

Association of Maternal Hypertension and Chorioamnionitis With Preterm Outcomes



WHAT'S KNOWN ON THIS SUBJECT: In very preterm infants, outcomes depend not only on the degree of immaturity, but also on the underlying pathologies that trigger preterm delivery. Studies that have addressed this issue have provided unclear results.



WHAT THIS STUDY ADDS: Patterns of outcomes differ between maternal hypertension and chorioamnionitis: hypertension is associated with greater risks for bronchopulmonary dysplasia and retinopathy of prematurity, and lower risks for brain injury, necrotizing enterocolitis, early-onset sepsis. For mortality, the effect changes across gestational age weeks.

abstract



OBJECTIVES: We compared the relative effect of hypertensive disorders of pregnancy and chorioamnionitis on adverse neonatal outcomes in very preterm neonates, and studied whether gestational age (GA) modulates these effects.

METHODS: A cohort of neonates 23 to 30 weeks' GA, born in 2008 to 2011 in 82 hospitals adhering to the Italian Neonatal Network, was analyzed. Infants born from mothers who had hypertensive disorders ($N = 2096$) were compared with those born after chorioamnionitis ($N = 1510$). Statistical analysis employed logistic models, adjusting for GA, hospital, and potential confounders.

RESULTS: Overall mortality was higher after hypertension than after chorioamnionitis (odds ratio [OR], 1.39; 95% confidence interval [CI], 1.08–1.80), but this relationship changed across GA weeks; the OR for hypertension was highest at low GA, whereas from 28 weeks' GA onward, mortality was higher for chorioamnionitis. For other outcomes, the relative risks were constant across GA; infants born after hypertension had an increased risk for bronchopulmonary dysplasia (OR, 2.20; 95% CI, 1.68–2.88) and severe retinopathy of prematurity (OR, 1.48; 95% CI, 1.02–2.15), whereas there was a lower risk for early-onset sepsis (OR, 0.25; 95% CI, 0.19–0.34), severe intraventricular hemorrhage (OR, 0.65; 95% CI, 0.48–0.88), periventricular leukomalacia (OR, 0.70; 95% CI, 0.48–1.01), and surgical necrotizing enterocolitis or gastrointestinal perforation (OR, 0.47; 95% CI, 0.31–0.72).

CONCLUSIONS: Mortality and other adverse outcomes in very preterm infants depend on antecedents of preterm birth. Hypertension and chorioamnionitis are associated with different patterns of outcomes; for mortality, the effect changes across GA weeks. *Pediatrics* 2014;134:e154–e161

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KEY WORDS

preterm infants, logistic models, risks, mortality, outcomes, pregnancy complications

ABBREVIATIONS

BPD—bronchopulmonary dysplasia
CI—confidence interval
FLT-1—fms-like tyrosine kinase-1
GA—gestational age
GIP—gastrointestinal perforation
INN—Italian Neonatal Network
IVH—intraventricular hemorrhage
NEC—necrotizing enterocolitis
OR—odds ratio
PVL—periventricular leukomalacia
RDS—respiratory distress syndrome
ROP—retinopathy of prematurity
SGA—small for gestational age
VEGF—vascular endothelial growth factor

Dr Gagliardi conceptualized and designed the study, supervised data collection, carried out statistical analyses, and drafted the initial manuscript; Dr Rusconi conceptualized and designed the study, contributed to interpretation of results, and critically reviewed and revised the manuscript; Drs Bellù and Zanini conceptualized and designed the study, supervised data collection, contributed to interpretation of results, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

These data were presented at the meeting of the European Society for Paediatric Research; October 9–14, 2013; Porto, Portugal.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-3898

doi:10.1542/peds.2013-3898

Accepted for publication Apr 7, 2014

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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In very preterm infants outcomes depend not only on the degree of immaturity, but also on the underlying pathologies that trigger preterm delivery.¹ Several studies have addressed this issue, but results have often been conflicting. For instance, both mortality and a common complication such as bronchopulmonary dysplasia (BPD) have been found to be higher,^{2–6} equal,^{7–10} or lower^{11–13} in infants born after preeclampsia compared with spontaneous preterm labor. There could be several reasons for these discrepancies, including differences in the populations studied, which often came from a single hospital, classification of antecedents of preterm birth, or adjustments made during the analysis stage. The topic is therefore worth further exploration.

