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ORIGINAL ARTICLE

Early cranial ultrasonographic findings of neonates born from mothers with premature rupture of membranes

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ABSTRACT

Objective: Premature rupture of membranes (PROM) has maternal, fetal, and neonatal implications. PROM can cause intrauterine infection and preterm birth. Maternal infection/chorioamnionitis is associated with neonatal neurodevelopment, cerebral palsy, and periventricular leucomalacia. In our study, we aimed to find out the rate of PROM associated-histologic chorioamnionitis (HCA) and corioamnionitis associated early neonatal brain damage findings with cranial USG.

Material and Methods: One hundred and fifteen neonates born in Zeynep Kamil Maternity and Children Hospital were enrolled to the study. Neonates were divided into four groups according to gestational age (term/preterm) and duration of PROM (>24 h). Data about route of delivery, birth weight, gender, and APGAR scores were collected and placentas were examined histopathologically. All neonates were evaluated with cranial USG by a radiologist unannounced of neonatal clinical condition and placental pathology. Term-preterm neonates, preterm PROM (+) and PROM (–) neonates and term PROM (+) and PROM (–) neonates were compared with each other.

Results: Total 115 neonates (52 female and 63 male), 50 term (mean: 39 GW) and 65 preterm (mean: 33.8±1.3 GW) neonates were enrolled to the study. Duration from PROM to birth was 2.2±2.7days in term group and 4.8±4.3 days in preterm group (p=0.014). APGAR scores of preterm neonates were lower than term neonates (p<0.01). There was no difference of placental examination results, timing of cranial USG examination and USG findings between term and preterm neonates (p>0.05). HCA rate was 30% in term and 26.2% in preterm group (p=0.648). Time of cranial USG imaging was 11.9±10.4 days in term and 9.1±7.7 days in preterm group (p=0.096). Four neonates (6.2%) in preterm PROM (–) group had abnormal cranial USG findings.

Conclusion: In our study, we cannot show early neonatal brain injury pathologic findings associated with HCA using cranial USG. Abnormal cranial USG findings in preterm group are due to prematurity independent of chorioamnionitis and PROM.

Keywords: Cranial USG, histologic chorioamnionitis, neonate, premature rupture of membranes.

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INTRODUCTION

Premature rupture of membranes (PROM) referred to as rupture of membranes before the onset of contractions can occur at term (≥37 weeks of gestation) and affects approximately 8–10% of term pregnancies. Preterm PROM refers to PROM before 37 + 0 weeks of gestation and is responsible for preterm birth with varying incidence.[1]

Chorioamnionitis, inflammation of the fetal membranes (chorion and amnion), is the most common cause of preterm birth (11–40%), and its incidence increases with decreasing gestational age.[2,3] Histologic chorioamnionitis (HCA) is more frequent than clinical chorioamnionitis. The most common route by which microorganisms invade the amniotic cavity is ascending passage from the lower genital tract,[4] especially in pregnancies with preterm PROM and with a longer duration of labor.[5]

Chorioamnionitis is associated with many short-term and long-term neonatal implications. Potential neonatal sequelae associated with chorioamnionitis are sepsis, pneumonia, respiratory distress, asphyxia, necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia (PVL), cerebral palsy (CP), long-term neurodevelopmental delay, and death.[6]

Full-term infants exposed to chorioamnionitis are at an increased risk of perinatal depression, encephalopathy, and CP,[7] while preterm infants are at an increased risk of intraventricular hemorrhage (IVH) and PVL, which can be ultimately lead to mental retardation and CP.[8,9]

The relation of HCA to neurodevelopmental defects is still being investigated. Proinflammatory cytokines produced during chorioamnionitis are essential in the pathogenesis of some neurodevelopmental defects (especially CP), PVL, IVH,[10] which can be detected and diagnosed with adequate imaging modalities (especially cranial ultrasonography) in the neonatal period.

Our study aimed to determine the PROM associated-HCA and chorioamnionitis associated early neonatal brain damage findings with cranial USG.

