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Chorioamnionitis Is a Risk Factor for Intraventricular Hemorrhage in Preterm Infants: A Systematic Review and Meta-Analysis

Eduardo Villamor-Martinez[1], Monica Fumagalli[2], Owais M. M. Mohammed Rahim[1], Sofia Passera[2], Giacomo Cavallaro[2], Pieter Degraeuwe[1], Fabio Mosca,[2] Eduardo Villamor[1*]

[1]Department of Pediatrics, Maastricht University Medical Center (MUMC+), School for Oncology and Developmental Biology (GROW), Maastricht, the Netherlands.

[2]Neonatal Intensive Care Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, 20122 Milan, Italy

***Correspondence**
Eduardo Villamor
e.villamor@mumc.nl

Abstract: Although chorioamnionitis (CA) is a well-known risk factor for white matter disease of prematurity, the association with intraventricular hemorrhage (IVH) is controversial and has not been yet systematically reviewed. We performed a systematic review and meta-analysis of studies exploring the association between CA and IVH. A comprehensive literature search was conducted using PubMed/MEDLINE and EMBASE, from their inception to 1 July 2017. Studies were included if they examined preterm infants and reported primary data that could be used to measure the association between exposure to CA and the presence of IVH. A random-effects model was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Of 1284 potentially relevant studies, 85 met the inclusion criteria (46,244 infants, 13,432 CA cases). Meta-analysis showed that CA exposure was significantly associated with all grades IVH (OR 1.88, 95% CI 1.61-2.19), with grades 1-2 IVH (OR 1.69, 95% CI 1.22-2.34), and with grades 3-4 IVH (OR 1.62, 95% CI 1.42-1.85). Both clinical and histological CA were associated with an increased risk for developing IVH in very preterm infants. In contrast, the presence of funisitis did not increase IVH risk when compared to CA in the absence of funisitis (OR 1.22, 95% CI 0.89-1.67). Additional meta-analyses showed that infants exposed to CA had significantly lower gestational age (GA; mean difference [MD] -1.20 weeks) and lower birth weight (BW; MD -55g) than the infants not exposed to CA. However, meta-regression and subgroup analysis could not demonstrate an association between the lower GA and BW and the risk of IVH in the CA-exposed infants. In conclusion, our data show that CA is a risk factor for IVH, but also a risk factor for being a younger and more clinically unstable preterm infant. In contrast to other complications of prematurity, such as patent ductus arteriosus, retinopathy of prematurity, or bronchopulmonary dysplasia, the effect of CA on IVH appears to be independent of CA as causative factor for very preterm birth.

Keywords: chorioamnionitis, intraventricular hemorrhage, very preterm infant, systematic review, meta-analysis

1. Introduction

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Germinal matrix hemorrhage–intraventricular hemorrhage (GMH-IVH) is one of the most common complications of prematurity (1-3). IVH typically initiates in the germinal matrix, which is a richly vascularized collection of neuronal-glial precursor cells in the developing brain and may disrupt the ependymal lining and extend into the lateral ventricle (1-3). Severe IVH consists of large amounts of intraventricular blood (usually termed grade 3 IVH) and may be complicated by hemorrhagic venous infarction in the periventricular white matter (usually termed grade 4 IVH) or by post–hemorrhagic hydrocephalus or both (1, 2). Severe IVH is associated with increased mortality as well as short- and long-term neurological morbidity, while the long-term neurological outcome of milder forms of IVH (grade 1-2) is still debated and remains an active area of research (1, 2, 4)

As extensively reviewed by Inder et al., the pathogenesis of IVH is multifactorial and may involve intravascular, vascular, and extravascular factors (2). Intravascular factors relate to the regulation of blood flow, pressure, and volume in the microvascular bed of the germinal matrix as well as to platelet-capillary function and blood clotting capability (2). Vascular factors refer to the intrinsic fragility and vulnerability of germinal matrix blood vessels (2). Extravascular factors include the poor support of the extravascular space surrounding the germinal matrix capillaries, the postnatal decrease in extravascular tissue pressure, and an excessive fibrinolytic activity (2). Of note, not all the pathogenetic factors are present in every IVH and "clinical circumstances dictate which factors are most critical in the individual infant"(2). Among these clinical circumstances, very preterm birth, generally defined as birth before 32 completed weeks of gestation, is the most consistently associated with the development of IVH. However, a number of risk factors including, among others, absent antenatal corticosteroid (ACS) treatment, vaginal delivery, peri- and postnatal hypoxic-ischemic events, severe respiratory distress syndrome (RDS), pneumothorax, hypercapnia, hemodynamic disturbances (either systemic hypertension or hypotension), rapid volume expansion, decreased hematocrit, glucose and/or electrolyte disturbances, seizures, patent ductus arteriosus (PDA), thrombocytopenia, inherited trombophilia, and infection may predispose to the development of IVH (1-3, 5-8).

Several studies suggest that IVH is unequally distributed among the different leading causes of very preterm delivery (9, 10). An estimated 40% of very preterm births are associated with placental inflammation, which is often subclinical. This inflammation may be localized to the maternal placenta or membrane (chorioamnionitis) or progress to a fetal inflammatory response, as evidenced by cord inflammation (funisitis) (11-16). Chorioamnionitis (CA) is not only a major risk factor for (very) preterm birth, but it is also considered a major contributor to prematurity-associated morbidity and mortality (11-16). The pathogenetic role of CA in the development of adverse outcomes of prematurity, such as bronchopulmonary dysplasia (BPD) (17), necrotizing enterocolitis (NEC), PDA, retinopathy of prematurity (ROP), or cerebral palsy has been addressed in a number of systematic reviews (17-23). Although intrauterine inflammation is a well-known risk factor for white matter disease of prematurity (24), the association with IVH is controversial and has not been yet systematically reviewed. We aimed to perform a systematic review and meta-analysis of studies exploring the association between CA and IVH. We used an extensive search strategy, which included not only studies describing IVH as outcome after exposure to CA, but also studies that assessed CA as potential risk factor for IVH. In addition, we analyzed the magnitude of the differences in potential confounders, such as GA, birth weight (BW), exposure to ACS, mode of delivery,

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sepsis, PDA, or RDS between the infants of the CA and the control group. Finally, we performed a meta-regression to investigate the effect of confounders on the association between CA and IVH.

2. Methods

The methodology of this study was based on that of earlier meta-analyses on CA and PDA (20), and CA and ROP (22). A protocol was developed prospectively that detailed the specific objectives, criteria for study selection, the approach to assessing study quality, clinical outcomes, and statistical methodology. The study was conducted and reported according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (25).

2.1 Sources and search strategy

A comprehensive literature search was conducted using the PubMed/MEDLINE and EMBASE databases from their inception to July 1, 2017. The search terms involved various combinations of the following keywords: “chorioamnionitis”, “intrauterine infection” “intrauterine inflammation”, “antenatal infection” “antenatal inflammation” “intraventricular hemorrhage”, “risk factors”, “outcome”, “cohort”, and “case-control”. No language limit was applied. Additional strategies to identify studies included manual review of reference lists of key articles that fulfilled our eligibility criteria and of reviews on chorioamnionitis, use of the “related articles” feature in PubMed, and use of the “cited by” tool in Google scholar and Web of Science.

2.2 Study selection

Studies were included if they examined preterm (<37 weeks) or low BW (<2500g) infants and reported primary data that could be used to measure the association between exposure to CA and the presence of IVH. We included both studies that described IVH as an outcome after exposure to CA, and studies that assessed CA as a risk factor for IVH. To identify relevant studies, two reviewers (O.M.R., E.V.) independently screened the results of the searches and applied inclusion criteria using a structured form. Discrepancies were resolved through discussion or in consultation with a third reviewer (P.D.).

2.3 Data extraction

Two investigators (E.V.-M., O.M.R.) independently extracted data from included studies using a predetermined data extraction form and another two investigators (P.D., E.V.) checked data extraction for accuracy and completeness. Discrepancies were resolved by consulting the primary report. Data extracted from each study included citation information, language of publication, location where research was conducted, objectives, study design, definitions of CA and IVH, inclusion/exclusion criteria, patient characteristics, and results (including raw numbers, summary statistics and adjusted analyses on CA and IVH where available).

