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Detection of Group B Streptococcus in pregnancy by vaginal volatile organic compound analysis: a prospective exploratory study

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Running Head: Detection of GBS in pregnancy by VOC analysis

Abbreviations

EOGBS - Early-onset group B Streptococcus

GC - Gas chromatograph

GC-IMS - Gas chromatograph ion mobility spectrometry

GCMS - Gas chromatograph mass spectrometer

GBS - Group B Streptococcus

IMS - Ion mobility spectrometry

VOC - Volatile organic compound

Abstract

Our objective was to assess whether volatile organic compound (VOC) analysis of vaginal swabs can detect maternal Group B Streptococcus during pregnancy in a prospective exploratory study. 243 women attending a high risk antenatal clinic at one university teaching hospital in the UK consented to take part and provide vaginal swabs throughout pregnancy. VOC analysis of vaginal swabs was undertaken and compared with the reference standard of GBS detected using enrichment culture method. The chemical components that emanated from the vaginal swabs were measured by gas chromatograph ion mobility spectrometry (GC-IMS). This platform has both high sensitivity and good specificity to a range of chemical compounds. Our main outcome was to determine the sensitivity and specificity of VOC analysis for the detection of maternal GBS in vaginal swabs during pregnancy. Our study has demonstrated that the sensitivity and specificity of the VOC analysis by GC–IMS for the detection of GBS from vaginal swabs was 0.81 (95% CI, 0.71-0.89) and 0.97 (95% CI, 0.91-1) respectively. We conclude that the use of VOCs as biomarkers for the detection of maternal GBS in the vagina is a novel tool. As this test produces results within minutes and is of low unit test cost it has the potential to be used in clinical settings, where fast diagnosis is important, for example, a patient in early labour.

Main research article

Introduction

Group B Streptococcus (GBS) is the most frequent cause of life-threatening early onset infection in newborn infants in the UK, known as early-onset group B Streptococcus (EOGBS) disease [1]. The incidence of EOGBS in the UK in 2015 was 0.57/1000 births [2]. GBS commonly colonises the gastrointestinal and genital tract of adults, with a global mean prevalence of 17%[3]. GBS only rarely causes disease in the immunocompromised adult, but it can pose a significant risk to newborn infants due to their immature immune systems.

The optimal screening strategy to prevent EOGBS is uncertain. Internationally there is a variation in guidelines, the 2019 ACOG recommends screening between 36+0-37+6 weeks gestation [4] but in the UK, universal screening is not currently recommended [5]. Maternal colonisation with GBS is the primary risk factor for disease (transmission to newborns is 40–70% and of these 1–2% will develop infection) [6, 7]. UK guidelines advocate offering intrapartum antibiotics to women found to be colonised during pregnancy and to those with other risk factors as this reduces the risk of culture positive EOGBS disease in the neonate [1, 8].

However, GBS colonisation status can be persistent but also intermittent and therefore transient during pregnancy. Up to 13% of women who are GBS positive in the before 37 weeks gestation receive unnecessary prophylatic antibiotics during labour [9, 10], which may contribute to increasing antibiotic resistance. The previous universal screening policy in the United States tested women between 35–37 weeks, studies of this had demonstrated that

among women who had a negative screening, 2–10% will become colonised before the onset of labour[10, 11].

The currently used diagnostic methods for colonisation with GBS utilise time-consuming enrichment culture methods (over 24 hours) [12] and therefore aren't appropriate for an intrapartum scenario. However, this method maximises GBS identification in cultures and is therefore the recommended technique in current guidance [4, 12]. Ideally, we would be able to screen for GBS colonisation at the start of labour so that only those women colonised in labour would be given antibiotics. Hence, there is a need to develop an accurate point of care test, which produces results within a few minutes, to reduce the burden of EOGBS disease.

An approach that could be applied to this medical need is to measure the volatile organic compounds (VOCs) that emanate from a vaginal sample. The concept of measuring VOCs for clinical applications is currently gaining momentum, with a broad range of biological materials and diseases being investigated. For example researchers have investigated diseases as diverse as colon cancer, pancreatic cancer, irritable bowel disease and respiratory tract infections in urine, stool, swabs and breath [13-16]. Such techniques hold considerable promise, as the test can be undertaken in a clinically relevant time period, the cost per test can be low and the instrument can be sited near or in the ward, thus ideal of point-of-care needs. The objective of this study was to determine the ability of VOC analysis to detect maternal GBS in vaginal swabs in pregnant women. Meeting this objective involved comparing GBS detected on vaginal swabs using the enrichment culture method to VOCs analysed by GC-IMS (gas chromatography ion mobility spectrometry).