MATERIAL AND METHODS

We enrolled 115 neonates (50 terms and 65 preterms) born in Zeynep Kamil Maternity and Children's Training and Research Hospital, Istanbul, from January to December 2002 to the study. Term (38–42 GW) and preterm (31–37 GW) neonates were grouped according to presence/absence of PROM (>24 h). Twin gestations and neonates with congenital anomalies were excluded from the study. Data about the mode of delivery, birth weight, gender, and APGAR scores (1 and 5 min) were collected from hospital records.

All placentas collected were delivered in a 10% formalin solution to the pathology department. An experienced perinatal pathologist unannounced on a neonatal clinical condition evaluated the materials according to an investigation protocol. At least two microscopic section slides were examined involving placental disc (center of the placental lobules), chorionic plate, and decidual ground. One of the section slides was drawn near the insertion of the umbilical cord, and the other one was from the region between the placental side and cord insertion. Additionally, one section slide was drawn from the umbilical cord, 2 cm away from the placental disc. All microscopic sections (slides) were stained with hematoxylin-eosin. HCA is defined as polymorphonuclear cell infiltration (>10 cells) in all placental areas and at least two regions of the chorionic plate and extraplacental membranes.

All neonates were assessed with cranial ultrasonography by a radiologist unannounced of neonatal clinical condition and placental pathology. During cranial USG examination, the neonate was held supine, and the head was fixed. 5–5.0 MHz convex probe, 7.0–8.5 mHz linear probe, and 6.0–9.0 MHz convex probe were used for sagittal, parasagittal, coronal, and paracoronal standard ultrasonographic sections. Especially 7.0–8.5 MHz linear ultrasonography probe sensible for white matter pathologies and PVL was used.

Term-preterm neonates, preterm PROM (+) and PROM (–) neonates, and term PROM (+) and PROM (–) neonates were compared with each other.

Statistical analyses were performed using SPSS 10 (IBM® SPSS Statistics, Chicago, IL). Descriptive statistical methods (mean and standard deviation), student t-test, Mann–Whitney U test was used to compare quantitative data. Chi-square test and Fisher exact Chi-square test were used for qualitative data comparison. Results were 95% confidence interval and $p<0.05$ as statistical significance.

RESULTS

Totally 115 neonates, 50 term and 65 preterm neonates were grouped according to PROM status. The characteristics of neonates are shown in Table 1. We compared (a) term neonates with preterms, (b) term PROM (+) neonates with term PROM (–) neonates, and (c) preterm PROM (+) neonates with preterm PROM (–) neonates.

There is no difference according to gender between the term and the preterm groups ($p>0.05$). Gender distribution is homogenous. The birth weight of preterm neonates is lower than the birth weights of term neonates, as expected ($p<0.01$). Preterm neonates are delivered mainly by the C/S route, and there is a significant difference in the mode of delivery between term and preterm neonates ($p<0.01$). APGAR scores (1 and 5 min.) are lower in preterm neonates than term neonates ($p<0.01$). HCA rates in term neonates and preterm neonates are 30% and 26.2%, respectively. The duration of PROM in the preterm group is longer (4.8±4.3 days) than of the term group (2.2±2.7 days) ($p<0.05$). There is no significant difference in the timing of cranial USG and USG results in placental pathology results ($p>0.05$). Time of cranial ultrasonographic imaging is 3–45 days (mean: 11.9±10.4 days) in term neonates and 3–46 days (9.1±7.7 days) in preterm neonates.

Abnormal cranial USG results observed in our study are bilateral cystic lesions in parietoccipital ve frontoparietal regions (n=1) (cystic PVL), ventriculomegaly (n=1), intraparenchymal hemorrhage in the right parietal corona radiata (n=1), and cavum septum pellucidum (n=1). These neonates are preterm PROM (–). We have not observed any pathologic cranial USG result by neonates with HCA.

