An evaluation into the use of procalcitonin levels as a biomarker of bacterial sepsis to aid the management of intrapartum pyrexia and chorioamnionitis

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BACKGROUND: Procalcitonin is an established biomarker for bacterial sepsis in the nonpregnant population with better diagnostic and prognostic value for bacterial infections.

OBJECTIVE: This study aimed to evaluate whether procalcitonin levels could be used in the diagnosis and management of intrapartum sepsis in women and their neonates suspected of intrapartum bacterial sepsis.

STUDY DESIGN: A prospective observational cohort study was conducted at the University Hospitals of Bristol and Weston NHS Foundation Trust. Overall, 117 women and their neonates managed for suspected intrapartum sepsis from June 2020 to October 2020 were included. Procalcitonin levels were measured in addition to routine biomarkers white cell count and C-reactive protein in women and their neonates during the initial septic screen and follow-up blood samples. The placentas underwent detailed histopathology. Maternal and neonatal parameters were used to categorize cases into “high-suspicion bacterial sepsis,” “equivocal bacterial sepsis,” and “low-suspicion bacterial sepsis.” The Kruskal-Wallis test was used to compare categories with biomarker values and placental histology scores.

RESULTS: Procalcitonin level was increased in 6 women in the initial septic screen sample, compared with 100 women with an increased C-reactive protein level. There was a significant difference in maternal postnatal procalcitonin results between “high-suspicion bacterial sepsis” and “low-suspicion bacterial sepsis” categories (P=.004). Moreover, 71.2% of placentas showed varying degrees of chorioamnionitis.

CONCLUSION: In our cohort of women, 94.6% had normal procalcitonin levels while in labor at the time of the septic screen, consistent with the low number of confirmed bacteremia. The result provided a basis that procalcitonin may complement clinical judgment and interpretation of already used prognostic and diagnostic tests, improving patient care in the management of intrapartum sepsis.

Key words: chorioamnionitis, intrapartum sepsis, procalcitonin, sepsis biomarkers

Introduction

Sepsis biomarkers have been the subject of several research studies, aiming to identify patients with bacterial sepsis (BS), differentiate sepsis from other noninfectious inflammatory pathologies, predict clinical severity, and guide antibiotic stewardship. The biomarkers predominantly used in the pregnant population include white cell count (WCC), C-reactive protein (CRP), and lactate, all known to be nonspecific for inflammation vs infection. Procalcitonin (PCT) is an established marker for sepsis in the nonpregnant population, with better diagnostic and prognostic value for bacterial infections. PCT, a precursor of calcitonin produced by C cells of the thyroid gland, is involved in maintaining calcium levels in the blood and released into the circulation in response to endotoxins and proinflammatory stimuli, specifically those originating from
bacteria. Levels are usually low in healthy people and people with viral infections, chronic inflammatory disorders, or autoimmune processes. PCT level increases significantly within the first hours in severe bacterial infections (latent period, 2–4 hours) and has a short half-life, helping guide and monitor response to antibiotic therapy.\(^3\),\(^4\) PCT used in diagnosing pregnancy-associated sepsis is relatively unexplored, and reference values for PCT in pregnancy have not been established.\(^5\),\(^6\)

Chorioamnionitis is reported to complicate 1% to 4% of births worldwide and is associated with significant maternal and perinatal adverse outcomes.\(^7\),\(^8\) Consequently, a low threshold to commence empirical broad-spectrum antibiotics in women developing intrapartum pyrexia is advised.\(^1\),\(^9\),\(^10\) The reported incidence of intrapartum pyrexia is high, ranging from 3% to 7%.\(^1\),\(^11\),\(^12\) The risk of neonatal sepsis in newborns delivered from mothers with intrapartum pyrexia is low at 0.24% (rate of <1 in 400 cases).\(^11\)

