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Examining the infectious aetiology and diagnostic criteria of maternal pyrexia in labour to improve antibiotic stewardship☆

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ABSTRACT

Objectives: To determine the infectious aetiology of peripartum maternal pyrexia and to assess the diagnostic accuracy of obstetric systemic inflammatory response syndrome criteria and cardiotocography as predictors of peripartum infection, in order to guide appropriate antibiotic management of mother and neonate.

Study Design: This study was carried out in a tertiary referral maternity hospital in Dublin, Ireland. A prospective cohort analysis was performed of 175 mother-newborn pairs with maternal pyrexia (≥38 °C) that developed after labour onset or within four hours postnatal. Infection was confirmed microbiologically in the case of sterile site infection, urinary tract infection (UTI) or growth of a significant perinatal pathogen from a placental swab. Infection was confirmed histologically by gross and microscopic examination of placentas in cases where there was growth of potentially pathogenic micro-organisms at a non-sterile site. Systemic inflammatory response syndrome criteria and cardiotocography in patients with confirmed infection versus those without evidence of infection were compared using independent samples t-test for continuous data and pearson chi-square test for nominal data. Diagnostic accuracy of obstetric systemic inflammatory response syndrome criteria (elevated maternal heart rate, elevated respiratory rate, decreased systolic blood pressure and elevated white cell count) for the identification of infection among women with peripartum pyrexia was determined using receiver operating characteristic curves.

Results: The infection rate was 17.1% (30/175). The rate was 22% (22/100) for pyrexia that occurred during labour and 10.7% (8/75) if it occurred within four hours after delivery. Obstetric systemic inflammatory response syndrome criteria and cardiotocography were not predictive of infection in women with peripartum pyrexia. No significant differences were observed in mean temperature, heart rate, respiratory rate, systolic blood pressure or white cell count between those with infections and those with no evidence of infection.

Conclusions: Peripartum pyrexia is predominantly of non-infectious origin. Improved diagnostic criteria are needed to identify infection for this indication. Early discontinuation of antibiotic treatment is appropriate in the majority of patients who develop term peripartum pyrexia after onset of labour.

Introduction

Maternal intrapartum pyrexia ≥38 °C has been associated with a risk of neonatal early-onset Group B Streptococcus (GBS) disease of 5.3 per 1000, compared to a background risk of 0.6 per 1000. [1] In an effort to avert these infections, guidelines in the US [2], UK [3], and Ireland [4] instruct healthcare providers to consider isolated maternal intrapartum fever of ≥38 °C as a sign of infective

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chorioamnionitis and an indication for antibiotic therapy. While maternal pyrexia during labour may be an indicator of chorioamnionitis, it is difficult to determine clinically owing to the range of other causes of pyrexia such as epidural use [5–7], direct physiological effects of labour, [8] dehydration [9], elevated ambient temperature [9], and use of misoprostol [10].

Diagnosing chorioamnionitis is an ongoing clinical challenge: signs and symptoms may be subtle and non-specific, while microbiological cultures and histology of the placenta are not available at the time of clinical suspicion. Hence, a clinical diagnosis of chorioamnionitis may be made when a combination (or even one) of the following are noted: maternal fever $\geq$38 °C, maternal tachycardia, fetal tachycardia, elevated white cell count, uterine tenderness, or purulent discharge from the cervical os. [4,9] In 2016, an expert panel of the National Institute of Child Health and Human Development (NICHD) contended that isolated maternal fever is not synonymous with chorioamnionitis. Furthermore, the panel argued that clinical use of the term chorioamnionitis is outdated as it implies presence of infection for what is in reality a heterogenous array of conditions characterized by infection or inflammation or both.[9]

Maternal intrapartum pyrexia leading to a clinical diagnosis of chorioamnionitis has significant implications for management of mothers and newborns, usually leading to intravenous antibiotic therapy and increased medical interventions. Since maternal intrapartum pyrexia is not always of infectious origin, treating all fevers with antibiotics results in overuse and may contribute to increased antimicrobial resistance. Furthermore, alterations in the neonatal microbiome caused by antibiotics have been linked to adverse effects later in childhood including obesity, diabetes and allergy. [11–13]