DISCUSSION

Our study aimed to determine the rate of PROM associated-HCA and chorioamnionitis associated early neonatal brain damage findings with cranial USG examination. PROM in term gestations is ac-

Table 1: The characteristics of neonates

	Term (%)	Preterm (%)	p
Gender (%)			
Male	28 (56)	35 (53.8)	0.818
Female	22 (44)	30 (46.2)	
Route of delivery			
NSVD	38 (76)	32 (49.2)	**0.004**
C/S	12 (24)	33 (50.8)	
APGAR 1.min	7.1±0.4	7.6±0.6	**0.001**
APGAR 5.min	9.1±0.3	8.9±0.5	**0.002**
Gestational age (mean±SD) (GW)	39.0±0.0	33.8±1.3	**0.001**
Duration of PROM (mean±SD) (days)	2.2±2.7	4.8±4.3	**0.014**
Placental pathology (%)			
Normal	35 (70)	48 (73.8)	0.648
Abnormal	15 (30)	17 (26.2)	
Timing of cranial USG (days)	11.9±10.4	9.1±7.7	0.096
USG results			
Normal	50 (100)	61 (93.8)	0.131
Abnormal	–	4 (6.2)	

NSVD: Normal spontaneous vaginal delivery; GW: Gestational week; USG: Ultrasonography; C/S: Cesarean section; SD: Standard deviation; PROM: Premature rupture of membranes.

cepted as a physiologic variant rather than a pathology. About 90% of term neonates are delivered in 24 h after rupture of membranes. After fetal membrane rupture, at least 50% of patients with preterm PROM give birth within 1 week.[11] Studies have demonstrated that PROM time is related to maternal infection and adverse outcomes of premature neonates, especially with membrane rupture time ≥72 h.[12,13] PROM occurred in 73.1% of pregnancies with an average gestational age of 33.0±2.4 weeks.[14] In our study, the time from rupture of membranes to delivery was 2.2±2.7days in term neonates, 4.8±4.3 days in preterm neonates (p=0.014). This difference is due to the therapeutical measures (antibiotics and tocolytics) in the management of preterm PROM.

When we compared the delivery route of term and preterm neonates, the rate of normal spontaneous vaginal delivery (NSVD) was 76% and C/S 24% in term neonates in our study. In preterm neonates, the rate of NSVD was 49.2%, and the rate of C/S was 50.8%. We had high C/S rates because our institution is a referral center for the follow-up and management of high-risk pregnancies. Apgar scores of preterm neonates (1 and 5 min) were lower than the scores of term neonates (p<0.05) due to the relatively higher complication risks of preterm infants during birth after the onset of labor.

Chorioamnionitis is present in 3–5% of deliveries at term; however, in deliveries between 21–24 weeks of gestation, chorioamnionitis is confirmed in 94% of placentas.[15] A study from China reported a high incidence of HCA as 84.8% in 19–36 GW pregnancies.[14] Çakır et al.[16] from Türkiye reported placental histopathologic status of preterm neonates <35GW: 33.8% normal findings, 12.3% HCA, and 53.9% findings of vasculopathy. In our study, the HCA rate was 30% in term neonates. The mean gestational age of our preterm neonates was 33.8±1.3 weeks, and the HCA rate was 26.2% (17/65). Our rates were higher than Çakır et al.,[16] which is due to our limited neonate number as we suppose. A study investigated 483 pregnancies between 34.5±5.6 GW for clinical/HCA and early neonatal brain damage. The time of the cranial imaging with USG was at 1st (0–3 days) and at 7th (5–14 days) postnatal days.[17] The abnormal cranial brain imaging findings were IVH, ventriculomegaly, increased periventricular echodensities and white matter echolucency. In the presence of HCA (rate: 37%), the incidence of these findings was increased. They observed a significant relation between chorioamnionitis and neonatal brain injury independent of gestational age. We performed cranial USG examination on 10.33±9.08 days (3–45 days), and our HCA rate was 27%.

