Intrapartum Fever at Term: Diagnostic Markers to Individualize the Risk of Fetal Infection: A Review

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and Gerard H. A. Visser, MD, PhD‡

Intrauterine infection is a serious complication during labor at term and is associated with adverse neonatal outcome. Early and accurate diagnosis is of great concern for both obstetrician and pediatrician with the use of current diagnostics. Clinical symptoms are often regarded as the main sign of intrauterine infection but this approach is highly unreliable and leads to both under- and overtreatment. Currently, no distinct fetal heart rate (FHR) patterns have been found that reliably identify neonates with intrauterine infection. Using a systematic literature search, this article reviews possible markers for the early detection of intrauterine or neonatal infection in maternal serum, amniotic fluid, and umbilical cord blood during labor at term. Maternal serum markers, with the possible exception of interleukin (IL)-8, are unreliable for the detection of intrauterine infection. In contrast, amniotic fluid levels of especially IL-6 and IL-8 are significantly associated with intrauterine infection. Umbilical cord blood IL-6 has been extensively investigated and is usually elevated in case of intrauterine or neonatal infection but shows only modest positive and negative predictive values (NPVs) for clinical use. Umbilical cord IL-8 concentration could be a valuable addition in the diagnostic process, as it has shown to have an NPV of 84% to 92% in the detection of neonatal infection and histological chorioamnionitis. Future research is essential and should focus on the combination of different markers and on the development of a prediction model, to improve the positive and NPVs of our arsenal to detect intrauterine and neonatal infections. Amniotic fluid and umbilical cord values of IL-6 and IL-8 levels are likely candidates for such a prediction model.

Target Audience: Obstetricians & Gynecologists and Family Physicians

Learning Objectives: After the completing the CME activity, physicians should be better able to evaluate the use of clinical chorioamnionitis with regard to histological evidence and as a diagnostic tool in early diagnosis of intra-amniotic infection. Asses the use of amniotic fluid IL-6 and IL-8 as diagnostic tools to detect early intra-amniotic infection and assess umbilical cord blood IL-8 in case of intrauterine- or neonatal infection using positive (PPV) and negative predictive values (NPV).
Maternal intrapartum fever is a frequent complication during labor at term and its association with adverse clinical neonatal outcome remains of great concern for pediatricians and obstetricians. Intrapartum fever, defined as a rectal body temperature of more than 38°C, occurs in up to 14.5% of term births\(^1\)\(^,\)\(^2\)\(^,\)\(^3\)\(^,\)\(^4\) and is considered a key sign of intrauterine infection.\(^4\) Although intrauterine infection is a common cause,\(^5\) there are many other explanations for intrapartum fever, such as epidural analgesia, an overheated delivery room, and dehydration.\(^2\)\(^,\)\(^6\)\(^,\)\(^7\) The use of epidural analgesia commonly increases maternal body temperature\(^2\)\(^,\)\(^3\)\(^,\)\(^6\)\(^-\)\(^9\)\(^,\)\(^10\)\(^,\)\(^11\) and therefore maternal fever during term labor is often attributed to epidural use. However, the underlying cause of this higher incidence of intrapartum fever remains controversial.\(^12\)\(^,\)\(^13\)\(^,\)\(^14\) Regardless of the etiology, there are far going implications of intrapartum fever for the fetus, and a rise of maternal core temperature may lead to an adverse neonatal outcome even in the absence of infection.\(^1\)\(^,\)\(^15\)\(^-\)\(^21\) Intrauterine infection is an important risk factor for neonatal sepsis, meningitis, pneumonia, increased mortality,\(^21\)\(^-\)\(^23\) and may have long-term consequences such as cerebral palsy.\(^25\) Early diagnosis is therefore crucial. However, previous studies have shown that clinically diagnosed chorioamnionitis is not supported by histological evidence in up to 38% of cases.\(^26\) This underlines the great difficulties of diagnosing intraamniotic infection accurately during labor.\(^5\) To minimize severe complications, in case of possible intrauterine infection, antibiotic prophylaxis together with sepsis evaluation is now done routinely.\(^2\)\(^,\)\(^27\) Yet, although early and easy accessible intervention is required it may lead to high numbers of neonates treated or evaluated unnecessarily. Lieberman et al. highlighted this by showing that out of 416 neonates evaluated for sepsis only 4 eventually proved to have sepsis.\(^2\) To prevent both over- and under-treatment, early diagnosis of infection in case of intrapartum fever is, therefore, required.

