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Full length article

Correlation between intrapartum CTG findings and interleukin-6 levels in the umbilical cord arterial blood: A prospective cohort study

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ABSTRACT

Objective: to investigate the correlation between the intrapartum CardioTocoGraphic (CTG) findings "suggestive of fetal inflammation" ("SOFI") and the interleukin (IL)-6 level in the umbilical arterial blood.
Study Design: prospective cohort study conducted at a tertiary maternity unit and including 447 neonates born at term.
Methods: IL-6 levels were systematically measured at birth from a sample of blood taken from the umbilical artery. The intrapartum CTG traces were retrospectively reviewed by two experts who were blinded to the postnatal umbilical arterial IL-6 values as well as to the neonatal outcomes. The CTG traces were classified into "suggestive of fetal inflammation (SOFI)" and "no evidence of fetal inflammation (NEFI) according to the principles of physiologic interpretation the CTG traces.
The CTG was classified as "SOFI" if there was a persistent fetal heart rate (FHR) increase > 10 % compared with the observed baseline FHR observed at the admission or at the onset of labor without any preceding repetitive decelerations. The occurrence of Composite Adverse Outcome (CAO) was defined as Neonatal Intensive Care Unit (NICU) or Special Care Baby Unit (SCBU) admission due to one or more of the following: metabolic acidaemia, Apgar score at 5 min ≤ 7, need of neonatal resuscitation, respiratory distress, tachypnoea/polypnea, jaundice requiring phototherapy, hypotension, body temperature instability, poor perinatal adaptation, suspected or confirmed early neonatal sepsis.
Main outcome measures: To compare the umbilical IL-6 values between the cases with intrapartum CTG traces classified as "SOFI" and those classified as "NEFI"; to assess the correlation of umbilical IL-6 values with the neonatal outcome.
Results: 43 (9.6 %) CTG traces were categorized as "SOFI"; IL-6 levels were significantly higher in this group compared with the "NEFI" group (82.0[43.4–325.0] pg/ml vs. 14.5[6.8–32.6] pg/mL; p <.001). The mean FHR baseline assessed 1 h before delivery and the total labor length showed an independent and direct association with the IL-6 levels in the umbilical arterial blood (p <.001 and p = 0.005, respectively). CAO occurred in 33(7.4 %) cases; IL-6 yielded a good prediction of the occurrence of the CAO with an AUC of 0.72 (95 % CI 0.61–0.81).
Conclusion: Intrapartum CTG findings classified as "SOFI" are associated with higher levels of IL-6 in the umbilical arterial blood.

Abbreviations: IL-6, Interleukin-6; FIRS, Fetal Inflammatory Response Syndrome; CTG, CardioTocography; ROM, Rupture of Membrane; FHR, Fetal Heart Rate; BE, Base Excess; NEFI, No Evidence of Fetal Inflammation; NICU, Neonatal Intensive Care Unit; SCBC, Special Care Baby Unit; SOFI, Suggestive of Fetal Inflammation.

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Introduction

Cardiotocography (CTG) was introduced into clinical practice to permit the timely recognition of an ongoing intrapartum hypoxic stress, so that appropriate actions could be taken to avoid hypoxic ischemic encephalopathy (HIE) or perinatal deaths [1–3]. However, intrapartum hypoxic injuries are not the only cause of adverse perinatal outcomes [4–6]. There are several "non-hypoxic" pathways such as inflammation which can also contribute to fetal compromise and resultant poor perinatal outcomes. The Early Notification Scheme Progress Report of the National Health Service (NHS) Resolution found that among the neonates with adverse outcome, evidence of infection in labor was observed in 15.6 % of these cases [7]. Recently, growing evidence has confirmed that intrauterine infection/inflammation leading to clinical chorioamnionitis is an emerging intrapartum pathway of "non hypoxic" fetal injury [8–11]. Bacterial toxins (e.g., lipopolysaccharides or LPS) and inflammatory cytokines (e.g., interleukins or IL-6) not only can cause direct injury to the developing fetal brain and other organs, but then can also potentiate the effects of the super-imposed hypoxic stress [10,12,13]. Furthermore, it has been demonstrated that following a microbial invasion of the amniotic cavity, a fetal inflammatory response syndrome (FIRS) may occur even in absence of clinical maternal signs (so-called "subclinical chorioamnionitis") [13,14]. Prompt detection and appropriate management of such cases can lead to a reduced incidence of adverse outcomes [15–17].

