Review Article

Fetal and early neonatal interleukin-6 response

Claudio Chiesa a,*, Lucia Pacifico b, Fabio Natale b, Nora Hofer c, John F. Osborn d, Bernhard Resch c

a Institute of Translational Pharmacology, National Research Council, 00133 Rome, Italy
b Department of Pediatrics and Child Neuropsychiatry, Sapienza University of Rome, 00161 Rome, Italy
c Research Unit for Neonatal Infectious Diseases and Epidemiology, Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, AT–8036 Graz, Austria
d Department of Public Health and Infectious Diseases, Sapienza University of Rome, 00161 Rome, Italy

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A B S T R A C T

In 1998, a systemic fetal cytokine response, defined as a plasma interleukin-6 (IL-6) value above 11 pg/mL, was reported to be a major independent risk factor for the subsequent development of neonatal morbid events even after adjustments for gestational age and other confounders. Since then, the body of literature investigating the use of blood concentrations of IL-6 as a hallmark of the fetal inflammatory response syndrome (FIRS), a diagnostic marker of early-onset neonatal sepsis (EONS) and a risk predictor of white matter injury (WMI), has grown rapidly. In this article, we critically review: IL-6 biological functions; current evidence on the association between IL-6, preterm birth, FIRS and EONS; IL-6 reference intervals and dynamics in the early neonatal period; IL-6 response during the immediate postnatal period and perinatal confounders; accuracy and completeness of IL-6 diagnostic studies for EONS (including the design, conduct, analysis and results of such studies according to the Standards for Reporting of Diagnostic Accuracy statement); and recent breakthroughs in the association between fetal blood IL-6, EONS, and WMI.

1. Introduction

Interleukin-6 (IL-6) is a pleiotropic cytokine that is produced by a variety of cells in response to infection and tissue injury. In the last two decades, the body of literature concerning the use of blood concentrations of IL-6 as a hallmark of the fetal inflammatory response syndrome (FIRS), a diagnostic marker of early-onset neonatal sepsis (EONS) [1] and a risk predictor of white matter injury (WMI) has grown rapidly, leading to improved understanding as well as new questions about the role of this cytokine in the perinatal period. In this article, we comprehensively review: (1) IL-6 biological functions; (2) current evidence on the association between IL-6, preterm birth, FIRS and EONS; (3) IL-6 reference intervals and dynamics in the early neonatal period; (4) IL-6 response during the immediate postnatal period and perinatal confounders; (5) accuracy and completeness of IL-6 diagnostic studies for EONS [including the design, conduct, analysis and results of such studies according to the Standards for Reporting of Diagnostic Accuracy (STARD) statement]; and (6) recent breakthroughs in the association between fetal blood IL-6, EONS, and WMI.

2. IL-6 biological functions and signaling pathways

Systemic inflammatory response syndrome, which is characterized by an excessive proinflammatory response, is a hallmark of sepsis [2]. Many proinflammatory cytokines including IL-6 have been implicated in the pathogenesis of sepsis [2]. Until recently, it was not known how the cytokine-driven inflammatory process is initiated. It is now known that microorganisms interact with a family of toll-like receptors (TLRs) belonging to the innate immune system, which trigger intracellular activation of nuclear factor kappa B and various kinases, leading to the production and release of cytokines [3]. Among these, IL-6 has been reported to be produced in the early phase of infectious inflammation by monocytes and macrophages immediately after the stimulation of TLRs, with distinct pathogen-associated molecular patterns [4]. In
noninfectious inflammatory conditions, such as tissue injury, damage-associated molecular patterns from damaged or dying cells stimulate TLRs to produce IL-6 [5]. This acute IL-6 expression plays a central role in the body’s defense against infection or injury by stimulating various cell populations [6].

IL-6 is produced by various cells, such as T-cells, B-cells, monocytes, fibroblasts, keratinocytes, endothelial cells, mesangial cells, adipocytes, and some tumour cells [7]. While serum concentrations of IL-6 in healthy donors are hardly detectable or in the low pg/mL range [8,9], during an inflammatory episode IL-6 is highly expressed, and circulating levels can rise dramatically from 1–5 pg/mL to several µg/mL in extreme cases [10,11]. Consequently, IL-6 is one of the most highly expressed mediators of inflammation [11].

IL-6 is a multifunctional cytokine involved in regulating the immune response, hematopoiesis, the acute phase response and inflammation. Its many biologic activities are at the root of its pathogenic properties. IL-6 engages in two distinct downstream signaling pathways to achieve these activities: classic and trans-signaling.

In classic signaling, IL-6 first binds to its specific membrane-bound α-receptor (IL-6R), which in turn associates with and activates the signal-transducing β-receptor chain gp130. Whereas gp130 is expressed by most, if not all, cells in the body [12], IL-6R is only expressed on a limited number of cell types including ephocytes, megakaryocytes and some leukocytes, namely monocytes, macrophages, B cells and subtypes of T cells [12,13]. In hematocytes, IL-6R expression is essential for the production of acute phase response proteins including C reactive protein (CRP) and fibrinogen. Being transiently expressed on lymphocytes, macrophages, and megakaryocytes, the IL-6R also orchestrates phases of the immune response [12]. All other cells, which do not express membrane-bound IL-6R, obtain IL-6 signals by trans-signaling. IL-6 binds to the soluble form of IL-6R (sIL-6R), and this complex not only protects IL-6 and prolongs its circulating half-life [14], but also acts as an agonist capable of directly activating many cell types via the ubiquitously expressed gp130 in a process termed trans-signaling [11]. It has been shown that sIL-6R strongly sensitizes target cells [14]. Embryonic stem cells, early hematopoietic progenitor cells, T cells, many neural cells, smooth muscle cells, mesothelial cells, and endothelial cells, among others, are only responsive to IL-6 in the presence of sIL-6R [12]. sIL-6R is present in the sera of healthy subjects at high concentrations (25–145 ng/mL), and these levels increase during inflammation [15–17]. sIL-6R in humans is generated through differential mRNA splicing but primarily through proteolytic cleavage and subsequent shedding of membrane-bound IL-6R [18,19]. In contrast to classic signaling, comprising the anti-inflammatory or regenerative activities of IL-6, evidence suggests that IL-6 trans-signaling via soluble IL-6R accounts for the proinflammatory properties of IL-6 [20]. In fact, while IL-6 classic signaling plays a role in developmental processes, tissue homeostasis, and acute phase response [21], trans-signaling is involved in many processes that include developmental processes, tissue homeostasis, and acute phase IL-6 [20]. In fact, while IL-6 classic signaling plays a role in soluble IL-6R accounts for the proinflammatory properties of IL-6 [20]. In fact, while IL-6 classic signaling plays a role in developmental processes, tissue homeostasis, and acute phase response [21], trans-signaling is involved in many processes that include developmental processes, tissue homeostasis, and acute phase IL-6 [20]. In fact, while IL-6 classic signaling plays a role in IL-6/sIL-6R complex in vivo [21], probably to prevent systemic IL-6 trans-signaling during inflammatory diseases [29].