Currently, the definitive diagnosis of histological chorioamnionitis can only be made after delivery and markers that could identify neonates at risk for complications are needed. Early onset sepsis starts in utero\(^28\) and current research is focused on early detection through maternal serum, amniotic fluid, or umbilical cord blood. Cytokines such as interleukin (IL)-1\(\beta\), IL-6, IL-8, tumor necrosis factor (TNF)-\(\alpha\), and sICAM-1, important in the response against infection, have been found elevated in neonatal serum in early onset sepsis\(^28\)\(^-\)\(^32\) and are therefore possible candidate markers for early detection of infection through screening. This review aims to give an overview of diagnostic markers to individualize the risk of fetal infection, in case of intrapartum risk factors for intrauterine infection at term.

### METHODS

Our search included a computerized English language literature search of Medline (1970–2010), the Cochrane library and a manual search of references and related articles. The following key words were used: (intrapartum OR labor OR labor OR delivery OR parturition OR maternal serum OR amniotic fluid OR cord blood OR cord plasma OR umbilical plasma OR umbilical blood) AND (cytokines OR markers OR marker chemokines OR inflammatory mediators OR IL-1\(\beta\) OR interleukin-1\(\beta\) OR interleukin-1 OR IL-6 OR interleukin-6 OR IL-8 OR Interleukin-8 OR TNF OR tumor necrosis factor OR TNF\(\alpha\) OR WBC OR white blood cell count OR CRP OR c-reactive protein) AND (chorioamnionitis OR funisitis OR amniotic infection OR intra uterine infection OR microbial invasion OR fetal inflammatory response syndrome OR perinatal infection OR perinatal complications OR fetal inflammation OR neonatal sepsis OR early onset sepsis).

Approximately 300 articles were found, after filtering doubles, 2 authors (A.E., L.N.) separately screened titles and abstracts of all selected studies to manually identify the articles investigating markers in maternal serum, amniotic fluid, or umbilical cord blood, to detect intrauterine or neonatal infection in term labor. Authors used inclusion criteria shown in Table 1. The full text of the remaining articles was retrieved. Articles with main focus on preterm labor or when gestational age could not be excluded as a confounding factor were not selected. In vitro or animal studies were not reviewed. Finally, 26 articles were selected.

### TABLE 1

<table>
<thead>
<tr>
<th>Category</th>
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<tr>
<td><strong>Diagnosis</strong></td>
<td><strong>Markers to individualize the risk of fetal infection</strong></td>
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<tr>
<td>Study population</td>
<td>Pregnant women in labor with risk factors for chorioamnionitis</td>
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<tr>
<td>Diagnostic markers</td>
<td>Gestational age 37 weeks or more</td>
</tr>
<tr>
<td>Duration of pregnancy</td>
<td>Markers in maternal serum, amniotic fluid or umbilical cord blood</td>
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<tr>
<td>Outcomes</td>
<td>Intrauterine (intra-amniotic) infection, neonatal infection, histological chorioamnionitis</td>
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<tr>
<td>Time period</td>
<td>1970 to 2010</td>
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<tr>
<td>Publication language</td>
<td>English</td>
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RESULTS

Clinical Signs

Signs of intra-amniotic infection like maternal fever, maternal tachycardia, uterine tenderness, foul-smelling amniotic fluid, and fetal tachycardia all contribute to the diagnosis of clinical chorioamnionitis and therefore cause great concern during labor. However, the diagnosis is highly susceptible to subjectivity26,33 and poorly supported by histological evidence.26 Furthermore, use of epidural and physical stress could interfere with maternal symptoms. Therefore, it was not surprising that none of these clinical signs alone were significantly associated with histological chorioamnionitis.26 However, clinical chorioamnionitis remains an important warning signal and should lead to further investigation to rule out intra-amniotic infection.26

