. The Prevention of Early-onset Neonatal Group B Streptococcal Disease: Green-top Guideline No. 36. 2nd ed. London: Royal College of Obstetricains and Gynaecologists; 2012.
6. Wyllie D, Paul J, Crook D. Waves of trouble: MRSA strain dynamics and assessment of the impact of infection control. *Journal of antimicrobial chemotherapy* 2011; **66**(12): 2685-8.
7. UK National Screening Committee. Screening for Group B streptococcal infection in pregnancy: external reveiw against programme appraisal criteria for the UK National Screening Committee (UK NSC). Version 5. 2012. http://legacy.screening.nhs.uk/policydb_download.php?doc=499 (accessed 1 August 2016).
8. Weston EJ, Pondo T, Lewis MM, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. *Pediatr Infect Dis J* 2011; **30**(11): 937-41.
9. Tudela CM, Stewart RD, Roberts SW, et al. Intrapartum evidence of early-onset group B streptococcus. *Obstetrics and gynecology* 2012; **119**(3): 626-9.
10. Schrag SJ, Verani JR. Intrapartum antibiotic prophylaxis for the prevention of perinatal group B streptococcal disease: Experience in the United States and implications for a potential group B streptococcal vaccine. *Vaccine* 2013; **31**: 20-6.
11. Le Doare K. Global maternal group B streptococcus colonisation. *The Lancet Infectious Diseases* 2016; **16**(9): 992-3.
12. Dangor Z, Kwatra G, Izu A, et al. Correlates of protection of serotype-specific capsular antibody and invasive Group B Streptococcus disease in South African infants. *Vaccine* 2015; **33**(48): 6793-9.
13. Madhi SA, Dangor Z, Heath PT, et al. Considerations for a phase-III trial to evaluate a group B Streptococcus polysaccharide-protein conjugate vaccine in pregnant women for the prevention of early- and late-onset invasive disease in young-infants. *Vaccine* 2013; **31 Suppl 4**: D52-7.
14. Madhi SA, Cutland CL, Jose L, et al. Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in healthy women and their infants:a randomised phase 1b/2 trial. *Lancet Infect Dis* 2016.
15. Chan WSW, Chua SC, Gidding HF, et al. Rapid identification of group B streptococcus carriage by PCR to assist in the management of women with prelabour rupture of membranes in term pregnancy. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 2014; **54**(2): 138-45.
16. Oddie S, Embleton ND. Risk factors for early onset neonatal group B streptococcal sepsis: case-control study. *Bmj* 2002; **325**(7359): 308.
17. Angstetra D, Fergusen D, Giles W. Institution of universal screening for group B streptococcus (GBS) from a risk management protocol results in reduction of early-onset GBS disease in a tertiary obstetric unit. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2007; **47**: 378-82.
18. Lin F, Weisman L, Azimi P, et al. Assessment of intrapartum antibiotic prophylaxis for the prevention of early-onset group B Streptococcal disease. *Pediatr Infect Dis J* 2011; **30**(9): 759-63.
19. Van Dyke M, Phares C, Lynfield R, Thomas A, Arnold K, Craig A. Evaluation of universal antenatal screening for group B streptococcus. *NEJM* 2009; **360**: 2626-36.

20. Sheehy A, Davis D, Homer CS. Assisting women to make informed choices about screening for Group B Streptococcus in pregnancy: a critical review of the evidence. *Women and birth* 2013; **26**(2): 152-7.
21. Kurz E, Davis D. Routine culture-based screening versus risk-based management for the prevention of early-onset group B streptococcus disease in the neonate: a systematic review. *JBI Database System Rev Implement Rep* 2013; **13**(3): 206-46.
22. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists Maternal Group B Streptococcus in pregnancy: screening and management. Melbourne: The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG); 2016
23. Schrag SJ, Farley MM, Petit S, et al. Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005 to 2014. *Pediatrics* 2016; **138**(6).
24. Centers for disease control and prevention. Prevention of Perinatal Group B Streptococcal Disease: revised guidelines: MMWR 59 In: (CDC) Cfdcap, editor.; 2010.
25. Azad M, Konya T, Maughan H, et al. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at four months. *CMAJ* 2013; **185**: 385-94.
26. Blaser M. Antibiotic overuse: Stop the killing of beneficial bacteria. *Nature* 2011; **476**(7361): 393-4.
27. Whittemore R, Knafl K. The integrative review: updated methodology. *Journal of Advanced Nursing* 2005; **52**(5): 546-53.
