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# Beyond neonatal seizures - epileptic evolution in preterm newborns: a systematic review and meta-analysis

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**ABSTRACT**

***Objective.*** To assess the potential risk of developing epilepsy in preterm newborns with neonatal seizures (NS). Two electronic databases (PubMed and Web of Sciences) were searched from inception to December 2020. Studies that investigated the outcome of epilepsy in neonates with NS were included.

***Methods.*** Case-control, cross-sectional and cohort studies were included. Data synthesis was undertaken via systematic review and meta-analysis of available evidence. All review stages were conducted by three independent reviewers. We analysed data on neonates with NS who developed post-neonatal epilepsy (PNE) based on the data reported in the selected articles. We then investigated the development of PNE in term and preterm neonates.

***Results.*** The initial search led to 568 citations, of which 12 were selected for the review and six were eligible for meta-analysis. Results of the meta-analysis showed no significant difference in the risk of developing PNE between full-term infants with NS (pooled OR [pOR]=0.92: 95% CI: 0.58-1.44) and preterm neonates.

***Significance.*** Gestational age does not seem to be an independent predictor for the development of PNE in neonates with NS. More data are needed to explore the relationship between seizures in the neonatal period and epilepsy later in life.

**Key words:** newborns, preterm infants, seizure

Seizures are the most frequent neurological diagnosis in neonatal intensive care units (NICU). The incidence of neonatal seizures (NS) is reported as 2.29/1,000 live births. Higher rates are seen in preterm neonates, with an incidence of 14.28/1,000 versus 1.10/1,000 in full-term infants, and the incidence increases with decreasing gestational age and birthweight [1-4]. The brain of preterm newborns is particularly vulnerable and NS constitute the most frequent and distinctive neurological symptom of acute cerebral [5-7]. The aetiological profile of seizures in preterm infants is different from that seen in term infants. Hypoxic-ischaemic encephalopathy is the most frequent cause of NS in term babies followed by stroke, cerebral malformations and metabolic disorders, while in preterm neonates, intraventricular/parenchymal haemorrhage and infections are the most common causes [8].

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## Mechanism of epileptogenesis in preterm newborns

The mechanisms and timing of epileptogenesis following preterm brain injuries are still poorly understood. Abnormal growth and maturation of some types of cells in preterm babies with very low birth weight, particularly neurons and oligodendrocytes, are associated with decreased cerebral and cerebellar volumes and increases in cerebral ventricular size [9]. The white matter of the preterm brain is particularly susceptible to injury that disrupts the normal progression of myelination. All these patho-mechanisms involved in the evolution of severe white matter injury (WMI) disrupt the development of neuronal networks and thereby induce epileptogenesis in preterm infants. Furthermore, it has been clearly demonstrated that in periventricular leukomalacia (PVL), there is a lack of balance between γ-aminobutyric acidergic synapses, from excitatory to inhibitory, or decreased expression of both NKCC1 and KCC2 in the subplate zone and subsequent white matter distribution [10-13].

## Development of post-neonatal epilepsy

Although experimental and clinical studies suggest specific and independent contribution of seizure-induced changes in determining long-term outcomes, none of these completely explain the risk of developing remote epilepsy. Very few papers have compared the two populations of preterm and full-term newborns with seizures. The more immature the brain, the more it appears to be susceptible to seizures [14]. The presence of seizures in neonatal age is suggested to be associated with an unfavourable outcome and significant morbidities. Among these, the development of post-neonatal epilepsy (PNE) has been reported but its relationship with NS is incompletely understood [15, 16]. Incidence of PNE following NS varies largely among published studies, ranging from 16% to 30% [17, 18]. Although there are many reports in the literature regarding the incidence of PNE in term infants who have suffered from NS, little is known about the incidence of PNE in preterm newborns, unfortunately, not all studies distinguished between preterm and term neonates. In this study, we specifically analysed the population of preterm newborns based on the hypothesis that the incidence of PNE is higher in preterm newborns with NS.