2.4 Quality assessment

Methodological quality was assessed using the Newcastle-Ottawa Scale for cohort or case-control studies (26). This scale uses a point rating system (range: 0-9 points) that scores three aspects of a study: selection (0-4 points), comparability (0-2 points) and exposure/outcome

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(0-3 points). Two reviewers (E.V.-M. and E.V.) independently assessed the methodological quality of each study. Discrepancies were resolved through discussion.

2.5 Statistical Analysis

Studies were combined and analyzed using COMPREHENSIVE META-ANALYSIS V 3.0 software (CMA, RRID:SCR_012779, Biostat Inc., Englewood, NJ, USA). For dichotomous outcomes, the odds ratio (OR) with 95% confidence interval (CI) was calculated from the data provided in the studies. ORs adjusted for potential confounders were extracted from the studies reporting these data. For continuous outcomes, the mean difference (MD) with 95% CI was calculated. When studies reported continuous variables as median and range or interquartile range, we estimated the mean and standard deviation using the method of Wan et al. (27). Due to anticipated heterogeneity, summary statistics were calculated with a random-effects model. This model accounts for variability between studies as well as within studies.

Subgroup analyses were conducted according to the mixed-effects model (28). In this model, a random-effects model is used to combine studies within each subgroup and a fixed-effect model is used to combine subgroups and yield the overall effect. The study-to-study variance (tau-squared) is not assumed to be the same for all subgroups. This value is computed within subgroups and not pooled across subgroups. Statistical heterogeneity was assessed by Cochran's Q statistic and by the I^2 statistic, which is derived from Q and describes the proportion of total variation that is due to heterogeneity beyond chance (29). We used the Egger's regression test and funnel plots to assess publication bias.

To explore differences between studies that might be expected to influence the effect size, we performed univariate random-effects meta-regression (method of moments) (30). The potential sources of variability defined a priori were: CA type (clinical or histological), funisitis, differences in GA and BW between the infants with and without CA, use of ACS, mode of delivery, rate of small for gestational age (SGA), rate of premature rupture of membranes (PROM), rate of preeclampsia, rate of early onset sepsis (EOS), rate of late onset sepsis (LOS), rate of RDS, rate of PDA and mortality. A probability value of less than 0.05 (0.10 for heterogeneity) was considered statistically significant.

3. Results

3.1 Description of studies

Of 1284 potentially relevant studies, 85 (7, 31-114) met the inclusion criteria. The flow diagram of the search is shown in Figure 1. The included studies evaluated 46,244 infants, including 13,432 cases of CA. The included studies and their characteristics are summarized in Supplementary Table 1. In 58 studies, the aim was to examine the outcomes, including IVH, of preterm infants with and without maternal CA. Twenty-four studies examined the risk factors for IVH, including maternal CA. Five studies studied the association between CA and IVH as their primary outcome (36, 73, 94, 114, 115). Fifty-four studies used a histological definition of CA and 24 studies used a clinical definition of CA. Only two studies (56, 62) provided data on microbiological CA and IVH. In one study (78) IVH was associated with clinical and histological CA separately. In four studies (49, 54, 63, 110) infants were assigned to the CA group if they had clinical and/or histological CA.

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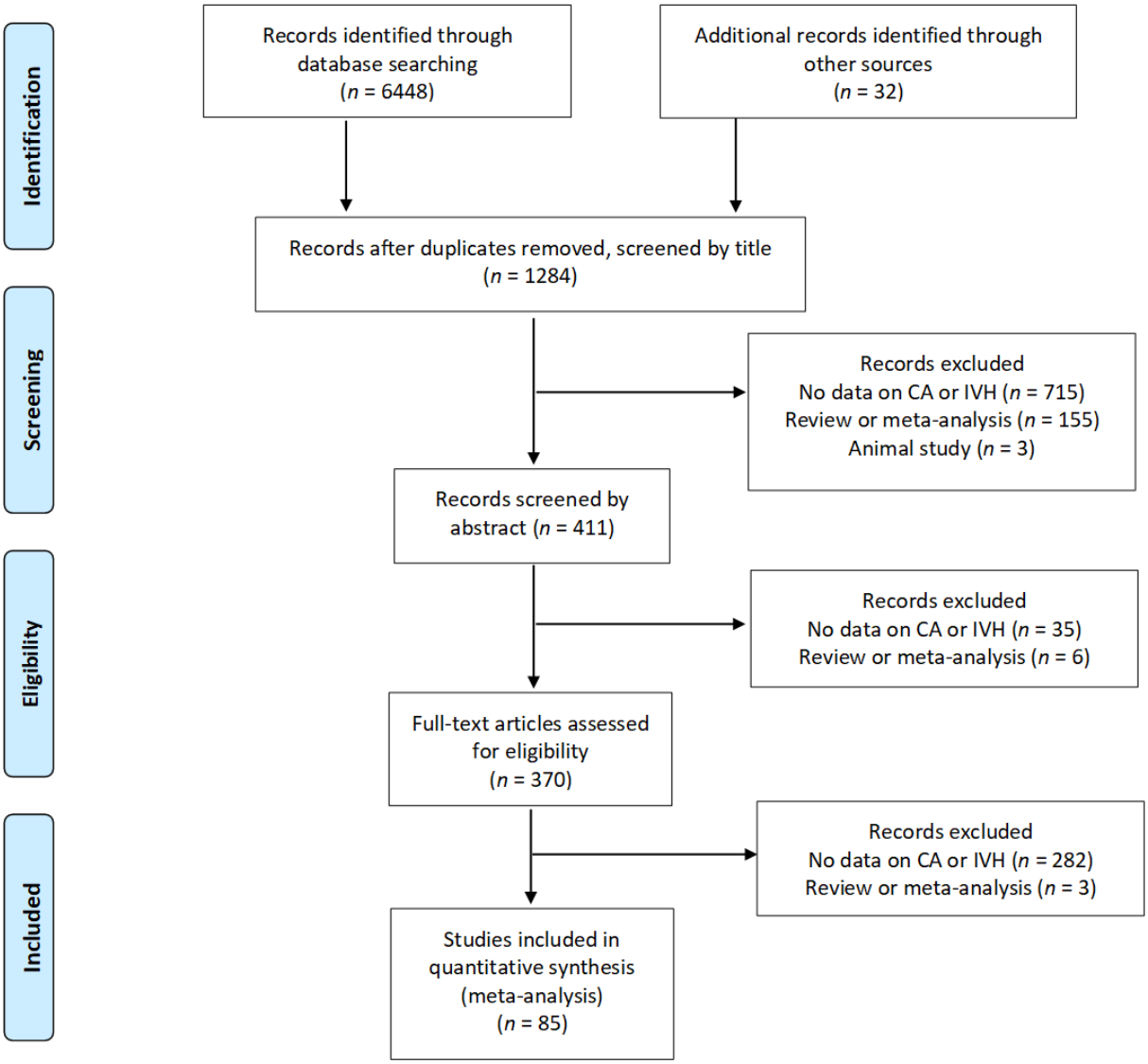

Figure 1. Flow diagram of search process.

3.2 Quality assessment

The quality of each study according to the Newcastle-Ottawa Scale is summarized in Supplementary Table 2. One study received a quality score of 5 points, 19 studies achieved a quality score of six points, 43 studies achieved a quality score of seven points, 11 studies achieved a quality score of eight, and 11 studies achieved the maximum score of 9 points. Studies were downgraded in quality for not adjusting the risk of IVH for confounders (k = 62), for not defining IVH clearly (k = 9), for only adjusting the risk of IVH for one confounding factor (k = 7), for not defining CA clearly (k = 6), and for losing a substantial portion of infants to follow-up (k = 4).

3.3 Analysis based on unadjusted data

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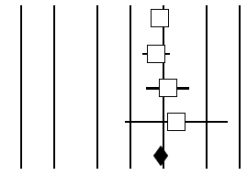
Meta-analysis showed that CA exposure was significantly associated with all grades IVH (Figure 2A), with grades 2-4 IVH (Figure 2B), with grades 1-2 IVH (2C), and with grades 3-4 IVH (Figure 2D). When the type of CA was analyzed separately, histological CA remained significantly associated with all grades IVH (Figure 3), with grades 2-4 IVH (Figure 2B), with grades 1-2 IVH (Figure 2C), and with grades 3-4 IVH (Figure 4). Clinical CA was significantly associated with all grades IVH (Figure 5) and with grades 3-4 IVH (Figure 6), but not with grades 1-2 IVH (Figure 2C). There was only one study providing data on the association of clinical CA and IVH grades 2-4 (Figure 2B). Neither visual inspection of the funnel plot (Figure 7) nor the regression test of Egger revealed evidence of publication bias.