In Ireland, maternal temperature $\geq$38 °C forms part of the obstetric systemic inflammatory response (SIRS) criteria utilised to identify women at risk of sepsis, along with temperature <36 °C, maternal heart rate (HR) $\geq$100 bpm, fetal heart rate >160 bpm, respiratory rate (RR) $\geq$20/min, white cell count (WCC) >16.9 or $<4.0 \times 10^9$/L, bedside glucose >7.7 mmol/L (in the absence of diabetes) or acutely altered mental status. [14] The presence of two or more of these SIRS criteria triggers escalation to medical review frequently leading to a septic workup (SWU). However, maternal vital signs (VS) undergo changes during pregnancy and labour [8]. In 2016 the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) task force considered the use of two or more SIRS criteria to identify sepsis to be unhelpful, as their presence may reflect the host response to inflammation, infection or other insults [15]. These obstetric SIRS criteria are in need of validation as markers of acute clinical deterioration around the time of labour.

The aims of this study were:

1 To determine the infection rate related to peripartum maternal pyrexia.
2 To evaluate the diagnostic accuracy of the obstetric SIRS criteria and cardiotocography (CTG) for identification of infection related to peripartum maternal pyrexia.

Materials and Methods

Study population and setting

Research ethics approval was granted by the National Maternity Hospital (NMH) Dublin Ethics Committee in September 2015. The study was conducted in a tertiary referral centre in the Republic of Ireland that had an average of 9247 births per annum between 2007 and 2016. This study aimed to investigate the clinical profile of women with peripartum pyrexia, which was defined as pyrexia that developed anytime after onset of labour until four hours after delivery. Pyrexia that developed immediately after delivery was included as it is likely to relate to infection or inflammation that was evolving during labour. A convenience sample size (n = 198) was chosen whereby data was collected on all women with peripartum pyrexia who delivered in the NMH over a four month period. Patients were excluded if they had any evidence of infection at the time of labour onset. Preterm births were more likely to have symptoms of infection prior to labour and therefore many, but not all, were excluded. Hence, a cohort of 175 mother-newborn pairs who presented with peripartum maternal temperature $\geq$38 °C on at least 1 occasion was included for prospective analysis from November 2015 to February 2016 (Fig. 1). There were 3006 deliveries ($\geq$500 g) during the study period. The prevalence of peripartum pyrexia that met the inclusion criteria was 5.8% (175/3006).

Data Collection

Information on maternal demographics, labour and delivery outcomes, maternal VS, white cell count and CTG, were collected from patient medical records, shortly after delivery during the postnatal inpatient stage. The laboratory information system was accessed prospectively for maternal and neonatal microbiological results and placental histology reports. Maternal VS were recorded

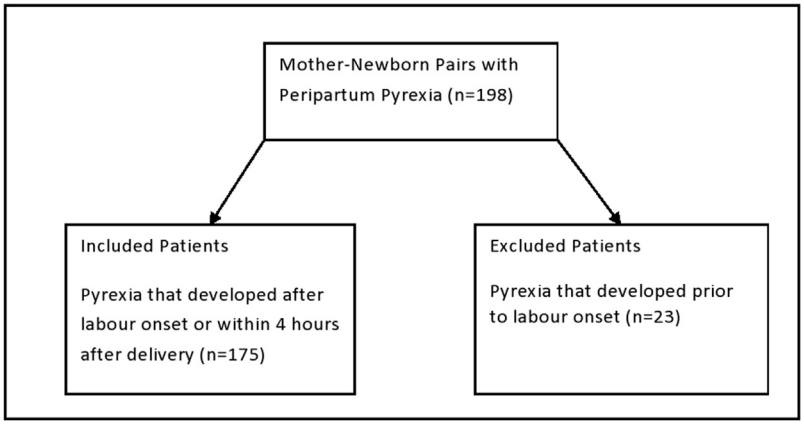

Fig. 1. Inclusion and Exclusion Criteria.

at maximum intervals of every two hours during labour and every four hours after delivery. Peripartum VS were selected at the same time that the highest temperature reading was observed. All VS recordings were performed by trained delivery ward staff.

