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ORIGINAL ARTICLE

Clinical impact of rapid polymerase chain reaction (PCR) test for group B *Streptococcus* (GBS) in term women with ruptured membranes

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Abstract

Background Early-onset group B *Streptococcus* (EOGBS/GBS) infection remains a significant cause of neonatal morbidity and mortality.

Aims Aiming to improve antimicrobial stewardship and reduce unnecessary maternal and infant exposure to intrapartum antibiotic prophylaxis (IAP), this study assessed the clinical use of a commercially available GBS polymerase chain reaction (PCR) assay for term women with pre-labour rupture of membranes.

Methods This was a retrospective study in a tertiary level maternity unit of term women with pre-labour rupture of membranes (ROM), without any clinical suspicion of infection performed between November and December 2017. GBS PCR tests were cross-referenced with patient clinical data. PCR test results, the impact of testing on antibiotic administration, pyrexia in labour, induction, interventional delivery rates and neonatal outcomes were analysed.

Results Of 200 patients included in the study, 29 were positive (14.5%) and 166 were negative (83%), with five invalid results (2.5%). One hundred and twenty three women had > 18-h ruptured membranes and 86 women (70%) who would have been eligible for IAP based on risk factors avoided antibiotic therapy following a negative PCR test. There were no significant differences in induction or interventional delivery rates between GBS-positive and GBS-negative women following PCR testing. During the study period, there were no cases of EOGBS.

Conclusions In a centre adhering to a risk-factor-based GBS policy, the introduction of limited rapid GBS screening for term women with pre-labour rupture of membranes resulted in a clinically significant reduction in prophylactic antibiotic use.

Keywords GBS · GeneXpert® · PCR · Term pre-labour ROM

Introduction

Group B *Streptococcus* is a beta-haemolytic, Gram-positive coccus which exists as part of the normal bacterial flora of the gastrointestinal, vaginal and urethral tracts in 15–35% of women. It can be chronic, intermittent or transient in nature [1, 2]. It is carried vaginally in approximately one in four women and can infect the amniotic fluid before or during labour which may be vertically transmitted to the foetus by aspiration [3]. Group B streptococcal (GBS) infection accounts for nearly 50% of serious early-onset neonatal bacterial infections manifesting as sepsis, pneumonia, respiratory distress and meningitis and 90% of cases occur within the first 24 h of life [3, 4]. The outcomes from early-onset GBS (EOGBS) infection can be devastating with a mean early onset case fatality of 12.1% [5].

The most significant risk factor for development of EOGBS sepsis is maternal colonisation at delivery with 12 infants per 1000 births born to colonised mothers developing EOGBS [6] and 40–50% of babies born to colonised mothers becoming colonised with GBS [4]. In Ireland, invasive EOGBS was reported at a rate of 0.66 in 1000 live births in 2016 [7]. The majority (74.4%) of EOGBS occurs in term infants [8].

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Intrapartum administration of prophylactic antibiotics has been proven to reduce vertical transmission of GBS [9, 10]. The Royal College of Obstetricians and Gynaecologists (RCOG) recommend that intrapartum antibiotic prophylaxis (IAP) is offered to women based on risk factors [11]. These risk factors are a previous infant infected with GBS, discovery of maternal GBS carriage through bacteriological investigation during pregnancy, preterm labour, suspected maternal intrapartum infection, maternal pyrexia and prolonged rupture of membranes (> 18 hours (h)) [11].

With the increasing threat of antimicrobial resistance [12], the appropriate use of antibiotics is paramount. Hospital-based stewardship has proven to be effective in reducing resistance rates, improving patient care and having a positive financial impact [13]. Screening for GBS at the onset of labour using rapid PCR testing is feasible [14], has a high sensitivity and specificity [15–18], may reduce the number of unnecessarily treatments [16] and is largely acceptable to women [19]. Currently universal GBS screening is not standard practice in the maternity ward of UK hospitals [11, 19] or Irish maternity units (personal communication).

The aim of this study is to evaluate the clinical use of rapid PCR testing for GBS in term women with pre-labour rupture of membranes and no evidence of infection who presented within the timeline for laboratory testing and assess use of intrapartum antibiotic prophylaxis.

Methods

This is a retrospective study of all women who underwent PCR testing for GBS in the National Maternity Hospital (NMH) during the months of November and December 2017. The NMH is a tertiary level unit with more than 9000 births per annum; antenatal options range from community midwifery home birth service to full multidisciplinary care.