To date, the overall ability to diagnose an ongoing intrapartum fetal inflammation or infection, particularly in the absence of maternal tachycardia and pyrexia is limited; recent studies have demonstrated that the classical Gibbs or the recently proposed Triple I criteria have a poor accuracy in the diagnosis of subclinical chorioamnionitis [18–21]. Moreover, several studies proved that the existing guidelines for the CTG interpretation fail in the diagnosis of chorioamnionitis [23–27]. According to the standard CTG classification [1,2], a suspicion of intrauterine infection should be raised only in presence of fetal tachycardia (>160 bpm), although it is clear that in case of infection some fetuses may rise their baseline without exceeding the cut off value of 160 bpm [28].

Some authors have recently described "inflammatory CTG patterns" which may indicate an ongoing subclinical chorioamnionitis [29–31]. These patterns include an inappropriately high baseline FHR for a given gestational age and/or a persistent FHR increase > 10 % compared with the previously observed baseline FHR at the time of admission or at the onset of labor without any preceding decelerations, both of which have been associated with a higher incidence of chorioamnionitis at histology [29–31].

Placental histopathological examination not only has a suboptimal accuracy in confirming an intraamniotic infection, but, it also does not enable a timely intervention during labor or in the management of the newborn as the results of this examination may not be available shortly after birth [21,22,32]. In contrast, an increase in the markers of fetal inflammation (e.g., IL-6) in the umbilical cord arterial blood is a strong indicator of an intrapartum fetal infection [33].

The aim of this study was to investigate the correlation between intrapartum CTG findings and neonatal IL-6 levels in a cohort of pregnant women at term gestation.

Methods

This was a prospective study including a non-consecutive cohort of women who gave birth at the University Hospital of Parma between March 2022 and February 2023.

The inclusion criteria were the following: singleton viable pregnancy with fetus in cephalic presentation, eligibility to vaginal delivery, diagnosis of active labor, gestational age ≥37 weeks, indication to continuous intrapartum fetal surveillance according to FIGO guidelines 2015 [2] (Supplement 1), normal CTG according to FIGO guidelines 2015 [2] classification at hospital admission and at the onset of active labor. All women were enrolled according to the laboratory availability for the IL-6 measurement (from Monday to Friday; 8 a.m. to 5p.m.).

Exclusion criteria were represented by pre-labor Cesarean delivery, suboptimal CTG recording, labor ward admission during the 2nd stage of labor, a total active labor length < 60 min, suspected or documented fetal arrhythmias, congenital anomalies detected before or after birth, maternal tachycardia (>120 bpm) or isolated pyrexia ≥ 38 °C at admission or during labor, fetal tachycardia (>160 bpm) at admission, diagnosis of clinical chorioamnionitis according to Gibbs [34] or Triple I [35] criteria before or during labor, assumption of drugs which can interfere with maternal or fetal heart rate (beta blockers, thyroid blockers). The administration of antibiotics in the week before labor was also among the exclusion criteria except for the use of intrapartum Ampicillin administered in women positive for GBS or with ruptured membranes for > 18 h as per internal protocol [36].

The labor was managed in accordance with the ACOG/SFMF guidelines for the management of the 1st and 2nd stage of labor [37]. Continuous CTG monitoring during labor was carried in each fetus until delivery using the FIGO 2015 guidelines on intrapartum CTG interpretation.

At birth, together with the paired arterial and venous sample for the blood gas analysis, 3 to 5 additional mL of blood from the arterial cord were collected and analyzed for IL-6 quantification. The decision to send the placenta for pathology was at discretion of the attending physician in charge for the labor management.

The CTG traces from labor admission to delivery were retrospectively evaluated by two senior obstetricians (TG, SF) who were blinded to the postnatal umbilical arterial IL-6 results as well as to the neonatal outcomes. The obstetricians used the principles of physiological CTG interpretation to classify the CTG traces into "suggestive of fetal inflammation (SOFI)" or "no evidence of fetal inflammation (NEFI)" [29,30].