The concentrations of IL-6, sIL-6R and sgp130 have to be considered. Under steady state conditions, levels of sIL-6R and sgp130 are roughly 1000 times higher than IL-6 levels [8]. However, during inflammatory conditions, IL-6 levels can increase up to a million-fold [10], whereas serum concentrations of sIL-6R and sgp130 show much smaller differences between healthy and diseased and in most cases do not rise by more than a factor of 2 [15]. These concentrations imply that IL-6, once secreted, will bind to sIL-6R in the serum and this complex will associate with sgp130, and thereby be neutralized [8]. Only when IL-6 levels exceed the levels of sIL-6R and sgp130, IL-6 can act systematically-as seen under septic conditions [10]. Because IL-6 alone does not interact with sgp130, with a molar excess of IL-6 over sIL-6R, sgp130 would only be able to block trans-signaling because free IL-6 will not, or will only, be partially trapped in IL-6/sIL-6R/sgp130 complexes. In contrast, under physiologic conditions, IL-6 is thought to act in a paracrine fashion [30]. Physiological conditions are a molar excess of serum sIL-6R over IL-6 characterized by free IL-6 and IL-6 found in IL-6/sIL-6R complexes. Under these conditions, the sgp130 protein can block both classic and trans-signaling because sgp130 would be able to trap all the free IL-6 molecules in IL-6/sIL-6R/sgp130 complexes [21].

3. Preterm birth and interleukin-6

Subclinical intrauterine infection and/or inflammation, represented by chorioamnionitis, is the most firmly established trigger of preterm delivery [31–33]. The etiology of preterm birth is complex but previous data indicate that chorioamnionitis induces an intra-amniotic inflammatory response involving the activation of a number of cytokines and chemokines which, in turn, may trigger preterm contractions, cervical ripening and rupture of the membranes [34]. Numerous studies have found that IL-6 is the most predictive and best candidate as a diagnostic tool for detecting pre-clinical chorioamnion inflammation and intra-amniotic inflammation leading to preterm birth [35–40]. Elevated levels of IL-6 in mid-trimester amniotic fluid have been associated with increased risk for spontaneous preterm birth (before 32 weeks), acute chorioamnionitis and funisitis [41]. In the recent Pregnancy Outcomes and Community Health cohort study, IL-6 levels in vaginal fluid at midtrimester had the greatest sensitivity for detecting spontaneous delivery at <35 weeks’ gestation and preterm delivery accompanied by chorioamnionitis [42]. Studies in tissue extracts from term and preterm deliveries have shown that IL-6 concentrations in the extraplacental membranes are modestly elevated with spontaneous term labor, but are dramatically elevated in preterm deliveries [43].

IL-6 is a proinflammatory cytokine known to be expressed by stimulated leukocytes [44]. In the tissues from preterm deliveries (with and without intrauterine infection), IL-6 concentrations correlate with the extent of leukocyte infiltration [45]. At the inflammatory site, leukocytes (predominantly neutrophils and macrophages) are recruited into the gestational membranes and activated, and eventually secrete proinflammatory cytokines including IL-6 [45,46]. Neutrophil infiltration to the chorionic plate, choriodedula, and umbilical cord can be measured through IL-6 concentrations of the amniotic fluid and cord blood [47]. The association between high IL-6 levels in the amniotic fluid and pregnancies complicated by prematurity rupture of membranes is especially strong when infection is present [48,49]. Elevated maternal serum IL-6 concentrations have been reported to be diagnostic for intrauterine infection-associated preterm labor, giving indirect evidence of a placental involvement in some instances of infection-associated preterm deliveries [45]. However, a decidual, or even cervical, source of this cytokine cannot be discounted [45].
The human amnion, choriodeciduala, and fetus have been proposed as potential sites of IL-6 synthesis and probable sources of IL-6 in the amniotic fluid [38,50,51]. Therefore, a relevant question is whether targeting amniotic fluid IL-6 signaling could be a promising option for the prevention of preterm delivery [31,38]. In a recent study, Lee et al. suggested that the IL-6 trans-signaling pathway plays a critical role in preterm birth and premature rupture of membranes by demonstrating an increase in amniotic fluid concentration of IL-6 and sIL-6R in women with intra-amniotic inflammation, and a decrease in the amniotic fluid concentration of sgp130 in women with preterm premature rupture of membranes (PPROM) [38]. In the same article, Lee et al. also showed that in physiologic gestations, amniotic fluid levels of sgp130 decline with gestational age [38]. These findings suggest that targeting the IL-6 trans-signaling pathway may prevent complications such as premature rupture of membranes and preterm birth.

4. Fetal inflammatory response, early-onset neonatal sepsis, and interleukin-6

FIRS is a systemic activation of the fetal innate immune system and was originally reported in pregnancies complicated by preterm labor (with intact membranes) and PPROM [52,53]. Affected fetuses had evidence of multisystemic involvement; they had a higher rate of adverse neonatal morbidity after adjustment for gestational age, and had a higher risk of subsequent spontaneous preterm delivery in cases of PPROM [53,54].