28. Polit D, Beck C. Essentials of nursing research. 8th ed. Philadelphia: Wolters Kluwer; 2014.
29. CASP. Critical Appraisal Skills Programme. 2014. http://www.casp-uk.net/ (accessed 27 May 2015).
30. Ohlsson A, Shah V. Intrapartum antibiotics for known maternal Group B streptococcal colonization (Review). *Cochrane Database Syst Rev* 2014; **6**: CD007467.
31. Edwards R, Clark P, Sistrom C, Duff P. Intrapartum antibiotic prophylaxis 1: relative effects of recommended antibiotics on Gram-negative pathogens. *American Journal of Obstetrics & Gynecology* 2002; **100**: 534-9.
32. Tuppurainen N, Hallman M. Prevention of neonatal group B streptococcal disease: intrapartum detection and chemoprophylaxis of heavily colonized parturients. *Obstetrics & Gynecology* 1989; **73**(4): 583-7.
33. Matorras R, Garcia-Perea A, Omenaca F, Diez-Enciso M, Madero R, Usandizaya J. Intrapartum chemoprophylaxis of early-onset group B streptococcal disease. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 1991; **40**(1): 57-62.
34. Nabhan AF, Elhelaly A, Elkadi M. Antibiotic prophylaxis in prelabor spontaneous rupture of fetal membranes at or beyond 36 weeks of pregnancy. *International Journal of Gynecology and Obstetrics* 2014; **124**(1): 59-62.
35. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *American Journal of Ophthalmology* 1996; **122**(6): 925-6.
36. Money D, Allen V. The prevention of early onset neonatal group B streptococcal disease. *Journal of Obstetrics and gynaecologists of Canada* 2013; **35**(10): 939-51.
37. Hannah M, Ohlsson A, Wang E, et al. Maternal colonisation with group B streptococcus and pre-labour rupture of the membranes at term: the role of induction of labor. *American Journal of Obstetrics and Gynecology* 1997; **177**(4): 780-5.
38. Ohlsson A, Shah V. Intrapartum antibiotics for known maternal Group B streptococcal colonization (Review). *Cochrane Database of Systematic reviews* 2009.
39. Ohlsson A, Shah V. Intrapartum antibiotics for known maternal Group B streptococcal colonization. *Cochrane Database of Systematic reviews* 2013; (1).
40. Centers for disease control and prevention. Prevention of Perinatal Group B Streptococcal Disease:Revised guidelines from CDC: MMWR 51. In: prevention Cfdca, editor.; 2002.
41. Lin FY, Brenner RA, Johnson YR, 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; **184**(6): 1204-10.

42. Coco AS. Comparison of two prevention strategies for neonatal group B streptococcal disease. *Journal of the American Board of Family Practice* 2002; **15**(4): 272-6.
43. Pinto NM, Soskolne EI, Pearlman MD, et al. Neonatal early-onset group B streptococcal disease in the era of intrapartum chemoprophylaxis: residual problems. *Journal of Perinatology* 2003; **23**(4): 265-71.
44. Berardi A, Lugli L, Rossi C, et al. Intrapartum antibiotic prophylaxis failure and group-B streptococcus early-onset disease. *Journal of Maternal-Fetal & Neonatal Medicine* 2011; **24**(10): 1221-4.
45. Fairlie T, Zell E, Schrag S. Effectiveness of intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal disease. *Obstetrics and gynecology* 2013; **121**(3): 570-7.
46. Evans D. Hierarchy of Evidence: a framework for ranking evidence evaluating healthcare interventions. *Journal of clinical nursing* 2003; **12**: 77-84.
47. Bienenfeld S, Rodriguez-Riesco LG, Heyborne KD. Avoiding Inadequate Intrapartum Antibiotic Prophylaxis for Group B Streptococci. *Obstetrics and gynecology* 2016; **128**(3): 598-603.
48. Blaser MJ. Harnessing the power of the human microbiome. *Proceedings of the National Academy of Sciences* 2010; **107**(14): 6125-6.
49. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J. The placenta harbors a unique microbiome. *Science translational medicine* 2014; **6**(237): 237ra65.
50. Azad MB, Konya T, Persaud RR, et al. Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. *BJOG : an international journal of obstetrics and gynaecology* 2016; **123**: 983-93.
51. Chu D, Antony K, Ma J, et al. The early infant gut microbiome varies in association with a maternal high-fat diet. *Genome Med* 2016; **8**(1): 77.