Fetal Monitoring

Fetal heart rate (FHR) monitoring with cardiotocography (CTG) is routinely used in case of high-risk pregnancies and essential in the detection of fetal stress and hypoxia. However, the value of CTG in the diagnosis of chorioamnionitis during labor at term is relatively unknown. A recent study on the relationship between histologic chorioamnionitis and FHR pattern measured by CTG has shown that there were no specific FHR patterns, like deceleration pattern and baseline variability, correlated to chorioamnionitis.34 These results are in agreement with 2 other studies were the relation between FHR patterns and intrauterine bacterial infection and/or neonatal sepsis was evaluated.35,36 However, in these studies, fetal tachycardia was present in 16% to 38% of cases of neonatal infection.34-37

Although there were no specific FHR patterns in case of intrauterine infection, the incidence of FHR abnormality was increased in one study.35 This in contrast with 2 smaller studies, in which the FHR pattern was normal in most cases of neonatal infection or histological chorioamnionitis.34,36

A relatively new method for continuous fetal monitoring is the STAN methodology in which classification of the FHR pattern is combined with ST analysis of the fetal electrocardiogram. Currently, little is known about the fetal electrocardiogram response to infection. In a consensus meeting of European experts on ST-analysis for fetal surveillance, it was concluded that in presence of maternal fever, ST-events even in combination with intermediary FHR changes should be regarded as indicative of fetal distress.38

Markers for Fetal Outcome

Tables 2 and 3 show an overview of IL-6 and IL-8 as a marker of infection in maternal serum (A), amniotic fluid (B), and umbilical cord blood (C), respectively.

Maternal Serum

A conventional marker commonly used in practice to detect infection is C-reactive protein (CRP). However, many studies have doubted the value of CRP in diagnosing intrauterine infection.39-41 Reason for doubt could be the low specificity of CRP, the fluctuating values at different gestational ages, and the correlation with duration of labor.39-41