Protocol for Determination of Infection Status

A SWU was obtained from women with fever ≥38 °C on at least one occasion. The maternal SWU included blood cultures, urine culture and vaginal swab. An incomplete SWU was defined as omission of one or more of the above tests. Placental swabs were taken where the obstetrician was suspicious of chorioamnionitis. Specimens from other sites were obtained if clinically indicated. A SWU was performed on all neonates born to mothers who had peripartum pyrexia. The standard neonatal SWU included a full blood count and blood culture. GBS polymerase chain reaction (PCR) on EDTA was performed if the neonatal blood culture was negative at 36 hours and the baby remained symptomatic with clinical evidence of early-onset sepsis. A lumbar puncture (LP) was performed in any baby with a clinical suspicion of meningitis, neurological findings associated with sepsis, a positive blood culture, a positive EDTA PCR, a maternal positive blood culture in labour, or failure to respond to treatment.

Cases were microbiologically categorised as "confirmed infection" if any of the following criteria were met:

- Sterile site infection in mother or neonate
- Maternal UTI defined as a pure or predominant growth of a single organism >100,000 organisms/ml
- A significant perinatal pathogen isolated from a placental swab i.e. pure or predominant growth of Group B *Streptococcus* (GBS), Group A *Streptococcus* (GAS), *Escherichia coli* (E.coli), *Listeria monocytogenes* or *Haemophilus influenzae.*

Mother-newborn pairs that had a full SWU were categorised as "no infection" in the absence of microbiological evidence of potential pathogens from any site.

Placentas were examined histologically if there was clinical chorioamnionitis, preterm birth <34 weeks gestation, preterm prelabour rupture of membranes or low APGAR score. Other placentas from women with PIL were examined only after consultant histopathologist review or clinical request. In non-sterile sites such as urine, vaginal, placental or rectal swabs, it was not always possible to distinguish between growth of potentially pathogenic micro-organisms and colonisation with normal microbiota; in addition, a small proportion of SWUs were incomplete. Examination of placentas was sought 47 times to determine infection status in these cases. All placentas were reported by placental pathologists who were blinded to microbiological results. Chorioamnionitis was reported using Society for Paediatric Pathology nomenclature. [16] Participants with no histological evidence of chorioamnionitis or subchorionitis were categorised as "no infection".

Statistical Analysis

Nominal data were reported as frequencies and proportions. Where appropriate, continuous demographic and labour outcome data were collapsed into clinically relevant nominal categories. Normally and non-normally distributed continuous data were reported as the mean ± standard deviation (SD) and the median ± interquartile range, respectively.

Study objectives were analysed as follows:

1 Infection outcomes were reported as frequencies and proportions.
2 SIRS criteria in patients with confirmed infection versus those without evidence of infection were compared using independent samples t-test for continuous data and pearson chi-square test for nominal data. Diagnostic accuracy of obstetric SIRS criteria as markers of infection related to peripartum pyrexia were evaluated using receiver operating characteristic (ROC) curves. Accuracy of SIRS criteria was reported as the area under the ROC curve (AUC), with the 95% confidence interval (CI) and significance level.

Statistical analysis was carried out using IBM SPSS Statistics version 22. A bonferroni correction was performed in order to reduce the risk of Type I error. Since twelve statistical tests were carried out on SIRS criteria and CTG as predictors of infection, a P-value threshold of <0.004 was chosen to claim statistical significance.

Results

Demographics

In this pyrexia cohort 79.4% (139/175) were nulliparous, and 99.4% (174/175) delivered at term (≥37 weeks gestation). The median duration of rupture of membranes (ROM) was 12.3 hours (IQR: 7.8 – 21.7), while 33.7% (59/175) of women had prolonged rupture of membranes greater than 18 hours. Pyrexia began during labour in 57.1% (100/175) of women and within four hours after delivery in 42.9% (75/175). There were no maternal admissions to critical care for infective reasons and there were no cases of maternal sepsis. APGAR scores were less than 7 at 1 minute in 9.1% (16/176) of neonates, and less than 7 at 5 minutes in 0.6% (1/176). A comparison of maternal demographics and delivery outcomes between those with confirmed infection and those with no evidence of infection are summarised in Table 1. The impact of antibiotic administration on neonatal management is summarised in Table 2.