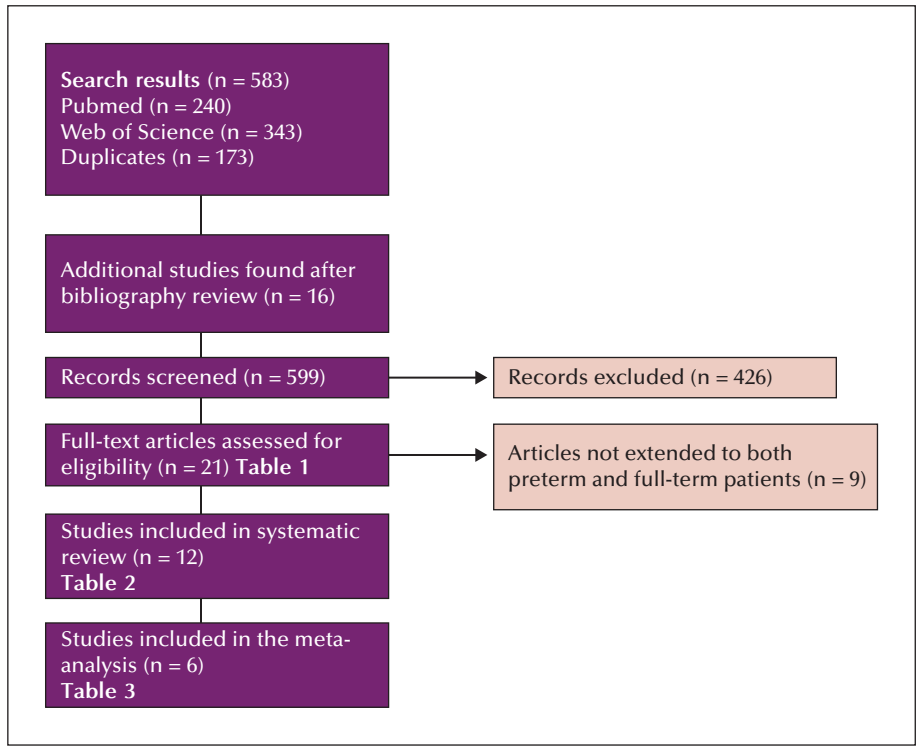
## Materials and methods

A systematic search was performed in PubMed and Web of Science, according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) using AMSTAR (A MeaSurement Tool to Assess systematic Reviews) guidelines. We searched for reports published from 1960 to December 2020. This large time frame was selected in order to obtain as many articles as possible for our analysis. The following search terms were used: "neonatal seizures AND preterm newborn AND neurological outcome", "neonatal seizures AND postneonatal epilepsy", and "neonatal seizures AND epilepsy AND preterm newborn". The filters used were "human studies", "English language" and "age under 18 months". Subsequently, we manually searched for pertinent studies cited in all relevant studies and not identified in our electronic search. Duplicates were removed after revision. All full texts were read by the same authors, and data were extracted and discussed within the group to assess for quality indicators and reliability. The following variables were extracted: full bibliographic reference, authors, study design, number of patients, number of full-term newborns, number of preterm newborns, degree of prematurity, use of EEG, follow-up duration, incidence and age at onset of PNE, and incidence of other neurological disorders. Only articles that focused on NS in term and preterm neonates, and commented on subsequent development of PNE were selected. Clinical or electro-clinical diagnosis of NS was required for inclusion. Review articles and studies on PNE and NS without a clear differentiation between term and preterm neonates were excluded. Reports without specific comment on the development of PNE were not included. A flow diagram of the applied search strategy is represented in *figure 1*.

Although there are many reports in the literature regarding the incidence of PNE in term infants who have suffered from neonatal seizures, little is known about the incidence of PNE in preterm newborns. Unfortunately, not all studies distinguished between preterm and term neonates, however, nonetheless we believe that our data are informative.

Selecting only those reports that included and specified preterm seizing newborns, 12 publications were selected, published between 1984 and 2020, and among these, six reports were excluded because they did not meet all the required inclusion criteria. Therefore, the meta-analysis was performed only on the six reports that contained complete and exhaustive clinical, electrographic and instrumental data. Moreover, all of these papers reported significant patient clinical follow-up information.

