Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Exposure to intrauterine inflammation and late-onset sepsis in very preterm infants

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BACKGROUND: Late-onset sepsis is an important cause of mortality and morbidity in preterm infants. As these infants rely mostly on their innate immune system to fight off infection, enhancing this immune system by appropriate stimuli may prevent late-onset sepsis. However, it remains unclear which stimuli can enhance the neonatal immune system. This study aims to investigate the influence of intrauterine inflammation on late-onset sepsis.
METHODS: This is a retrospective cohort study in a Neonatal Intensive Care Unit in the Netherlands. Between 2005 and 2016, 1014 infants with ≤32 weeks gestational age and/or with a birth weight ≤1500 g were included. Intrauterine inflammation was subdivided into histological chorioamnionitis, fetal inflammatory response, and funisitis. Logistic and Cox regression analyses were performed to investigate the influence of intrauterine inflammation on late-onset sepsis.
RESULTS: Thirty-six percent of the included infants developed late-onset sepsis; 24% of placentas showed intrauterine inflammation. Late-onset sepsis incidence did not differ between infants with or without exposure to intrauterine inflammation after adjustment for gestational age (histological chorioamnionitis aHR 0.928 [CI: 0.727–1.185], $p = 0.551$; fetal inflammatory response aHR 1.011 [CI: 0.793–1.288], $p = 0.930$); funisitis aHR 0.965 [CI: 0.738–1.263], $p = 0.797$).
CONCLUSIONS: Late-onset sepsis in very preterm infants seems not to be associated with intrauterine inflammation.

Pediatric Research (2022) 91:230–234; https://doi.org/10.1038/s41390-021-01455-0

IMPACT:

- Intrauterine inflammation is not protective of developing late-onset sepsis in premature infants.
- A large cohort study on the effect of intrauterine inflammation on neonatal outcome.
- This study adds to existing knowledge on finding appropriate stimuli to enhance the immune system of premature infants to improve neonatal outcome.

INTRODUCTION

Late-onset sepsis (LOS) is an important cause of death and morbidity among preterm born infants.[1,2] Although the mechanisms underlying this vulnerability are not yet fully understood, it is increasingly acknowledged that the innate immune system is important to withstand infection. Emerging evidence shows that, besides the humoral and cellular immune system, the innate immune system also has adaptive characteristics and memory.[3] Exposure to appropriate stimuli may result in an enhanced immune response as seen by epigenetic changes in innate immune cells. This is referred to as trained immunity and may reduce susceptibility to infection.[3,4] Intrauterine inflammation (IUI) due to histological chorioamnionitis (HCA) is characterized by infiltration of neutrophils into the chorionic disc of the placenta or extraplacental membranes. Fetal inflammatory response is defined as infiltration of neutrophils of the fetus into chorionic or umbilical blood vessels.[5,6] IUI is a major risk factor for preterm birth and therefore contributes to neonatal morbidity and mortality.[7,8]

Previous studies indicate an effect of IUI on infection independently of prematurity. Most studies indicate that HCA increases the risk of developing early-onset sepsis (EOS).[9,10] To date, nevertheless, data on the influence of IUI on LOS are conflicting. Strunk et al. found HCA to decrease LOS incidence in very low birth weight (VLBW) infants,[11] while others did not find difference in incidence of LOS.[12,13] Confirming the association between IUI and LOS could be an important step to gain more insight into the innate immune response. Therefore, the aim of this study was to investigate whether there is an association between IUI and the incidence of LOS in VLBW infants. Furthermore, we investigated the influence of IUI on early postnatal morbidities like EOS, respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH).