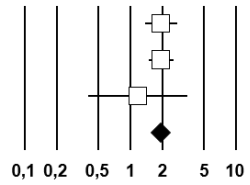
A. All grades IVH

CA type	Studies (k)	Patients (n)	Odds ratio	Lower limit	Upper limit	p-Value	Heterogeneity *p*-value	I^2
Histological	36	13080	1,87	1,54	2,28	0,000	<0.001	70.3
Clinical	14	5564	1,72	1,28	2,32	0,000	0.007	54.7
Histological and/or clinical	4	789	2,21	1,39	3,49	0,001	0.274	22.9
Microbiological	1	151	2,64	0,89	7,85	0,081		
Overall	53	**19189**	**1,88**	**1,61**	**2,19**	**0,000**	**<0.001**	**64,0**



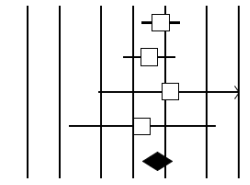
B. Grades 2-4 IVH

CA type	Studies (k)	Patients (n)	Odds ratio	Lower limit	Upper limit	p-Value	Heterogeneity p-value	I^2
Histological	10	1335	1,98	1,39	2,81	0,000	0.669	0,0
Clinical	1	1111	1,97	1,51	2,58	0,000		
Histological and/or clinical	1	88	1,18	0,40	3,49	0,763		
Overall	**12**	**2564**	**1,94**	**1,57**	**2,39**	**0,000**	**0,715**	**0,0**



C. Grades 1-2 IVH

CA type	Studies (k)	Patients (n)	Odds ratio	Lower limit	Upper limit	p-Value	Heterogeneity *p*-value	I^2
Histological	16	4909	1,84	1,21	2,80	0,004	<0.001	81.5
Clinical	5	806	1,43	0,80	2,55	0,226	0.079	52.3
Histological and/or clinical	2	246	2,25	0,46	10,95	0,314	0.043	75.5
Microbiological	1	151	1,23	0,24	6,18	0,804		
Overall	**24**	**5933**	**1,69**	**1,22**	**2,34**	**0,002**	**<0.001**	**75.5**



D. Grades 3-4 IVH

CA type	Studies (k)	Patients (n)	Odds ratio	Lower limit	Upper limit	p-Value	Heterogeneity *p*-value	I^2
Histological	31	11376	1,62	1,39	1,87	0,000	0.001	48.2
Clinical	15	19067	1,50	1,06	2,13	0,022	<0.001	83.9
Histological and/or clinical	2	246	1,64	0,54	5,02	0,385	0.951	0,0
Microbiological	2	195	5,01	1,50	16,72	0,009	0.738	0,0
Overall	**49**	**31301**	**1,62**	**1,42**	**1,85**	**0,000**	**<0.001**	**63,8**

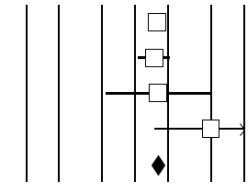


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Figure 2. Meta-analyses of the association between chorioamnionitis (CA) and intraventricular hemorrhage (IVH), according to definition of IVH.

Study name	ALL IVH-Yes / Total		Statistics for each study				Relative Weight (%)
	CA-Yes	CA-No	Odds ratio	Lower limit	Upper limit	p-Value	
Sarkar 2005	3 / 29	6 / 33	0.52	0.12	2.30	0.388	1.31
Kosuge 2000	4 / 44	5 / 37	0.64	0.16	2.58	0.531	1.44
Seong-Hee 2015			0.72	0.23	2.18	0.555	1.95
Dempsey 2005	11 / 130	21 / 200	0.79	0.37	1.69	0.542	2.90
Watterberg 1999	8 / 22	7 / 18	0.90	0.25	3.25	0.870	1.61
Ecevit 2014	4 / 21	3 / 15	0.94	0.18	5.00	0.943	1.10
Suppiej 2009	5 / 41	8 / 63	0.95	0.29	3.15	0.940	1.78
Richardson 2006	66 / 292	78 / 368	1.09	0.75	1.57	0.665	4.36
Mu 2008	15 / 64	11 / 55	1.22	0.51	2.95	0.651	2.55
Tsiartas 2013	31 / 142	16 / 89	1.27	0.65	2.49	0.480	3.22
Liu 2014	23 / 49	18 / 46	1.38	0.61	3.11	0.443	2.74
Elimian 2000	169 / 527	170 / 733	1.56	1.22	2.01	0.000	4.75
Zanardo 2008	11 / 68	22 / 219	1.73	0.79	3.78	0.170	2.85
Logan 2013	26 / 335	27 / 586	1.74	1.00	3.04	0.050	3.65
Miyazaki 2016	243 / 1235	350 / 2843	1.74	1.46	2.09	0.000	4.94
Lee. Hyun Ju 2011	33 / 71	25 / 76	1.77	0.91	3.46	0.093	3.24
Rocha 2006	31 / 125	50 / 327	1.83	1.10	3.03	0.019	3.85
Been 2009	24 / 121	21 / 180	1.87	0.99	3.54	0.054	3.35
Mehta 2006	30 / 64	31 / 100	1.96	1.03	3.76	0.041	3.31
Dexter 2000	60 / 157	28 / 118	1.99	1.17	3.39	0.011	3.74
Nasef 2013	26 / 95	23 / 146	2.02	1.07	3.80	0.030	3.36
Babnik 2006	23 / 49	23 / 76	2.04	0.97	4.29	0.061	2.97
Bermick 2016	58 / 88	62 / 128	2.06	1.17	3.61	0.012	3.64
Dalton 2015	58 / 88	62 / 128	2.06	1.17	3.61	0.012	3.64
Sato 2011	54 / 158	28 / 144	2.15	1.27	3.65	0.004	3.76
Yanowitz 2006	16 / 24	12 / 25	2.17	0.68	6.88	0.190	1.86
Soraisham 2013	55 / 197	27 / 187	2.30	1.37	3.83	0.002	3.82
van Vliet 2012	9 / 21	12 / 51	2.44	0.83	7.17	0.106	2.02
Lu 2016	21 / 60	12 / 77	2.92	1.29	6.57	0.010	2.75
Erdemir 2013	3 / 12	4 / 45	3.42	0.65	18.00	0.147	1.11
Polam 2005	36 / 102	10 / 75	3.55	1.63	7.73	0.001	2.85
Ohyama 2002	11 / 90	2 / 53	3.55	0.76	16.68	0.108	1.23
Perrone 2012	31 / 48	13 / 44	4.35	1.81	10.45	0.001	2.55
Bordigato 2010	6 / 14	2 / 15	4.88	0.78	30.29	0.089	0.95
Bry 2015	4 / 16	0 / 8	6.12	0.29	129.08	0.244	0.39
Ogunyemi 2003	181 / 254	120 / 520	8.26	5.88	11.61	0.000	4.47
HISTOLOGICAL OVERALL			**1.87**	**1.54**	**2.28**	**0.000**	

Heterogeneity: Q = 114; I^2 = 70.3%; p < 0.00001

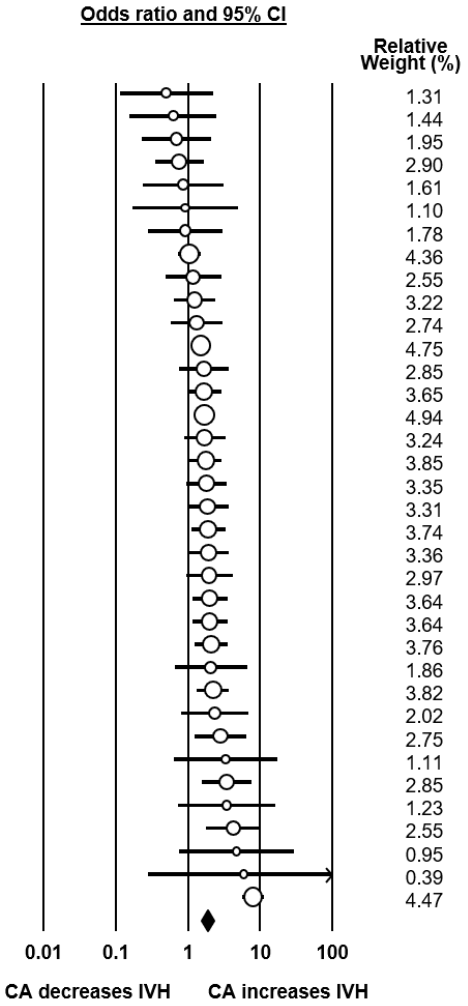

Figure 3. Meta-analysis of the association between histological chorioamnionitis (CA) and all grades intraventricular hemorrhage (IVH).