Infection Outcomes

The infection rate for women with peripartum pyrexia was 17.1% (30/175). Subgroup analysis found that pyrexia in labour was associated with an infection rate of 22% (22/100) while pyrexia occurring within four hours after delivery was associated with a rate of 10.7% (8/75). Of the 175 women with pyrexia, 13.2% (23/175) had chorioamnionitis, the majority of which were diagnosed histologically (10.9%, 19/175) as opposed to microbiologically (2.3%, 4/175). The rate of chorioamnionitis was 16% (16/100) among women with intrapartum pyrexia and 9.3% (7/75) among women who developed pyrexia within four hours after delivery. Blood stream infection (BSI) occurred in 2.3% of the cohort (4/175). These consisted of 3 maternal blood stream infections and one neonatal infection identified by PCR in blood. UTIs occurred in 1.7% of women (3/175). A further 14.3% (25/175) had microbial colonisation at a non-sterile genito-urinary site but were not deemed to have chorioamnionitis histologically. There was no evidence of infection or colonisation in 68.6% (120/175) of the cohort (Fig. 2).

GBS was the most prevalent pathogen, accounting for 43.3% (13/30) of infections, the majority of which were chorioamnionitis. *E. coli* accounted for 16.7% (5/30) of infections, anaerobic bacteria 10% (3/30), *Enterococcus faecalis* 6.7% (2/30) and one each by Proteus mirabilis and Peptostreptococcus asaccharolyticus. No pathogen was isolated in 16.6% (5/30) of histologically confirmed infections.

Diagnostic Accuracy of Obstetric SIRS Criteria and CTG

Two or more obstetric SIRS criteria consisting of pyrexia ≥ 38 °C plus at least one of maternal heart rate ≥ 100bpm, respiratory rate

Table 1
Demographic Data, Labour and Delivery Outcomes in "Confirmed Infections" versus "Colonisation / No Infections".

	Confirmed Infections (*n* = Confirmed Infections (mean, SD) *(n = 30)*	Colonisation / Colonisation / No Infection (mean, SD) *(n = 145)*	Statistical Statistical Significance
Maternal Age (years)	31.5, 4.7	32.9, 4.2	0.49
Gestation at Delivery (weeks)	39.6, 1.7	39.6, 1.9	0.76
	Confirmed Infections *(n = 30)*	Colonisation / No Infection *(n = 145)*	Statistical Significance
Post-partum Haemorrhage (ml):			
Normal (<500)	21 (70%)	95 (65.5%)	0.38
Minor (500 – 1000)	8 (26.7%)	42 (29%)	
Major (1001 – 2000)	0 (0%)	7 (4.8%)	
Severe (> 2000)	1 (3.3%)	1 (0.7%)	
Sepsis (life-threatening organ dysfunction caused by a dysregulated host response to infection)	0 (0%)	0 (0%)	–
Spontaneous Vaginal Delivery	10 (33.3%)	57 (39.3%)	0.74
Instrumental Delivery	10 (33.3%)	49 (33.8%)	
Caesarean Section in Labour	10 (33.3%)	39 (26.9%)	
	Confirmed Infections Delivered by SVD or Instrumental *(n = 20)*	Colonisation / No Infection Delivered by SVD or Instrumental *(n = 106)*	Statistical Significance
Episiotomy	13 (65%)	68 (64.2%)	0.94
3rd / 4th Degree Tear	1 (5%)	2 (1.9%)	0.40
Manual Removal of Placenta	0 (0%)	3 (2.8%)	0.45
Neonatal Outcomes:	Neonates Born in Confirmed Infection Group *(n = 30)*	Neonates Born in Colonisation / No Infection Group *(n = 146)*	Statistical Significance
Live Births	30 (100%)	146 (100%)	–
Immediate NICU / SCBU admission	5 (16.7%)	20 (13.8%)	0.68

NOTE: all continuous data was normally distributed

Table 2
Impact of Antibiotic Administration on Neonatal Management

Neonatal Investigations performed	Number
Blood Cultures	175
PCR on EDTA	1
Lumbar Punctures	5
WCCs	170
	Mean (SD)
WCC[a]	19.2×10^9/L (5.2)

[a] data was normally distributed.

$\geq$ 20 breaths/min, or WCC > 16.9×10^9/L were observed in 70.9% (124/175) of mothers. The rate of infection in this group was 16.1% (20/124). No significant differences were observed in mean temperature, heart rate, respiratory rate, systolic blood pressure or WCC between the groups with "confirmed infection" and "no evidence of infection"(Table 3).