The CTG was classified as "SOFI" if there was:

- a persistent increase in the baseline FHR > 10 % compared with the observed baseline FHR at the time of admission or at the onset of labor without any preceding, repetitive decelerations **with or without**
  A reduced baseline FHR variability (≤5 bpm for > 50 min)
  - OR
  - an increased baseline FHR variability (≥25 bpm for at interval of at least 1 min, which has been described as the "Zig Zag" pattern)
  - OR
  - an absence of FHR cycling (alternating epochs of reduced and normal FHRV reflecting quiet and active fetal sleep cycles) or the presence of sinusoidal pattern (Supplement 2).

In the "SOFI" group, abnormally reduced or increased variability as well as loss of cycling and/ or sinusoidal pattern were considered as CTG findings of neuroinflammation [38,39]. The characteristics of the uterine activity were deliberately not included among the CTG findings suggestive of inflammation as the external tocography is considered to be of limited reliability [40].

All the CTG traces which did not present the features of "SOFI" as described above were classified as "NEFI".

Cases with repetitive decelerations of each type (late, variable, or prolonged) were classified in the "SOFI" or in the "NEFI" group based on their appearance on the CTG trace before or after the increase of the baseline FHR, respectively.

For all the CTG traces of both groups the mean FHR baseline in the last hour before delivery was calculated as the mean between the highest and the lowest FHR on at least ten minutes of stable segments, excluding accelerations and decelerations.

Inconsistencies were discussed by the two Obstetricians and in the event of disagreement the final decision was made by the most

experienced obstetrician (TG), based on the principles of physiological interpretation of intrapartum CTG.

The demographic and clinical characteristics of each woman were retrieved from the medical records. In particular, the following data was collected: total labor length, interval from rupture of membranes (ROM) to delivery, augmentation with oxytocin, meconium-stained amniotic fluid, antibiotics prophylactically administered during labor, operative delivery (both cesarean and instrumental vaginal delivery).

The clinical data of each neonate including birthweight, Apgar score at 5 and 10 min, umbilical cord artery and vein pH and base excess (BE), need of resuscitation and admission to Neonatal Intensive Care Unit (NICU) or to Special Care baby Unit (SCBC) were also collected.

The occurrence of a Composite Adverse Outcome (CAO) was defined as the NICU or SCBU admission due to one or more of the following: metabolic acidosis (arterial pH < 7.00 and/or BE $\leq$ -12 mEq/L); Apgar score at 5 min ≤ 7, need for neonatal resuscitation, respiratory distress, tachypnoea/polypnea, jaundice requiring phototherapy, hypotension, body temperature instability, poor perinatal adaptation, confirmed (by positive blood cultures) early onset neonatal sepsis (EONS) < 72 h after birth. The postnatal management of the infant was not influenced by the IL6 levels which became available on average a week after birth.

Sample collection and analysis

The umbilical cord was clamped 60 to 180 s after delivery as per local standard practice for uneventful birth to assess the blood gases [41]. An additional amount of about 3–5 mL of the arterial blood was sampled using a vacutainer collecting system and then centrifugated. Supernatants were stored at −70° C until the testing. A solid phase Enzyme Amplified Sensitivity Immunoassay (ELISA) (Demeditec, Diagnostics GmbH, Lise-Meitner-Straße 2, 24,145 Kiel, Germany) using monoclonal antibodies directed against distinct epitopes of IL-6 was used to assess the levels of this cytokine in the umbilical blood. Analysis were performed on Gemini Combo automated microplate and slide processor (Diatron, Tablas u.39, H-1097, Budapest, Hungary). The limit of detection for this assay declared by the manufacturer was 2 pg/mL and inter-assay and intra-assay coefficients were less than 10 % (4.2 and 4.4 respectively).

Outcome

The primary outcome of the study was to compare the IL-6 values in the umbilical cord arterial blood the cases with intrapartum CTG traces classified as “SOFI” and those classified as “NEFI”. As a secondary outcome the association between the IL-6 levels and the incidence of neonatal CAO was investigated.