In preterm neonates, maternal serum IL-6 concentration has shown to be a sensitive and specific marker for chorioamnionitis.42 In line with this, Smulian et al have shown that histologic chorioamnionitis is associated with higher maternal IL-6 levels in term pregnancies43 (Table 2 [A]). These data also demonstrated that IL-6 is associated with maternal temperature.43 The process of labor itself has been associated with a rise in maternal IL-6 levels.44 The correlation between IL-6 and histologic chorioamnionitis is weaker.43 Furthermore, several studies have pointed out that maternal IL-6 levels are a poor reflection of umbilical cord or neonatal serum IL-6.40,45-47 Other studies found no relationship between maternal IL-6 and chorioamnionitis or neonatal infection39,40 (Table 2 [A]). These results indicate that maternal IL-6 is a nonspecific marker of intrapartum fever and should not be used to screen for intrauterine infection. For maternal serum IL-8 levels, the relationship with intrauterine infection may be different because one study showed that IL-8 levels were only associated with chorioamnionitis, not with the process of labor40 (Table 3 [A]). The significant association with chorioamnionitis40 makes maternal IL-8 a promising marker for the early detection of intra-amniotic infection. When compared with other maternal markers, such as white blood cell count (WBC), CRP, IL-1α, IL-1β, TNF-α, and IL-6, IL-8 had the highest sensitivity and specificity for detection of intrauterine infection.40 In contrast with these finding, Berner et al showed TNF-α and CRP levels to be higher in mothers with septic infants, but not G-CSF, IL-1β, IL-6, IL-8, and sICAM-139 (Table 2 [A]). WBC and leukocyte es-
<table>
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<tr>
<th>First Author (Reference)</th>
<th>Study Size</th>
<th>Study Population</th>
<th>Marker of Intrapartum Fever</th>
<th>Marker of Clinical Chorioamnionitis</th>
<th>Marker of Histopathological Chorioamnionitis</th>
<th>Marker of MIAC/Intra-Amniotic Microbial Infection</th>
<th>Marker of Neonatal Infection</th>
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<tr>
<td><strong>A. In maternal serum</strong></td>
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<tr>
<td>Berner et al³⁹</td>
<td>171 neonates</td>
<td>1. Neonates with sepsis 2. Neonates with suspected but not confirmed sepsis 3. Healthy neonates</td>
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<tr>
<td>Shimoya et al⁴⁰</td>
<td>22 cases, 81 controls</td>
<td>Term labor, + or – histopathological chorioamnionitis</td>
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<tr>
<td>Smulian et al⁴¹</td>
<td>47 cases, 47 controls</td>
<td>Women with intrapartum fever at term</td>
<td>+ +</td>
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<td><strong>B. In amniotic fluid</strong></td>
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<tr>
<td>Roos et al⁵⁸</td>
<td>33 women</td>
<td>Women undergoing CS at term</td>
<td></td>
<td></td>
<td>+</td>
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<tr>
<td>Gomez et al⁶⁰</td>
<td>148 women</td>
<td>Women at term with spontaneous labor or PROM</td>
<td>+ +</td>
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<td><strong>C. In umbilical cord blood</strong></td>
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<tr>
<td>Berner et al³⁹</td>
<td>136 cases</td>
<td>As described in Table 1A</td>
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<tr>
<td>Shimoya et al⁴⁰</td>
<td>103 neonates</td>
<td>As described in Table 1A</td>
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<tr>
<td>Smulian et al⁴¹</td>
<td>47 cases, 47 controls</td>
<td>As described in Table 1A</td>
<td>+</td>
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<tr>
<th>First Author (Reference)</th>
<th>Study Size</th>
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<th>Marker of Intrapartum Fever</th>
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<th>Marker of Histopathological Chorioamnionitis</th>
<th>Marker of MIAC/Intra-Amniotic Microbial Infection</th>
<th>Marker of Neonatal Infection</th>
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</thead>
</table>
| Singh et al72           | 32 neonates| 1. Elective CS  
2. Spontaneous labor  
3. PROM  
4. Labor with chorioamnionitis | + (IL-6) - (IL-6 mRNA) | + | | | |
| Santana et al73         | 256 neonates| 1. Neonates with sepsis  
2. Neonates with non infectious pathology  
3. Healthy neonates | | | | | + |
| Dollner et al74         | 184 neonates| 1. Neonates with sepsis  
2. Neonates with non infectious pathology  
3. Healthy neonates | | | | | + |
| Shalak et al75          | 61 neonates| Mature and premature neonates who were exposed to clinical chorioamnionitis and admitted to the NICU | | | | | + |
| Chaiworapongsa76        | 36 cases, 111 controls | Neonates of mothers with clinical chorioamnionitis | | | | | + |
| Dollner et al77         | 221 neonates| 1. Uncomplicated delivery  
2. Delivery complicated by PROM, clinical signs of infection or preterm labor | | | + (Only in severe not mild) | | |
| Perenyi et al78         | 22 neonates| Neonates admitted to NICU with clinical signs of sepsis or with risk factors for sepsis | | | + | | |
| Weimann et al79         | 87 neonates| 1. Neonates with sepsis  
2. Neonates with perinatal stress  
3. Healthy neonates | | | | | + |

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TABLE 2
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<tr>
<th>First Author (Reference)</th>
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<th>Study Population</th>
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<th>Marker of Histopathological Chorioamnionitis</th>
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<th>Marker of Neonatal Infection</th>
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<tbody>
<tr>
<td>Berner et al(^8^3)</td>
<td>99 neonates</td>
<td>1. Neonates with suspected sepsis 2. Premature infants 3. Control group</td>
<td>+ (IL-6-mRNA)</td>
<td>Sensitivity: 56%</td>
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<tr>
<td>Tasci et al(^6^8)</td>
<td>40 cases, 30 controls</td>
<td>PROM at term</td>
<td>+</td>
<td>Il-6 &gt; 39 pg/mL  Sensitivity: 100%, PPV 36.9%, Specificity: 81%, NPV 100%</td>
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<tr>
<td>Mestan et al(^8^0)</td>
<td>506 neonates</td>
<td>Preterm and term labor + or − histopathological chorioamnionitis</td>
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<tr>
<td>Duncombe et al(^8^1)</td>
<td>55 neonates</td>
<td>Term labor, + or − histopathological chorioamnionitis</td>
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+, positive relation with outcome; ++, strong relation with outcome; −, negative relation with outcome.