Diagnosing chorioamnionitis and managing intrapartum sepsis present unique diagnostic difficulties and are ongoing clinical challenges. Although intrapartum pyrexia may be an indicator of chorioamnionitis, most cases are secondary to noninfectious factors, including epidural analgesia, prolonged labor, increased ambient temperature, use of prostaglandins, and activation of the proinflammatory cascade during parturition.\(^1\),\(^12\) Furthermore, pregnancy causes physiological adaptations, which mimic those of early infection, including increased heart rate and reduced blood pressure. These challenges lead to overdiagnosis and treatment of sepsis in labor.\(^1\)

There is growing evidence suggesting that exposure to intrapartum antibiotics is associated with alterations in infant intestinal microbiome, influencing early immune development and increasing the risk of immunemediated diseases, such as asthma, allergy, and atopy.\(^13\),\(^14\)

This study aimed to evaluate whether PCT levels could be used in the diagnosis and management of intrapartum sepsis in women and their neonates suspected of intrapartum BS.\(^1\)

**Materials and Methods**

A prospective observational cohort study was conducted at St. Michael’s Hospital, University Hospitals of Bristol and Weston (UHBW) NHS Foundation Trust, Bristol, United Kingdom, averaging 5000 deliveries a year. The hospital research ethics committee approved the study protocol, and funding was provided by the department.

Over a 4-month period (June 2020 to October 2020), all women who developed intrapartum pyrexia and were started on the sepsis pathway, according to local and national guidance, were included in the study. The recommendations were for 1 temperature of >38°C on 1 occasion or >37.5°C on 2 consecutive occasions at least an hour apart to administer paracetamol. Blood cultures were performed and intravenous (IV) antibiotics were started in women with persistent pyrexia an hour after paracetamol administration.\(^9\),\(^10\) To determine the severity of infection and a possible source, these women routinely had samples taken for blood cultures, full blood count, urea and electrolytes, liver function, lactate, and CRP. PCT levels were added to this initial sample (denoted by the term “septic screen (SS)” blood sample) together with subsequent CRP samples (“postnatal (PN)” blood sample) to avoid additional sampling. The PCT results were concealed from clinicians to avoid influencing the management of intrapartum sepsis.

At the UHBW NHS Foundation Trust, all neonates born to women treated for intrapartum pyrexia routinely have blood collected for blood cultures, full blood count, and CRP and are started on IV antibiotics for at least 36 hours. Treatments are stopped according to repeat inflammatory marker results and clinical appearance. For this study, initial samples were also tested for PCT levels (“time 0” blood sample) together with subsequent CRP samples (“day 1” blood sample). The PCT results were concealed from the clinicians.

The PCT was measured with the Elecsys BRAHMS PCT assay, with a value of <0.25 ng/mL considered normal for patients not in the intensive care unit (ICU) and a cutoff value of <0.5 ng/mL considered normal for patients in the ICU.\(^15\),\(^16\)

Women treated for intrapartum pyrexia routinely have a urine sample, low vaginal swab (LVS), and throat swab sent for microbiology, and all women in this cohort were tested for COVID-19. The placenta were sent for histopathologic assessment and examined by a consultant perinatal pathologist who scored any inflammation present using published criteria.\(^17\) The staging and grading of chorioamnionitis were scored using the following criteria:
Correlations were performed between each biomarker value and placental score from initial and follow-up samples (0 = no correlation and 1 = complete correlation). The Kruskal-Wallis test was performed to correlate each clinical category with the individual biomarker values and placental histology scores. A P value of <.05 was considered significant.

Results
A total of 117 women along with their neonates were included in the study (7% of our delivered population in the study period). Table 1 A previous audit performed in the department demonstrated the rate of intrapartum pyrexia at 13.5%, and therefore, we estimated that we included approximately 53% of the cases. The exclusion criteria included incomplete data and factors that may skew sepsis biomarkers, gestational age of <37 weeks, women with immunocompromising conditions, and known chronic infection.

Blood cultures were performed in 98.3% of women, and all blood cultures were taken before the start of antibiotics. Of note, 2 blood cultures were positive with clinically significant organisms (1.7%). Moreover, 1 blood culture grew Proteus mirabilis, which correlated to an increased PN maternal PCT level of 2.6, but normal PCT level in the neonate. The other blood cultures grew GBS (as did microbiology for the LVS and placental swab), which correlated to an increased PCT level of 3.6 in the neonate.