FIRS was originally defined as a level of IL-6 >11 pg/mL in samples of fetal plasma obtained by cordocentesis [52,53]. Following this precept, Hofer et al. have recently demonstrated that in preterm neonates FIRS is an independent predictor of adverse neonatal outcome and some primary outcome parameters including EONS [55]. In an observational study of 176 consecutive preterm neonates admitted to the neonatal intensive care unit (NICU) [62 (35%) with FIRS (cord blood IL-6 > 11 pg/mL), and 114 without], Hofer et al. [55] demonstrated that FIRS was significantly associated with EONS [odds ratio 10.26, 95% confidence interval (CI) 2.95–35.68; \( P < 0.001 \)] independently of gestational age and idiopathic respiratory distress syndrome. The receiver operating characteristic curve analysis for cord blood IL-6 showed an area under the curve (AUC) 0.75 (95% CI 0.68–0.84; \( P < 0.001 \)) for the prediction of overall adverse neonatal outcome, and specifically an AUC 0.80 (95% CI 0.70–0.90; \( P < 0.001 \)) for the prediction of EONS [55].

In view of the clinical importance of FIRS (defined by a fetal blood IL-6 concentration) as a predictor for morbidity in preterm neonates, a major topic to be addressed is whether the level of IL-6 depends on the severity of intra-amniotic inflammation. Also the paper by Buhimschi et al. [56] may be of great interest. This addressed the issue in a prospective observational cohort involving 132 consecutive mothers [median gestational age (interquartile range): 29.6 (24.1–33.1) weeks] who had clinically indicated amniocentesis to rule out infection. The intensity of intra-amniotic inflammation was graded on the presence of four inflammatory proteomic biomarkers (neutrophil defensins 2 and 1 and calgranulins C and A) in the amniotic fluid that have been previously [57,58] reported as highly predictive of histologic chorioamnionitis, funisitis and EONS. The three grades used were: none of the 4 biomarkers, “no inflammation”; 1-2 biomarkers, “minimal inflammation”; and 3-4 biomarkers, “severe inflammation”. Results showed that neonates with severe intra-amniotic inflammation had significantly elevated cord blood IL-6 levels but not those delivered by women with no or minimal inflammation. Because the level of IL-6 was highly associated with the degree of placental histologic chorioamnionitis, one can conclude that at the stage of no or minimal amniotic fluid inflammation, the fetus is usually protected. However, detection of a positive blood culture and umbilical cord IL-6 levels well above the mean in several neonates delivered by women with no or minimal intra-amniotic inflammation [56], suggested that the hematogenic infection of the human fetus and increasing fetal inflammatory response, in the absence of concurrent amniotic fluid colonization and inflammation, are possible. Thus, the early and accurate recognition of neonates who have already had in utero a robust inflammatory response in the context of minimal intra-amniotic inflammation remains a major clinical concern. Additional studies of the genetic and perinatal factors accounting for the differential maternal and fetal inflammatory response are needed.

5. IL-6 reference intervals and dynamics in the early postnatal period

As a prerequisite for analyzing the IL-6 neonatal response associated with early-onset sepsis, there is a need to establish the IL-6 reference intervals and dynamics in the healthy neonate during the early postnatal period, counterbalanced by a greater awareness of the potential confounding factors that may affect them.

In a longitudinal study to assess upper reference limits for IL-6 in 148 healthy babies (113 term, 35 near-term) during the early postnatal period, Chiesa et al. [59] showed that gestational age was negatively associated with IL-6 values obtained at three fixed neonatal ages (0, 24, and 48 h after birth). In fact, the geometric mean IL-6 concentration in the healthy near-term babies at birth and at 24 and 48 h of life was 6.40 (95% CI 3.61–11.50; \( P = 0.0001 \)), 2.38 (95% CI 1.41–3.99; \( P = 0.001 \)) and 2.40 (95% CI 1.49 –3.88; \( P < 0.001 \)) times higher, respectively, than the concentration observed in the healthy term babies [59]. They also showed that the kinetics of IL-6 during the first 48 h of life in healthy infants, are different in the near-term infant compared with the term neonate, suggesting different physiologic processes [59]. Among the term babies, the geometric mean IL-6 values were significantly lower at birth [1.69 pg/mL (95% CI 1.28–2.23)] than at 24 h [4.09 (3.13–5.33)] of life, with no significant change from 24 to 48 h [3.45 (2.70–4.43)] of life. In the term neonate, the surge of IL-6 at 24 h of age probably reflects a physiological stress reaction induced at birth. Similar data regarding IL-6 dynamics in healthy term neonates have also been reported by other investigators [60]. In contrast, within the subgroup of near-term babies, the geometric mean IL-6 concentrations were already increased at the time of birth [10.9 (6.53–18.4)] being not significantly different from those found at 24 [9.3 (6.2–14.1)] and 48 h [8.4 (5.97–11.9)] of life, therefore suggesting that a physiological stress reaction had already begun before birth. Taken together, these data demonstrate the effects of development on IL-6 reference intervals and dynamics during the 48-h period after birth. Different gestational age- and postnatal-dependent physiologic processes may be potential confounding factors when interpreting IL-6 reference intervals and dynamics throughout the early postnatal period.

In view of the latest advances in neonatal care, these reference intervals derived from only 35 near-term and 113 term newborns need additional refinement in a larger sample of healthy neonates including, in particular, those born before 35 weeks of gestation, that is, those that now populate most NICUs [61].

6. Studies of IL-6 diagnostic accuracy for early-onset neonatal sepsis: quality of reporting

6.1. Data sources

We systematically reviewed PubMed, Scopus, and the Cochrane Library databases up to June 1, 2014. The PubMed combined search
term used was: (Interleukin-6 OR IL-6) AND (neonatal sepsis OR neonatal infection OR sepsis). The search terms applied to the Scopus and the Cochrane Library were “Interleukin-6 and sepsis” and “Interleukin-6”, respectively.

6.2. Study selection criteria

Articles were eligible for inclusion in our review if they provided measures of IL-6 accuracy for diagnosing EONS, defined by the National Institute of Child Health and Human Development and Vermont Oxford Network, as sepsis with onset at <3 days of age. We excluded studies that used IL-6 measurements that were made only on maternal blood samples. We also excluded duplicate articles. Conference abstracts or studies written in languages other than English were also excluded.