Statistical analysis

Statistical analysis was performed by using the Statistical Package for Social Science (SPSS), release 21.0 and Jamovi release 1.6.23. The Kolmogorov–Smirnov test was used to assess the normality of the distribution of the data. Continuous variables were reported as median [IQR], categorical variables were reported as n (%). Categorical variables were compared using the Chi-square or Fisher exact test, while comparison of continuous variables included *T* test for independent sample and 2-tailed t-tests. Between-group comparison of continuous variables was under- taken using *t* test and the Mann-Whitney nonparametric equivalent test. Comparisons between more than two groups were performed using Kruskal-Wallis or analysis of variance test as appropriate. Spearman’s coefficient was used to test the correlation between IL and 6 values and the following variables: total labor length, interval time between ROM and delivery, gestational age at delivery and mean FHR baseline during the last hour before delivery. Multivariable logistic analysis was used to control for potential confounders. The prediction of the secondary outcome (CAO) was determined by receiver operating characteristic (ROC) curve analysis. $P < 0.05$ was considered as statistically significant. The study was conducted following the STROBE Guidelines [42].

The research protocol was approved by the local ethics committee (nr 0000205) and informed consent obtained from each subject involved.

Results

Overall, 2935 deliveries were recorded during the study period, among whom 680 fulfilling the inclusion criteria were assessed for eligibility. Of these, 447 were included in the final analysis (Supplement 3) with 43(9.6 %) of them presenting a CTG trace classified as “suggestive of fetal inflammation (SOFI)”. The comparison of the maternal and labor characteristics between the cases with intrapartum CTG traces classified as “SOFI” and those classified as “NEFI” is shown in Table 1.

The cases with intrapartum CTG classified as SOFI had significantly higher levels of IL-6 (82.0[43.4–325.0] pg/mL vs. 14.5[6.8–32.6] pg/mL respectively; $p < 0.001$), a longer interval between ROM and delivery (540.0 [344.0–960.0] vs 279.0[84.0–575.0] min; $p < .001$) as well as a longer total length of labor (477[385.0–630.0] vs 280.0 [156.0–445.0] min; $p < 0.001$) compared with the NEFI group. Also, in the former group, a higher rate of meconium-stained amniotic fluid (23.2 % vs. 7.2 %; $p < 0.001$) was noted.

A significant direct correlation was found between the IL-6 levels in the umbilical arterial blood and the following variables: gestational age at delivery (Spearman’s coefficient 0.17p <.001), total labour length (Spearman’s coefficient 0.33p <.001), ROM to delivery interval (Spearman’s coefficient 0.29p <.001), mean FHR baseline 1 h before delivery (Spearman’s coefficient 0.21; p <.00) (Table 2). Moreover, an inverse correlation between IL and 6 levels and the umbilical arterial BE was also found (Spearman’s coefficient −0.11; $p = 0.03$) (Table 2).

Table 1
Maternal demographics and labor characteristics in the group with CTG findings defined as “Suggestive of Fetal Inflammation” (SOFI) and in that with “No Evidence of Fetal Inflammation” (NEFI).

Variables	NEFI (n = 404)	SOFI (n = 43)	p-value
Maternal age (years)	32.0[28.0–35.0]	31.0[26.5–35.0]	0.31
Caucasian	311(77.0)	37(86.0)	0.17
Pre-pregnant BMI	22.6[20.3–26.0]	22.1[21–0-25.0]	0.79
Weight gain (Kg)	12.1[9.5–15.0]	12.0[10.0–15.0]	0.78
Nulliparous	225(55.8)	29(67.4)	0.14
Gestational age at delivery (weeks)	39.6[39.0–40.4]	40.4[39.3–41.0]	0.05
PROM	108(26.7)	14(32.6)	0.42
IOL	156(38.6)	18(41.8)	0.67
• PGE1 + mechanical method	78(19.3)	9 (20.9)	0.08
• PGE1	39(9.6)	9 (20.9)	
• Mechanical method	22(5.4)	0	
• Oxytocin	17(4.2)	0	
Prophylactic antibiothic	121(30.0)	18(41.9)	0.11
Caesarean Section in labor	11(2.7)	2(4.7)	0.81
Interval ROM to delivery (min)	279.0 [84.0–575.0]	540.0 [344.0–960.0]	<0.001
Total length of labor (min)	280.0 [156.0–445.0]	477[385.0–630.0]	<0.001
GBS status	72(17.9)	6(13.9)	0.52
Meconium-stained amniotic fluid	29(7.2)	10(23.2)	<0.001
Augmentation with oxytocin	153(37.8)	22(51.1)	0.09
Epidural analgesia	215(53.3)	28(65.1)	0.14
IL-6 pg/mL	14.5[6.8–32.6]	82.0[43.4–325.0]	<0.001
Arterial pH	7.25[7.21–7.30]	7.24 [7.19–7.26]	0.04
BE mmol/L	−2.1[-4.6 to 0.2]	−4.6[-5.4 to −2.0]	<0.001