Compared with an increased CRP level of ≥10 mg/L in 100 women (86%) and an increased WCC of >11 × 10⁹/L in 112 women (96%), an increased PCT level of ≥0.25 µg/L in “SS” blood samples was found in 6 women (5.4%). Compared with an increased CRP level of ≥10 mg/L in all women (100%; range, 13–304 mg/L), an increased PCT level in “PN” blood samples was found in 39 women (41.5%; range, 0.3–38.5 µg/L).

An increased PCT level of ≥0.25 µg/L was found in 47 neonates (55.3%; range, 0.3–4.6) in the “time 0” blood samples and 95 neonates (98.9%; range, 0.3–58.5 µg/L) in the “day 1” blood samples. Moreover, an increased CRP level of ≥20 mg/L was found in 7 neonates (5.98%; range, 10–58 mg/L) in the “time 0” blood samples and 41 neonates (35.04%; range 10–88 mg/L) in the “day 1” blood samples (Table 2).

Statistics
The correlations were performed to compare the values of maternal and neonatal biomarkers from initial and follow-up blood samples. When the CRP level was increased for the mother and neonate on initial sampling, it was likely to be increased on the second sample. Moreover, there was a positive correlation between both “time 0” and “day 1” PCT levels with the CRP results for the neonate, +0.509 and +0.409, respectively. There was a positive correlation between maternal “SS” PCT level and neonatal “time 0” PCT level (+0.305) and neonatal “day 1” PCT level (+0.404). This was a higher correlation compared with maternal “SS” CRP level and neonatal “time 0” CRP level (+0.098) or neonatal “day 1” CRP level (+0.141).

Table 3 shows the number of maternal and neonatal participants that were divided into the 3 determined categories. The spread of biomarker results for the maternal “SS” and “PN” blood samples according to the 3 categories are illustrated in Figure 1.

Figure 2 shows the mean PCT results for the 3 categories for both maternal and neonatal blood tests taken during their initial and follow-up blood samples. When performing the Kruskal-Wallis test among the categories, there was no significant difference in maternal “SS” PCT results among the 3 categories, which would be expected as the “SS” PCT levels were only increased in 6 women (PCT level of ≥0.25 µg/L). However, for the “PN” PCT results, there was a significant difference between the “high-suspicion BS” and “low-suspicion BS” categories (P = .004). For neonates, there was a significant difference between the “high-suspicion BS” and “low-suspicion BS” categories for both “time 0” (P = .0349) and “day 1” (P = .008) PCT results.
There was no significant difference between the CRP and WCC results in the 3 categories for maternal results and no significant difference between the CRP and WCC results in the 3 categories for neonatal results. However, there was a significant difference in CRP results between “high-suspicion BS” and “equivocal BS” for the neonatal “time 0” (P=0.022) and “day 1” (P=0.0002) CRP results.

A total of 80 women (68.3%) had completed placental histopathology and were scored a total of 24 for their grading and staging of chorioamnionitis. A high proportion of women (57 of 80 [71.2%]) showed varying degrees of chorioamnionitis (range, 5–18; mean score, 10.6). Figure 3 shows the placental histopathology scores for the 3 maternal categories. In the maternal categories, there was a significant difference between “high-suspicion BS” and both “equivocal BS” (P=0.02) and “low-suspicion BS” (P=0.00018). There was a weak correlation between maternal “PN” PCT level and placental score (+0.17) and neonatal “day 1” PCT level and placental score (+0.234).

Comment

Principal findings

We sought to analyze PCT levels in a cohort of women who presented with possible intrapartum sepsis. We hypothesized that a small number of women would have a proven bacteremia but that a proportion of women would display features highly suggestive of BS. We set out to determine if there was a relationship between PCT and BS. The results showed a significant difference in PCT results between the “low-suspicion BS” and “high-suspicion BS” categories for maternal and neonatal follow-up PCT results. In addition, there seems to be a linear correlation between maternal and neonatal PCT levels with maternal and neonatal clinical conditions (Figure 1). This suggests that PCT could be of diagnostic and prognostic values for bacterial infections in the management of intrapartum pyrexia.