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Study name	Grades 3-4 IVH-Yes / Total		Statistics for each study				Relative Weight (%)
	CA-Yes	CA-No	Odds ratio	Lower limit	Upper limit	p-Value	
Wirbelauer 2011	0 / 17	6 / 54	0.21	0.01	3.98	0.301	0.25
Nasef HC 2013	0 / 95	3 / 146	0.21	0.01	4.20	0.311	0.24
Zanardo 2008	0 / 68	3 / 219	0.45	0.02	8.85	0.600	0.24
Trevisanuto 2013	2 / 71	4 / 71	0.49	0.09	2.74	0.413	0.71
Smit 2015	5 / 135	8 / 165	0.75	0.24	2.36	0.629	1.59
Been 2009	5 / 121	8 / 180	0.93	0.30	2.90	0.896	1.59
Mu 2008	11 / 64	9 / 55	1.06	0.40	2.79	0.905	2.18
Rodríguez-Trujillo 2016	11 / 111	5 / 54	1.08	0.35	3.27	0.895	1.67
Lee. Ju Young 2010	18 / 79	21 / 98	1.08	0.53	2.21	0.829	3.81
Sarkar 2005	2 / 29	2 / 33	1.15	0.15	8.71	0.894	0.52
Pappas 2014	259 / 1063	179 / 855	1.22	0.98	1.51	0.073	20.39
Tsiartas 2013	2 / 142	1 / 89	1.26	0.11	14.07	0.853	0.37
Seliga-Siwecka 2013	69 / 141	103 / 242	1.29	0.85	1.96	0.227	9.28
Liu 2014	5 / 49	3 / 46	1.63	0.37	7.24	0.522	0.95
Watterberg 1999	2 / 22	1 / 18	1.70	0.14	20.42	0.676	0.35
Ogunyemi 2003	17 / 254	21 / 520	1.70	0.88	3.29	0.112	4.40
Elimian 2000	79 / 527	66 / 733	1.78	1.26	2.52	0.001	11.99
Hendson 2011	58 / 298	38 / 319	1.79	1.15	2.79	0.010	8.44
Kim 2015	7 / 92	6 / 143	1.88	0.61	5.78	0.271	1.64
Dexter 2000	19 / 156	8 / 117	1.89	0.80	4.48	0.149	2.69
Arayici 2014	20 / 145	9 / 136	2.26	0.99	5.15	0.053	2.93
Salas 2013	35 / 148	24 / 199	2.27	1.28	4.02	0.005	5.61
Rocha 2006	18 / 125	22 / 327	2.33	1.20	4.52	0.012	4.36
Lau 2005	32 / 403	29 / 893	2.53	1.51	4.23	0.000	6.67
Soraisham 2013	20 / 197	8 / 187	2.53	1.09	5.89	0.032	2.79
Yamada 2015	18 / 73	4 / 39	2.86	0.89	9.17	0.076	1.53
Yanowitz 2006	1 / 24	0 / 25	3.26	0.13	83.90	0.476	0.20
Bordigato 2010	1 / 14	0 / 15	3.44	0.13	91.79	0.460	0.20
Mestan 2010	6 / 94	3 / 162	3.61	0.88	14.80	0.074	1.06
Polam 2005	11 / 102	2 / 75	4.41	0.95	20.54	0.059	0.89
Ahn 2012	5 / 89	1 / 168	9.94	1.14	86.45	0.037	0.46
HISTOLOGICAL OVERALL			**1.62**	**1.39**	**1.87**	**0.000**	

Heterogeneity: Q = 33; I^2 = 10.0%; p =0.308

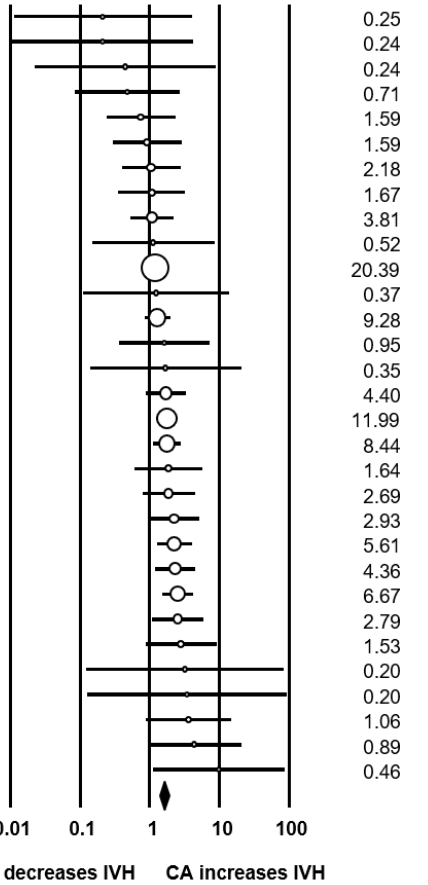

Figure 4. Meta-analysis of the association between histological chorioamnionitis (CA) and grades 3-4 intraventricular hemorrhage (IVH).

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Study name	All IVH-Yes / Total		Statistics for each study				Relative Weight (%)
	CA-Yes	CA-No	Odds ratio	Lower limit	Upper limit	p-Value	
Ryckman 2011	6 / 33	41 / 186	0.79	0.30	2.03	0.619	5.74
Botet 2010	44 / 165	45 / 163	0.95	0.59	1.55	0.848	10.09
Holcroft 2003	16 / 45	61 / 168	0.97	0.49	1.92	0.926	7.96
Morales 1987	37 / 43	37 / 43	1.00	0.30	3.39	1.000	4.16
Rong 2012	16 / 44	63 / 188	1.13	0.57	2.25	0.719	7.98
Gawade 2013	6 / 12	28 / 66	1.36	0.40	4.65	0.627	4.10
Gonzalez-Luis 2002	11 / 45	16 / 90	1.50	0.63	3.57	0.363	6.35
Baumert 2008	21 / 101	371 / 2574	1.56	0.95	2.55	0.078	10.02
Vaihinger 2013	16 / 47	33 / 151	1.85	0.90	3.78	0.094	7.68
Poralla 2012	30 / 52	28 / 80	2.53	1.24	5.19	0.011	7.67
Barrera-Reyes 2011	11 / 23	19 / 81	2.99	1.14	7.86	0.026	5.62
Vergani 2004	12 / 73	33 / 580	3.26	1.60	6.64	0.001	7.72
Nasef 2013	13 / 33	23 / 146	3.48	1.52	7.96	0.003	6.68
Suarez 2001	22 / 52	34 / 228	4.18	2.16	8.09	0.000	8.23
CLINICAL OVERALL			**1.72**	**1.28**	**2.32**	**0.000**	

Heterogeneity: Q = 29; I^2 = 54.7%; p =0.007

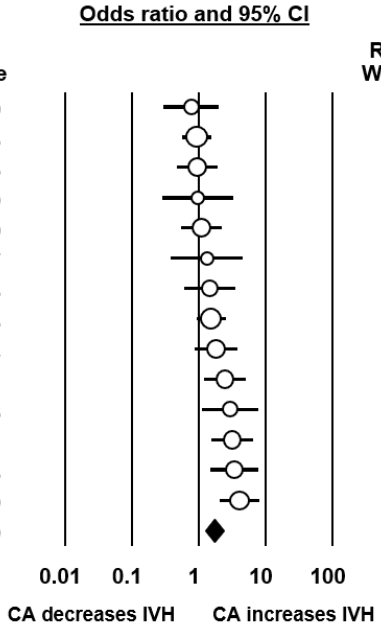

Figure 5. Meta-analysis of the association between clinical chorioamnionitis (CA) and all grades intraventricular hemorrhage (IVH).