Prior to the introduction of PCR testing, IAP against EOGBS was offered to patients based on RCOG risk factors. In July 2017, rapid GBS testing was introduced with the intention to reduce unnecessary antibiotic exposure in term women with prolonged rupture of membranes > 18 h who were GBS-negative and did not have any other risk factors for EOGBS. Women with any other identified risk factors followed previous hospital protocol in keeping with RCOG guidelines [11].

A rectal and low vaginal PCR swab (COPAN Transystem) was obtained from term women at risk of prolonged rupture of membranes > 18 h, either following spontaneous rupture of membranes (SROM) or following artificial rupture of membranes (ARM), prior to the onset of labour. The recto/vaginal swab was sent to the laboratory and processed using the GeneXpert® PCR system according to manufacturer's instructions (Cepheid Europe SAS, Vira Solelh, 81470, Maurens-Scopont, France). All testing took place during routine laboratory hours (Monday to Friday 08.00–18.00, Saturday 09.00–13.00) and results were phoned to the antenatal ward. Unlike previous studies [19], no women declined to have swabs obtained once the purpose of testing was explained to them.

Data was obtained from the microbiology laboratory database and included information pertaining to the date and time the sample was taken, the date and time the sample was processed and the result of the test, i.e. positive, negative or invalid. Delivery reports for each woman were accessed through an internal patient database (PAS system). Patient demographics were included as follows: age; gestation; parity and method of membrane rupture (spontaneous or artificial); time of rupture of membranes; time of delivery; duration of ruptured membranes; antibiotic therapy received, i.e. intrapartum antibiotic prophylaxis; treatment for suspected infection or none; the indication for this, i.e. GBS-positive or a clinical indication; delivery method; and whether they underwent induction of labour. Each mother was matched to her infant and recorded whether the neonate underwent a septic work-up within the first 7 days of life and whether neonatal cultures or PCR obtained were positive for GBS.

The criteria for inclusion or exclusion for analysis is shown in Table 1. Analysis of data was carried out to investigate the clinical significance of the utilisation of the rapid GBS PCR test compared to the previous practice based specifically on duration of rupture of membranes [11]. Comparisons were made between the GBS-positive and GBS-negative cases based on parity, vaginal birth after caesarean section and method of delivery (spontaneous, instrumental or caesarean delivery) with a comparison also drawn regarding the rates of induction of labour and caesarean deliveries in the spontaneous rupture of membrane subgroup. The cases were analysed based on the duration of membrane rupture prior to delivery (< 18 h and > 18 h), and antibiotic administration and their indication (prophylactic or therapeutic). Finally, analysis was carried out regarding each infant born to mothers of the study, whether they had a neonatal septic screen and the results of this.

Ethical approval was not sought as this was an audit of a change management that had been introduced routinely in the hospital earlier that year. Nominal data was reported as frequencies and proportions. A 95% confidence interval (CI) is calculated where relevant, and a p value of < 0.05 is considered statistically significant. A core outcome set (COS) was

Table 1 Criteria for study inclusion

Included in analysis	Excluded from analysis
≥ 37 weeks of gestation	< 37 weeks of gestation
Ruptured membranes (SROM/ARM)	In labour prior to rupture of membranes
Not in labour	Pyrexia > 38 °C or symptoms and signs of chorioamnionitis or sepsis
No clinical suspicion of infection at time of swab	

not used in designing this study as a relevant COS did not exist at the time of design [20]; patients were not involved in the design of the study, but patient involvement and opinion are suggested for future studies.

Results

Of the 218 women who had PCR tests conducted during the study period, 16 were excluded as they did not fulfil the inclusion criteria. A further two women delivered by the time of the PCR test and were also excluded from analysis. Of the 200 women included, eight received repeat testing following initial invalid results. Five results remained invalid after repeat testing (2.5%) (Fig. 1).

The median age of the study participants was 33 years (range, 19–47 years), with a median gestation of 40 weeks (37–42 weeks). Table 2 provides the maternal characteristics of the participants. Fifty-one women had artificial rupture of membranes (ARM) and 149 women had spontaneous rupture of membranes (SROM). This latter group was used to compare the induction rates between women who tested GBS-positive and GBS-negative by PCR. Of the 23 women presenting with SROM who subsequently tested GBS-positive by PCR, 12 (52.2%) underwent induction of labour with oxytocin. The corresponding rate of induction among women presenting with SROM who tested GBS-negative was 52/122 (42.62%; $p = 0.4935$). Comparison of delivery methods between women found to be GBS-positive or GBS-negative following SROM revealed no significant differences in the rates of spontaneous vaginal delivery, instrumental delivery or caesarean section between the two groups (Table 3).