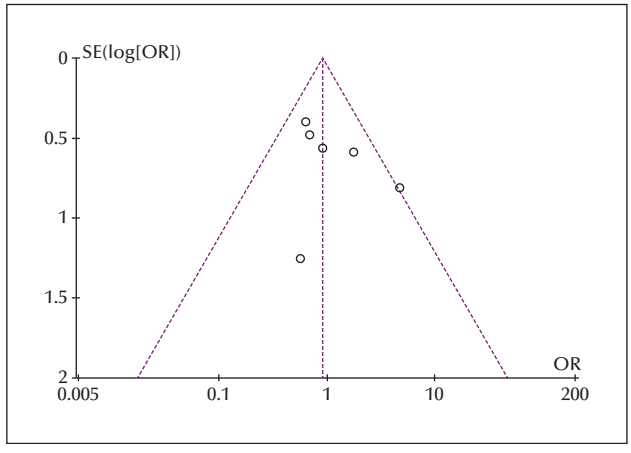
The possible influence of publication bias was revealed using funnel plots that graph precision versus magnitude of effects. The horizontal axis shows the event effect, while the vertical axis shows the standard (*figure 2*). When publication bias is limited, the points representing the included studies are symmetrically distributed around the mean effect size.




■ **Figure 1.** Flow diagram of search strategy.

The individual and pooled point effect were graphically summarised using forest plots with Mantel-Haenszel odds ratios (OR) for dichotomous data. Each study is represented by a square and a line. The square indicates the OR and its size depends on the weight assigned to each included study; the line represents the 95% confidence interval. The pooled effect is displayed by the black diamond [19].

Statistical heterogeneity was investigated using the $\lambda^2$ test, with a significance level of $p<0.05$, and with an $I^2$ test was considered significant for values higher than 70%. Therefore, a random effect model was used when heterogeneity was significant; otherwise, a fixed effect model was adopted. The 5.3 version of RevMan was used for meta-analysis.




■ **Figure 2.** Funnel plot for publication bias demonstrating a lack of studies with small sample size.

## Results

The search identified 583 records, through database searching of PubMed and Web of Science. Of all 583 articles, 343 were found on the Web of Science and 240 on PubMed. Of these, 41 (Web of Science) and 90 (PubMed) were found based on "neonatal seizures AND preterm neonates AND neurological outcomes", 244 (Web of Science) and 45 (PubMed) based on "neonatal seizures AND postnatal epilepsy" and 56 (Web of Science) and 109 (PubMed) based on "neonatal seizures AND epilepsy AND preterm newborns". Furthermore, 16 articles were manually added from references of pertinent studies which were not identified in our electronic search. We also included studies in which NS were diagnosed on clinical