6.3. Data extraction

Data extraction included the country of the research, year of publication, journal, reference standard employed, the type of study design, the number and specific characteristics of the patients in the septic and non-septic groups (Table 1), and items related to the quality of the methods and reporting (Table 2). Specific data regarding the IL-6 cut-off level used, the sensitivity, specificity, and AUC for the diagnosis of EONS were also extracted (Table 1). In cases in which estimates of uncertainties around the observed values of sensitivities and specificities were not calculated using Wilson’s method [62], we calculated them.

6.4. Quality assessment of the included studies

In 2003, the STARD statement was published in 13 biomedical journals [63–65]. The STARD initiative was developed in response to accumulating evidence of poor methodological quality. Therefore, a data extraction form based on the STARD checklist and adapted for neonates with EONS was used to appraise the overall quality of the included studies. All articles were closely examined on the extent to which they adhered to the STARD checklist by assigning a yes or no response to each item.

Twenty-five items make-up the STARD checklist. When the papers considered in this study were assessed, only those STARD items that have been empirically shown to have a potentially biasing effect on diagnostic accuracy [66–69] and those items we deemed may account for variation between estimates of diagnostic accuracy for neonatal sepsis, were evaluated.

The checklist of STARD items we used is shown in Table 2. Adequate reporting of three key domains, that is, descriptions of participant recruitment, reference standard and index test, and study population, was considered essential for capturing the global and integrative quality of the estimated accuracy of the diagnostic tests. As these were used for ruling in or for ruling out a multiform diagnostic entity such as EONS, they were split into various complementary items. Two investigators (CC, BR) independently assessed the methodological quality of all eligible studies.

6.5. Methodological quality of the included studies

We found 19 articles which were eligible for inclusion in our review [61,70–87]. Papers were published between 1995 and 2014. All were studies of diagnostic accuracy, and stated this as the research objective in the introduction. Most studies were performed in single perinatal centers. The IL-6 accuracy for the diagnosis of EONS yielded discrepant results (Table 1). Potential sources of the wide variation in IL-6 sensitivity and specificity include the lack of consistent IL-6 cut-off values regardless of the time of sampling; and differences in study sample sizes, patient demographic and clinical characteristics, and participant recruitment.

We therefore evaluated the extent to which IL-6 accuracy studies adhered to the STARD initiative. Agreement between the two reviewers was almost perfect with an overall agreement percentage of 98.8%. The kappa statistic had a value of 0.98 (95% CI 0.96–0.99), indicating very good agreement.

Overall, the quality of IL-6 diagnostic accuracy studies on EONS over the last two decades was sub-optimal. Information on the key elements of design, conduct, analysis, and interpretation of test accuracy were frequently missing. The importance of describing how eligible subjects were identified cannot be overemphasized. It is crucial to describe the populations from which patients and patient controls originated, as it allows an assessment of the “spectrum of disease”, which is likely to influence the diagnostic performance of the test. Reported estimates of diagnostic accuracy may have limited clinical applicability (generalizability) if the spectrum of tested patients is not similar to the patients for whom the test will be used in practice. While some IL-6 accuracy studies enrolled neonates who were suspected of having the disease because of presenting symptoms, other studies recruited neonates who were (initially asymptomatic and) only at risk of developing the disease because of a history of maternal risk factors. Other studies included neonates already diagnosed with sepsis and those in whom sepsis had been already excluded. Finally, there were also designs starting with: two separate selection processes to sample patients with sepsis and patients without sepsis (a case-control design with limited spectrum [66,88]); non-consecutive sampling of patients (a method leading to the “limited challenge bias” [89]); retrospective data collection; and identification of patients by searching hospital records. These alternative study designs are likely to influence the spectrum of disease. Spectrum bias also results from differences in the severity of sepsis/EONS between populations. Clinical and birth characteristics (as proxy measures of morbidity) of the septic and non-septic neonatal populations were reported in only half of the IL-6 diagnostic accuracy studies. As individual clinical and demographic attributes, such as gestational age and birth weight, do not capture the overall morbidity status, it is of greater concern that reporting of the distribution of scores of the major measures of illness severity was remarkably poor in neonates with and without sepsis.

Differential verification bias is a key issue in any diagnostic accuracy study. It occurs if some patients receive a different reference standard. Studies that relied on 2 or more reference standards to verify the results of the index test, have reported estimates of diagnostic accuracy on average 60% higher than those found in studies that used a single reference standard [68]. The origin of this difference probably resides in differences between the reference standards in how they define sepsis, or in their quality. Reference standards are not interchangeable. They may not have the same degree of error, and may not identify the same segment of the disease spectrum. Thus it is worrying that in most of the included IL-6 diagnostic accuracy studies, different reference standards were used to diagnose (or exclude) EONS and verify index test results.

A further step in the critical appraisal of the reference standard is whether the index test or the comparator of the index test formed part of the reference standard [90,91]. Unfortunately, in six of the 19 included studies the comparator of the index test such as CRP test was also a component of the reference standard (incorporation bias). In such situations it is likely that the person interpreting the results of the comparator will have knowledge of the results of the other test (index test and reference standard).

In order to make a valid comparison between the index test and the standard test, it is essential that the criteria (cut-off values etc) are defined before the start of the study. If the cut-offs are decided after the results are obtained, the likelihood that another study will
Table 1  
Characteristics of IL-6 accuracy studies (1995-2014) for diagnosing early (< 72 h) -onset neonatal infection.