We recently addressed this issue in an area-based epidemiologic study on 2085 newborn infants <32 weeks' gestational age (GA), and showed that different patterns of adverse outcomes were associated with different pregnancy complications that led to preterm delivery.¹⁴ In particular, we found that complications associated with infection/inflammation (eg, spontaneous preterm labor) increased the risk for neurologic outcomes, whereas complications associated with placentation disorders (eg, hypertensive disorders of pregnancy) increased the risk for BPD, retinopathy of prematurity (ROP), and in-hospital mortality. This epidemiologic work followed an important study by McElrath et al,³ in which the authors, based on both clinical information and histologic and bacteriological data, suggested the clustering of pregnancy complications into 2 main groups: placentation disorders and intrauterine infection/inflammation.

Whether the effect of various complications of pregnancy on outcomes varies by weeks of GA remains to be clarified. To address this question, studies have to enroll large numbers of very preterm

infants. In Italy, the Italian Neonatal Network (INN), a voluntary collaboration of neonatal units adhering to the Vermont Oxford Network, has been active since 2005. Within this framework, we collected information on 2 main antecedents of preterm birth, namely chorioamnionitis (the prototypic condition belonging to the "infection/inflammation" group according to McElrath's classification³), and hypertensive disorders of pregnancy (the main complication belonging to the "placentation disorder" group).

The aims of this study were: (1) to describe in a large data set the pattern of adverse outcomes in very preterm infants, comparing those born from pregnancies with chorioamnionitis with those born from mothers who had hypertensive disorders of pregnancy; and (2) to investigate the effect of GA on the relationship between these antecedents of preterm delivery and the outcomes.

METHODS

From a cohort of 16 236 neonates <1501 g and/or <30 weeks' GA, born in 2008 to 2011, and treated in 82 hospitals adhering to the INN, we excluded infants <23 weeks' GA ($N = 164$) owing to the uniformly poor prognosis, and those >30 weeks' GA ($N = 4909$) because of the increasing proportion of small for gestational age (SGA) infants, as well as those who had congenital anomalies ($N = 493$), thus leaving 10 670 infants (eligible cohort). For this study we selected infants born either after hypertensive disorders of pregnancy or after chorioamnionitis; infants who had both complications ($N = 111$) were not analyzed.

All variables were defined according to the Vermont Oxford Network (www.vtoxford.org). In particular, hypertensive disorders of pregnancy comprised chronic or pregnancy-induced hypertension, defined as a systolic blood pressure above 140 mm Hg or a diastolic blood pressure above 90 mm Hg

recorded before or during the current pregnancy, with or without edema and proteinuria. Chorioamnionitis was coded as present if a diagnosis of chorioamnionitis was recorded in the maternal or infant medical record.

The following outcomes were considered: mortality before discharge from hospital; BPD, defined as oxygen dependency at 36 weeks' postmenstrual age; respiratory distress syndrome (RDS) defined as hypoxia requiring supplemental oxygen plus a chest radiograph consistent with RDS (reticulogranular appearance in lung fields with or without low lung volumes and air bronchograms) within the first 24 hours of life; need for mechanical ventilation; pneumothorax; grade 3 to 4 intraventricular hemorrhage (IVH)¹⁵; cystic periventricular leukomalacia (PVL) defined as presence of 1 or more periventricular white matter echolucencies; severe ROP defined as stage III to V or need for ROP surgery; necrotizing enterocolitis (NEC) requiring surgery, or focal gastrointestinal perforation (GIP); and early sepsis (if a bacterial pathogen was recovered from a blood and/or cerebrospinal fluid culture obtained on day 1 to 3 of life), and late sepsis (after day 3).