grounds only, because there were only three reports on electro-clinical diagnosis of NS and subsequent PNE development (*figure 1*) [5, 20, 21].
According to our inclusion and exclusion criteria, 21 studies published between 1960 and 2020 were selected, including 14 retrospective studies and seven prospective studies (*table 1*).
The total number of newborns with seizures was 2,794, of whom 317 developed PNE (11.3%). The number of preterm patients with NS was 970; 15.4% of them (*n*=150) developed PNE. NS diagnosis was based on EEG alone in 19 studies and based on combined clinical observation and video-EEG polygraphy in two studies. The length of post-NICU follow-up was specified in 19 reports as between three months and 12 years [22]. Only a few reports specified the intervals between clinical examinations, and none of the studies described the methods of the assessments during follow-up. Four studies documented gestational age [23-27]. In six publications [17, 25, 28-31], only preterm neonates were reported. Eleven reports further described the presumed aetiology of prematurity. Only one publication reported birthweight [32]. The age at onset of PNE was specified in 11 publications, with most patients developing PNE within the first year of life. Three publications commented on PNE only, although most children also developed multiple disabilities such as cerebral palsy and/or intellectual impairment. Eleven studies showed stratified symptomatology according to the type of prematurity. In one study [33], the preterm neonates developed NS, febrile seizures and epilepsy but the incidence of PNE could not be obtained.
Only 12 publications clearly differentiated between preterm and full-term patients with PNE (*table 2)*, with a follow-up ranging from three months to seven years. The age at onset of PNE was reported in six studies [23, 26-28, 31, 32] (range: 4 months - 3.6 years). In 11 publications, prematurity was not correlated with incidence of PNE [6, 15, 16, 24, 34-39].
Six publications presenting full data on PNE in preterm (*n*=201) and term (*n*=350) newborns [3, 5, 24, 26, 27, 32] were suitable for meta-analysis. The main characteristics of the aforementioned studies are summarised in *table 3*.
According to our meta-analysis, there was no significant difference in the risk of developing PNE between preterm and full-term infants with NS, and *figure 3* shows a Forest plot with no difference in the odds of neonatal epilepsy between term and preterm infants (OR: 0.92, 95% CI: 0.58-1.44; $\lambda^2$: 6.61; *p*=0.25; $I^2$: 24%). The cumulative meta-analysis indicated no evidence of statistical difference in the odds of having epilepsy between full-term and preterm infants, however, the number of studies (six) may be insufficient to determine a reliable estimate. While most of these studies are concordant, only two papers [26, 27] show a higher risk for full-term infants than for preterm infants; this result could lead us to think that prematurity acts as a protective factor. In our analysis, the average rate of PNE in preterm was 20.4% (range: 3.7-27.3%; IQR: 7.3%) versus 16.3% for PNE in full-term babies (range: 6.4-37.3%; IQR: 13.6%).
Inspection of the funnel plot revealed that the studies deemed eligible for meta-analysis are relatively homogeneous, as shown by *figure 2*. Based on comparison of the percentages of patients with PNE in the studies included in the meta-analysis, little variability in PNE rate was found in preterm infants [3, 7, 23-26, 28-32, 38, 39] (with the exception of the study of Hellstrom *et al*. [24]) as compared to full-term infants, who showed a fluctuation from 6.45% to 37.35% (*table 3*) [3, 7, 24, 26, 32].
See *figure 2 and 3* for forest plot and funnel plot representations.

## Discussion

We conducted this systematic review and meta-analysis aiming to examine the relationship between the presence of NS and the development of PNE in preterm infants.
In the literature, the incidence of epilepsy in infants who have had seizures in the neonatal period is reported at around 17% [17], however, the risk of PNE varies significantly among the 12 studies included in our systematic review.
While performing our search, we found that there are relatively few papers reporting specifically on the incidence of epilepsy in preterm newborns with seizures, however, we believe that the results of our analysis are nevertheless very informative. In fact, it was our belief that PNE was more frequent in seizing preterm newborns than in term newborns, pointing to prematurity as the cause of PNE, but our meta-analysis demonstrates that prematurity may not be considered a predisposing factor for PNE in seizing newborns.
NS could be either overestimated if non-epileptic paroxysmal events are considered to be seizures, or underestimated if electrographic-only seizures are not detected without synchronized video-EEG-recordings. Nonetheless, the semiology of seizures in preterm neonates is somewhat different. Glass *et al*. [7] reported that 24% of preterm neonates had exclusively subclinical seizures (and 66% had at least one subclinical seizure) and seizures tended to be shorter with unlikely propagation in the more immature preterm brain. Furthermore, the variability in the reported incidence could also be due to the different inclusion criteria used, such as the duration of EEG monitoring, selection of babies to be monitored, and

▼ **Table 1.** Full-text articles assessed for eligibility.