PATIENTS AND METHODS

This retrospective hospital-based cohort study was conducted at the level III Neonatal Intensive Care Unit (NICU) of the Amsterdam UMC location VU medical center (VUmc) in Amsterdam, the Netherlands. All infants admitted between January 1, 2005 and December 31, 2016 with a gestational age (GA) ≤ 32 weeks and/or

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Received: 8 October 2020 Revised: 16 February 2021 Accepted: 17 February 2021
Published online: 17 March 2021

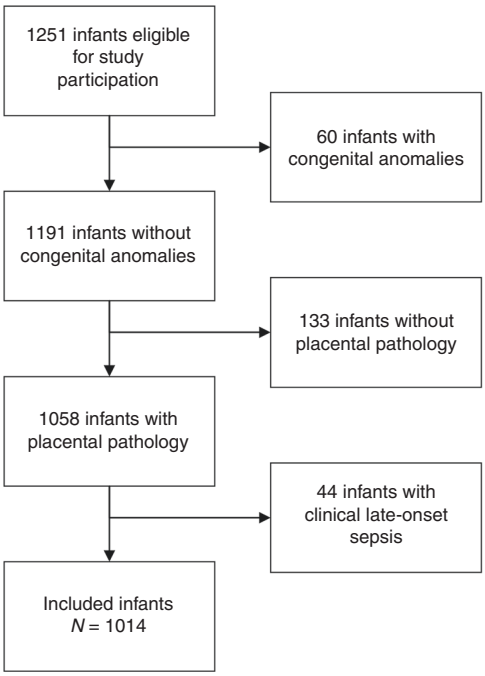

Fig. 1 Flowchart of patient selection for the cohort. N number of patients.

with a birth weight (BW) of ≤1500 g were included in the study. Demographic and clinical data were obtained from the patient records and electronic health record. Infants with major congenital anomalies, infants without placental histologic examination, and infants with culture-negative LOS were excluded from analysis.

In total, 1251 VLBW infants or premature infants with a GA ≤ 32 weeks and/or with a BW ≤ 1500 g were admitted to the level III NICU between January 1, 2005 and December 31, 2016. One thousand and fourteen infants were eligible for study participation after applying the exclusion criteria (Fig. 1). If infants suffered more than one episode of LOS, only the first episode was taken into analysis.

According to the Medical Ethical Review Committee of the VUmc, the Medical Research Involving Human Subjects Act (WMO) does not apply to this study. Therefore, no informed consent from the subjects was required.

Placental pathology

In general, placentas of all infants were examined. Histological slides of placentas previously diagnosed with an inflammatory response were reassessed to determine the location and severity of inflammation. The pathologist was blinded toward clinical outcomes. Semi-quantitative histologic scoring of the extraplacental membranes, umbilical cord, and placenta was performed by using a standardized diagnostic framework according to Redline et al. and the consensus statement of the Amsterdam Placental Workshop Group.[5,6] The maternal inflammatory response was defined as an inflammatory reaction characterized by infiltration of neutrophils of maternal origin into the subchorionic fibrin, the chorion, or the amnion. It is subdivided into three stages: (1) subchorionitis or chorionitis, (2) acute chorioamnionitis, and (3) necrotizing chorioamnionitis. Only stage two and three are regarded as HCA. The fetal inflammatory response is defined as an inflammatory reaction characterized by infiltration of neutrophils of fetal origin into the wall of chorionic blood vessels, the umbilical vein, or umbilical arteries. It is subdivided into three stages: (1) chorionic vasculitis, (2) umbilical vasculitis, and (3) concentric umbilical perivasculitis. Funisitis is defined as inflammation of the umbilical vein or arteries, and sometimes the Wharton jelly (stages two and three).[5,6]

Outcome

LOS was defined by the following: (1) a positive peripheral blood culture >72 h after birth, (2) clinical signs of sepsis, and (3) appropriate antibiotic treatment for at least 5 days.[1] If culture was negative, a LOS episode was defined as clinical and excluded. EOS was defined by clinical signs of sepsis within 72 h after birth, appropriate antibiotic treatment for at least 5 days, and a positive peripheral blood culture.[1] Because many mothers receive antibiotics prior to birth, blood cultures in the first days of life may be false negative. We therefore decided to report EOS including clinical suspect cases who received >5 days of antibiotics with a negative blood culture. IVH was defined according to the grading by Papille et al.[14] The diagnosis of RDS was based on the clinical judgment of the physician on call and/or typical findings on the X-ray. NEC was defined by Bell's stages; only infants who developed NEC stage IIa or more were considered as NEC.[15]