Material and Methods

Study design

We conducted a prospective exploratory study at one UK hospital (University Hospitals Coventry & Warwickshire) serving a diverse population. The study protocol was approved by the NHS Research Ethics Committee West Midlands Birmingham South on 14th January 2014 (13/WM/0486) and all participants gave written informed consent. The Group B Strep Support charity were consulted prior to the application for funding regarding a patient perspective about the study. Research was carried out according to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Participants and test methods

From 25th January 2017, women between 14–36 weeks gestation were consented during their attendance to a high risk antenatal clinic for women at an increased risk of spontaneous preterm birth. A speculum examination was performed as per patient routine care. No specific hygiene advice was given. As part of routine screening in the preterm prevention clinic, a vaginal swab (reference standard) for microbiology culture and sensitivity testing using the enriched culture method was taken and placed into a non-nutritive transport medium, and concurrently two cotton swabs were used to obtain index test vaginal samples. The index test swabs were then placed in a universal containers and snap frozen in liquid nitrogen and stored at −80°C. Specimens were obtained by gently rotating the swabs across the mucosa of the vagina. Biomedical scientists independently interpreted the reference swab cultures. Demographic data including age at booking pregnancy, BMI, parity and ethnicity were collected about each woman (Table 1). Samples were taken in a consecutive

series from all women who consented in the clinic, some women consented to samples being taken during every attendance to the clinic.

Chemical analyser

Chemical vapour analysis of the index swabs was undertaken in the BioMedical Sensors Laboratory, School of Engineering, University of Warwick. Here a Gas Chromatograph-Ion Mobility Spectrometer (GC-IMS) was used. Our group have previously used this instrument on a range of medical conditions including respiratory tract infections, Coeliac's disease and irritable bowel disease [16-18]. This instrument was chosen over more traditional gas chromatograph mass spectrometer (GCMS) as the basic sensitivity of the instrument is much higher than GCMS, it can use nitrogen/air as the carrier gas (so no need for expensive carrier gases such as helium), has a lower purchase/test cost than GCMS and has a much smaller form factor, making it applicable for a ward setting.

The GC-IMS instrument used was manufactured by G.A.S. (GC-IMS is also the product name, Dortmund, Germany). In use the samples, in this case formed of a mixture of VOCs that emanate from the vaginal swab, are injected into the GC-IMS. These VOCs are preseparated by the gas chromatograph (GC) column, which takes the complex mix of chemicals and separates them based on their interaction with the long column coated with a rententive layer. Thus chemicals elude from the column at different times (known as the retention time). These pre-separated chemicals exit the GC and enter a drift tube ion mobility spectrometry (IMS) detector. Here the molecules are ionized using a radioactive source (in this case tritium) and then released into the drift tube in a controlled manner. The ions are then moved along the drift tube using an electric field. At the same time a buffer gas (nitrogen) is fed in the

opposite direction to the ions. The resultant impacts between the ions and the buffer gas reduce the velocity of the ions. Thus ions achieve different velocities due to its interaction with both the electric field and the buffer gas, which is inversely proportional to their size, mass and charge and then are collected on a Faraday plate, to provide a time-dependent signal corresponding with ion mobility. The device can measure substances in the low ppb range. The instrument was suitable for a clinical setting and was placed on a work surface (dimensions: 45 x 50 x 20 cm; mass: 20 kg).

Chemical testing and analysis

In total 607 samples from 243 women were tested using the G.A.S. GC-IMS system. Swabs were thawed and transferred to a 20ml glass vial in batches of 20. The vials were then sealed with a crimp top lid fitted with a PTFE septum. The index samples were then placed in a vial tray cooled and maintained at 4^{o}C to reduced unwanted odour emission and sample degradation, whilst other samples were being tested. Prior to the sample measurement, samples were heated to 40^{o}C for 10 minutes. The sample line for the GC-IMS was inserted into the septa of the vial using a needle and 2mls of sample were then extracted from the vial and injected into the analytical platform. The machine settings were as follows: E1: 150 ml/min (for the drift tube IMS), E2: 20 ml/min (for the GC column) and the pump at 25%. The total run time was 10 minutes. The temperatures were set to: T1: 45^{o}C, T2: 80^{o}C, and T3: 70^{o}C.