<table>
<thead>
<tr>
<th>Country, year [reference]</th>
<th>Recruitment</th>
<th>Reference standard in infected neonates</th>
<th>Reference standard in control neonates</th>
<th>Sample studied</th>
<th>IL-6 Cutoff (pg/mL)</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany, 1995 [72]</td>
<td>46 NICU preterm and term babies: 13, infected; 33, uninfected</td>
<td>1) ≥ 3 categories of clinical signs, and positive blood culture; or 2) ≥ 3 categories of clinical signs, and ≥ 2 abnormal laboratory results in the first 48 h of life</td>
<td>NA</td>
<td>Cord blood</td>
<td>150</td>
<td>69 (42–87)</td>
<td>91 (76–97)</td>
<td>NA</td>
</tr>
<tr>
<td>Switzerland, 1996 [73]</td>
<td>199 preterm and term babies (enrolled from the Obstetric Unit, or the NICU): 18, infected; 181, uninfected</td>
<td>1) Positive culture of blood and/or CSF, abnormal WBC and CRP, and clinical signs; or 2) ≥ 3 categories of clinical signs</td>
<td>Neither clinical nor biological signs of infection</td>
<td>≤ 1 h</td>
<td>100</td>
<td>100 (82–100)</td>
<td>92.3 (87–95)</td>
<td>NA</td>
</tr>
<tr>
<td>USA, 1997 [71]</td>
<td>23 preterm and term babies with suspected EONS: 8, infected; 15, uninfected</td>
<td>1) Positive blood or CSF culture; or 2) clinical signs and positive laboratory (WBC, I:T ratio, or spinal tap) results</td>
<td>NA</td>
<td>UA</td>
<td>&gt;7</td>
<td>87.5 (52.9–97.8)</td>
<td>66.7 (41.7–84.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Italy, 1997 [74]</td>
<td>60 NICU preterm and term babies: 13, infected; 47, uninfected</td>
<td>Positive blood culture, clinical signs, and/or radiographic evidence of pneumonia</td>
<td>Babies with various types of distress who were well within 48–72 h</td>
<td>≤ 24 h</td>
<td>70</td>
<td>69 (42–87)</td>
<td>36 (24–51)</td>
<td>NA</td>
</tr>
<tr>
<td>USA, 1999 [75]</td>
<td>28 preterm babies with either spontaneous preterm labor or PPRM: 14, infected; 14, uninfected</td>
<td>1) Autopsy; or 2) clinical signs and ≥ 2 laboratory (WBC, I:T ratio, PC, spinal fluid) abnormalities</td>
<td>NA</td>
<td>UV blood</td>
<td>25</td>
<td>92.9</td>
<td>92.9</td>
<td>NA</td>
</tr>
<tr>
<td>USA, 2000 [76]</td>
<td>43 NICU singleton, very preterm babies: 21, infected; 22, uninfected</td>
<td>Positive culture of blood and/or CSF; or ≥ 3 maternal/neonatal risk factors for infection</td>
<td>Negative blood culture, and &lt;3 maternal/neonatal risk factors for infection</td>
<td>UV blood</td>
<td>100</td>
<td>81</td>
<td>90.9</td>
<td>NA</td>
</tr>
<tr>
<td>Norway, 2001 [77]</td>
<td>24 NICU preterm neonates: 11, infected; 13, uninfected</td>
<td>1) Clinical signs, and a positive blood culture; or 2) ≥ 3 categories of clinical signs, and CRP ≥ 3 mg/dL; or 3) radiographic evidence of pneumonia and CRP ≥ 3 mg/dL.</td>
<td>Clinical conditions apparently noninfectious</td>
<td>Cord blood</td>
<td>33</td>
<td>82 (52–95)</td>
<td>69.2 (42–87)</td>
<td>0.86 (0.66–0.96)</td>
</tr>
<tr>
<td>Sweden, 2001 [78]</td>
<td>32 NICU preterm and term babies with suspected sepsis: 20, infected; 12, uninfected</td>
<td>1) Positive culture of blood and/or CSF; or 2) abnormal CRP, WBC, and ≥ 1 category of clinical signs (i.e. oliguria, metabolic acidosis, or hypoxemia)</td>
<td>Clinical conditions apparently noninfectious</td>
<td>≤ 24 h</td>
<td>&gt;160</td>
<td>100 (84–100)</td>
<td>69 (42–87)</td>
<td>NA</td>
</tr>
<tr>
<td>Spain, 2001 [79]</td>
<td>31 preterm and term babies: 10, infected; 11, uninfected; 10, healthy controls</td>
<td>≥ 2 categories of clinical signs, ≥ 1 abnormal laboratory finding, and a positive blood culture</td>
<td>Clinical conditions apparently noninfectious; and normal postnatal course through the 1st month of life</td>
<td>Cord blood</td>
<td>100.8</td>
<td>50 (24–76)</td>
<td>91 (62–98)</td>
<td>0.5</td>
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<td>Germany, 2001[80]</td>
<td>136 preterm and term babies: 68, infected; 68, uninfected. Of the 136 babies, 77 were preterm: 40, infected; 37, uninfected</td>
<td>1) Clinical signs and positive blood culture; or 2) clinical signs, and abnormal laboratory (CRP, I:T ratio) results, biological fluids positive for bacteria, or signs of inflammation in placenta</td>
<td>Noninfectious clinical conditions</td>
<td>Cord blood</td>
<td>80</td>
<td>87 (77–93)</td>
<td>90 (80–95)</td>
<td>NA</td>
</tr>
<tr>
<td>Italy, 2003[81]</td>
<td>134 NICU preterm and term babies: 19, infected; 115, uninfected</td>
<td>1) Positive blood culture and clinical signs; or 2) ≥3 clinical signs prompting ≥5 d of antibiotic therapy, and historical and clinical risk factors for EONS</td>
<td>Symptomatic babies who had negative body fluid cultures, and were apparently well within 24–48 h</td>
<td>At birth</td>
<td>≥200</td>
<td>74 (51–88)</td>
<td>89 (82–93)</td>
<td>NA</td>
</tr>
<tr>
<td>Austria, 2003[82]</td>
<td>68 NICU preterm and term babies with suspected sepsis: 41, infected; 27, uninfected</td>
<td>1) Positive blood culture; or 2) ≥3 categories of clinical signs, positive sepsis screen and/or risk factors, and antibiotic therapy ≥7 d</td>
<td>Negative blood culture, negative sepsis screen, and antibiotic therapy &lt;3 d</td>
<td>24 h</td>
<td>≥30</td>
<td>63 (41–81)</td>
<td>71 (63–79)</td>
<td>NA</td>
</tr>
<tr>
<td>Denmark, 2008[83]</td>
<td>123 NICU babies with at least 1 clinical sign suggesting EONS: 29, infected; 94, uninfected</td>
<td>1) Positive blood culture; or 2) ≥2 categories of clinical signs, or clinical chorioamnionitis, and positive blood or CSF culture; or 3) ≥2 categories of clinical signs, or clinical chorioamnionitis, and a haematologic sepsis score &gt;3; or 3) radiographic evidence of pneumonia and a haematologic sepsis score &gt;3</td>
<td>Clinical signs, CRP ≤5 mg/dL, and antibiotic therapy for 3 days; or clinical signs, but no antibiotic therapy</td>
<td>0 h ‡</td>
<td>≥150</td>
<td>46 (32–61)</td>
<td>100 (88–100)</td>
<td>NA</td>
</tr>
<tr>
<td>Brazil, 2010[84]</td>
<td>144 NICU preterm babies presenting RDS during the first 24 h of life: 44, infected; 100, uninfected</td>
<td>1) ≥2 categories of clinical signs, or clinical chorioamnionitis, and positive blood or CSF culture; or 2) ≥2 categories of clinical signs, or clinical chorioamnionitis, and a haematologic sepsis score &gt;3; or 3) radiographic evidence of pneumonia and a haematologic sepsis score &gt;3</td>
<td>No clinical signs, and a haematologic sepsis score &lt;3</td>
<td>≤36 h</td>
<td>&gt;36</td>
<td>82 (68–91)</td>
<td>44 (35–54)</td>
<td>0.72 (0.62–0.83)</td>
</tr>
</tbody>
</table>
France, 2011