Statistical analysis

Statistical analysis was performed by using the SPSS statistical software version 24.0 for Windows (Chicago, IL, USA). All analyses were two sided, and a p value of <0.05 was considered statistically significant. Frequencies were used to summarize categorical data, whereas means and standard deviations or medians and interquartile ranges (IQRs) were used to summarize continuous data. Contingency tables were analyzed by using Fisher's exact tests. Means were compared using the unpaired Student's t test. Effects of IUI on LOS and time until infection were examined using Cox proportional hazards regression. The effects were summarized using hazard ratios (HRs) and 95% confidence intervals (CIs) and adjusted for GA and EOS. Logistic regression analysis was performed to evaluate the effect of IUI on other neonatal outcomes (EOS, IVH, RDS, and NEC) and adjusted for GA. Data are represented as odds ratios (ORs) and 95% CIs.

RESULTS

The 1014 infants eligible for study participation had a mean GA of 29 weeks (SD ±2.1 weeks and with a range of 23–37 weeks), a mean BW of 1217 g (SD ±337 g), and 54% was male. Of the 1014 infants, 364 (36%) developed one or more LOS episodes, with coagulase-negative Staphylococci as the most common pathogen (Table 1). Seventy-five percent of infants developed the first episode of LOS within the first 11 days of life, with the median postnatal age of 7 days (IQR 6–11). Infants with LOS had significantly lower GA and BW (GA (mean ± SD): 28.1 ± 2.0 vs. 29.4 ± 2.1, $p < 0.001$, BW (mean ± SD): 1091 ± 294 vs. 1287 ± 342 g, $p < 0.001$; Table 2) but no significant difference in BW z-score ($p = 0.526$; Table 2). Apgar scores at 1 and 5 min were significantly lower in the infants with LOS (Table 2), and RDS and NEC were more prevalent in the LOS group (Table 2). Furthermore, infants in the LOS group in comparison to infants without LOS required longer mechanical ventilation (48 h, IQR 0–288 vs. 0 h, IQR 0–48 h, $p < 0.001$; Table 2) and continuous positive airway pressure (360 h, IQR 144–696 vs. 96 h, IQR 0–312 vs., $p < 0.001$; Table 2). EOS was more prevalent in the non-LOS group, whereas NEC and RDS were more prevalent in the LOS group (Table 2).

IUI and outcome

HCA was found in 240 of the 1014 (24%) placentas. A fetal inflammatory response was present in 242 placentas; in 4 cases, information on fetal involvement was not available. Seventeen placentas had a fetal inflammatory response without HCA; however, only two placentas had a fetal inflammatory response without any maternal inflammatory response. Neutrophilic

Table 1. Causative pathogens of first late-onset sepsis episode.

	N (%)
Total infants with LOS	364 (100)
Pathogen	
Gram positive	331 (90.9)
CoNS	272 (74.7)
Staphylococcus aureus	48 (13.2)
Other	11 (3.0)
Gram negative	30 (8.3)
Escherichia coli	9 (2.3)
Serratia marcescens	7 (1.9)
Klebsiella oxytoca	5 (1.4)
Other	9 (2.7)
Yeast	3 (0.8)
Candida albicans	3 (0.8)

CoNS coagulase-negative Staphylococci, *LOS* late-onset sepsis.

Table 2. Risk factors and outcomes for infants with and without late-onset sepsis.

Risk factors/outcomes	LOS		*p* value
	No $n = 650$ (64%)	Yes $n = 364$ (36%)	
GA (weeks)	29.4 ± 2.1, range 23–37	28.1 ± 2.0, range 24–34	<0.001
BW (g)	1287 ± 342	1091 ± 294	<0.001[a]
BW *z*-score	−0.21 ± 0.98	−0.17 ± 0.98	0.526
SGA	92 (14%)	50 (15%)	0.849
Gender (male)	332 (51%)	197 (58%)	0.052
Apgar at 1 min <7	307 (48%)	196 (58%)	0.003
Apgar at 5 min <7	109 (17%)	84 (25%)	0.004
Mechanical ventilation (h)	0 (IQR 0–48)	48 (IQR 0–288)	<0.001[a]
CPAP (h)	96 (IQR 0–312)	360 (IQR 144–696)	<0.001[a]
Antibiotics in the first 3 days postpartum	516 (79.9%)	286 (79%)	0.745
Intrauterine inflammation			
HCA	144 (22.2%)	96 (26.4%)	0.144
Any fetal inflammatory response	142 (22%)	100 (27.5%)	0.055
Funisitis	106 (16.4%)	68 (18.7%)	0.386
HCA and funisitis	103 (15.9%)	65 (17.9%)	0.429
Neonatal morbidity			
EOS	64 (9.9%)	20 (5.5%)	0.017
IVH stage ≥2	47 (7.5%)	39 (10.7%)	0.08
RDS	316 (49%)	278 (76.6%)	<0.001
NEC stage ≥2	14 (2.2%)	40 (11.1%)	<0.001
Mortality	79 (12.2%)	31 (8.5%)	0.092