In the ROC curve analysis (Fig. 3), the 95% confidence intervals for all peripartum maternal pyrexia related clinical observations (HR, RR, SBP, WCC) included an AUC of 0.5 (Table 4), indicating that these variables have poor predictive value as markers of infection. A non-reassuring cardiotocograph (NRCTG) was associated with an infection rate of 18.2% (14/77); for normal CTGs the infection rate was 16.4% (16/98). For NRCTGs there was no significant difference between those with infections and those with no evidence of infection (Table 3).

Comment

Utilising a broad range of diagnostic information from SWUs and histological examination of placentas, we found a low rate of infection among mother-newborns pairs where maternal pyrexia

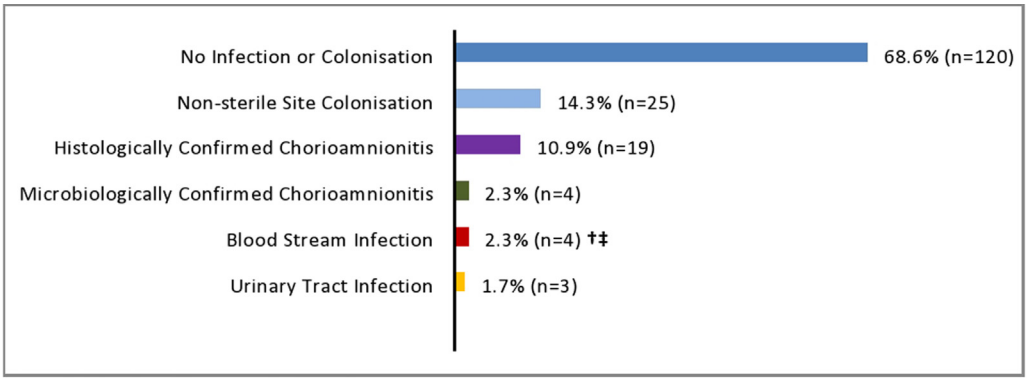

Fig. 2. Infection Outcomes in Pyrexia Cohort.
†One Maternal blood stream infection was associated with a UTI.
‡One Neonatal blood stream infection was associated with histologically confirmed chorioamnionitis.

Table 3
Comparison of SIRS criteria and CTG between "Confirmed Infections" versus "Colonisation / No Infection".

Maternal Vital Sign	Confirmed Infections (mean, SD)	Colonisation / No Infections (mean, SD)	Statistical Significance
Temperature (°C)	38.30, 0.24	38.30, 0.29	0.53
Heart Rate (bpm)	96, 15	93, 16	0.51
Respiratory Rate (breaths per min)	17, 1	17, 2	0.62
Systolic Blood Pressure (mmHg)	118, 13	123, 13	0.99
White Cell Count (WCC)	18, 5	18, 4	0.32
Maternal Vital Sign / CTG	Confirmed Infections (%) *n = 30*	Colonisation / No Infections (%) *n = 145*	Statistical Significance
WCC > 16.9 × 10 [9]/L	16 (53.3%)	86 (59.4%)	0.54
WCC < 4.0 × 10 [9]/L	0 (0%)	0 (0%)	–
Non-reassuring CTG	14 (46.7%)	63 (43.4%)	0.75

SIRS (systemic inflammatory response syndrome); CTG (cardiotocography); bpm (beats per minute); WCC (white cell count).
NOTE: all continuous data was normally distributed.