213 NICU preterm babies with a presumptive diagnosis of EONS: 31, infected; 182, uninfected

1) Positive culture of blood or CSF, and clinical signs; or

Positive superficial culture without abnormal CRP; alternative diagnosis (obstetrical trauma, perinatal asphyxia, meconium aspiration syndrome, pneumothorax, etc); neither positivesuperficial culture nor abnormal CRP

6 h 300 87.1 (71.1–94.9) 81.9 (75.6–86.8) 0.89 (0.84–0.95)

2) Clinical signs, CRP > 10 mg/L, positive superficial or placental cultures, and no alternative diagnosis

Iran, 2012

65 NICU preterm and term babies with clinical signs of sepsis or maternal risk factors for EONS: 49, infected; 16, uninfected

1) Positive blood culture; or Negative blood culture, < 3 categories of clinical signs, and a negative sepsis screen

6 h 60 53 (39–66) 100 (81–100) NA

2) ≥ 3 categories of clinical signs, and positive sepsis screen or maternal risk factors

Spain, 2012

128 preterm and term babies with prenatal risk factors for EONS (77% asymptomatic at birth): 10, infected; 118, uninfected

1) Positive blood culture and clinical signs; or

NA Cord blood 255.87 90 87.3 0.88

2) ≥ 3 categories of clinical signs (94–96) (80.1–92.3) (0.70 –1.06)

Spain, 2013

213 NICU preterm babies with a presumptive diagnosis of EONS: 31, infected; 182, uninfected

1) Positive blood culture; 2) ≥ 3 categories of clinical signs; or

3) ≥ 1 category of clinical signs, and 1 laboratory (WBC, I:T ratio, CRP) abnormalities

NA Cord blood 15.85 73.3 (56–86) 84 (78–89) 0.81 (0.67–0.95)

Austria, 2014

218 NICU preterm babies with risk factors for EONS: 30, infected; 188, uninfected

1) Positive blood culture; 2) ≥ 3 categories of clinical signs; or

3) ≥ 1 category of clinical signs, and 2 laboratory (WBC, I:T ratio, CRP) abnormalities

NA Cord blood 38 83 (55–95) 82 (75–87) 0.91 (0.85–0.97)

2) Clinical signs, CRP > 10 mg/L, positive superficial or maternal cultures, and no alternative diagnosis categories of clinical signs, and a negative sepsis screen

24 h 10 71 (58–82) 62.5 (39–82)

36 h 150 46.9 (34–61) 100 (81–100)

AUC = Area under the curve; CSF = Cerebrospinal Fluid; CRP = C reactive protein; EONS = Early-onset neonatal sepsis; I:T = Immature-to-total neutrophil; NA = Not available; NICU = Neonatal Intensive Care Unit; PC = Platelet count; PPROM = Preterm Premature Rupture of Membranes; RDS = Respiratory Distress Syndrome; UA = Umbilical artery; UV = Umbilical Vein; WBC = White Blood Cells.
We also determined whether the interpretation of the index test or reference standard was influenced by knowledge of the results of the other test. Review biases, including test review bias (knowledge of the outcome of the reference standard when reviewing the index test) and diagnostic review bias (knowledge of the outcome of the index test when reviewing reference standard) can lead to inflation of the measures of diagnostic accuracy. Information about masking was reported in a minority of reports (4/19). Information regarding methods for calculating IL-6 test reproducibility, as well as the number, training and expertise of the persons executing and reading the index test and the reference standard were among the least commonly reported items from the STARD guidelines. There may be a lack of understanding of the effects of poor reproducibility or low level of expertise on the final outcome of the diagnostic accuracy of a test.

Measures of diagnostic accuracy will be biased if the result of the index test influences the decision to order the reference standard [90]. It is therefore important to state how many participants satisfying inclusion criteria failed to undergo the index tests and/or the reference standard and the reasons for failing to do so. This item was reported in over half of the publications included (11/19). A flow diagram is highly recommended to illustrate the design of the study and provide the exact number of participants at each stage of the study [63,64]; none of the 19 IL-6 diagnostic accuracy studies had a flow diagram.

As the absolute values of diagnostic accuracy are only estimates, when evaluations of diagnostic accuracy are reported the precision of the sensitivity and specificity should be reported. Reporting of CIs is critical to allow a physician to know the range within which the true values are likely to lie [92]. Only 7 (37%) of the 19 included studies reported CIs.