Numbers are expressed as Median[IQR] or n(%).
BMI = body Mass Index; PROM = Premature Rupture of Membranes; IOL = Induction of Labor; ROM = Rupture of Membranes; GBS = Group B Streptococcus, IL-6 = Interleukin-6; BE = Base Excess, PGE1 = Prostaglandin E1.

Table 2
Correlation between the IL-6 in the umbilical artery and labor characteristics.

Variable	Spearman's coefficient	p-value
Gestational age at delivery (weeks)	0.17	<0.001
Birthweight (g)	0.04	0.40
Total labor length (min)	0.33	<0.001
Interval time ROM to delivery (min)	0.29	<0.001
Mean FHR baseline 1 h before delivery (bpm)	0.21	<0.001
Arterial pH	−0.10	0.05
Arterial BE (mmol/L)	−0.11	0.03

ROM = Rupture of Membranes; FHR = Fetal Heart Rate; BE = Base Excess.

At the multivariable logistic analysis, the mean FHR baseline in the last hour before delivery and the total labor length remained the only variables independently associated with the IL-6 levels in the umbilical arterial blood (p <.001 and p =.005 respectively) (Supplement 4).

In the group of fetuses whose intrapartum CTG was classified as SOFI the IL-6 values were significantly higher in those cases with CTG features consistent with fetal neuroinflammation (abnormally increased or reduced FHR variability and/or loss of cycling (n = 21)) compared with those with normal cycling and normal FHR variability (n = 22) (202 [78.8–994.0] vs. 48.8[36.8–148.0]pg/mL p < 0.001).

Overall, 33/437 (7.6 %) of neonates had a CAO. The characteristics of the neonates with and without CAO are compared on Table 3. In the group of neonates with a CAO a significantly longer interval from ROM to delivery (705[343.0–1010.0] vs. 286[84.0–569.0]; p <.001) as well as a higher incidence of intrapartum CTG classified as SOFI (27.3 % vs 8.2 %; p <.001),a higher incidence of meconium-stained amniotic fluid (21.2 % vs. 7.7 %; p = 0.008), higher IL-6 values on arterial cord (43.3 [22.6–260.0] pg/mL vs. 15.9[7.3–38.9] pg/mL respectively; p <.001) and significantly lower BE values in umbilical arterial blood (-4.0[-6.3 to −1.8] mmol/L vs −1.92[-4.6 to −0.1] mmol/L p = 0.006) were found.

Binomial logistic regression including all the variables that were significantly different at the univariate analysis showed that IL-6 level on umbilical artery was the only independent predictor of CAO (p = 0.04) (Table 4).When comparing the diagnostic accuracy of the IL-6 values in predicting the risk of CAO an AUC of 0.72 (95 % CI 0.61–0.81) was found with a best-cutoff value of 20.9 pg/mL which yielded a 81.2 % sensitivity, 58.2 % specificity 13.5 % PPV and 97.6 % NPV (Fig. 1).

Discussion

Our study suggests that an intrapartum CTG trace categorized as suggestive of fetal inflammation "SOFI" is associated with higher levels of IL-6 in the umbilical arterial blood as well as with a longer labor duration, a longer interval between ROM and delivery and a higher incidence of meconium-stained amniotic fluid. Moreover, the mean FHR baseline in the last hour before delivery and the total labor length were positively and independently correlated with the IL-6 levels in the umbilical artery. In the group of fetuses whose intrapartum CTG was classified as SOFI, the IL-6 values were significantly higher in the presence of features suggestive of fetal neuroinflammation (abnormally increased or reduced FHR variability and/or loss of cycling, and /or sinusoidal patterns in association with > 10 % increase in the baseline FHR). Lastly, this study suggests that an increased IL-6 level in the umbilical arterial blood at birth is a good predictor of CAO.