| Year | Study design | Author | Total patients | Born a term | Born preterm | Prematurity type | EEG | Follow-up | Total patients | Other neurological deficit | Incidence P/T | Age of onset | PNE in preterm |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1960 | P | R. Harris | 41 | 27 | 14 | NA | Yes | 1-4 yrs | 3 | MR, CP | NA | NA | NA |
| 1966 | P | F.J. Schulte | 57 | 55 | 2 | 1 (35 W)-1 (36 W) | Yes | 1-4 yrs | 6 (14.2%) | MR | NA | 5-8 mos. | NA |
| 1982 | R | K. watanabe | 264 | 264 | NA | NA | Yes | 3-9 yrs | 68 (25.8%) | MR, CP | NA | 0-4.5 yrs. | NA |
| 1992 | R | J.L.D. Gherpelli | 23 | 21 | 2 | NA | Yes | 2-24 mos | 7/23 (30%) | NA, CP, DD | NA | 2-6 mos. | NA |
| 1995 | R | Hellstrom-Westas | 58 | 31 | 27 | 29 | Yes | 19 mos | 3 (1 preterm) (8.3) | NA | 1/3 | NA | 1 (27) |
| 1996 | R | E.L. Ortibus | 81 | 67 | 14 | NA | Yes | 2-48 mos | 15 (18.5%) | DD | NA | NA | NA |
| 2002 | R | Brunquell | 77 | 31 | 22 | NA | Yes | 6 mos-7 yrs | 11 (14.4%) | NA | NA | 3.5 yrs. | NA |
| 2004 | R | Garcias Da Silva | 158 | 83 | 44 | NA | Yes | 48 mos | 43 (28.4%) | NA | 4/44 P (0.85) 14/83 T (P 0.19) | 22% (12 mos.), 33% (48 mos.) | 4 (44) |
| 2004 | P | Pisani | 28 | / | 28 | 29 W | Yes | 6 mos | 7/27 (25.9%) | CP | NA | NA | 7 (27) |
| 2006 | P | Herrgard EA | 621 | / | 60 | <32 W | Yes | 5 yrs | 4 | NA | NA | NA | 4 (60) |
| 2007 | R | R. Guillet | 196 | NA | NA | NA | Yes | 12 yrs | 21 (15.9%)) | CP | NA | <4 mos. | NA |
| 2007 | P | Ronen GM | 88 | 62 | 26 | 32 | Yes | 10 yrs | 17 (19.3%) | NA | 48% P/29% T | 4-10 mos. | 13 (48%) |
| 2007 | R | Pisani | 106 | 55 | 51 | 29 (<29 W), 22 (>29 W) | Yes | 24 mos | 22 (18.8%) | NA | 3 P, 13 T | NA | 9 (51) |
| 2008 | P | M.L. Nunes | 101 | 73 | 28 | NA | Yes | 11.9-53.5 mos | 19/64 (21.3%) | DD | NA | <48 mos. | NA |
| 2008 | R | Pisani | 51 | / | 51 | 29 (24-29 W)/22 (30-36 W) | Yes | 30-91 mos | 9 (18%) | MR, CP | NA | 4 mos. | 9 (51) |

▼ **Table 1.** Full-text articles assessed for eligibility (*continued*).

| Year | Study design | Author | Total patients | Born a term | Born preterm | Prematurity type | EEG | Follow-up | Total patients | Other neurological deficit | Incidence P/T | Age of onset | PNE in preterm |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2010 | R | Davis | 414 | / | 414 | 401-1000 g | 22% | 18-22 mos | 47 (16%) | NA | NA | NA | 47/414 (16%) |
| 2012 | P | Pisani | 85 | 44 | 41 | 8 (34-36 W)-25 (29-33 W)-18 (<28 W) | Video EEG | 7 yrs | 15 (17.6%) | NAn CP, MR | 17% P/18% T | NA | 7/41 (17%) |
| 2015 | CR | Spagnoli | 2 | / | 2 | 24/28 | Yes | RS | Focal febrile seizures | NA | NA | NA | 2 (2) |
| 2016 | R | Pisani | 154 | / | 76 | 29 | Video EEG | 3-6-9-12 mos | 11 (15%) | CP, DD | NA | <1 year | 19 (15%) |
| 2018 | R | Glass | 87 | 75 | 12 | 30/34 | Yes | 1 yrs | 1 (7%) | NA | 3/12 (25%) P; 5/75 (7%) T (p-value 0.04) | 3.6 yrs (median age) | 3 (12) |
| 2018 | R | Pisani | 102 | 46 | 56 | NA | Yes | Population study | 7 (14.3%) | NA | NA | NA | 25 (14.3%) |

R: retrospective; P: perspective; CR: case report; NA: not available; W: week of gestational age; CP: cerebral palsy; DD: developmental disorder; MR: mental retardation; PNE: postneonatal epilepsy; P: preterm newborns; T: term newborns.

▼ **Table 2.** Thirteen studies included in the systematic review.