Results: clinical implications

Clinical utilization of the host response, blood infection biomarker PCT has gained attention and has already been approved for the guidance of antimicrobial therapies and antimicrobial stewardship in patients with respiratory infection and sepsis. More recently,
it has been shown as an indicator of superimposed bacterial infection in COVID-19 and guided reduced antibiotic use in COVID-19. Clinical application in maternity and neonates is relatively unexplored and remains unvalidated.

All women had an SS PCT level of <0.25 ug/L except 6 women (5.4%). This result supported other studies, which showed that PCT as a biomarker is not influenced by pregnancy or labor. Our results showed that CRP and WCC were increased in a significant proportion of women in labor, in stark contrast to the small number of women with an increased PCT level (86%, 96%, and 5%, respectively). Although our numbers were small, this study suggested that PCT may identify BS in the obstetrical population with greater specificity. Moreover, PCT could be used as an antibiotic stewardship tool, aiding cessation of antibiotics in women with a low likelihood of infection and 2 negative serial PCT measurements.

**Results: research implications**

Here, the neonates had an increased PCT level of $\geq 0.25$ ug/L in 55.3% in “time 0” blood samples and 98.9% in “day 1” blood samples. However, an increased CRP level of $\geq 10$ mg/L was found in 5.98% in “time 0” blood samples and in 35.04% in “day 1” blood samples. This study supported recent evidence suggesting a physiological rise in PCT in a well neonate.

Blood cultures are used to diagnose bacteremia and identify pathogens, to provide information about the type of microorganism and antimicrobial susceptibility. Here, only 2 blood cultures (1.7%) were positive with clinically significant organisms. Furthermore, when looking at the total number of blood cultures received from our obstetrical population in 2020, of 723 blood cultures, only 13 (1.8%) were positive. The result supported the theories of low yield or low levels of bacteremia in this population.
Other studies have sought to address this issue with <10% of cultures showing growth of bacteria. Moreover, contamination limits their specificity, as was the case for 1 woman in this study. A study by Laukemann et al analyzed 1083 patients with suspected infection who had blood culture sampling on admission to the emergency department. Only 9.6% of patients had positive blood cultures, and PCT proved to be the most reliable predictor of blood culture positivity, being 8.5-fold higher in positive blood cultures. The study suggested a cutoff for their PCT assay level of <0.1 U/L to identify patients with a low risk of bacteremia; consequently, unnecessary blood culture sampling could be avoided in these patients.

Here, detailed placental histopathology found that most placentas (71.2%) have varying degrees of inflammation. Placental histopathology has long been the “gold standard” for the diagnosis of chorioamnionitis. Evidence is emerging that challenges the correlation between clinical chorioamnionitis and histologic chorioamnionitis. A study by Smulian et al focused on clinical chorioamnionitis and histologic placental inflammation in 139 pregnancies. They concluded that clinical chorioamnionitis and possible neonatal infection were not supported by histologic evidence of infection in 38.1% and 26.8% of cases, respectively, suggesting other noninflammatory causes of signs and symptoms. Another study by Roberts et al concluded that 96% of histologic chorioamnionitis cases occurred without infection, suggesting that there may be alternative causes among low-risk women at term.

Here, the presence of inflammation in a substantial proportion of the “low-suspicion BS” group could be supportive of the assertion that not all placental
inflammations are the result of an infection. An alternative, and perhaps more likely, explanation of the findings is that although inflammation in the placenta is caused by local infection, this may be limited to the placenta, cord, and membranes and does not always lead to significant infection in the mother or baby. When inflammation in both maternal and fetal aspects of the placenta was graded, there was a correlation between clinical condition and scores for placental inflammation, with mean scores of 5.5 for “low-suspicion BS,” 8.186 for “equivocal BS,” and 12.214 for “high-suspicion BS” (Figure 3). This suggests that the more severe the placental inflammation, the more likely it is to represent a clinically significant infection. However, the spread of the scores in each group limits the use of this scoring system in individual cases.