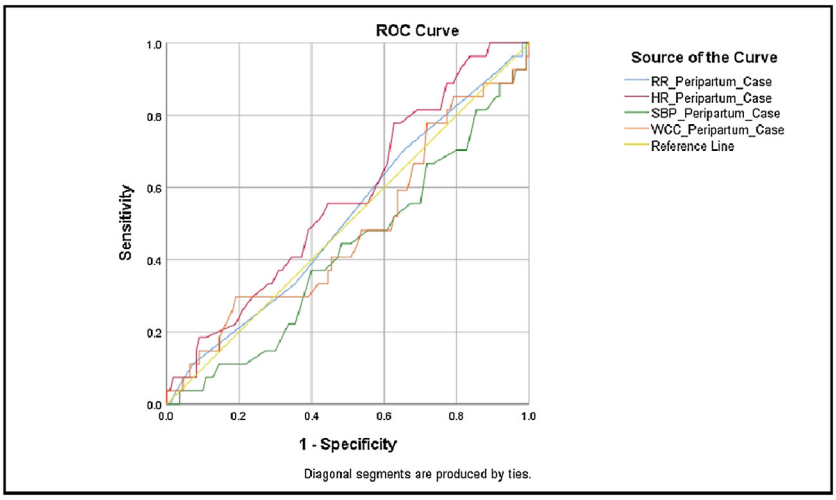

Fig. 3. ROC Curves for maternal RR,HR,SBP,and WCC as predictors of infection in cases with peripartum pyrexia.

Table 4
Receiver Operator Characteristic (ROC) Curve Analysis.

Area under the ROC Curve			
Peripartum Pyrexia Related Maternal Vital Sign	AUC	95% Confidence Interval	Statistical Significance
Elevated Heart Rate	0.542	0.43 to 0.65	*P* = 0.48
Elevated Respiratory Rate	0.515	0.40 to 0.63	*P* = 0.81
Decreased Systolic Blood Pressure	0.399	0.29 to 0.51	*P* = 0.09
Elevated White Cell Count	0.505	0.39 to 0.62	*P* = 0.93
Null hypothesis: true area = 0.5			

ROC (receiver operator characteristic curve).

≥ 38 °C on at least one occasion occurred after onset of labour or within four hours after delivery, at term gestation, with or without two or more obstetric SIRS criteria. Infection was more commonly diagnosed when pyrexia occurred during labour compared to pyrexia that occurred shortly after delivery. The most commonly identified infection was histologically confirmed chorioamnionitis (10.9%; 19/175). [16] Our findings call into question the view that peripartum maternal pyrexia, especially in the presence of two or more obstetric SIRS criteria, is a sign of infection.

The low rate of infection (17.1%; 30/175) associated with peripartum pyrexia confirms that aetiologies other than infection were the cause in the majority of cases. These findings support the assertion of the expert panel of the NICHD that maternal fever alone should not automatically lead to a diagnosis of infective chorioamnionitis. The panel propose to replace the use of the intrapartum term chorioamnionitis with the term "intrauterine inflammation or infection or both" or "Triple I". [9]

We found that the combination of two obstetric SIRS criteria consisting of temperature ≥38 °C plus any one of HR ≥100bpm, RR ≥ 20 breaths/minute, systolic blood pressure <100 mmHg, or WCC > 16.9×10^9/L were poor predictors of infection in women with peripartum pyrexia. At a time when doubts have been expressed about the diagnostic accuracy of SIRS criteria for the identification of sepsis [15], our findings highlight the inadequacy of the approach to escalate to medical review and SWU based solely on the presence of two or more obstetric SIRS criteria around

the time of labour. In addition, our findings suggest that CTG may not be useful in identifying infection related to peripartum pyrexia.

The neonatal "sepsis calculator" of Puopolo et al [17] can be used to guide decisions on whether or not antibiotics should be used in late preterm and term neonates born to mothers who had intrapartum pyrexia. In the UK, NICE provide guidance on the duration of such courses of antibiotics for neonates, suggesting discontinuation at 36 hours if the blood culture is negative [18]. No such tools or guidance exist to aid decision-making in the initiation or de-escalation of antibiotic therapy for women with intrapartum pyrexia. There is a need for future research to accurately identify infection in women during term labour, making use of biomarkers and prediction models similar to those utilised for neonates. This could greatly reduce exposure to antibiotics among women in labour and their newborns as well as reduce interventional delivery.

While there may be a low rate of infection among women with peripartum pyrexia at term, the presence of bloodstream infections in 2.3% (4/175) of mother-newborn pairs means that it may still be prudent to initiate SWUs in these patients, until such time as we can accurately diagnose infection at the time of peripartum pyrexia. However the findings of this study provide evidence to support the safe discontinuation of antibiotics in mothers with peripartum pyrexia $\geq 38\,^{\circ}C$ on at least one occasion, with or without two or more obstetric SIRS criteria, at term, without signs of infection prior to labour, provided the 48 hour blood culture is negative and the patient remains well in the postnatal period.

Disclosure of Interests

No conflicts of interest declared. No funding was sought for this study.

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