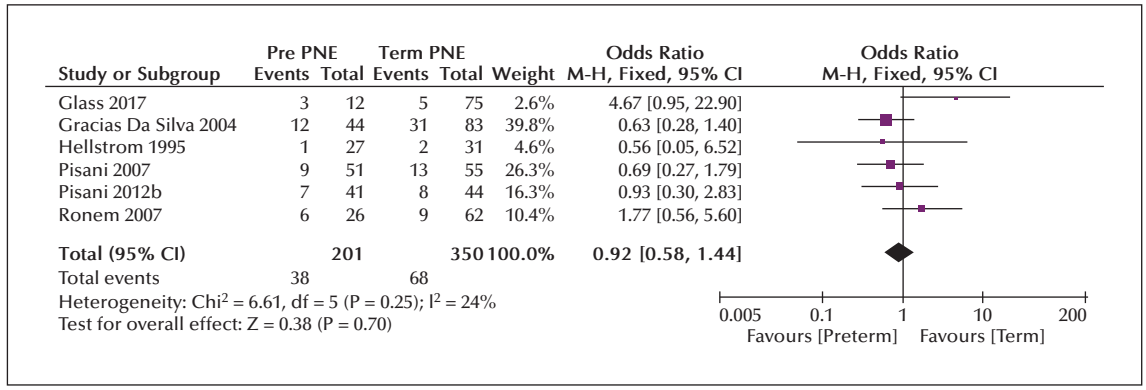
| Year | Author | Total patients PNE | Other neurological deficit | Incidence P/T | PNE in preterm |
|---|---|---|---|---|---|
| 1995 | Hellstrom-Westas | 2 (1 preterm) (8.3) | NA | 1/3 | 2 (27) |
| 2004 | Garcias Da Silva | 43 (28.4%) | NA | 4/44 P (0.85) 14/83 T (P 0.019) | 4 (44) |
| 2004 | Pisani | 7/27 (25.9%) | CP | NA | 7 (27) |
| 2007 | Ronen GM | 17 (19.3%) | NA | 48% P/29% T | 13 (48%) |
| 2007 | Pisani | 22 | NA | 9 P, 13 T | 9 (51) |
| 2008 | Pisani | 9 (18%) | MR, CP | NA | 9 (51) |
| 2010 | Davis | 47 (16%) | NA | NA | 47/414 (16%) |
| 2012 | Pisani | 15 (17.6%) | NA, CP, MR | 17% P/18% T | 7/41 (17%) |
| 2015 | Spagnoli | Focal febrile seizures | NA | NA | 2 (2) |
| 2016 | Pisani | 11 (15%) | CP, DD | NA | 19 (15%) |
| 2018 | Glass | 1 (7%) | NA | 3/12 (25%) O; 5/75 (7%) T (p-valus 0.04) | 3 (12) |
| 2018 | Pisani | 7 (14.3%) | NA | NA | 25 (14.3%) |

NA: not available; CP: cerebral palsy; DD: developmental disorder; MR: mental retardation; PNE: postneonatal epilepsy.

▼ **Table 3.** Six studies evaluated in the meta-analysis.

| Author | Preterm (n) | Term (n) | PNE at preterm (n) | PNE at term (n) | Total with epilepsy | PNE at preterm (%) | PNE at term (%) |
|---|---|---|---|---|---|---|---|
| Garcias Da Silva *et al.* [32] | 44 | 83 | 12 | 31 | 43 | 27.27 | 37.35 |
| Glass *et al.* [27] | 12 | 75 | 3 | 5 | 8 | 25.00 | 6.67 |
| Hellstrom-Westas *et al.* [24] | 27 | 31 | 1 | 2 | 3 | 3.70 | 6.45 |
| Pisani *et al.* [28] | 51 | 55 | 9 | 13 | 22 | 17.65 | 23.64 |
| Ronen *et al.* [26] | 26 | 62 | 6 | 9 | 15 | 23.08 | 14.52 |
| Pisani *et al.* [38] | 41 | 44 | 7 | 8 | 15 | 17.07 | 18.18 |
| Total (n) | 201 | 350 | 38 | 68 | 106 | | |
| Median (%) | | | | | | 20.36 | 16.35 |
| IQ range (%) | | | | | | 7.30 | 13.64 |

n: number; IQ: interquartile; PNE: postneonatal epilepsy.




■ **Figure 3.** Forest plot of the odds ratio for epilepsy in preterm versus full-term babies with NS.

type of neurophysiological method (ambulatory EEG versus conventional EEG) [40].