Statistical analysis

The data was analysed using the statistical pipeline successfully used in [16-18]. In summary, the GC-IMS data was first extracted using the L.A.V. software (v2.2.1, G.A.S, Germany), which

converts the data from its native file format to a text file. This was followed by a pre-processing step to reduce the dimentionality of the data, making the statistical analysis less computationaly intensive. A typical GC-IMS output file (of a single sample) contains typically 11 million data points. Though the number of data points is high, the information content is sparse, with the all of the values containing non-background information being located around the centre of the dataset. Thus, we are able to crop the central section of the data and then apply a threshold to make the background values all be zero. These values are selected by visual inspection of the data using the LAV software and results in around a 500 fold reduction in the number of non-zero data points. Once completed, the data was analysed using a 10-fold cross validation approach. In each fold, the data was split into a 90% training set and a 10% test set. Features with discriminary power were identified form the training set using a rank-sum test and 50 features with the lowest p-value were taken forward for classification. Here, five different classifiers we used, specifically sparse logistic regression, random forest, Gaussian process classifier, support vector machine and neural network (this set is commonly used within our pipeline). Once the training models had been created, they were applied to the same features in the test set. This process is repeated ten times until all the data has a test result. This process provided test probabilities for each sample and from this, statistical values, including sensitivity and specificity were calculated.

Results

Between January 2017 and August 2018, 243 women had vaginal swabs taken throughout pregnancy. The demographic data of these women shows the majority of women were white (79.0%) and two thirds were multiparous and one third nulliparous (Table 1). The maternal

GBS colonisation rates as defined by a positive enriched culture from vaginal swabs was 13.6% (corresponding to 33 women).

Figure 1 shows a typical output of the GC-IMS to a positive swab. The background is represented in blue with the non-blue areas showing that the instrument is detecting chemicals. The intensity of the peak (with red being the highest intensity) represents the amount of ions (and thus the chemical) detected. In general, each of the circular areas of higher intensity represent a different chemical. Furthermore, it can be see that the majority of the reponse is in the central section of the output. What was found is that the number of chemical peaks changed significantly across the cohort (independent of them being GBS positive or negative), which is likely to reflect vaginal biome, but were not investigated further in this study. The data from the G.A.S. GC-IMS was analysed as described and the statistical output is shown in Table 2. The high sensitivity and specificity indicates a strong signal is associated with GBS colonisation. The shape of the ROC curve illustrates the test has an excellent ability to discriminate between those with GBS from those without (Figure 2, Table 2) To help visualise these differences, we have also created a box plot of the probabilities generated by the classifier for each sample, as shown in figure 3. The line in the centre of the box plot is the median and the upper/lower boundaries are the 25^{th} and 75^{th} percentiles and error bars defining the 10^{th} and 90^{th} percentiles. Data points outside this region are individually plotted as outliers. The plot shows that there are significant differences in the probabilities of GBS and non-GBS samples.

Discussion

This is the first exploratory study to our knowledge to report the use of VOC analysis to detect GBS. In our prospective cohort study we investigated the potential of VOCs in the detection of GBS on vaginal swabs taken at the same time as samples for traditional GBS testing methods. The ultimate aim is to be able to implement this technology as a point of care test for women intrapartum, reducing the incidence of EOGBS disease by appropriate administration of antibiotic prophylaxis.

VOC profiles from vaginal swabs taken from pregnant women discriminated those whose swabs grow GBS from those who did not with a high sensitivity and specificity. Our results suggest that women who are colonised with GBS have chemically different vaginal swabs to those who are not colonised. The vagina has its own varied microbiome, but our data suggests that despite this, there are differences in VOCs from vaginal swabs in those who are colonised with enough GBS to be detected by the enriched culture method. These GBS associated differences in VOCs were demonstrated and are detectable with this novel technology. The VOCs detected are believed to be the gaseous waste products produced from the metabolic pathways of the bacteria in the vaginal, which occur as a result of the complex interactions in the vagina between, the vaginal and cervical epithelial cells, the vagina flora and invading pathogens. False positive tests could be driven by alterations in either the vaginal flora or the maternal host response. This study suggests that GBS produces a unique VOC fingerprint in pregnancy. A recent meta-analysis of the VOC literature found that VOCs could differentiate 11 other microbial pathogens in multiple disease states, but did not include the detection of GBS in pregnancy [19, 20].