Of 266 term neonates without PROM history, 27 neonates had abnormal cranial USG findings. There was no difference between neonates with normal and abnormal USG findings in birth weight and gestational age. Abnormal USG findings were as follows: Ependymal cysts (13/27), ventricular dilatation (6/27), plexus choroideus cysts (3/27), ventricular dilatation with choroid cysts (2/27), midline cyst in the posterosuperior region of the third ventricle (1/27), and subependymal hemorrhage+increased ventricular dimension + thalamic calcification (1/27).[18] In our study, none of the neonates in the term PROM (–) group had abnormal cranial findings. Abnormal cranial USG results that we observed are bilateral cystic lesions in parietoccipital ve frontoparietal regions (n=1) (cystic PVL), dilatation in lateral ventricles (n=1), intraparenchymal hemorrhage in the right parietal corona radiata (n=1), and cavum septum pellucidum (n=1). All these cases were preterm neonates without HCA.

Cavum septum pellucidum, observed in one neonate in our study, is a cavity containing CSF and localized between the two lateral ventricles of the brain. It is accepted as a normal brain variation without clinical implication.[19] Cavum septum pellicidum is present in early gestational ages and typically closes within 3–6 months after birth in 85% of term neonates.

Up to date, there is still controversy between maternal infection/chorioamnionitis and neonatal neurodevelopmental status. While some studies show an association between maternal infection/chorioamnionitis and neonatal neurodevelopmental status,[20–22] some studies report no relation.[9,23] Xiao et al.[24] collected the studies in different medical databases and reported a meta-analysis to clarify the discrepancy about pathologic neuroimaging and neurodevelopmental outcomes. They wrote that developmental mental index of neonates <28 GW and <34 GW is lower in the presence of HCA (p<0.05).

Neuroimaging for the neurodevelopmental prognosis of high-risk neonates is still under investigation.[25] White matter injury (WMI) is the most common type of brain injury of premature infants. WMI includes cystic and diffuse PVL and periventricular hemor-

rhagic infarct. Cranial USG examination can detect IVH, cystic PVL, ventriculomegaly, and large infarct areas. Still, it can be inadequate to see diffuse non-cystic PVL, posterior fossa lesions, myelination, and metabolic disturbances.[26]

There is a strong association between cystic PVL and adverse motor outcomes, especially CP. Non-cystic WMI, which is less commonly diagnosed on cranial USG imaging in the early neonatal period, is associated with cognitive, hearing, and visual deficits in some studies.[25,27–29] Inflammatory responses of maternal-fetal dyads can cause preterm PROM and adverse neurologic outcomes in infants. In a study, despite high serum inflammatory cytokine levels due to histologic inflammation of the fetal region, findings of brain damage on cranial USG of neonates 24–34 GW gestational age could not be shown. Still, adverse neurologic outcome had been observed.[30] High-risk infants with normal cranial USG imaging can have neurodevelopmental disturbances later in life, so clinical and neuroimaging follow-up of these infants is strongly recommended.[25,27–29]

There is a need for modalities that could precisely and specifically assess central nervous system structure and function in preterm neonates to promote optimal neurodevelopment, and the early prediction/long-term of outcome.[5] We think that our limitation is the low case number in our study. Studies with a high number of patients will help the clinicians better understand the subject.

CONCLUSION

In conclusion, our study cannot show early neonatal brain injury pathologic findings associated with HCA using cranial USG examination. Abnormal cranial USG findings in our preterm group are due to prematurity independent of chorioamnionitis and PROM.

Statement

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – NUK, ZAS, HAT, ZGK, HÇ; Design – NUK, ZAS, HAT, ZGK, HÇ; Supervision – NUK, ZAS, HAT, ZGK, HÇ; Resource – NUK, HAT, ZAS; Materials – NUK, HAT, HÇ, ZGK; Data Collection and/or Processing – NUK, HAT, HÇ, ZGK; Analysis and/or Interpretation – NUK, HAT, ZAS, HÇ, ZGK; Literature Search – NUK, HAT, ZAS; Writing – NUK, ZAS; Critical Reviews – NUK, ZAS, HAT, HÇ, ZGK.

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