MIAC indicates microbial invasion in the amniotic cavity.
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<tbody>
<tr>
<td><strong>A. In maternal serum</strong></td>
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</tr>
<tr>
<td>Berner et al(^39)</td>
<td>171 neonates</td>
<td>As described in Table 1 A</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Shimoya et al(^40)</td>
<td>22 cases, 81 controls</td>
<td>As described in Table 1 A</td>
<td>+</td>
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<td><strong>B. In amniotic fluid</strong></td>
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<td>Roos et al(^58)</td>
<td>33 women</td>
<td>As described in Table 1 B</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Puchner et al(^61)</td>
<td>80 women</td>
<td>1. Amniocentesis at 14–15 weeks</td>
<td>+</td>
<td>++</td>
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<td></td>
<td></td>
<td>2. Preterm labor</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Romero et al(^59)</td>
<td>205 women</td>
<td>1. Amniocentesis midtrimester</td>
<td>+</td>
<td>++</td>
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<td>2. Preterm labor</td>
<td>+</td>
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<td>3. Term labor</td>
<td>+</td>
<td>++</td>
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<td>4. Term in labor</td>
<td>+</td>
<td>++</td>
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<td><strong>C. In umbilical cord blood</strong></td>
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<td>+</td>
<td>++</td>
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<tr>
<td>Santana et al(^73)</td>
<td>256 neonates</td>
<td>As described in Table 1 C</td>
<td>+</td>
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terase were correlated to the duration of labor and were not a marker for infection. In summary, there is no complete agreement on the diagnostic value of immunological mediators in maternal serum to detect intrauterine infection. They seem to be elevated during intra-amniotic infection but specificity is not high enough for actual use in practice. Research on CRP and IL-6 has shown many contradictory findings. More research is necessary regarding WBC, leukocyte esterase, TNF-α, IL-1α, IL-1β, and IL-8, before their potential as a sensitive and specific intrapartum marker will be known. Of all maternal cytokines, IL-8 appears the most consistent diagnostic marker.

Amniotic Fluid

The role of cytokine detection in amniotic fluid in the diagnostic process of intra-amniotic infection has been examined extensively in preterm labor and a positive correlation between chorioamnionitis and IL-1, TNF, IL-8, and IL-6 in particular has been found. In term pregnancies, IL-6 is physiologically present in amniotic fluid and is slightly elevated during labor but significantly elevated in case of intra-amniotic microbial infection (Table 1B). Moreover, amniotic fluid cytokine determination can be determined more rapidly than gram stain and WBC, for the detection of microbial invasion in the amniotic cavity (MIAC) in patients at term (Table 2 [B]). However, clear cut off values with positive (PPVs) and negative predictive values (NPVs) have not been established yet, and more research is necessary before IL-6 can be used as a diagnostic marker.

Similar to IL-6, elevated IL-8 levels have also been associated with clinical or histological signs of intrauterine infection (Table 3 [B]). IL-8 is significantly increased during labor, but even higher values have been detected when labor was associated with positive amniotic fluid cultures (Table 3 [B]). A study by Roos et al showed that elevation of both IL-6 or IL-8 levels was strongly associated with microbial invasion of the amnion cavity (Table 1B). They also found that lipopolysaccharide binding protein (LBP), an acute phase protein, and soluble CD14, a surface protein released by monocytes, are normal constituents of amniotic fluid. Although CD14 had no association with microbial infusion of the amniotic cavity or histologic chorioamnionitis, LBP was elevated in association with MIAC, labor, intrapartum fever, chorioamnionitis, and the presence of cytokines. However, LBP was increased during
labor even in the absence of infection, which makes it a less useful marker to diagnose intrauterine infection during labor.