Table 3
Labor characteristics according to the presence/absence of a neonatal Composite Adverse Outcome (CAO).

Variables	No CAO (n = 414)	CAO (n = 33)	p-value
Gestational age at delivery (weeks)	39.6[39.0–40.4]	39.3[38.6–40.3]	0.12
Birthweight (g)	3375 [3120–3566]	3425[2971–3805]	0.98
Interval ROM-delivery (min)	286[84.0–569.0]	705 [343.0–1010.0]	<0.001
Total labor length (min)	290 [163.0–474.0]	383[253.0–454.0]	0.08
Meconium-stained amniotic fluid	32(7.7)	7(21.2)	0.008
Caesarean Section	10(2.4)	3(9.1)	0.20
CTG features defined as SOFI	34(8.2)	9(27.3)	<0.001
Arterial pH	7.22[7.21–7.20]	7.21[7.16–7.27]	0.88
Arterial BE mmol/L	−1.92[-4.6–0.1]	−4.0[-6.3–1.8]	0.006
IL-6 (pg/mL)	15.9[7.3–38.9]	43.3[22.6–260.0]	<0.001

Numbers are expressed as Median[IQR] or n(%).
ROM = Rupture of Membranes; BE = Base Excess; SOFI = suggestive of fetal inflammation

Table 4
Binomial logistic regression of the variables associated with the occurrence of a neonatal Composite Adverse Outcome.

Predictor	Estimate	SE	Z	p
Meconium-stained amniotic fluid	0.88400	0.5515	1.603	0.10
Interval ROM-delivery	4.81e-4	2.62e-4	1.834	0.07
Arterial BE (mmol/L)	−0.10826	0.0599	−1.807	0.07
CTG features defined as SOFI	0.48886	0.5825	0.839	0.40
IL-6 pg/ml	**0.00118**	**5.71e-4**	**2.061**	**0.04**

ROM = Rupture of Membrane;BE = Base Excess; SOFI = suggestive of fetal inflammation

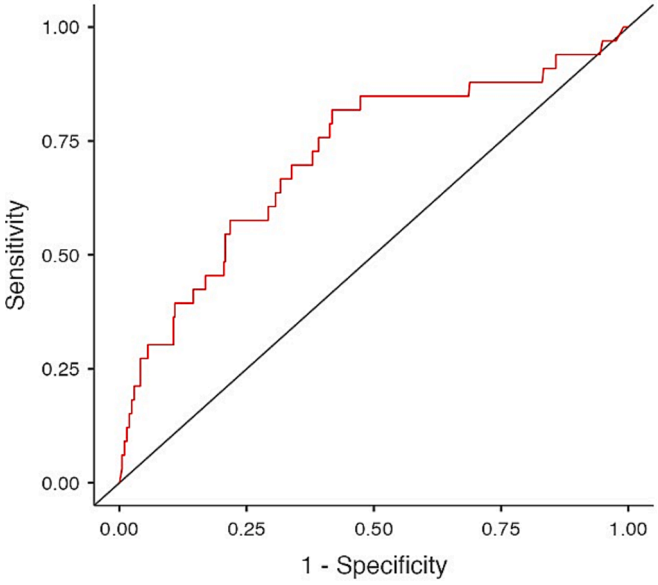

Fig. 1. Receiving Operating Characteristics (ROC) curves of the IL-6 (pg/mL) in predicting the risk of a neonatal Composite Adverse Neonatal Outcome.

Strengths and limitations

The main strengths of our study are represented by its original design and by the large number of cases prospectively included. Based on the authors' best knowledge, it is the first study which correlated the intrapartum CTG features suggestive of fetal inflammation with the IL-6 levels in the umbilical arterial blood collected immediately after birth. These may be considered as an objective hallmark of intrapartum fetal inflammation. Moreover, all the recent studies which described the intrapartum CTG features suggestive of fetal inflammation based on physiological interpretation of CTG were retrospective with smaller numbers.