Most of the included studies only documented a short follow-up period. In fact, in four reports, the follow-up stopped at between six months and 19 months [7, 24, 25, 31], which may be insufficient as PNE may develop later in life.

In the literature review performed by Pisani *et al*. [39], the total incidence of PNE in full-term and preterm newborns was estimated at 17.9%. In this systematic review, we calculated an incidence of PNE at 20.36% in preterm and 16.35% in full-term newborns. This is close to the previously reported incidence of 17-25%, with a lower risk in preterm (17%) compared to full-term infants (30%) [34, 35, 41, 42].

Based on comparison with the previous studies, the percentage of preterm infants who develop PNE is relatively homogeneous (interquartile range), while in term infants, the percentages fluctuate significantly, ranging from 6.45% to 37.35% (*table 3*).

These results could be due to involvement of the subcortical plate, subsequent to the severe intraventricular/parenchymal haemorrhage that represents the first cause of seizures in extremely and very preterm neonates [17, 43-47]. We could not find reports on the thresholds of seizure burden, which would be relevant, since hypothetically, the higher the seizure burden in the neonatal period, the higher the risk of developing PNE.

Instead, in preterm neonates, the focus of the studies seems to be more on the outcome following NS such as death or neurodevelopmental impairment [23]. The literature suggests that in premature neonates, PNE is frequently associated with intellectual disability and/or cerebral palsy [3]. This association has already been reported in newborns with NS and is perhaps indicative of the severity of brain damage in preterm neonates [22, 36, 37, 40, 48].

## Limitations

The conclusions of our study are limited by the low number of reports with complete electro-clinical diagnosis of seizures. Some papers included seizures that were only diagnosed clinically and two reported only video EEG-confirmed diagnosis. Ten reports included patients with both EEG and/or clinical diagnosis. The method of seizure (or clinical) diagnosis is an important point, as in most preterm newborns, seizures are only detectable by EEG, however, many movement patterns in these subjects may appear as suspicious for NS and electrographic-only seizures are not visible at all.

The gestational age was not always reported and therefore we cannot categorize the selected population as very early preterm, early preterm, or late preterm. Furthermore, the details of therapeutic interventions for seizures were also not always reported, and unfortunately this could influence the outcome. The comorbidities were not always well specified in the reported studies either, nor were the tests used to assess them. Also, the age at onset of epilepsy was not always reported, thus we cannot extrapolate any difference in the age at onset between term and preterm neonates. Finally, the duration of the follow-up represents a major limit of our research, because it was very variable among the studies (three months to 12 years, with an average of 4.6 years); some patients were followed for three months which is insufficient to look for and report on PNE.

## Conclusions

Preterm newborns are widely recognised to have a higher incidence of NS compared to full-term babies. Our aim was to analyse whether the incidence of PNE

in preterm seizing newborns was different from that of term neonates. The information for the analysis was more difficult to obtain than expected because the gestational age of newborns or the differentiation between preterm and term seizing newborns were not specified in the published papers. Despite these limits, our study highlights that the literature lacks sufficient information on the incidence of epilepsy in preterm infants. Notwithstanding this, there does not seem to be any difference in the incidence of PNE between preterm and full-term newborns with seizures. We hope our study will be the stepping stone for further research on this topic, as further knowledge on seizures and subsequent PNE in premature neonates will improve our approach in the acute setting and during long-term follow-up for this complex population. ■

**Supplementary material.**
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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## TEST YOURSELF

**(1) Neonatal convulsions:**

A. are more common in full-term infants
B. have the same incidence in term infants and preterm infants
C. show increased incidence with decreasing gestational age and birth weight

**(2) What is the incidence rate of epilepsy in patients who have had neonatal seizures?**

A. The incidence varies widely between published studies (16% to 30%)
B. Less than 16%
C. The incidence increases with decreasing gestational age and birth weight

**(3) Is there a difference in the incidence of post-neonatal epilepsy in preterm infants who have had neonatal seizures, compared to full-term infants?**

A. The incidence is higher in term infants
B. There is no significant difference between the two groups
C. The incidence is higher in preterm infants

*Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.*