Our results demonstrate that the G.A.S. GC-IMS instrument has a very high specificity and negative predictive value for the detection of GBS in vaginal swabs. This technology could now be developed as a bedside test for GBS colonisation. Previous studies have demonstrated high patient acceptability for intrapartum testing for GBS [21]. In the acute intrapartum scenario, women could have a swab taken and analysed in a hand held device in minutes. Where the results are positive, this could guide clinicians to prompt and appropriate administration of intrapartum antibiotics, reducing the risk of EOGBS. This would reduce residual GBS disease as it would allow us to treat the 10% women who may be negative at screening but convert to positive by the time of labour. The high negative predictive value of the test could be used to counsel families about the low likelihood of colonisation with GBS and bring into question whether administration of antibiotic prophylaxis is necessary, reducing unnecessary antibiotic exposure to both the mother and infant. Furthermore, a large number of women need to be tested for a screening program and the cost of this test is minimal.

Strengths of the study include the large number (n=607) of swabs analysed using the G.A.S. GC-IMS instrument and compared to the reference standard. We complied with the STARD statement and minimised bias as far as possible. However, there were a few limitations to our study. Our prevalence of colonisation with GBS is lower than expected at 13.6%, compared with the global average of 17.9% and European average 19.0% [3]. In the clinic women have a vaginal swab only (as part of their screening for risk of spontaneous preterm birth), this is not in keeping with recommendations for specimen collection for detection of colonisation of GBS. Swabbing both the lower vagina and rectum increases the culture yield when compared to sampling the vagina only [6, 22]. Previous studies sub-analysis has illustrated

that colonisation from low vaginal swabs only had a mean prevalence of 14.2%[3], this has more similarity to our cohort. In future studies we would aim to comply with the recommendations of a low vaginal and rectal swab to identify which women are colonised both for our reference and index test. Furthermore, we have not attempted to identify the specific biomarkers associated with GBS. This would require the use of a more sophisticated measurement platform (such as GCMS), which we were unable to undertake within this study.

The Centre for Disease Control and Prevention recommend that in order to be considered clinically useful in the intrapartum period, a point of care test should have sensitivity and specificity equal to or greater than 90% [6]. It is possible that optimising our sample collection (for both the index and reference test) as recommended may further increase our sensitivity to reach this threshold. Furthermore, due to logistical issues, samples were not analysed on site and therefore had to be frozen and then transferred for analysis at a later date. This may have caused degradation of the VOCs and influenced the fingerprints obtained as has been shown in previous studies[23].

At present an optimal screening strategy to prevent EOGBS has not been established, the high specificity and sensitivity obtained in this study suggest that with further work, it could be possible to implement this type of technology into a clinically useful screening pathway. It would allow the timely initiation of therapeutics by clinicians to prevent EOGBS and furthermore prevent women and their babies unnecessarily remaining in hospital for observation and/or antibiotic administration to the neonate when not indicated. This type of analysis and use of VOCS as biomarkers has huge potential in medical diagnostics, VOCs are thought to reflect complex changes in the vagina and therefore this technology has the

potential to be utilised in the assessment of a variety of diseases in obstetrics and gynaecology.

In conclusion, EOGBS disease remains the leading infectious cause of morbidity and mortality amongst neonates. Preventative efforts have reduced the burden of this disease over time but at present worldwide no universal screening tool or pathway can be agreed. This study has shown that the VOC signature present in vaginal swabs of pregnant women distinguished those swabs from which GBS was detected. Using the G.A.S. GC-IMS analytical platform with a sensitivity and specificity for GBS colonisation of 0.81 and 0.97 respectively. Development of this technology has the potential to provide clinically useful and cost-effective universal screening intrapartum for colonisation with GBS.

Disclosure of interests

None declared

Contribution of authorship

Conception: JC & SQ. Planning: LL, JC and SQ. Carrying out: LL, ED, AW, JC and SQ. Writing: LL, JC and SQ. Supervision: JC and SQ

Details of ethics approval

The study protocol was approved by the NHS Research Ethics Committee West Midlands Birmingham South on 14th January 2014 (13/WM/0486)

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Table/Figure caption list

Table 1: Demographic characteristics of the women taking part in the study, the booking BMI of six patients is not known.

Table 2: Statistical output from G.A.S. GC-IMS analytical platform using a sparse logistic regression classifier.

Figure 1: Typical output of the GC-IMS to a swab positive for GBS. The x axis represents the drift time of the IMS and the y axis the retention time of the same eluding out of the GC. The non-blue areas are chemical signals be detected by the instrument.

Figure 2: ROC output for G.A.S. GC-IMS instrument for women colonised with GBS in pregnancy versus those who are not colonised

Figure 3: The boxplot representing the distribution of level of probabilities of assigning VOC'S outputs, of patients with and without GBS using the classifiers described. The closer the probability is to 1, the more certainty the classification model has to define the sample group. The probability of assigning swabs to GBS positive or negative are clearly separated indicating high assurance of the classification model to classify the patient to the correct group.