Intermediate, indeterminate, and uninterpretable results may not always be included in final assessment of the diagnostic accuracy of a test. The frequency of these results, by itself, is an important pointer of the overall usefulness of the test. Only two of the 19 included studies reported this item.

Since the technology for existing tests is rapidly improving, it is important to report the actual dates when the study was performed. This will allow the reader to consider any technologic advances since the study was done. Fortunately, most publications provided this information.

In general, the results of our analysis show that over the last two decades the quality of reporting on IL-6 diagnostic accuracy studies for EONS was sub-optimal leaving ample room for improvement. Studies of the same test can produce different estimates of diagnostic accuracy depending on the design, conduct and data analysis. Readers should be aware of the STARD criteria before starting a study in this field.

7. IL-6 response in the early postnatal period and perinatal confounders

Previous studies have suggested that interpretation of the IL-6 response in early life may be affected and confounded by concurrent factors associated with stress, systemic infection and infection [74,79,93]. Absent from most publications on IL-6 accuracy studies for the diagnosis of EONS, however, are data on how the interpretation of the IL-6 response in the infected and uninfected neonates might have been hampered by the severity of the underlying illnesses (and their extent of inflammatory reaction). Clinical severity was described in only half of these publications, and most of them used gestational age and birth weight as simple proxies for more elaborate measures of illness severity (Table 2). Although birth weight and gestational age may be adequate for some purposes, they do not completely account for variations in the severity of illness. Previous reports have emphasized apparent variations in morbidity and mortality among NICUs despite controlling for birth weight and gestational age. Substantial residual variation is still evident after such adjustments [94]. Hence, it is worrying to think that Cobo et al. have considered prematurity and related factors, such as the use of maternal steroids and antibiotics, as the only

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**Table 2**

Quality of reporting of IL-6 accuracy studies (1995–2014) for diagnosing early (<72 h)–onset neonatal infection.

<table>
<thead>
<tr>
<th>Category and Item No.</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>METHODS-PARTICIPANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Describe the study population:</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>1A. the inclusion and exclusion criteria,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1B. setting, and locations where data were collected</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Describe participant recruitment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2A. Was enrollment of patients based only on clinical signs suggesting infection?</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>2B. Were such patients consecutively enrolled?</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>2C. Was enrollment of patients based only on maternal risk factors for infection?</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>2D. Were such patients consecutively enrolled?</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>2E. Were patients identified by searching hospital records?</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>2F. Did the study include both patients already diagnosed with sepsis and participants in whom sepsis had been excluded?</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Describe data collection:</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>3. Was data collection planned before the index test and reference standard were performed (prospective study)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TEST METHODS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methods pertaining to the reference standard and the index test:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4A. Was a composite reference standard used to identify all newborns with sepsis, and verify index test results in infected babies?</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>4B. Was a reference standard used to exclude sepsis?</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>4C. Was a composite reference standard used to identify all newborns without sepsis, and verify index test results in uninfected babies?</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>4D. Did the index test or its comparator form part of the reference standard?</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>5. Were categories of results of the index test (including cut-offs) and the reference standard defined after obtaining the results?</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>6. Did the study report the number, training and expertise of the persons executing and reading the index tests and the reference standard?</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>7. Was there blinding to results of the index test and the reference standard?</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td><strong>STATISTICAL METHODS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Describe the statistical methods used to quantify uncertainty (i.e. 95% confidence intervals)?</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>9. Describe methods for calculating test reproducibility</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td><strong>RESULTS-PARTICIPANTS AND TEST RESULTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10A. Describe when the study was done, including beginning and ending dates of recruitment</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>10B. Did the study report clinical and demographic (postnatal hours or days, gestational age, birth weight, gender) features in those with and without sepsis?</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>10C. Did the study report distribution of illness severity scores in those with and without sepsis?</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>11. Report the number of participants satisfying the criteria for inclusion that did or did not undergo the index tests and/or the reference standard; describe why participants failed to receive either test</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>12. Report a cross-tabulation of the results (including indeterminate and missing results) by the results of the reference standard; for continuous results report the distribution of the test results by the results of the reference standard</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td><strong>RESULTS-ESTIMATES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Report measures of statistical uncertainty (i.e. 95% confidence intervals)</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>14. Report how indeterminate results, missing responses and outliers of index tests were handled</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>15. Report estimates of test reproducibility</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>
possible confounding factors to be adjusted for when assessing the independence of umbilical cord IL-6 in predicting EONS [70]. Moreover, risk factors such as antenatal corticosteroid and antimicrobial use are influenced by the interval between maternal presentation and delivery and by access to care [95]. In a few IL-6 accuracy studies, Apgar scores have also been used as simple proxies for measuring illness severity in neonates with and without early-onset sepsis [76,77,80,83,86]. However, Apgar scores are known to be dependent on gestational age [96], and may actually reflect intrapartum obstetric or anesthesia practices. Low Apgar scores may also suggest a pattern of suboptimal resuscitation or of greater antecedent fetal sedation or compromise [95]. Thus the use of appropriate measures of illness severity is essential for assessing clinical severity in the comparison of results of diagnostic accuracy studies [94,97,98]. To this end, in a study on IL-6 accuracy in diagnosing sepsis in critically ill neonates admitted to the NICU during the first 48 h of life [81], Chiesa et al. used two objective, validated measures of neonatal illness severity, the Score for Neonatal Acute Physiology and its perinatal extension [94,97]. They found that IL-6 levels increase at birth and at 24 and 48 h of life in the presence of bacterial infection, and that the increases are independent of illness severity [81]. They also found that illness severity has the potential to confound IL-6 concentrations in that, among newborns without infection, the higher the illness severity and risk indices, the greater the IL-6 response at birth.

Previous studies have sought to identify which prenatal and perinatal variables would mimic or mask alterations in the IL-6 response caused by infection. Prolonged exercise has been associated with increased production of IL-6 from the stimulated blood monocytes [99]. This observation can possibly explain the higher IL-6 levels during vaginal delivery, where the parturient makes a stronger effort than that during an elective cesarean section. Thus, IL-6 has been consistently found to increase in the fetus in circulation to response to labor or other labor-related events both with and without histologic chorioamnionitis [100–104].