Data shown as *n* (%), mean ± SD, or median (IQR). *p* Value for continuous data were calculated by independent *T* test, for categorical data by Fisher's exact.
LOS late-onset sepsis, *GA* gestational age, *BW* birth weight, *SGA* small for gestational age, *IQR* interquartile range, *CPAP* continuous positive airway pressure, *HCA* histological chorioamnionitis, *EOS* early-onset sepsis, *IVH* intraventricular hemorrhage, *RDS* respiratory distress syndrome.
[a]Independent *T* test, equal variances not assumed.

infiltration in the umbilical cord, funisitis, was found in 174 of the 1014 placentas (17%). HCA and funisitis were found to be inversely correlated to GA; at 25 weeks, 49% had HCA and 21% funisitis, compared with 8 and 8%, respectively, at 32 weeks (HCA: $p < 0.001$, funisitis: $p < 0.001$) (Fig. 2). Preterm premature rupture of membrane was more common in infants exposed to HCA compared to infants not exposed to HCA (60 vs. 14%, $p < 0.001$).

Risk and time to developing LOS was analyzed with Cox hazard regression and censored for death and loss to follow-up (for example, because of transfer to another hospital). Cox regression showed no significant difference in the risk of developing LOS after adjustment for GA and after adjustment for GA and EOS (Table 3). When investigating the association between IUI and other neonatal morbidities, a significant higher incidence of EOS and a lower incidence of RDS were found after adjustment for GA (Table 4). When NEC and LOS were taken together, no association was found with IUI (data not shown).

DISCUSSION

This large retrospective study could not confirm an association between exposure to IUI and LOS in preterm infants.

Recently, there has been a wide interest in the adaptive characteristics of the innate immune system. It is increasingly recognized that the innate immune response can be enhanced by appropriate stimuli, which may contribute to preventing LOS. Whether IUI is such an appropriate stimulus and can protect against LOS is uncertain. Strunk et al. did find lower incidences of LOS in infants who were exposed to HCA in utero after adjustment for GA.[11] However, most of the studies published on this topic could not confirm this hypothesis, as well as our study presented here.[12,13,16–18] Nonetheless, many of these studies lack power due to low numbers of the included infants, and there is considerable heterogeneity between the studies concerning population and incidences of LOS or IUI. Therefore, results have to be interpreted with caution. A recent meta-analysis on the association between HCA and LOS showed that exposure to HCA not only is not protective of developing LOS but also is even increasing the risk of LOS. After adjustment for GA, however, no association between HCA and LOS was found.[19] In animal models that simulate exposure to IUI by injecting lipopolysaccharide (LPS), the number of immune cells, such as neutrophils, monocytes, and lymphocytes, significantly increases and these cells produce more anti-inflammatory cytokines.[20,21] However, after repeated doses of LPS in sheep a reduction in anti-inflammatory cytokines is seen, which suggests tolerance to the stimulus.[22] If such an effect also occurs in human fetuses, this could explain why IUI is not an appropriate stimulus for preventing LOS. Another explanation could be that the pro-inflammatory response in preterm infants when stimulated by exposure to IUI is not enough to prevent LOS. In vitro exposure of innate immune cells of neonates to endotoxins lead to significantly reduced expression of pro-inflammatory T-helper1-polarizing cytokines, while relatively preserving anti-inflammatory T-helper2-polarazing cytokines, compared to adult innate immune cells.[23] In term born infants, responses of tumor necrosis factor-alpha and interleukin-6 to stimulation of innate immune cells with Bacillus Calmette-Guérin were comparable with adults.[24] Since maturation of the innate immune system takes place mostly during third trimester, the innate immune system of extreme prematures is less developed compared to that of late preterm or term infants and might explain the absence of the association between IUI and LOS in this cohort.[23–26]