Study name	Grades 3-4 IVH-Yes / Total		Statistics for each study				Relative weight
	CA-Yes	CA-No	Odds ratio	Lower limit	Upper limit	p-Value	
Kidokoro 2014			0.51	0.11	2.43	0.398	3.16
Linder 2003	6 / 25	30 / 80	0.53	0.19	1.46	0.219	5.24
Nasef CC 2013	0 / 33	3 / 146	0.61	0.03	12.13	0.747	1.11
Aden 2013	69 / 223	154 / 389	0.68	0.48	0.97	0.033	9.35
Lim 2011	4 / 9	32 / 63	0.78	0.19	3.16	0.722	3.64
Botet 2010	17 / 165	21 / 163	0.78	0.39	1.53	0.466	7.26
Morales 1987	12 / 43	12 / 43	1.00	0.39	2.57	1.000	5.67
De Felice CC 2001	11 / 81	43 / 402	1.31	0.65	2.67	0.454	7.06
Gonzalez-Luis 2002	4 / 45	6 / 90	1.37	0.37	5.11	0.643	3.95
Austeng 2010			1.40	0.71	2.75	0.329	7.29
Garcia-Muñoz 2014	215 / 1480	575 / 6850	1.85	1.57	2.19	0.000	10.15
Soraisham 2009	105 / 477	311 / 2617	2.09	1.63	2.67	0.000	9.86
Alexander 1998	23 / 95	145 / 1272	2.48	1.51	4.09	0.000	8.43
Gawade 2013	3 / 12	6 / 66	3.33	0.71	15.75	0.129	3.18
Gagliardi 2014	274 / 1510	120 / 2096	3.65	2.91	4.58	0.000	9.95
Osmanagaoglu 2005	6 / 31	8 / 223	6.45	2.07	20.10	0.001	4.70
CLINICAL OVERALL			**1.49**	**1.07**	**2.08**	**0.019**	

Heterogeneity: Q = 93; I^2 = 83.9%; p < 0.001

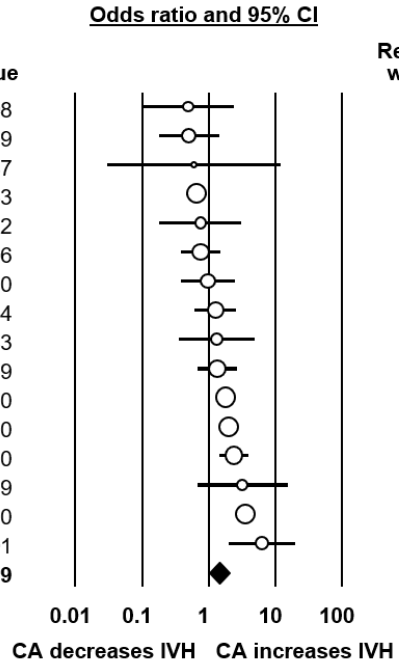

Figure 6. Meta-analysis of the association between clinical chorioamnionitis (CA) and grades 3-4 intraventricular hemorrhage (IVH).

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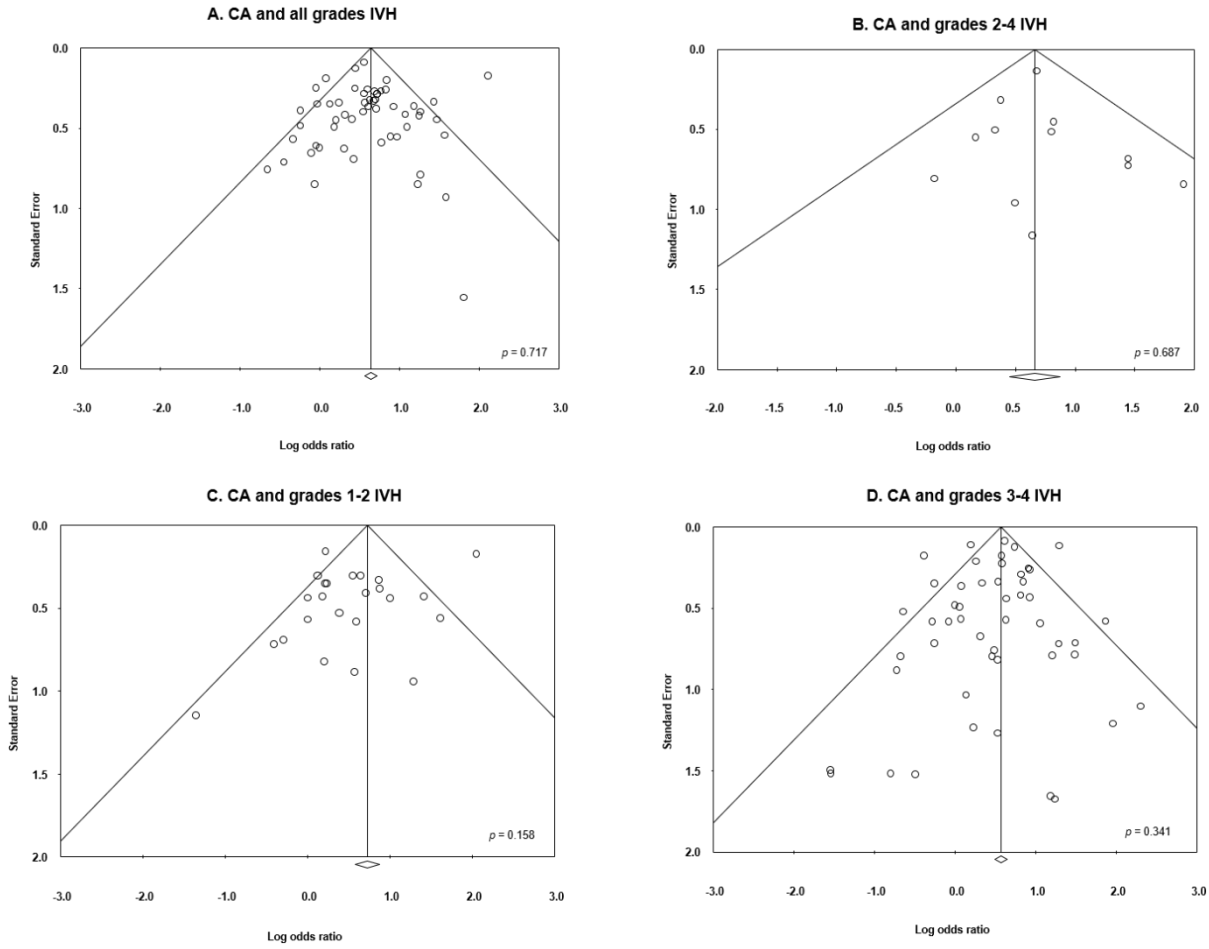

Figure 7. Funnel plots assessing publication bias for the association between chorioamnionitis (CA) and intraventricular hemorrhage (IVH).

3.4 Analysis of covariates

To explore the possible differences in baseline characteristics between the groups of exposed and non-exposed to CA, we performed additional meta-analyses. As summarized in Table 1, infants exposed to CA showed significantly lower GA and BW. Moreover, infants with CA had significantly higher rates of exposure to ACS, significantly higher rates of premature rupture of membranes (PROM), significantly higher rates of EOS, significantly higher rates of LOS, and significantly higher rates of PDA (Table 1). Infants with CA also had significantly lower rates of cesarean delivery, significantly lower rates of small for gestational age (SGA) and significantly lower rates of preeclampsia (Table 1).

To analyze the possible influence of the GA and BW on the unadjusted association between CA and IVH, we performed meta-regression analysis. As depicted in Table 2, this analysis showed that the differences in GA or BW between the CA exposed and non-exposed groups were not significantly correlated with the effect size of the association between CA and IVH.

To further analyze the effect of GA on the risk of IVH, we carried out subgroup analyses. We found that in the group of studies where the CA-group did not differ significantly ($p>0.05$) in GA from the control group, CA was a risk factor for all grades IVH but not for grades 3-4 IVH (Table 4). We analyzed a subgroup of studies where the CA-group had a MD in GA of ≤0.5 weeks, and we found that CA was a risk factor for all grades IVH and for grades 3-4

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IVH (Table 4). We also found a that in studies where the CA-group had a MD in GA of less than 1 week, CA was a risk factor for all grades IVH and for grades 3-4 IVH (Table 4).

We carried out further meta-regression analysis to examine the role of other covariates in the association between CA and IVH. Meta-regression could not find a significant difference in IVH risk between infants with clinical and infants with histological CA (Table 3). Meta-regression did find a significant association between the CA-associated risk of grades 3-4 IVH and the risk of preeclampsia (Supplementary Figure 1), mortality (Supplementary Figure 2), risk of LOS (Supplementary Figure 3) and risk of PDA (Supplementary Figure 4) Other meta-regressions could not find a significant association between the CA-associated risk of IVH and other covariates (Table 3).