TNF is a marker which, in contrast to IL-6, is not always detectable in amniotic fluid of normal pregnant women and has been associated with chorioamnionitis in both preterm and term pregnancies.52 However, although a TNF-α rise was found in relation to microbial invasion of the amniotic cavity, this correlation was only weak.58 IL-1β but not IL-1α has been found to be elevated in relation with microbial invasion of the amniotic cavity63; nevertheless, this needs to be confirmed by other studies. Likewise, more research is necessary for leukemia inhibitory factor, which was found to be raised in intra-amniotic infection64 and leukocyte esterase that was not associated with microbial invasion of the amniotic cavity.41 One of the conventional markers, WBC was associated with microbial invasion of the amniotic cavity,60 but not significantly elevated when intra-amniotic infection was used as outcome variable.60 Furthermore, little is known about its sensitivity and specificity as a diagnostic marker.

Recently, CXCL13 (B lymphocyte chemoattractant), a chemokine produced by macrophages, has been proposed as a marker of intrauterine infection.56 CXCL13 is present in amniotic fluid in normal pregnant women at term and is significantly increased with intra-amniotic infection in preterm pregnancies,66 but its role during infection in term pregnancies has not yet been studied.

In summary, little is known about potential markers for intra-amniotic infection at term. IL-6 and IL-8 might be sensitive and specific markers in amniotic fluid and are possibly useful as diagnostic markers, but clear cut-off values still have to be investigated. IL-1β, leukemia inhibitory factor WBC, TNF-α CXCL13 could be promising but also need to be further investigated in term pregnancies before conclusions can be made. In the studies summarized earlier, amniotic fluid was retrieved by transabdominal needle aspiration (intact membranes), transvaginally (intact membranes), or during cesarean section.

**Umbilical Cord Blood**

As maternal serum may give information about intrauterine infection, umbilical cord blood is likely to give a better idea about early neonatal infection, as infections are expected to be of intrauterine origin.28,67 Of all potential umbilical cord blood diagnostic cytokines for intra-amniotic infection, IL-6 is perhaps the most extensively studied.28,68,39,40,43,57,69–79,80,81 (Table 2 [C]). Many studies have shown that umbilical cord blood IL-6 is elevated in relation to clinical chorioamnionitis,75,76,78 histopathological chorioamnionitis,68,40,77,80,81 and early-onset neonatal infection39,57,69,70,73,74,79 (Table 2 [C]). Labor and intrapartum fever alone can not account for this large increase in umbilical cord blood IL-6, which is in contrast to IL-6 in maternal blood.43,72 Therefore, umbilical cord blood IL-6 seems to be a rather specific marker. However, the sensitivity and specificity to predict neonatal infection varies from 50% to 87% and 87% to 93%, respectively39,73 (Table 2 [C]). Furthermore, 2 studies have found in large groups of neonates that the capacity of IL-6 to distinguish between infection or noninfectious pathology is questionable.73,74 This corresponds with data from preterm neonates in whom IL-6 was raised in infectious and noninfectious pathology.82 In contrast with these results, Miller et al and Weimann et al have shown that IL-6 levels discriminated between infants with infection and sick infants without infection70,79 (Table 2 [C]).

It has been proposed that there is a direct fetal contribution to IL-6 production71,46,76, therefore, IL-6 mRNA would be expected to be raised in cord blood of neonates with sepsis. This has indeed been found by Berner et al.83 However, Singh et al found more ambiguous result,72 but both state that IL-6 mRNA is likely to be a more specific predictor of neonatal infection than IL-6 plasma levels.72,83

Cord blood IL-8 concentration has shown to be a sensitive and specific marker for detection of neonatal infection in preterm and term neonates39,40,73,74,83,80 (Table 3 [C]). A recent study suggested IL-8 to be a better marker in the diagnosis of neonatal infection than IL-6 or CRP, and a cutoff value of 112 pg/mL, showing a PPV of 100%, has been proposed.73 This is in line with earlier findings of Shimoya et al who found that umbilical cord IL-8 at a cutoff value of 100 pg/mL showed to be more sensitive and specific marker to detect histological chorioamnionitis than IL-6.50 The combined use of IL-8 with other cytokines or other variables such as CRP or leukocyte values did not improve its diagnostic capability.73 Particularly, the high NPV of 92% and 84%, respectively, could make IL-8 a reliable and useful marker.40,73 Although IL-8 differentiates well between infected and healthy neonates,73,74 there are contradictions about the discriminating capacity of IL-8 between infection and noninfectious pathology.73,74