IUI is correlated with an increase in EOS incidence, which is comparable to findings of other studies.[9,10] This can be explained by the hypothesis that vertical transmission of pathogens responsible for developing IUI can cause EOS in preterm infants.[27] Exposure to HCA or a fetal inflammatory response decreased the incidence of RDS as reported in previous research, since cortisol production increases after exposure to IUI, which stimulates surfactant synthesis.[28,29] No significant effect was seen for IVH. Some studies suggest that IUI increases the incidence of IVH; however, this remains controversial.[30] Since multiple factors

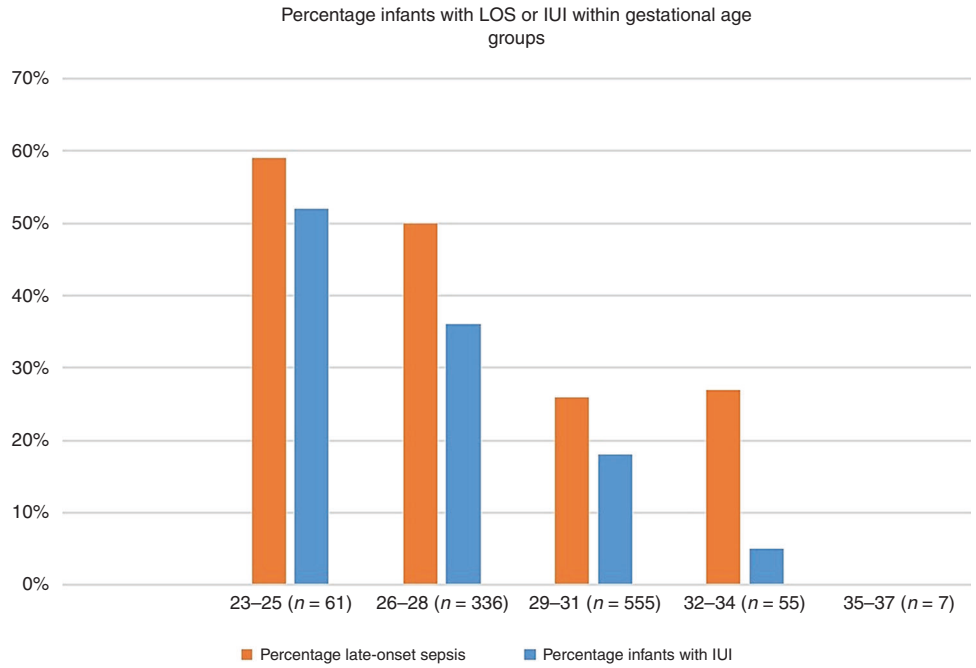

Fig. 2 Late-onset sepsis and intrauterine inflammation. Percentage of infants with late-onset sepsis (LOS) or intrauterine inflammation (IUI) within gestational age groups (in weeks). n number of patients; IUI intrauterine inflammation; LOS late-onset sepsis.

Table 3. Histological chorioamnionitis, any fetal inflammatory response, funisitis, and risk of LOS.

Predictive risk factors for LOS	*N* (%)	Adjusted for GA		Adjusted for GA and EOS	
		Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
HCA	240 (23.7%)	0.928 (0.727–1.185)	0.551	0.930 (0.727–1.189)	0.562
Any fetal inflammatory response	242 (23.9%)	1.011 (0.793–1.288)	0.930	1.021 (0.800–1.304)	0.865
Funisitis	174 (17.2%)	0.965 (0.738–1.263)	0.797	0.984 (0.752–1.289)	0.908

LOS late-onset sepsis, *HCA* histological chorioamnionitis, *EOS* early-onset sepsis, *CI* confidence interval, *GA* gestational age.