3.5 Analysis of funisitis

We performed additional analyses aimed at evaluating the role of the presence of a fetal inflammatory response (i.e. funisitis) on the development of IVH. Thirteen studies reported on IVH (36, 39, 61, 65, 70, 71, 74, 82, 88, 89, 98, 103, 104) in infants with histological CA with or without funisitis. As shown in Figure 8, meta-analysis could not show a significant difference in IVH risk between infants with funisitis and infants with CA without funisitis (OR all grades IVH: 1.22, 95% CI 0.89 to 1.67; grades 3-4 IVH: 1.17, 95% CI 0.74 to 1.85). Using meta-regression, we also found no significant difference in IVH risk between infants with funisitis, and infants with CA without funisitis (Table 3).

	Study name	IVH-Yes / Total		Statistics for each study			
		CA-Yes. Fun-Yes	CA-Yes. Fun-No	Odds ratio	Lower limit	Upper limit	p-Value
All gardes IVH	Ohyama 2002	0 / 8	11 / 82	0.37	0.02	6.78	0.499
	Logan 2013	9 / 147	17 / 188	0.66	0.28	1.52	0.324
	Rocha 2006	10 / 44	21 / 81	0.84	0.35	1.99	0.693
	Tsiartas 2013	11 / 45	20 / 97	1.25	0.54	2.88	0.608
	Richardson 2006	43 / 178	23 / 114	1.26	0.71	2.23	0.428
	Babnik 2006	14 / 27	9 / 22	1.56	0.50	4.85	0.446
	Been 2009	17 / 68	7 / 53	2.19	0.83	5.76	0.112
	Liu 2014	15 / 26	8 / 23	2.56	0.80	8.14	0.112
	All IVH			**1.22**	**0.89**	**1.67**	**0.226**
	Heteregeneity: Q = 7; I^2 = 0.0%; p = 0.467						
Grades 3-4 IVH	Trevisanuto 2013	1 / 44	1 / 27	0.60	0.04	10.09	0.726
	Rocha 2006	10 / 44	21 / 81	0.84	0.35	1.99	0.693
	Smit 2015	2 / 55	3 / 80	0.97	0.16	6.00	0.973
	Lau 2005	20 / 250	12 / 153	1.02	0.48	2.15	0.955
	Been 2009	3 / 68	2 / 53	1.18	0.19	7.31	0.861
	Kim 2015	3 / 31	4 / 61	1.53	0.32	7.29	0.596
	Mestan 2010	5 / 54	1 / 40	3.98	0.45	35.48	0.216
	Liu 2014	4 / 26	1 / 23	4.00	0.41	38.70	0.231
	Tsiartas 2013	2 / 45	0 / 97	11.21	0.53	238.38	0.121
	Severe IVH			**1.17**	**0.74**	**1.85**	**0.490**
	Heteregeneity: Q = 5; I^2 = 0.0%; p = 0.705						

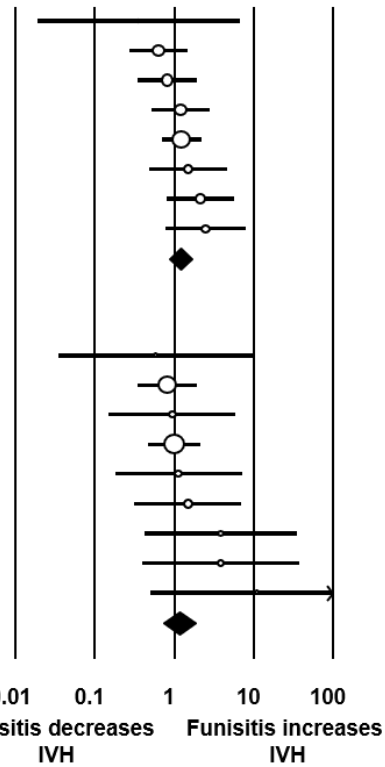

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Figure 8. Meta-analysis of the association between funisitis and intraventricular hemorrhage (IVH). Fun: funisitis; CI: confidence interval.

3.6 Analysis based on adjusted data

Thirteen studies adjusted the association between CA and the risk of IVH for confounding factors. As shown in Supplementary Table 3 and 4, studies adjusted for different covariates. Meta-analysis pooling this adjusted data found that CA was significantly associated with a higher risk of all grades IVH (OR 1.25, 95% CI 1.02 to 1.53, Supplementary Table 3). This association became non-significant when only analyzing studies which used a histological definition of CA (Supplementary Table 3). Meta-analysis of adjusted data also found a significant association between CA and grades 3-4 IVH (OR 1.22, 95% CI 1.04 to 1.43, Supplementary Table 4). This association became non-significant when grouping studies by clinical or histological CA definition (Supplementary Table 4).

4. Discussion

The current systematic review and meta-analysis demonstrates that both clinical and histological CA are associated with an increased risk for developing IVH in very preterm infants. In contrast, the presence of funisitis did not increase IVH risk when compared to CA in the absence of funisitis. Additional meta-analyses showed that infants exposed to CA had significantly lower GA and lower BW than the infants not exposed to CA. However, meta-regression and subgroup analysis could not demonstrate an association between the lower GA and BW and the risk of IVH in the CA-exposed infants. This suggests that the effects of CA on HIV risk might be at least partially independent on the role of CA as etiological factor for very preterm birth.

The association between CA and increased risk of HIV is biologically and clinically plausible. IVH generally occurs within the three first days of life and affects the infants with higher hemodynamic and respiratory instability, frequently associated with extreme prematurity and/or severe perinatal infections (2, 116). Therefore, the clinical circumstances around birth and during the first days of life are critical for the development of IVH. Our study confirms previous reports showing that these clinical circumstances are different in CA-exposed and CA–unexposed very preterm infants (17, 20, 22). Thus, infants exposed to CA were born significantly earlier (≈1.2 weeks), were lighter (≈55 g), and had a higher rate of exposure to antenatal corticosteroids, PROM, vaginal delivery, early and late onset sepsis, and PDA. As mentioned in the introduction, some of these factors may have affected IVH risk.

The degree of prematurity is the most important predisposing factor for the occurrence of IVH (1-3), as well as for other complications of prematurity such as BPD, ROP, NEC, or PDA (20, 22, 23, 117, 118). Nevertheless, very preterm birth is always a pathological event and very preterm infants carry a mortality/morbidity risk conferred by whatever condition led to their early delivery (119-122). Therefore, CA may affect infant morbidity through inducing very preterm birth or through the deleterious effects of infection/inflammation. Interestingly, previous meta-analyses showed an association between the lower gestational age of the CA-exposed group and the CA-associated risk of BPD (117), PDA (20), and ROP (22, 23). In

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contrast, our meta-regression could not show that the difference in GA between CA-exposed and CA-unexposed infants significantly correlated with IVH risk. Moreover, we performed subgroup analyses in which we only included the studies showing small or no differences in GA between the CA-exposed and the control group and we observed that the significant IVH risk was maintained in this subgroup of studies. In contrast, this was not the case when the same subgroup analysis was performed for PDA (20) or ROP (22, 23). Altogether this suggests that CA may increase complications such as PDA or ROP through GA-dependent mechanisms, whereas the effect on IVH may be mediated by GA-independent mechanisms.

Besides GA, several other factors potentially confound the association between CA and IVH. A number of studies adjusted for important potential confounders, although the number and nature of confounders varied between studies. We performed separate analyses aggregating adjusted association measures. This reduced or made non-significant the association between CA and IVH (Supplementary Table 3 and 4). Previous meta-analyses on the relationship between CA and BPD (17), cerebral palsy (18), and ROP (22) also showed that the positive association observed with unadjusted data was significantly reduced, or became non-significant, when adjusted data were pooled. Moreover, the significant positive association between CA and PDA became a significant negative association when only adjusted data were analyzed (20).