Although, IL-8 and IL-6 are the best known cytokines in relation to intra-amniotic infection, other potential markers have been also investigated.39,73,74,77,79,84,85
TNF-α, IL-1β, p55, p75, IL-1-RA, and CRP have been found to be raised in relation to severe chorioamnionitis, but not in mild cases. G-CSF was raised significantly in case of neonatal infection. One of the conventional markers, CRP, although raised in case of intrapartum fever and chorioamnionitis, has been shown to be of no diagnostic value of neonatal infection in several studies. Several studies have shown that TNF-α is elevated in relation to neonatal infection, but other studies showed no increase or even a decrease. The same contraindications exist for IL-1β, where one study showed no association, another showed a decrease of IL-1β, and several showed an increase with neonatal infection. SICAM-1 has been found to be elevated in preterm neonates at risk for infection, and to be a sensitive marker in neonatal serum in combination with CRP. However, those promising results did not apply for umbilical cord blood, and UV-sICAM-1 has been shown to be of no significant relevance in the diagnosis of early neonatal sepsis. Umbilical cord levels of LBP are increased in relation to histologic chorioamnionitis and are not increased in association with MIAC or with labor itself, which is in contrast to the findings in amniotic fluid. Because this has only been investigated in one study, more research is necessary to establish the role of LPB as a potential marker of intra-amniotic infection.

In conclusion, IL-6 and IL-8 levels in umbilical cord blood appear to be promising markers for detection of intra-amniotic infection, with IL-8 being more specific than IL-6. Controversy remains about the specificity of certain markers; however, in contrast to what is seen in maternal serum, a rise in IL-6 and IL-8 indicates pathology although perhaps not completely specific for infection. Therefore, the negative predictive value of UV IL-6 and IL-8 could be of great importance to decrease overtreatment of neonates. SICAM-1 has shown to be a poor diagnostic marker and should not be used. CRP is probably of no value in early detection of infection either. Other markers such as TNF-α and IL-1β have not been investigated sufficiently, and the same holds for G-CSF, sIL-2R, IL-1RA, p55, p75, MIP-1α, RANTES, sTrem-1, and LPB. Mestan et al were the first who used a multiplex immunoassay to measure 27 biomarkers in cord blood to identify markers that are strongly associated with fetal inflammatory response syndrome. Among these 27 biomarkers, IL-1β, IL-6, and IL-8 were selectively associated with fetal inflammatory response syndrome. Further interpretation will require more targeted studies that are powered to detect interactions among these important biomarkers.

Epidural Analgesia

The use of epidural analgesia commonly increases maternal body temperature, however, the underlying cause of this higher incidence of intrapartum fever remains controversial. One theory is that fever is attributable to a noninfectious inflammatory process initiated or enhanced by labor epidural analgesia. Some studies have demonstrated elevated IL-6 levels associated with this fever. Goetzl et al have examined the relationship between epidural-related fever and the endogenous pyrogens and inflammatory mediators IL-1β, IL-6, IL-8, and TNF-α. They concluded that epidural fever is associated with maternal and fetal inflammation in the absence of neonatal infection. Higher levels of cytokines in maternal serum suggest that the maternal compartment is the primary inflammatory source. In line with this, Riley et al have shown that women receiving labor epidural analgesia developed more frequently fever but were not more likely to have placental infection, suggesting that epidural-related fever results from a noninfectious inflammatory process. In both studies, it was found that women with higher IL-6 levels on admission in labor were at increased risk for developing fever. These findings suggest that women who have an “activated” immune system on admission may react differently to epidural analgesia, leading to fever. Although maternal IL-6 levels on admission are associated with later development of fever, admission IL-8 levels and cord blood IL-8 were not significantly higher in the setting of fever. In most studies summarized in Tables 2 and 3, the use of epidural analgesia during labor was not mentioned, nor was a distinction made between epidural and otherwise. In summary, studies have shown that women receiving labor epidural analgesia developed more frequently fever but were not more likely to have placental infection, suggesting that epidural-related fever results from a noninfectious inflammatory process. Higher levels of cytokines in maternal serum suggest that the maternal compartment is the primary inflammatory source, whereby women with higher IL-6 levels on admission in labor are at increased risk for developing fever, without increases in cord blood IL-8. Future research is needed to elucidate the underlying inflammatory process associated with epidural analgesia. Although the lack of infectious neonatal morbidity, mounting evidence suggests that intrapartum maternal fever in the absence of infection may lower the threshold for hypoxic brain injury. In addition to the potential fetal risks from temperature elevation, elevated amniotic fluid IL-6 has...
been linked to an increased risk of cerebral palsy independent of infection in preterm infants.  