Strengths and limitations
This study analyzed PCT together with the routine SS investigations in both maternal and neonatal patients, thus reflecting a “real-world” clinical context. We collected a detailed dataset for each patient, ensuring accurate interrogation of each clinical episode.

We did not anticipate such a low number of increased PCT levels in this cohort of women, necessitating a larger cohort to adequately power a study investigating clinical outcomes with PCT levels. However, this finding was important, demonstrating that PCT does not seem to be altered by the physiology of labor, unlike other inflammatory markers in clinical use.

We chose to categorize our cases into “low-suspicion BS,” “equivocal BS,” and “high-suspicion BS.” This approach has been adopted in other studies.26 We were careful to include validated methods of categorization, such as “Sepsis in Obstetrics Score” and the “Kaiser” scoring for neonates.19,21 Moreover, we acknowledge that the routine investigation results formed part of this categorization and so any effect may have been artificially strengthened. However, as in the case of CRP, this would have led to an enhanced correlation, where if high

**TABLE 1**

**Maternal and neonatal demographics of results**

| Maternal demographics | n (%) |
|------------------------|-------|
| N                      | 117   |
| Multiparous            | 26 (17.7) |
| Primiparous            | 91 (82.3) |
| Mean age (y)           | 29.8  |
| Mean gestation (wk)    | 39.6/7 |
| Mean BMI (kg/m²)       | 26.1  |
| Maternal comorbidities |       |
| Preeclampsia           | 5     |
| Fatty liver disease, n | 1     |
| Gestational diabetes mellitus, n | 6 |
| Inflammatory bowel disease, n | 2 |
| Known vaginally colonized GBS, n | 7 |
| Risk factors for intrapartum pyrexia | |
| Epidurals              | 95 (81.2) |
| Fetal blood samples    | 11 (8.4) |
| Induction of labor     | 76 (64.9) |
| Mean time from ruptured membranes and delivery (h) | 23.8 |
| Augmentation of labor with oxytocin infusion, n/N (%) | 20/41 (48.8) |
| Location of delivery   |       |
| Obstetrical theater    | 58 (49.6) |
| Obstetrical-led delivery suite | 56 (47.8) |
| Midwifery-led unit     | 3 (2.6) |
| Mode of delivery       |       |
| Normal vaginal delivery| 26 (22.2) |
| Ventouse-assisted delivery | 10 (8.5) |
| Forcep-assisted delivery | 41 (35.1) |
| Emergency cesarean delivery | 40 (34.2) |
| Maternal intravenous antibiotic length of course | |
| 24 h                   | 88 (73.5) |
| 48 h                   | 25 (21.4) |
| 72 h                   | 6 (5.1) |
| Completed a 5- to 7-day course of oral antibiotics during discharge from the hospital | 117 (100) |
| Neonatal demographics  |       |
| N                      | 117   |
| Female                 | 62 (52.9) |
| Male                   | 55 (47.1) |
| Mean birthweight (g)   | 3458  |
| Other features         |       |
| Meconium               | 29 (24.8) |
| Fetal tachycardia before delivery | 47 (40.2) |
| Admission to the NICU  | 15 (12.8) |
| Neonates requiring assisted ventilation | 11 (9.4) |
| Average day of discharge (d), median (interquartile range) | 6.6 (2–13) |
| Neonatal intravenous antibiotic length of course | |
| 36 h                   | 46 (39.3) |
| 48 h                   | 29 (24.8) |
| 72 h                   | 10 (8.5) |
| 5 d                    | 29 (24.8) |
| 7 d                    | 3 (2.6) |

Data are presented as number (percentage), unless otherwise specified.
BMI, body mass index; GBS, group B Streptococcus; NICU, neonatal intensive care unit.
Walker. Procalcitonin levels in intrapartum pyrexia and suspected chorioamnionitis. Am J Obstet Gynecol Glob Rep 2022.
### TABLE 2