Adjustment for potential confounders, particularly for GA and/or BW, is widely used in observational studies examining predictors of neonatal outcomes after preterm birth. However, this approach is controversial and can lead to biased conclusions (119, 121). As mentioned above, neonatal adverse outcomes depend both on immaturity and on the conditions that caused preterm birth (119-121). Therefore, very low GA would represent both a risk factor per se and a mediator in the causal pathway linking cause of preterm birth to outcome (119, 121). Adjustment for an intermediate variable might introduce bias unless all mediator–outcome confounders are taken into account in the analysis (119, 121, 123, 124). As assessed by Gagliardi et al. (121), the difficulty of achieving, at least at the current level of knowledge of etiology of preterm birth, full control of all mediator–outcome confounders limits the possibility of causal interpretation of the associations found, but it does not limit their descriptive value. In this sense, our meta-analysis may be a valuable contribution to the understanding of CA as etiopathogenic factor of both prematurity and IVH.

Our data suggest that CA-exposed infants are not only younger but also more clinically unstable than the non-exposed infants. This is reflected in the higher mortality and the higher rate of sepsis and PDA in CA-exposed infants (Table 1). Of note, meta-regression showed a correlation between the effect size of the association between CA and grade 3-4 IVH and the effect sizes of the association between CA and PDA. As mentioned elsewhere, the presence of a hemodynamically relevant PDA has been correlated with the occurrence of IVH and the proposed mechanism is the disturbance of cerebral blood flow (2, 3, 8, 125). Our data support this association between IVH and PDA in CA-exposed infants.

The biological plausibility of the association between CA and IVH is supported by the direct and indirect effects of inflammatory mediators. Hemodynamic disturbances in preterm infants with CA have been correlated with elevated cord blood concentrations of proinflammatory cytokines such as IL-6, IL-1beta and TNF-alfa (126). Cytokines can act directly on the vascular smooth muscle, producing vascular relaxation and hypotension or indirectly by

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increasing vascular endothelial production of prostacyclin and nitric oxide (126). In addition, cytokines can eventually promote a neuro-inflammatory cascade in the fetal brain penetrating across the blood brain barrier or activating specific receptors such as CD14 and TLR4 which are constitutively expressed in the circumventricular organs, choroid plexus and leptomeninges (127, 128). Inflamed glial or endothelial cells, challenged by external stimuli, enhance the release/expression of various chemoattractants and adhesion molecules which may promote the platelet and neutrophil activation and adhesion determining possible endothelial cell damage and changes in blood rheology and flow (129, 130). These changes, occurring inside the fragile germinal matrix capillaries or within the vascular connection between germinal matrix and the subependimal venous network, may increase the likelihood of IVH in preterm infants with CA.

It should be noted that not all intraamniotic infections will lead to an inflammatory process extending to the fetal component (131). Funisitis is considered the histologic counterpart of the fetal inflammatory response syndrome (16, 132). Our study showed that the presence of funisitis combined with CA did not significantly increase the odds of having IVH, when compared with CA in the absence of funisitis. This is an argument against the fetal inflammatory response as etiopathogenic factor for IVH. We have previously reported that funisitis is not an additional risk factor for developing PDA (20) but the presence of funisitis significantly increased the risk of developing severe ROP (22).

Our meta-analysis has several limitations that should be considered. First, the published literature showed great heterogeneity in definition of CA, and in assessment of confounders. Particularly, criteria for the use of the term clinical CA are highly variable and recent recommendations propose to restrict the term CA to pathologic diagnosis (133). Second, in most of the included studies the analysis of the association between CA and IVH was not the main objective. Third, adjusted data were available only from 13 of the 85 studies included in the meta-analysis. In addition, we had to rely on the adjusted analyses as presented in the published reports and the variables which they included, which were not consistent across studies. On the other hand, the strengths of the present study are the large number of included studies; the use of rigorous methods including extensive and comprehensive search; duplicate screening, inclusion, and data extraction to reduce bias; the use of meta-analysis of baseline and secondary characteristics and the use of meta-regression to control for potential confounders.

One important limitation, inherent to any meta-analysis on IVH, is the possible heterogeneity of the definition of the condition. The grading system most commonly used for IVH in the infant was first reported by Papile et al. and later modified by Volpe and is based on the presence and amount of blood in the germinal matrix, lateral ventricles, and periventricular white matter (1). Grade 1 represents germinal matrix hemorrhage only with no or minimal IVH (<10% of ventricular area on parasagittal view). Grade 2 represents IVH occupying 10–50% of ventricular area on parasagittal view. Grade 3 is IVH with hemorrhage occupying > 50% of ventricular area on parasagittal view. Grade 4 represents severe IVH with associated periventricular echodensity (1). Although grade 4 IVH is a periventricular hemorrhagic infarction rather than an extension of IVH per se, the 1-4 grading system remains pervasive in the literature and clinical setting despite debate regarding appropriate nomenclature (134). In addition grade 3 and 4 IVHs are frequently grouped together as severe or high grade IVH (134). Nevertheless, our meta-analysis shows a significant increased risk of both severe and

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less severe (grade 1-2) IVH in CA-exposed infants. Therefore, potential differences in IVH classification may not have affected the results.

In conclusion, IVH is a multifactorial complication that is more common in the youngest and sickest preterm infants. Our data show that CA is a risk factor for IVH, but also a risk factor for being a younger and more clinically unstable preterm infant. In contrast to other complications of prematurity, such as PDA, ROP, or BPD (20, 22, 23, 117), the effect of CA on IVH appears to be independent of CA as causative factor for very preterm birth.

5. Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

6. Author Contributions

E.V.-M. carried out data collection, carried out statistical analyses, assessed methodological quality, contributed to interpretation of results, drafted the initial manuscript, and reviewed and revised the manuscript. M.F. contributed to statistical analysis and interpretation of results and reviewed and revised the manuscript. O. M. R. selected studies for inclusion, carried out data collection and carried out statistical analyses. S.P. contributed to interpretation of results and reviewed and revised the manuscript. G.C. contributed to interpretation of results and reviewed and revised the manuscript. P.D. carried out and supervised data collection and contributed to interpretation of results. F.M. contributed to interpretation of results and reviewed and revised the manuscript. E.V. conceptualized and designed the study, carried out the search and selected studies for inclusion, supervised data collection, contributed to statistical analyses and interpretation of results, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

7. Data Availability Statement

The datasets generated and analyzed for this study can be found in the Supplementary Material linked to this article, at….

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1 Tables

Table 1. Meta-analysis of the association between chorioamnionitis and covariates.

Meta-analysis	Chorioamnionitis	*k*	Effect size	95% CI	Z	*p*	Heterogeneity		
							Q	*p*	I^2
Gestational age (weeks)	Clinical	11	MD -0.73	-1.16 to -0.30	-3.35	0.001	140	<0.001	92.9
	Histological	42	MD -1.27	-1.49 to -1.05	-11.42	<0.001	495	<0.001	91.7
	Any type	56	MD -1.20	-1.40 to -1.00	-11.66	<0.001	839	<0.001	93.4
Birth weight (g)	Clinical	11	MD -29.14	-77.66 to 19.39	-1.18	0.239	107	<0.001	90.6
	Histological	41	MD -70.21	-96.71 to -43.72	-5.19	<0.001	362	<0.001	89.0
	Any type	55	MD -55.00	-74.89 to -35.12	-5.42	<0.001	474	<0.001	88.6
Antenatal corticosteroids	Clinical	5	OR 1.10	0.76 to 1.60	0.52	0.605	55	<0.001	92.8
	Histological	31	OR 1.20	1.01 to 1.42	2.03	0.043	95	<0.001	68.3
	Any type	38	OR 1.19	1.02 to 1.38	2.28	0.023	155	<0.001	76.1
Cesarean section	Clinical	8	OR 0.53	0.30 to 0.93	-2.23	0.026	316	<0.001	97.8
	Histological	28	OR 0.33	0.25 to 0.45	-7.32	<0.001	177	<0.001	84.8
	Any type	36	OR 0.37	0.29 to 0.47	-8.06	<0.001	495	<0.001	92.9
SGA	Histological	15	OR 0.33	0.23 to 0.49	-5.53	<0.001	79	<0.001	82.3
	Any type	16	OR 0.34	0.23 to 0.50	-5.64	<0.001	80	<0.001	81.2
Preeclampsia	Clinical	3	OR 0.16	0.09 to 0.29	-5.98	<0.001	2	0.369	<0.001
	Histological	23	OR 0.15	0.11 to 0.20	-13.09	<0.001	65	<0.001	66.2
	Any type	27	OR 0.15	0.12 to 0.20	-15.25	<0.001	69	<0.001	62.2
PROM	Clinical	3	OR 5.02	2.71 to 9.31	5.12	<0.001	2	<0.001	18
	Histological	27	OR 3.14	2.54 to 3.87	10.63	<0.001	149	<0.001	82.6
	Any type	30	OR 3.29	2.70 to 4.02	11.76	<0.001	155	<0.001	81.3
Male sex	Clinical	8	OR 1.10	0.80 to 1.53	0.58	0.560	80	<0.001	91.2
	Histological	35	OR 0.99	0.89 to 1.11	-0.15	0.881	91	<0.001	62.8
	Any type	46	OR 1.00	0.90 to 1.12	0.07	0.941	193	<0.001	76.7
Maternal diabetes	Any type	9	OR 0.81	0.65 to 1.01	-1.92	0.055	5	0.725	0.0
EOS	Clinical	7	OR 4.41	3.58 to 5.42	14.08	<0.001	9	0.197	30.3
	Histological	18	OR 2.62	1.88 to 3.65	5.68	<0.001	48	<0.001	64.9
	Any type	25	OR 3.81	3.20 to 4.54	14.96	<0.001	87	<0.001	72.4
LOS	Clinical	5	OR 1.41	1.10 to 1.81	2.68	0.007	17	0.002	76.8
	Histological	30	OR 1.53	1.27 to 1.84	4.45	<0.001	134	<0.001	78.3
	Any type	37	OR 1.55	1.34 to 1.80	5.82	<0.001	174	<0.001	79.3
PDA	Clinical	4	OR 1.30	1.04 to 1.64	2.27	0.023	7	0.062	59.0
	Histological	26	OR 1.41	1.15 to 1.72	3.35	0.001	144	<0.001	82.6
	Any type	31	OR 1.60	1.35 to 1.80	6.00	<0.001	195	<0.001	84.6
RDS	Clinical	3	OR 2.01	0.48 to 8.41	0.95	0.341	11	0.004	82.0
	Histological	15	OR 1.09	0.81 to 1.45	0.55	0.582	89	<0.001	84.3
	Any type	21	OR 1.00	0.78 to 1.29	0.01	0.990	149	<0.001	86.6