This study was carried out as an analysis of the INN database, for which all hospitals sought local ethics committee approval. A written consent to data collection was obtained from parents as per Italian law. No protected health care information was collected.

Neonates born after hypertension and those born after chorioamnionitis were compared on their relative odds of selected outcomes, by using multivariate logistic regression. The analyses were adjusted for GA and other possible prenatal confounders, such as antenatal steroids, gender, location of birth (inborn/outborn), mode of delivery (vaginal/cesarean), and multiple pregnancies. Random-effects logistic models were used to take into account

the multilevel structure of the data (hospitals-neonates). Results are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Statistical analyses were performed by using statistical software Stata 11.1 (Stata Corp, College Station, TX).

RESULTS

We studied 3606 very preterm infants, with a mean GA of 27.4 weeks (SD, 2.1), and a mean birth weight of 938 g (SD, 281 g); of these, 1510 infants (14.1% of the eligible cohort) were born after chorioamnionitis, and 2096 (19.6%) after hypertensive disorders of pregnancy. The characteristics and main outcomes of infants are reported in Table 1; several aspects of infants born from mothers who had hypertensive disorders differed from those born after chorioamnionitis, most notably GA, with a mean difference of almost 2 weeks.

As expected, the lower the GA, the higher the frequency of all adverse outcomes (Table 2). The number of infants exposed to either hypertensive disorders or chorioamnionitis varied across GA weeks, with hypertensive disorders of pregnancy increasing, and chorioamnionitis remaining constant until at least 29 weeks' GA (Fig 1); for this reason, we adjusted for GA in all of the analyses.

Table 3 illustrates the ORs for several outcomes, adjusted for GA and the other potential confounders. Infants born after hypertensive disorders of pregnancy, when compared with those born after chorioamnionitis, had an increased risk for in-hospital death, acute and chronic respiratory problems (RDS, pneumothorax, mechanical ventilation, BPD), and ROP, and a lower risk for severe IVH, cystic PVL, surgical NEC or GIP, and early-onset sepsis.

When we looked at ORs for mortality in infants born after hypertensive

TABLE 1 Characteristics of the Infants Studied (Mean [SD] or Percentage) According to Maternal Complications

	Chorioamnionitis (N = 1510)	Hypertension (N = 2096)	P ^a	Total (N = 3606)
GA, weeks	26.3 (2.1) (range, 23–30)	28.1 (1.8) (range, 23–30)	<.001	27.4 (2.1) (range 23–30)
Birth wt, g	933 (284)	942 (278)	.34	938 (281)
Antenatal steroids	81.70	85.98	<.001	84.19
Males	52.58	47.38	.002	49.56
Twin (any order)	22.19	18.46	.006	20.02
Location of birth: inborn	94.77	92.60	.009	93.51
Caesarean section	58.68	96.28	<.001	80.53
Apgar score at 1 min	4.6 (2.3)	5.6 (2.2)	<.001	5.2 (2.3)
In-hospital death	24.45	12.43	<.001	17.47
RDS	87.80	90.37	.02	88.87
Mechanical ventilation	71.85	64.60	<.001	67.64
Pneumothorax	4.44	5.34	.28	4.96
BPD	28.37	21.89	<.001	24.39
Severe ROP	15.06	6.35	<.001	9.81
Surgical NEC or GIP	6.34	2.31	<.001	3.99
Grade 3–4 IVH	18.16	5.73	<.001	10.94
Cystic PVL	6.58	4.24	.02	5.21
Early-onset bacterial sepsis	16.86	5.06	<.001	9.97
Late-onset sepsis ^b	26.72	17.70	<.001	21.36

^a Student's *t* test or χ^2 .

^b Including bacterial and fungal sepsis.