The main limitation of our study is represented by the lack of a systematic placental analysis; however, the correlation of intrapartum

CTG or of the IL-6 levels with the placental histology did not represent an outcome of our study. In addition, the placental analysis is known to have a suboptimal reliability in the confirmation of an intrapartum chorioamnionitis [21,22]. This is because chorioamnionitis has been shown to occur secondary to amniotic fluid inflammation without the presence of bacteria, and inhalation of this amniotic fluid may result in fetal inflammation without any changes in placental histopathology [13]. In contrast, detection of IL-6 in the umbilical blood truly reflects an ongoing fetal systemic inflammatory response (FIRS).

Due to the exclusion of cases with isolated maternal pyrexia or diagnosis of clinical chorioamnionitis according to Gibbs [34] or Triple I [35] criteria before or during labor, no case of EONS has been reported in our series; therefore, we were not able to assess the correlation between the IL-6 levels and the occurrence of this complication which has an estimated incidence of 0.4/1000 live births [43].

Also, the lack of a systematic assessment of the inflammatory markers on the neonate (e.g., white blood cells count, C-reactive protein) may be seen as a potential weakness. However, the neonatal management and the request of additional laboratory tests or therapies was at discretion of the clinician in charge of the individual case. This was because the IL-6 cord values were not made available to the neonatal team to the pediatricians after birth as per our study protocol.

Interpretation in the context of what is known

IL-6 is widely acknowledged as a major mediator of the acute phase response to a tissue inflammation/injury and FIRS is currently defined as its elevation on the fetal plasma [13,14,33]. Based on several studies conducted on preterm fetuses, a cut-off of 11 pg/mL in samples of fetal plasma obtained by cordocentesis has been shown to identify those fetuses at increased risk of severe neonatal morbidity [44,45].

The few existing studies on term neonates have confirmed that cord blood IL-6 levels are reliable in confirming the occurrence of fetal infection and predicting the risk of EONS [46,47]. Tasci et al. [48] reported that IL-6 values $>$ 39 pg/mL had 100 % sensitivity and 81 % specificity in predicting funisitis and positive newborn cord blood cultures. This higher cut-off reported in term neonates at birth compared with fetuses submitted antenatally to cordocentesis probably reflects a physiological raise of the IL-6 levels due to the stress reaction induced by labor itself [49]. Rogers et al. [50] also found that umbilical IL6 levels had greater elevations in term infants compared to preterm infants and proposed that this difference may be related to the relative immaturity of the preterm immune system. In our own study higher values of IL-6 (about 20 pg/mL) were found to be associated with adverse perinatal outcome compared with those reported in preterm infants [44].

Our findings have confirmed that IL-6 may be considered a reliable marker of fetal inflammation as its levels increase according to the presence of a CTG trace classified as "SOFI". Moreover, the IL-6 levels in the umbilical arterial blood seem higher in fetuses with CTG features suggestive of neuroinflammation which indicates a more severe fetal inflammation. This finding may have an important impact on clinical practice in avoiding or limiting superimposed hypoxic stress in the presence of features of neuroinflammation.

To date, few studies have investigated the relationship between intrapartum CTG features and the occurrence of clinical or subclinical chorioamnionitis. Aina-Mumuney et al found that selected CTG parameters (i.e., tachycardia, decelerations, variability) had a sensitivity of 29–65 % and a specificity of 46–93 % in identifying fetal systemic inflammation defined as the presence of findings of chorioamnionitis or funisitis at placental histology [23]. More recently, Sukumaran et al. analysed the CTG features of 57 cases of histologically confirmed chorioamnionitis and/or funisitis. A baseline FHR increase $\geq$ 10 % compared with the values observed at the onset of labor was noted in all these cases and loss of cycling in the vast majority of them (54 or 94.7 %) [29]. Galli et al. [30] reported that the intrapartum CTG features which in accordance with the Physiological CTG interpretation are considered suggestive of chorioamnionitis (inappropriately high FHR for a give gestational age or persistent FHR increase $>$ 10 % compared with the values at admission or at labor onset without preceding repetitive decelerations) were associated with a higher incidence of adverse perinatal outcome. The main limitation of most of these studies was that the occurrence of an intrapartum intraamniotic inflammation/infection was defined solely on the basis of placental histology whose reliability is acknowledged to be suboptimal [22,32].