Other noninfectious causes can lead to an increase in IL-6. Cord serum or cerebrospinal fluid levels of IL-6 have been reported to be elevated during the immediate postnatal period in infants with perinatal asphyxia in the presence as well as absence of infection [81,105–110], and have been correlated to the degree of encephalopathy and neurodevelopmental outcome [106]. In a group of 20 infants with fetal acidemia, respiratory depression, and low Apgar scores, cerebrospinal fluid levels of IL-6 were higher among infants with more severe neonatal encephalopathy [105]. This elevation of IL-6 levels could be attributable to brain damage manifesting as neonatal encephalopathy and/or antecedents (including chorioamnionitis) of encephalopathy [111]. The association between elevated IL-6 levels and encephalopathy was found even among infants born to mothers without the diagnosis of chorioamnionitis [112]. Thus, antecedents of neonatal encephalopathy other than chorioamnionitis (that is, hypoxia-ischemia) might lead to elevated levels of IL-6 in the neonatal blood [113].

8. Association of FIRS and EONS with brain injury

Brain injury in the premature infant consists of multiple lesions, principally germinal matrix/intraventricular hemorrhage (IVH), posthemorrhagic hydrocephalus, and periventricular leukomalacia (PVL) [114]. The last of these now appears to be the most important determinant of the neurologic morbidity observed in survivors with birth weight <1500 g, of whom about 10% later exhibit cerebral palsy, and about 50%, suffer cognitive and behavioral deficits [115,116].

The pathogenesis of PVL is multifactorial and probably involves damage, either related to ischemia/reperfusion injury in the critically ill premature infant with impaired regulation of cerebral blood flow, or to inflammation-induced brain injury associated with infection [117]. Relating to the latter, a recent study has shown that maternal intrauterine infection and fetal systemic inflammation play a role in the pathogenesis of PVL [118]. An association between WMI and/or cerebral palsy and maternal, placental, or fetal infections [119–121] with high levels of IL-6 in the amniotic fluid and cord blood, has been demonstrated [122]. Martinez et al. showed that mothers of neonates who developed PVL and IVH within the first week of life had higher median amniotic fluid IL-6 levels (42,795 pg/ml versus 8,020 pg/mL; P = 0.009), more positive amniotic fluid cultures (64% versus 21%; P < 0.003), and a shorter median amniocentesis-to-delivery interval (16 h versus 24 h; P = 0.045) than women who delivered neonates without PVL or IVH [123]. The hypothesis is that the fetal systemic inflammatory response leads to WMI. Indeed, neuropathologic examination has shown that an inflammatory reaction is detected at the early stage of PVL in the brain that persists until the late phase of cystic cavitation [124]. This process is characterized by the presence of active astroglial and microglial proliferation in the brains of infants with PVL and cytokine production [124,125]. The intensity of cytokine production observed in the brains of infants with PVL is higher than in anoxic lesions without PVL, particularly at the early stage of PVL [124]. Whether this brain inflammatory response is secondary to systemic inflammation, hypoxia-ischemia, or both, remains unclear.

Surprisingly, what is emerging is that a significant increase of WMI including a progressive form of WMI that is more readily evident on magnetic resonance imaging scans at term-equivalent age [126], may arise from postnatal infections through a systemic inflammatory response [127–129]. Postnatal infections have been linked to altered development of white matter pathways [130] and widespread impairments in brain development. The increased risk of early WMI with postnatal infection is consistent with the observation that recurrent postnatal sepsis is a risk factor for progressive WMI [126,129]. A few studies have observed that during the immediate postnatal period WMI in preterm infants is associated with an altered equilibrium in the inflammatory IL-6 response to early-onset sepsis and that proinflammatory cytokines such as IL-6 act as part of a larger systemic response. In a prospective cohort study examining the association between cytokines including IL-6 and WMI in 84 very-low-birth weight infants with early-onset sepsis and necrotizing enterocolitis (NEC), Procianoy and Silveira [131] showed that neonates with proven early-onset sepsis, NEC, and high plasma levels of IL-6 were at high risk for WMI. Proven EONS and NEC carried a high risk for WMI even after adjustment for gestational age and birth weight [relative risk, 3.04 (95% CI 1.93–4.80) and relative risk, 2.2 (95% CI 1.31–3.74), respectively]. IL-6 levels obtained during the first 24 h of life were higher in infants with WMI than in control subjects. Using ROC analysis, a plasma level of IL-6 ≥ 116 pg/mL was a good risk predictor for WMI with sensitivity, specificity and negative predictive value being 96%, 77%, and 98%, respectively. Thus these data support the hypothesis that neonatal sepsis leads to an extracerebral inflammatory stimulus and WMI in the immature brain, without bacterial antigen gaining access to the brain. More recently, in an observational study of 176 preterm infants, Hofer et al. [55] showed that elevated cord blood IL-6 concentrations were significantly associated with EONS as well as neonatal mortality, respiratory morbidity, and neurologic morbidity including IVH and PVL.

9. Conclusions

IL-6 has consistently been found to be the best candidate as a diagnostic tool for detecting pre-clinical chorioamnion inflammation and intra-amniotic inflammation leading to preterm birth.
Determination of FIRS (and fetal blood IL-6 concentration) provides a means to recognize neonates who are at risk for adverse neonatal outcome, in particular EONS. Physiologic processes and perinatal confounders in the early life should be taken into account to optimize use of IL-6 in the diagnosis of EONS. The reliability of this cytokine for the differential diagnosis of infectious versus noninfectious systemic inflammatory response during the immediate postnatal period has yielded variable results. Some of this variation reflects differences in reporting quality of IL-6 diagnostic accuracy for EONS. Future well-reported studies showing information on key elements of design, conduct, and analysis would be useful resources to guide decisions on the use and interpretations of IL-6 test results in the diagnosis of neonates with early-onset sepsis. Future studies are also needed to clarify how systemic inflammatory IL-6 response in utero and postnatally, may increase the risk of WMI in postnatal sepsis.

References


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