Of 200 women who had GBS PCR tests processed in the study period, all were performed at the time of confirmation of rupture of membranes. Of these, 77 (38.5%) delivered their baby within 18 h of rupture of membranes: 51 (66.23%) with SROM and 26 (33.77%) with ARM. Of the 77 women delivering within 18 h of ROM, 17 women tested GBS-positive, 58 were GBS-negative and two tests were invalid. Regarding the provision of antibiotics in this group, 60 received no antibiotics (prophylactic or therapeutic), 12 (15.58%) received IAP, all of whom tested GBS-positive, while five women received therapeutic antibiotic therapy as part of septic work-up in labour (Table 4).

One hundred and twenty-three women (61.5%) who underwent GBS PCR testing experienced prolonged rupture of membranes greater than 18 h duration before birth. Ninety-eight of these 123 women (79.7%) had SROM, while 25 (20.3%) had undergone ARM. In this group, there were 3 invalid results, 12 GBS-positive and 108 GBS-negative results. Under the previous protocol, every woman at term with prolonged rupture of membranes would have been offered IAP. Following GBS PCR testing, 86 (70%) received no antibiotics (prophylactic or therapeutic), 21 (17.1%) received IAP (11 women tested GBS-positive, 9 tested GBS-negative, and 1 returned invalid results), while 15 (12.2%) received

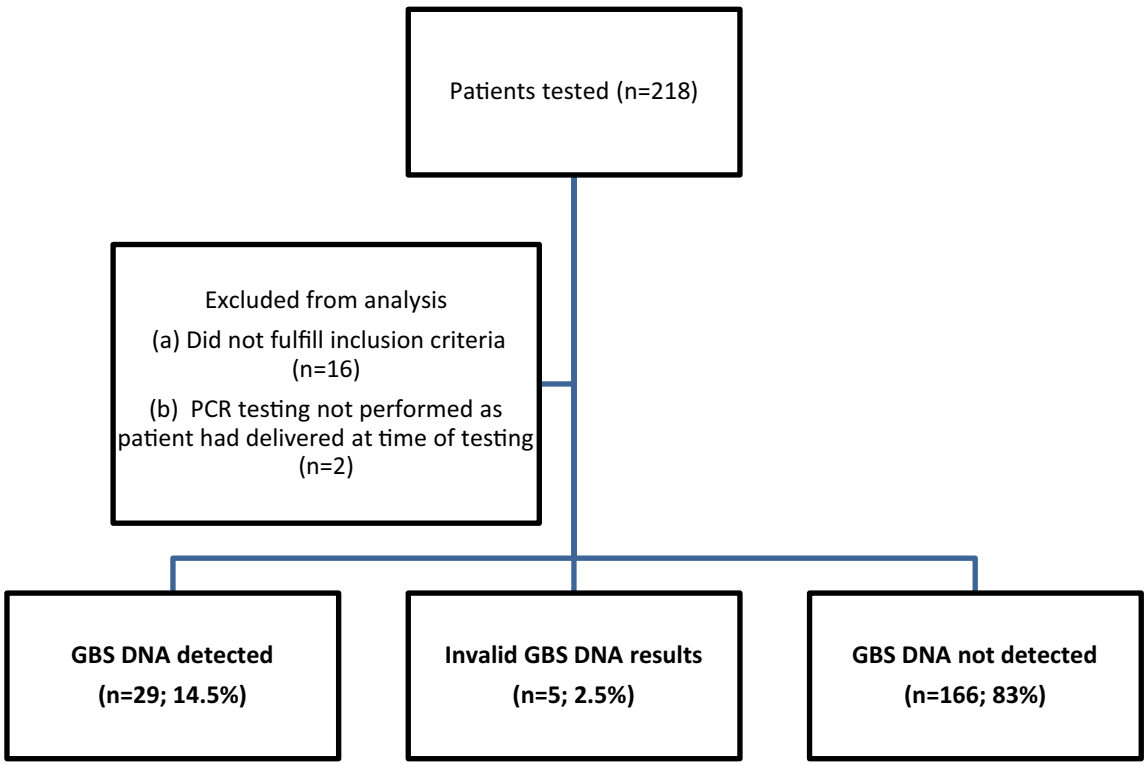

Fig. 1 Flow-sheet of testing by recto-vaginal swabs with results of group B *Streptococcus* (GBS) rapid testing. DNA, deoxyribonucleic acid; PCR, polymerase chain reaction

Table 2 Maternal demographics ($n = 200$)