TABLE 2 Frequency of Selected Outcomes by GA Week (Percentage)

GA Week	In-hospital Death	RDS	BPD	ROP	NEC or GIP	Grade 3–4 IVH	PVL	Early-Onset Sepsis	Late-Onset Sepsis
23	68.7	99.4	70.0	45.2	4.2	43.8	5.3	16.2	40.0
24	49.5	97.4	65.2	37.3	8.7	30.8	4.0	16.2	42.9
25	33.8	97.0	49.3	30.8	10.2	21.2	9.7	14.4	38.9
26	22.3	96.4	43.6	15.9	6.7	14.1	6.9	14.2	30.8
27	14.8	94.9	31.2	9.4	3.8	7.8	7.2	11.3	26.1
28	8.3	88.0	15.0	4.6	2.7	5.9	4.1	8.9	14.9
29	4.3	86.3	11.8	1.0	1.7	3.0	3.6	5.4	12.0
30	2.5	73.6	8.2	0.5	0.9	2.0	3.6	5.7	8.8
Overall	17.5	88.9	24.4	9.8	4.0	10.9	5.2	10.0	21.4

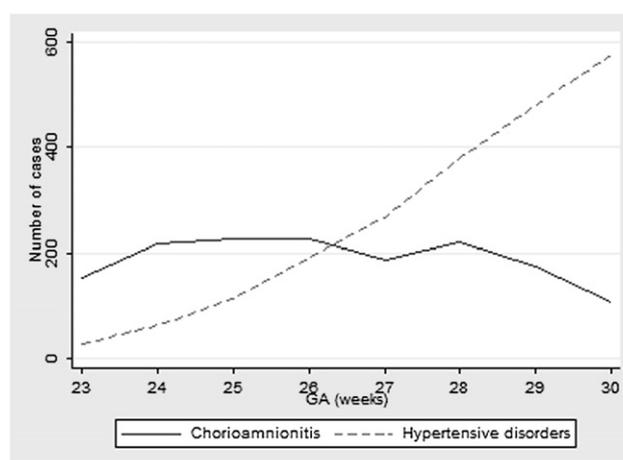


FIGURE 1

Absolute frequency of chorioamnionitis and hypertensive disorders by GA week.

TABLE 3 OR of Various Outcomes for Infants Born After Hypertensive Disorders; Reference Group Are Infants Born After Chorioamnionitis

	OR (95% CI) ^a	P
In-hospital death	1.39 (1.08–1.80)	.011
RDS	1.93 (1.44–2.61)	<.001
Need for mechanical ventilation	1.82 (1.44–2.29)	<.001
Pneumothorax	1.60 (1.09–2.37)	.018
BPD	2.20 (1.68–2.88)	<.001
Severe ROP	1.48 (1.02–2.15)	.040
Surgical NEC or GIP	0.47 (0.31–0.72)	.001
Stage 3–4 IVH	0.65 (0.48–0.88)	.006
Cystic PVL	0.70 (0.48–1.01)	.056
Early-onset bacterial sepsis	0.25 (0.19–0.34)	<.001
Late-onset sepsis ^b	1.19 (0.94–1.50)	.152

^a Adjusted for GA, antenatal steroids, gender, multiple pregnancies, inborn/outborn, and mode of delivery.

^b Including bacterial and fungal sepsis.

disorders in comparison with those born after chorioamnionitis at each GA week (Fig 2), a clear trend was evident; at 23 to 26 weeks' GA, infants born after hypertensive disorders showed a significantly higher risk for mortality. The effect tended to gradually disappear with increasing GA, and from 28 weeks' GA onward, the ORs were <1, indicating that being born after hypertensive disorders was less unfavorable than being born after chorioamnionitis (ie, an interaction between GA and exposure was present) (*P* for interaction <0.02).