Total number of maternal and neonatal biomarker and microbiology samples performed and whether the biomarkers were increased or microbiology had positive culture growth

| Maternal septic screen blood sample Biomarker | n (%) | Number increased |
|---------------------------------------------|-------|------------------|
| WCC                                         | 115 (98.3) | 112 (96.0) |
| CRP                                         | 115 (98.3) | 100 (86.0) |
| PCT                                         | 111 (94.9) | 6 (5.4) |
| Lactate                                     | 103 (88.1) | — |

| Maternal postnatal blood sample Biomarker | n (%) | Number increased |
|------------------------------------------|-------|------------------|
| WCC                                      | 100 (85.5) | 90 (82.6) |
| CRP                                      | 98 (83.8) | 117 (100.0) |
| PCT                                      | 94 (80.4) | 39 (41.5) |

| Maternal microbiology results Microbiology sample | n (%) | Positive culture growth |
|-------------------------------------------------|-------|-------------------------|
| Bloods cultures                                 | 115 (98.3) | 2 (1.7) |
| Urine culture                                   | 107 (91.5) | 2 (1.9) |
| Low vaginal swabs                               | 100 (85.5) | 15 (15.0) |
| Throat swabs                                    | 86 (73.5) | 2 (2.3) |
| Placental swabs                                 | 21 (17.9) | 6 (28.6) |
| COVID-19                                        | 107 (91.5) | 2 (1.9) |

| Neonatal time 0 blood sample Biomarker | n (%) | Number increased |
|--------------------------------------|-------|------------------|
| WCC                                  | 108 (92.30) | 102 (94.40) |
| CRP                                  | 117 (100.00) | 7 (5.98) |
| PCT                                  | 85 (72.70) | 47 (55.40) |

| Neonatal day 1 blood sample Biomarker | n (%) | Number increased |
|--------------------------------------|-------|------------------|
| CRP                                  | 117 (100.0) | 41 (35.04) |
| PCT                                  | 96 (82.1) | 95 (86.0) |

| Neonatal microbiology results Microbiology sample | n (%) | Positive culture growth |
|-------------------------------------------------|-------|-------------------------|
| Blood cultures                                  | 117 (100.0) | 0 (0) |
| Lumbar puncture CSF                             | 26 (22.2) | 0 (0) |

Data are presented as number (percentage), unless otherwise specified. Increase PCT level $\geq 0.25 \mu g/L$; increased CRP level $\geq 10 \text{ mg/L}$; and increased WCC $> 11 \times 10^9/\text{L}$.

CRP, C-reactive protein; CSF, cerebrospinal fluid; PCT, procalcitonin; WCC, white cell count.

Walker. Procalcitonin levels in intrapartum pyrexia and suspected chorioamnionitis. Am J Obstet Gynecol Glob Rep 2022.

### TABLE 3

The number of maternal and neonatal participants (N=117) in the 3 determined categories for “low-suspicion BS,” “equivocal BS,” and “high-suspicion BS”

| Categorization Variable | Low-suspicion BS | Equivocal BS | High-suspicion BS |
|-------------------------|------------------|--------------|------------------|
| Maternal                | 37 (32)          | 63 (54)      | 17 (15)          |
| Neonatal                | 20 (17)          | 55 (47)      | 42 (36)          |

Data are presented as number (percentage), unless otherwise specified.

BS, bacterial sepsis.

Walker. Procalcitonin levels in intrapartum pyrexia and suspected chorioamnionitis. Am J Obstet Gynecol Glob Rep 2022.
CRP was used to denote “high-suspicion BS,” one would anticipate a higher correlation coefficient for CRP.

Conclusion
In a cohort of women managed for intrapartum sepsis during labor, 94.6% had normal PCT levels at the time of the SS, compared with the normal adult population, supporting the evidence that PCT as a biomarker is not influenced by pregnancy or labor. Moreover, 58.5% of women had normal serial PCT levels, consistent with the low number of confirmed bacteremia in this population. The result provided a basis that PCT may complement clinical judgment and interpretation of already used prognostic and diagnostic tests, improving patient care in the management of intrapartum sepsis. Serial PCT measurements may be useful in antibiotic stewardship, predicting the prognosis, monitoring patients, and tailoring therapy to the individual needs of the patients.

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