Maternal characteristics	Number (Percentage)	GBS-positive	GBS-negative	Invalid result
Nulliparous women	138/200 (69%)	19/138 (13.7%)	117/138 (84.8%)	2/138 (1.5%)
Multiparous women (no previous caesarean)	53/200 (26.5%)	9/53 (17%)	42/53 (79.25%)	2/53 (3.75%)
Multiparous women (previous caesarean)	9/200 (4.5%)	1/9 (11.11%)	7/9 (77.78%)	1/9 (11.11%)
Spontaneous rupture of membranes	149/200 (74.5%)	23/149 (15.44%)	122/149 (81.88%)	4/149 (2.68%)
Artificial rupture of the membranes	51/200 (25.5%)	6/51 (11.76%)	44/51 (86.28%)	1/51 (1.96%)
Total	200 (100%)	29 (14.5%)	166 (83%)	5 (2.5%)

GBS group B *Streptococcus*

antibiotic therapy as part of septic work-up as management of pyrexia in labour. One further woman (0.81%) received initially prophylactic antibiotics and subsequently antibiotic treatment due to pyrexia in labour. The provision of IAP to nine women who tested GBS-negative may be explained by staff following the previous protocol, or undocumented clinical circumstances. With the use of GBS PCR screening, 12 women received IAP that previously would have not been indicated (ROM < 18 h) as they tested positive for GBS.

Of the 200 babies born to the study group, 45 (22.5%) underwent postnatal septic screens. Twenty (44.4%) of these 45 infants were born to mothers who had received treatment antibiotic therapy for pyrexia in labour. Six of these infants (6/45, 13.3%) were born to mothers who had tested positive for GBS in labour, and all six received IAP. Among the 155 infants who did not require septic work-ups, 23 (23/157, 14.6%) were born to GBS-positive mothers. No babies had positive blood cultures or developed EOGBS during the study period.

Discussion

In this study, PCR for GBS was positive in 14.5% of term women with pre-labour rupture of the membranes. This is consistent with rates reported in similar studies [15, 16, 18]. There was no difference in induction rate or mode of delivery between GBS-positive and GBS-negative groups. There was a clinically significant reduction in women exposed to IAP without any corresponding increase in neonatal investigations or infection.

Table 3 Comparison of delivery methods by group B *Streptococcus* (GBS) polymerase chain reaction (PCR) result in term women with spontaneous rupture of the membranes alone (excluding ARM for induction of labour; four invalid excluded from comparison; NS, not statistically significant)

Delivery method	GBS-positive ($n = 23$)	GBS-negative $n = 122$	p
Vaginal delivery	14/23 (60.9%)	71/122 (58.2%)	NS
Instrumental delivery	5/23 (21.7%)	29/122 (23.77%)	NS
Caesarean delivery	4/23 (17.4%)	22/122 (18.03%)	NS

The main strength of this study is the real-life applicability of the conclusions which can be drawn from the results, namely the significant decrease in inappropriate antimicrobial use without compromising neonatal outcomes. Previous studies have focused on sensitivity and specificity of the results [11, 17, 18], with clinicians blinded to the PCR results [19] and on the potential economic impacts associated with the introduction of rapid GBS PCR testing [21].

The limitations of the study are firstly the sample size and the timing (2 months); although there was no case of neonatal EOGBS infection detected, the study was not powered to analyse the use of rapid PCR test in the prevention of EOGBS disease. Furthermore, the samples were only able to be processed during routine laboratory hours. In the future, we aim to make the test available out-of-hours and thus only screen women who are close to 18 h ruptured membranes. In addition, this is a retrospective study with the limitations inherent to retrospective data collection.

Clinical implications of rapid GBS PCR testing include the sensitivity and specificity compared with enrichment culture, the impact on induction, mode of delivery, neonatal septic screen rate and infections. GBS PCR was validated in our laboratory and compared with 48-h enrichment culture. The sensitivity was 84%, specificity 99%, positive predictive value 94.4%, negative predictive value 96.4% and invalid rate 1.6%, which is similar to rates reported in the literature [17, 18]. Nevertheless, clinical staff must be particularly aware of false-negative PCR results and provide appropriate broad spectrum antibiotic therapy if there are clinical signs of infection in a mother or neonate. Attention was also paid to the potential impact of rapid testing on induction rates, with positive PCR results supporting the administration of IAP in conjunction with expedited induction of labour [13]. As elevated induction rates are associated in some studies with a secondary rise in interventions, such as instrumental and caesarean deliveries [22], it is prudent to assess and quantify any excess risk that PCR testing may possibly infer. The findings of the study reveal a statistically non-significant increase in the rates