Such a pattern was not observed in the other outcomes, and interaction was

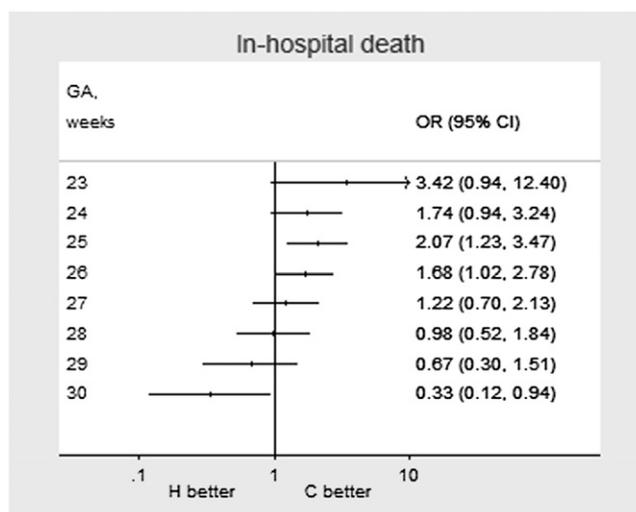
always non-significant (*P* always >0.6), with the exception of late onset sepsis, for which an interaction was present, although the overall effect did not differ from the null value. Supplemental Figures 3–10 illustrate these results.

DISCUSSION

This study demonstrates that in very preterm infants several neonatal outcomes depend both on immaturity and on the underlying mechanisms that led to preterm birth, namely, hypertensive disorders of pregnancy and chorioamnionitis. In addition, it shows how for in-hospital mortality the relationship

between the relative exposures and the outcome is not constant, even in the small GA strata considered in this study (23–30 weeks' GA).

Our data largely confirm the results of a previous area-based study that we carried out in another population and in another GA span (23–32 weeks' GA), in which several antecedents of preterm delivery were ascertained.¹⁴ This other study showed that grouping together complications such as hypertensive disorders of pregnancy, intrauterine growth restriction, acute fetal distress as a cause of preterm delivery under “placentation disorders”,³ and other complications (spontaneous preterm labor, preterm prelabor rupture of membranes, chorioamnionitis, hemorrhage) under “infection/inflammation”³ allowed us to gain a clearer picture of the relation with main outcomes such as mortality, IVH, cystic PVL, BPD, and ROP. Given the greater sample size of this study, which only focused on 2 main antecedents of preterm delivery, namely hypertensive disorders of pregnancy (placentation disorders) and chorioamnionitis (infection/inflammation), we confirmed those results and were able to focus on other outcomes such as acute lung injury (RDS, need for mechanical ventilation, and pneumothorax), early- and late-onset sepsis, and NEC or GIP. Moreover, in the current study we also dealt with a problem left open in our previous study and unsettled in literature, that is, the possibility of a modulation of different outcomes by GA. In this respect, we showed a gradient of effect of exposures on mortality across GA weeks (infants of lower GA weeks showing greater mortality after hypertension), but not for the other outcomes studied. Several studies suggest that in very preterm infants, inflammatory antecedents of birth increase lung maturity, reducing RDS and other acute respiratory illnesses, and thus increasing

**FIGURE 2**

OR (95% CI) for mortality in infants born from mothers who have hypertensive disorders (H) in comparison with those born after chorioamnionitis (C) at various GA weeks.

immediate probability of survival. Some authors also suggest that inflammation provides the fetus with the ability to withstand extrauterine conditions that would otherwise prove lethal,^{16,17} especially for its effects on the lungs. Inflammation is a key stimulus for lung maturation; experimental studies show that intra-amniotic injection of several pro-inflammatory agents induced lung maturation.¹⁸ Other studies performed exclusively in extremely preterm infants (22 to 26–27 weeks' GA) have shown that chorioamnionitis lowers the risk for mortality.^{3,19} These findings are consistent with the fact that the first causes of death in very preterm infants are respiratory.^{19,20}

Although for mortality we observed an interaction between exposures and GA, this was not evident for other outcomes. Across the entire GA strata, chorioamnionitis was always associated with increased cerebral injury and NEC/GIP, and less BPD and ROP.