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CI: confidence interval; MD: mean difference; OR: odds ratio; SGA: small for gestational age; PROM: premature rupture of membranes; EOS: early-onset sepsis; LOS: late-onset sepsis; PDA: patent ductus arteriosus; RDS: respiratory distress syndrome.

Table 2. Random effects meta-regression of IVH risk in the chorioamnionitis group, and mean difference in gestational age and birth weight.

IVH grade	**Meta-regression**	***k***	**CC**	**95% CI**	**Z**	***p***	**R^2**
All grades IVH	Mean difference gestational age (per week)	35	-0.02	-0.19 to 0.16	-0.17	0.863	0.00
	Mean difference birth weight (per 100 g)	35	0.00	-0.001 to 0.001	0.07	0.942	0.00
Grades 1-2 IVH	Mean difference gestational age (per week)	20	0.05	-0.15 to 0.25	0.51	0.613	0.00
	Mean difference birth weight (per 100 g)	20	0.13	-0.07 to 0.33	1.27	0.203	0.54
Grades 3-4 IVH	Mean difference gestational age (per week)	37	-0.19	-0.43 to 0.04	-1.62	0.105	0.29
	Mean difference birth weight (per 100 g)	37	-0.10	-0.30 to 0.10	-1.01	0.312	0.00

IVH: intraventricular hemorrhage; *k*: numer of included studies; CC: coefficient; CI: confidence interval;

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Table 3. Random effects meta-regression of IVH risk in the chorioamnionitis group, and predefined covariates.

IVH grade	Meta-regression	k	CC	95% CI	Z	P	R^2
All grades IVH	Chorioamnionitis type (histological/clinical)	49	-0.08	-0.45 to 0.29	-0.42	0.673	0.00
	Funisitis (CA+F+ vs. CA+F-)	9	-0.12	-0.62 to 0.38	-0.49	0.627	0.00
	ACS (log OR)	25	0.01	-0.46 to 0.49	0.05	0.964	0.00
	Cesarean section (log OR)	22	-0.07	-0.47 to 0.32	-0.36	0.717	0.00
	Maternal age (MD)	17	-0.08	-0.24 to 0.07	-1.09	0.276	0.00
	SGA (log OR)	11	0.39	-0.09 to 0.88	1.59	0.111	0.54
	PROM (log OR)	20	-0.40	-1.06 to 0.26	-1.19	0.233	0.08
	Preeclampsia (log OR)	16	0.03	-0.40 to 0.45	0.13	0.897	0.00
	Mortality (log OR)	26	0.18	-0.15 to 0.50	1.07	0.285	0.07
	Early onset sepsis (log OR)	14	0.13	-0.47 to 0.73	0.42	0.672	0.00
	Late onset sepsis (log OR)	24	-0.04	-0.39 to 0.32	-0.19	0.846	0.00
	PDA (log OR)	22	0.13	-0.21 to 0.48	0.75	0.453	0.00
	RDS (log OR)	21	0.02	-0.22 to 0.27	0.22	0.827	0.00
Grades 3-4 IVH	Chorioamnionitis type (histological/clinical)	46	-0.07	-0.44 to 0.30	-0.37	0.708	0.00
	Funisitis (CA+F+ vs. CA+F-)	8	0.07	-0.29 to 0.44	0.40	0.691	0.00
	ACS (log OR)	28	-0.11	-0.60 to 0.38	0.42	0.672	0.00
	Cesarean section (log OR)	27	0.08	-0.09 to 0.26	0.92	0.358	0.06
	Maternal age (MD)	18	-0.01	-0.25 to 0.22	-0.11	0.911	0.00
	SGA (log OR)	12	0.24	-0.19 to 0.67	1.08	0.280	0.22
	PROM (log OR)	22	-0.09	-0.35 to 0.17	-0.65	0.515	0.00
	Preeclampsia (log OR)	18	0.41	0.20 to 0.63	3.74	0.0004	1.00
	Mortality (log OR)	30	0.42	0.17 to 0.67	3.33	0.001	0.58
	Early onset sepsis (log OR)	20	0.11	-0.32 to 0.54	0.51	0.613	0.00
	Late onset sepsis (log OR)	26	0.35	0.01 to 0.70	1.99	0.047	
	PDA (log OR)	21	0.40	0.04 to 0.76	2.18	0.029	0.48
	RDS (log OR)	27	-0.06	-0.34 to 0.21	-0.49	0.627	0.14

k: number of studies included; CA: chorioamnionitis; F: funisitis; CC: coefficient; CI: confidence interval; MD: mean difference; OR: odds ratio; ACS: antenatal corticosteroids; SGA: small for gestational age; PROM: premature rupture of membranes; PDA: patent ductus arteriosus; RDS: respiratory distress syndrome.

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Table 4. Subgroup meta-analyses based on difference in gestational age (GA).

Subgroup of studies	IVH definition	k	OR	95% CI	*p*
Studies where CA-group did not differ significantly in GA from control (p>0.05)	All grades IVH	15	1.59	1.20 to 2.10	0.001
	Grades 3-4 IVH	14	1.54	0.99 to 2.39	0.055
Studies where CA-group did differ significantly in GA from control (p<0.05)	All grades IVH	20	1.71	1.46 to 2.01	<0.001
	Grades 3-4 IVH	23	1.90	1.56 to 2.33	0.000
Studies where CA-group had a MD in GA of ≤0.5 weeks compared to control	All grades IVH	11	1.66	1.25 to 2.22	<0.001
	Grades 3-4 IVH	13	1.36	1.03 to 1.80	0.028
Studies where CA-group had a MD in GA of >0.5 weeks compared to control	All grades IVH	24	1.68	1.43 to 1.98	<0.001
	Grades 3-4 IVH	23	1.99	1.64 to 2.41	<0.001
Studies where CA-group had a MD in GA of <1 weeks compared to control	All grades IVH	16	1.72	1.37 to 2.15	<0.001
	Grades 3-4 IVH	18	1.52	1.21 to 1.92	<0.001
Studies where CA-group had a MD in GA of ≥1 weeks compared to control	All grades IVH	19	1.65	1.37 to 1.97	<0.001
	Grades 3-4 IVH	18	2.00	1.60 to 2.50	<0.001

CA: chorioamnionitis; GA: gestational age; IVH: intraventricular hemorrhage; k: number of studies included; CI: confidence interval; MD: mean difference.