Table 4 Characteristics by duration of ruptured membranes (RM) at delivery and antibiotic administration

	All women	ROM < 18 h	ROM > 18 h
Total	200	77 (38.5%)	123 (61.5%)
GBS-positive	29 (14.5%)	17 (22.08%)	12 (9.76%)
GBS-negative	166 (83%)	58 (75.32%)	108 (87.8%)
Invalid result	5 (2.5%)	2 (2.6%)	3 (2.44%)
SROM	149 (74.5%)	51 (66.23%)	98 (79.68%)
ARM	51 (25.5%)	26 (33.77%)	25 (20.32%)
Nulliparous	138 (69%)	50 (64.94%)	88 (71.55%)
Multiparous (Including VBAC)	62 (31%)	27 (35.06%)	35 (28.45%)
Multiparous undergoing VBAC only	9 (45%)	3 (3.9%)	6 (4.88%)
No antibiotics required	146 (73%)	60 (77.92%)	86 (69.92%)
Intrapartum antibiotic prophylaxis (IAP)	33 (16.5%)	12 (15.59%)	21 (17.07%)
Antibiotic treatment in labour for clinical signs of infection	20 (10%)	5 (6.49%)	15 (12.2%)
IAP + therapeutic antibiotics	1 (0.5%)	0	1 (0.81%)

$n = 200$ (all women who met inclusion criteria with processed GBS PCR test)

GBS, group B *Streptococcus*; *SROM*, spontaneous rupture of the membranes; *ARM*, artificial rupture of the membranes; *VBAC*, vaginal birth after caesarean section; *IAP*, intrapartum antibiotic prophylaxis

of induction among GBS-positive women presenting with SROM at term, in comparison to similarly described GBS-negative women (52.2% vs 42.6%), though the clinical impact on work of induction on the staff and the woman was not assessed. In keeping with the statistically non-significant difference in induction rates between GBS-positive and GBS-negative women in our study, rates of spontaneous vaginal delivery, instrumental delivery and caesarean section were similar between the two groups, suggesting that rapid testing for GBS status, in term women presenting with SROM, does not infer additional risk of intervention during labour.

The key objective was the assessment of prophylactic antibiotic provision among term women presenting with SROM or undergoing ARM who had GBS PCR testing during the study period. The impact of GBS PCR testing on the use of antibiotics to prevent EOGBS, from both a clinical and health economics perspective, has been described in several studies [11, 15–20]. These studies were mainly prospective, evaluating the accuracy of PCR testing compared to cultures, both in universal screening programs and at the time of labour and then assessing the potential impact from a clinical and financial perspective. While the percentage of unnecessarily treated women was significantly reduced using the rapid test when compared to conventional culture, the study group with conventional universal culture was tested between 34 and 38 weeks gestation. Following GBS PCR testing, we found a reduction in the administration of IAP among term women with prolonged rupture of membranes. With this reduction in antibiotic administration, there may have also been a reduction in the possible risks of IAP, including anaphylaxis, increased medicalisation of labour, effects on the foetus and the possibility of infection by antibiotic resistant organisms [11]. Some women in this study delivered < 18 h rupture of membranes ($n = 77$) and 17 of these women were GBS-positive and were offered IAP to prevent EOGBS. This cohort of women would not have received IAP based on risk factors alone. This was an unexpected benefit of the study as we had swabbed women at the time of pre-labour rupture of membranes and not at the time of 18-h rupture of membranes.

In attempting to assess the potential harms associated with reducing inappropriate IAP administration, neonatal outcomes were studied. GBS-negative mothers who received antibiotic therapy in labour due to maternal pyrexia or suspicion of infection were the most likely to have babies requiring early neonatal septic screens. There was no adverse neonatal outcome detected from the reduction in IAP, but there may be clinical benefit to the reduction in antibiotic exposure to the foetus, reduction in septic screens and the possible effects of antibiotic use on the foetal and neonatal microbiome [23].

Even without 24-h access to testing, there was a clinical difference in care with use of the test prior to onset of labour in a group that would be expected to labour within the next day or so. We aim to make this test available out-of-hours also. Future studies could include the impact of a 24-h service on clinical outcomes as well as a detailed cost benefit analysis. As patient involvement is crucial for medical research, a qualitative piece investigating women's opinion of the test would be valuable, especially in the context of refusal in previous studies [19, 20].

Conclusion

There was a clinically significant reduction in prophylactic antibiotic use for term women, with ruptured membranes > 18 h and no clinical suspicion of infection. No adverse effects

were detected although caution is advised as the study numbers were small.

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Author contribution All four authors meet all the criteria for authorship.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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