As far as BPD is concerned, this study supports the greater overall importance of the "vascular hypothesis"²¹ over the "infectious" hypothesis on the development of BPD. Several recent reports have shown that maternal hypertensive disorders of pregnancy are associated with a higher risk for BPD^{5,6,14,22}; however, the underlying mechanism has only recently been clarified in experimental animal studies. Preeclampsia is characterized by maternal endothelial dysfunction that leads to hypertension, proteinuria, and other complications.²³ In preeclampsia, a disturbed regulation of vascular growth in the fetal-maternal unit leads to an overproduction of anti-angiogenic factors, such as the soluble form of the vascular endothelial growth factor (VEGF) receptor antagonist fms-like tyrosine kinase-1 (FLT-1). FLT-1 is also markedly increased in amniotic fluid; it has been shown to disrupt lung development through impaired VEGF signaling in utero, and to reduce

alveolarization and pulmonary vascular growth in infants.²⁴ These findings demonstrate the biological plausibility of the epidemiologic evidence that links preeclampsia to BPD.

ROP, which is primarily a vascular disease, also seems to follow the pattern of BPD in being linked to maternal hypertension rather than chorioamnionitis.¹⁴ ROP is a 2-stage disease, with a first stage characterized by reduced intrauterine retinal vascular development, followed by an exaggerated postnatal response to hypoxia, with subsequent excessive secretion of VEGF causing a second vasoproliferative stage of the disease.²⁵ According to this model, hypertension exerts its noxious effect in the anti-angiogenic, first stage of disease. The mechanism of delayed retinal development could include a reduced intrauterine level of VEGF.²⁵ Very preterm infants of preeclamptic mothers have lower levels of VEGF and higher levels of anti-angiogenic factor FLT-1.²⁶ Zayed et al²⁷ provided direct confirmation to this hypothesis by showing that maternal hypertension/preeclampsia interfered with the infant's retinal vascular development during the first stage of the disease, resulting in an increased risk for severe ROP during the second stage.

Although we and other authors^{14,27,28} found a detrimental role played by hypertension on ROP, others showed a protective one.^{29–31} A possible explanation for these discordant results lies in the data analysis. It is known that SGA infants (a condition the risk for which is increased by hypertension)²⁵ have a higher frequency of ROP.^{31–33} We should therefore expect an increased risk for ROP for conditions that increase intrauterine growth restriction/SGA, such as hypertension, and certainly not decrease. If being SGA is both caused by hypertension/preeclampsia and associated with ROP, then adjusting for birth weight in studies analyzing the

role of hypertensive disorders could give rise to a problem of "overadjustment." In fact, studies that investigate the role played by hypertension on ROP and correct-for-birth weight in their analysis find that hypertension is protective,^{29–30} whereas others that do not adjust (eg, this study and refs 14, 27, 28) find the opposite.

In regards to neurologic outcomes, in recent years the association between antenatal infection and cerebral white matter damage has gained wide acceptance.^{34,35} Our study confirmed the negative effect of chorioamnionitis on ultrasound-diagnosed cerebral lesions.

Although the association between chorioamnionitis and early sepsis was expected,³⁶ the association with NEC is more problematic. The pathogenesis of NEC is multifactorial, and both infectious and vascular factors are involved.³⁷ To the best of our knowledge, no large-scale study has ever addressed the associations of antecedents of preterm delivery and NEC. Although it is unlikely that a prenatal infection is directly responsible for the increased relative risk for NEC found in chorioamnionitis, innate immunity upregulation in the gut toward bacterial antigens plays a key role in the pathogenesis of NEC.³⁸

One limitation of our study, which is common to all studies looking at conditions associated with very preterm delivery, is the lack of a proper "control" group of normal infants,^{17,36} because preterm birth is always the result of a pathologic process. Consequently, we can only compare the risks after hypertension with those after chorioamnionitis. A lower risk after hypertension, as with IVH/PVL, only means that the risk after chorioamnionitis is higher, not that it is lower in absolute value than the risk that a hypothetical "normal" fetus would experience. We can legitimately conclude however, that among

infants being born at 23 to 30 weeks' GA after hypertension or chorioamnionitis, the risks are not equal, owing to the fact that for some outcomes the risks are higher after hypertension, whereas for others they are higher after chorioamnionitis.