Table 4. Histological chorioamnionitis, any fetal inflammatory response, funisitis, and neonatal outcome.

All infants ($n = 2014$)			aOR (95% CI)[a]	*p* value
	EOS			
	No ($n = 929$), *N* (%)	Yes ($n = 84$), *N* (%)		
HCA	205 (22.1%)	35 (41.7%)	1.865 (1.144–3.038)	0.012
Any fetal inflammatory response	206 (22.2%)	36 (43.4%)	2.054 (1.264–3.337)	0.004
Funisitis	147 (15.9%)	27 (32.1%)	2.058 (1.246–3.401)	0.005
	IVH			
	No ($n = 906$), *N* (%)	Yes ($n = 86$), *N* (%)		
HCA	198 (21.9%)	36 (41.9%)	1.235 (0.744–2.051)	0.415
Any fetal inflammatory response	202 (22.4%)	34 (40%)	1.165 (0.701–1.936)	0.556
Funisitis	150 (16.6%)	21 (24.4%)	1.072 (0.612–1.876)	0.809
	RDS			
	No ($n = 414$), *N* (%)	Yes ($n = 594$), *N* (%)		
HCA	81 (19.6%)	156 (26.4%)	0.567 (0.386–0.833)	0.004
Any fetal inflammatory response	86 (20.8%)	153 (25.9%)	0.508 (0.345–0.746)	0.001
Funisitis	63 (15%)	107 (19%)	0.641 (0.424–0.970)	0.036
	NEC			
	No ($n = 957$), *N* (%)	Yes ($n = 54$), *N* (%)		
HCA	226 (23.7%)	14 (25.9%)	0.756 (0.390–1.466)	0.408
Any fetal inflammatory response	228 (23.9%)	13 (24.5%)	0.723 (0.369–1.418)	0.345
Funisitis	167 (17.5%)	7 (13%)	0.547 (0.240–1.246)	0.151

HCA histological chorioamnionitis, *EOS* early-onset sepsis, *IVH* intraventricular hemorrhage, *RDS* respiratory distress syndrome, *aOR* adjusted odds ratio, *CI* confidence interval, *GA* gestational age.
[a]Logistic regression analysis, adjusted for GA.

contribute to developing IVH, differences in incidence of risk factors such as GA, BW, mechanical ventilation, and infection could be an explanation for the different outcomes of studies on IVH and IUI.[28,31] This study does have some limitations. In 11%, placental histology was unavailable, which could affect the results by selection bias although many characteristics of the cohort and incidence of IUI are comparable with previous studies.[11,32,33] The Dutch policy on the management of extremely preterm infants before October 2010 (infants <25 weeks were not treated actively) made that the age distribution in our cohort differs from others.[11] However, mean GA and BW is comparable.[12,13,18] Furthermore, we did not investigate whether some children developed LOS after discharge from the NICU to regional hospitals, therefore some LOS cases could potentially have been missed. The strength of this study is the large sample size for a single-center study.

This study investigated the association of exposure to IUI on LOS incidence. We did not find any association between them. Understanding underlying mechanisms why some factors stimulate the innate immune system, and some do not, may direct future strategies to actively enhance the neonatal innate immune response in order to prevent LOS and to improve neonatal outcome of preterm infants. Further research should provide the evidence necessary to draw firm conclusions.

ACKNOWLEDGEMENTS

We would like to thank O. Tjoa and T. Knol for assisting in the completion of the database and C.F. Peeters for support on statistical analyses. Furthermore, we thank the staff of the Department of Neonatology and the Department of Pathology of the VUmc for their assistance in the logistics of this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the study design and interpretation of the data. M.B.v.D. completed the database, assisted in analysis of placental pathology, performed statistical analyses, drafted the manuscript, and revised it before final approval. J.P.v.d.V. analyzed placental pathology and revised and approved the final version before publication. D.H.V. contributed significantly to the conception of the design of the research, the interpretation of the results, and revising the manuscript before publication. M.M.v.W. contributed to the study design, interpretation of the results, and revision of the manuscript before publication. H.L.T. revised the manuscript and contributed to the interpretation of the results.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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