**Long-Term Outcome**

Cytokines have also been found to be related to long-term outcome of the neonate. In term asphyxiated children, preserved dried neonatal blood spots increased IL-1, IL-6, IL-8, TNF, and RANTES levels—detected by chemiluminescence detection—were associated with cerebral palsy. This is consistent with experimental and clinical observations relating cytokine elevations with white matter lesions, and linking intrauterine infection with risk of CP in term infant. In a different study, term infants umbilical cord IL-6 levels were increased 376 times in infants with asphyxia who developed hypoxic-ischemic encephalopathy (HIE) compared with healthy infants and were increased 5.5 times compared with infants with asphyxia who did not develop HIE. Moreover, in the neonates who developed HIE higher IL-6 cord levels were associated with a worse long-term outcome as compared with a relatively more favorable outcome in infant with HIE and lower IL-6 levels. The same study showed that maternal IL-6 levels, although correlated with asphyxia in neonates, did not predict HIE or adverse outcome. These results imply that umbilical vein IL-6 levels in neonates with asphyxia can be used to predict HIE and to detect neonates at risk for brain injury and therefore in need of early intervention. However, these studies do not show a specific association between intrauterine infections and adverse outcome and suggest other pathways. The same may hold for umbilical vein sICAM-1 levels, which are not increased in case of infections but may well be associated with cerebral trauma or hypoxia.

**DISCUSSION**

Intrauterine infection is a common and severe complication of labor. Its diagnosis is currently depending on nonspecific, indistinct, and late clinical symptoms. Because early diagnosis and treatment of neonatal infection is crucial, a significant degree of overtreatment exists. The aim of this review was to give an overview of the available research on markers other than IL-6 or IL-8 in maternal serum, amniotic fluid, or umbilical cord blood has shown to be either too contradicting or too limited to rely on by clinicians. Thus, future challenges are to confirm predictive values of biomarkers, especially IL-6 and IL-8, in prospective studies not only to detect but also to prevent neonatal infection. One could anticipate on a predictive model based on clinical signs, fetal tachycardia in combination with maternal serum, and/or amniotic fluid markers. If such a model would reach high sensitivity and specificity levels, a stepwise strategy might be proposed in which the pregnant woman could be treated with antibiotics in case of a high suspicion of intrauterine infection followed by neonatal interven-
tions such as medium care admission in case of elevated IL-8 levels in umbilical cord blood. With such a protocol, amniotic fluid should preferably be obtained vaginally after rupture of the membranes. Cytokine determination following rupture of membranes is feasible, and cytokine values of vaginally obtained amniotic fluid are highly correlated to those determined in amniotic fluid obtained through an intrauterine pressure catheter. A reduction in overtreatment during labor and especially in admissions of the newborn should most likely reduce costs also if the costs of cytokine measurements will be taken into account.

In conclusion, most data on predictive value of various markers for intrauterine infection have shown disappointing results. The high negative predictive value of IL-8 in umbilical cord blood indicates that IL-8 can be used to prevent overtreatment of healthy neonates. Future research is essential and should focus on the combination of different markers and on the development of a prediction model, to improve the PPVs and NPVs of our arsenal to detect intrauterine and neonatal infections. Amniotic fluid and umbilical cord values of IL-6 and IL-8 levels are likely candidates for such a prediction model.

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