Another potential limitation of our study is that, as with all observational studies, we are unable to distinguish between causation and association in explaining our results. Even so, our results and line of reasoning help clarify pathophysiological mechanisms suggested by other studies on these main maternal complications of pregnancy in very preterm infants.

We only focused on 2 exposures (hypertension and chorioamnionitis), disregarding any other antecedent of delivery at 23 to 30 weeks' GA. The fact that the exposures studied are only a subset of those experienced by this population does not, however, reduce the validity of the study; similarly, in a randomized clinical trial, the investigator chooses the type and dose of drugs to be compared to improve inference without loss of internal validity.³⁹ This line of reasoning is gaining momentum in epidemiologic studies, where a "lack of representativeness" has been shown to provide unbiased estimates of effects under most conditions, and indeed to be often advantageous in terms of efficiency.^{40,41}

Moreover, although we employed definitions widely used in clinical practice and research (those of the Vermont Oxford Network, the largest neonatal network worldwide), we admit that exposures were defined without any clinical detail, as is always the case in large epidemiologic studies, and consequently there is the possibility of some misclassification. In particular for chorioamnionitis, our classification probably detected the more severe/manifested cases for the exposures under examination and not the whole

spectrum of the disease. Again, the fact of focusing only on more severe degrees of exposure (or differently severe degrees in the 2 arms of study) does not bias the results,^{39–41} as long as there is not differential misclassification (that is, different recording of exposure owing to the presence/absence of outcomes, for example, preferentially recording chorioamnionitis instead of hypertension in case of PVL). Given that we collected our data prospectively, and the outcomes were recorded without knowledge of the aim of this study, diagnostic bias and differential misclassification were probably low. The multicenter structure of data also probably helped reduce differential misclassification.

Our study also had several strengths. We collected our data prospectively from a large number of hospitals. The data collection time frame is recent, thereby reflecting contemporary clinical practice. Because of the large sample size, we were able to demonstrate the effects of exposures, even though misclassification may be present.

CONCLUSIONS

Our study provides evidence of a different effect of different pregnancy complications on neonatal outcomes, and in more general terms, it highlights the importance of intrauterine life on future health and disease.

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(Reggio Emilia); Massimo Bellettato, Roberta Pesavento, Alessandra Cesaro, Massimo Scollo (Thiene); Isabella Mondello (Reggio Calabria); Aniello Pugliese, Claudio Iervolino (Napoli Cardarelli); Giovanni Corsello, Mario Giuffrè (Palermo Policlinico Giaccone); Pasqua Betta, Mario Giuseppe Romeo, Alessandro Saporito (Catania Policlinico Rodoligo); Maria Grazia Leone, Alessandro Rodonò (Catania Ospedale Santo Bambino); Alessia Franceschi, Francesco M. Risso (Genova Gaslini); Mauro Carpentieri, Teresa Vecchiano, Maria Pia Cigliano (Napoli SS Annunziata); Piermichele Paolillo, Simonetta Picone (Roma Casilino); Antonio Marra, Gessica Rossetti, Tiziana Testa (Moncalieri); Fernando Del Cuore (Lecce); Francesco Crescenzi (Terni); Gianna Poloni, Maria Chiara Russo (Torino Maria Vittoria); Francesco Nigro, Gabriella Lucia Tina (Catania Ospedale Garibaldi); Patrizia Brindisino (Chieti); Raffaele Gurrado (Ospedale SS. Annunziata); and Maurizio Felice, Isabella Formica (Ospedale Bolognini Seriate).

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(Continued from first page)

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding. Participation of centers to the Italian Neonatal Network is aided by an unrestricted grant by Chiesi pharmaceuticals.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Association of Maternal Hypertension and Chorioamnionitis With Preterm Outcomes

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Pediatrics 2014;134:e154

DOI: 10.1542/peds.2013-3898 originally published online June 9, 2014;

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DOI: 10.1542/peds.2013-3898 originally published online June 9, 2014;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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