On the contrary, cord IL-6 might be considered a valuable marker of intrapartum intraamniotic infection/inflammation. Its concentration on the umbilical artery is higher in the fetuses who exhibited intrapartum CTG features defined as SOFI and correlates with the risk of neonatal morbidity associated with infectious/inflammatory injury.

In addition, our study found that the IL-6 levels were higher among those cases of intraamniotic infection characterized by an abnormal (reduced or increased) variability and/or loss of cycling thus indicating that IL-6 may be considered also as a marker of severity of FIRS [51]. These results were consistent with those reported by Pereira et al. [38] in a study on 648 intrapartum CTG traces. Absence of cycling from the beginning of the intrapartum recording occurred in 5 % of the included cases and these infants were more likely to have poorer perinatal outcome despite a normal pH at birth.

To date, a clear correlation between intrapartum fetal infection and adverse neonatal outcome has been made only in those cases presenting with maternal signs of infection. Based on recent literature findings, it is plausible to speculate that the fetal injury may start long before the appearance of overt signs of infection in the mother [52–55]. However, the identification of isolated fetal infection (i.e. subclinical chorioamnionitis) may represent a challenge for the clinicians; in this context, the findings of our study are likely to have a significant impact on intrapartum care of fetuses exposed to both clinical and subclinical chorioamnionitis by enabling the timely diagnosis of those CTG features defined as SOFI which are associated with an increased levels of IL-6 in the fetal blood. Fetal inflammation is not an "intermittent" stress, but a continuous fetal stress with enhanced metabolic rate and fetal inflammatory response syndrome. Therefore, this will permit the clinicians to avoid superimposed hypoxic stress which has been shown by experimental animal models and observational human studies to worsen perinatal and long-term neurological outcomes.

Similarly, when considering the postnatal assessment, few reliable tools are currently available to promptly identify those neonates exposed to an intrauterine infection/inflammation who are at higher risk of perinatal complications and may require an intensive surveillance [56]. Among them, the Kaiser score based on clinical information is considered as the most promising screening tool to predict the risk of EONS [57–59]. The increased levels of IL-6 in umbilical cord arterial blood at birth may be a useful tool to confirm or exclude an intrapartum fetal inflammation and to predict the risk of neonatal morbidity. In this perspective the implementation of a rapid test to quantify the levels of IL-6 on the arterial cord may be envisaged as a possible new strategy to confirm intrapartum fetal inflammation which can be combined with the blood gas analysis used for the diagnosis of neonatal acidemia due to intrapartum hypoxia.

Conclusion

Increased levels of IL-6 in the umbilical cord arterial have been found to be associated with CTG features suggestive of fetal inflammation (SOFI) during labour. Moreover, features of neuroinflammation (loss of cycling, abnormally increased or reduced FHR variability and/or sinusoidal patterns) are associated with a further increase in the IL-6 levels, possibly indicating a worsening severity of the fetal systemic inflammatory response (FIRS). These findings are very likely to have an impact on clinical practice by enabling the frontline clinicians to avoid superimposed hypoxic stress to improve short term and long-term perinatal outcomes. Larger studies are needed to assess if this marker may be

introduced in the routine clinical practice to help modify neonatal care.

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CRediT authorship contribution statement

Elvira di Pasquo: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Stefania Fieni:** Conceptualization, Supervision. **Edwin Chandraharan:** Conceptualization, Writing – review & editing. **Andrea Dall'Asta:** Writing – review & editing, Formal analysis. **Giovanni Morganelli:** Data curation. **Marta Spinelli:** Data curation. **Maria Laura Bettinelli:** Data curation. **Rosalia Aloe:** Data curation, Formal analysis, Methodology. **Annalisa Russo:** Data curation, Investigation, Methodology. **Letizia Galli:** Conceptualization, Writing – review & editing. **Serafina Perrone:** Conceptualization, Data curation, Supervision. **Tullio Ghi:** Conceptualization, Formal analysis, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2024.01.018.

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