Background: Birth asphyxia is a leading cause of neonatal mortality. Ischemia-modified albumin (IMA) levels may have a predictive role in the identification and prevention of hypoxic disorders, as they increase in cases of ischemia of the liver, heart, brain, bowel, and kidney.

Purpose: This study aimed to assess the value of IMA levels as a diagnostic marker for neonatal hypoxic-ischemic encephalopathy (HIE).

Methods: Sixty newborns who fulfilled 3 or more of the clinical and biochemical criteria and developed HIE as defined by Levene staging were included in our study as the asphyxia group. Neonates with congenital malformation, systemic infection, intrauterine growth retardation, low-birth weight, cardiac or hemolytic disease, family history of neurological diseases, congenital or perinatal infections, preeclampsia, diabetes, and renal diseases were excluded from the study. Sixty healthy neonates matched for gestational age and with no maternal history of illness, established respiration at birth, and an Apgar score ≥7 at 1 and 5 minutes were included as the control group. IMA was determined by double-antibody enzyme-linked immunosorbent assay of a cord blood sample collected within 30 minutes after birth.

Results: Cord blood IMA levels were higher in asphyxiated newborns than in controls (250.83±36.07 pmol/mL vs. 120.24±38.9 pmol/mL). Comparison of IMA levels by HIE stage revealed a highly significant difference among them (207.3±26.65, 259.28±11.68, 294.99±4.41 pmol/mL for mild, moderate, and severe, respectively). At a cutoff of 197.6 pmol/mL, the sensitivity was 84.5%, specificity was 86%, positive predictive value was 82.8%, negative predictive value was 88.3%, and area under the curve was 0.963 ($P<0.001$).

Conclusion: IMA levels can be a reliable marker for the early diagnosis of neonatal HIE and can be a predictor of injury severity.

Key message

Questions: What is the value of ischemia modified albumin (IMA) as a diagnostic marker for neonatal hypoxic-ischemic encephalopathy (HIE)?

Finding: IMA levels were significantly higher (nearly double elevation) in hypoxic than healthy newborns in the first few hours after birth in the full-term neonates.

Meaning: IMA can be a reliable marker for the early diagnosis of neonatal HIE and can be a predictor of injury severity.

Introduction

Birth asphyxia is the second leading cause of neonatal mortality after sepsis. Perinatal asphyxia is an insult to the fetus due to oxygen insufficiency (hypoxia) and/or reduction of perfusion (ischemia) to various organs. It is associated with tissue lactic acidosis and hypercapnia. It is the most significant cause of cerebral damage and long-term neurological consequences in the perinatal period both in term and preterm infants. Its incidence is approximately 1 to 6 every 1,000 live term births in developing countries, 20%–50% of asphyxiated newborns die within the neonatal period. Up to 25% of the survivors will display permanent neuropsychological handicaps, including cerebral palsy, mental retardation, epilepsy, or learning disability. Several biochemical predictors of hypoxic brain damage have been researched in the last decade such as activin A, creatine kinase, neuron-specific enolase, and protein S-100. Ischemia modified albumin (IMA) is a modification of human serum albumin (HSA). Hypoxia, acidosis, or ischemia alter the N-terminal amino acids of HAS and decrease the binding capacity of HSA to metals such as cobalt, nickel, and copper. It is known that ischemia of liver, heart, brain, bowel, and kidney raise the IMA level. IMA rapidly elevated within 5 to 10 minutes after the ischemic event and stays high for 30 minutes then it returns to baseline 12 hours after the ischemia event. Therefore, it may have a predictive value in the identification and
This study aimed to assess the value of IMA as a diagnostic marker for neonatal hypoxic-ischemic encephalopathy (HIE).

Methods

1. Study sample

This prospective study was performed at the department of Obstetrics and Gynecology of Zagazig University Hospital in the period between 2017 and 2018. This case-control study was approved by the Institutional Ethical Committee of Zagazig University (approval number: ZU-IRB# 2510-5-7-2017) and in accordance with the Helsinki declaration after a full explanation of the purpose and nature of all procedures used. Written informed consent was obtained from the parents of the patients involved in the study. Further information and documentation to support this are available on request.

We studied 60 full-term consecutive asphyxiated neonates who delivered at the obstetric department of Zagazig University Hospital due to nonreassuring fetal status (bradycardia, late deceleration of the fetal heart rate, repetitive variable deceleration of the fetal heart rate, and reduced beat-to-beat variability). Asphyxia was defined according to an Apgar score less than 3 at the 5 minutes, pH less than 7.0, or base excess less than 12 in cord blood or venous blood taken from newborns within 60 minutes of birth or the need for positive pressure ventilation (more than 3 minutes) or the presence of postnatal clinical complications attributed to hypoxia and/or ischemia such as shock, altered tone, depressed level of consciousness and convulsion.

We included the neonates who fulfilled 3 or more of the clinical and biochemical criteria and developed HIE, as defined by Levene staging and born between September 2017 to September 2018 (asphyxia group). An HIE diagnosis based on the Finer classification cannot diagnose the disease until 48 hours after the occurrence of the hypoxic/ischemic events has occurred. Sixty healthy neonates with matched gestational age, without a history of maternal illness, established respiration at birth and Apgar score ≥7 at 1 and 5 minutes were included as (a control group).

Infants with congenital malformation, cardiac or hematological diseases, sepsis, intrauterine growth retardation, low birth weight were excluded from the study. Other exclusion criteria were familial history of neurological diseases, perinatal infections, multiple pregnancies, preeclampsia, and maternal diabetes or renal diseases to remove the effect of these factors on the oxidative stress.

All studied neonates exposed to full history taking including maternal and delivery history with focus on perinatal asphyxia, mode of delivery, gestational age, neonatal Apgar score of at 1 and 5 minutes and type of resuscitation used: oxygen with face mask, a self-inflating bag with positive pressure, cardiac massage and medications for staging the severity of the asphyxiated group.

Clinical assessment included general examination, gestational age estimation using new Ballard score, body weight, head circumference, vital signs, and neurological examination within the first 24 hours after birth and for 7 days to classify HIE according to the criteria of Sarnat and Sarnat. The alertness, posture, activity, tone, neonatal reflexes, seizures, the number of anticonvulsant drugs were assessed.

Laboratory investigations including: complete blood count was done using Cell-Dyn_1700 (Abbott Diagnostics, Abbott Park, IL, USA), blood gases, C-reactive protein (CRP) was determined using the Tina-Quant C-Reactive protein Gen 3 assays (Roche Diagnostics, Indianapolis, IN, USA) on Roche Modular P800 system. Cord blood samples were collected as early as possible immediately after birth and analyzed for arterial blood gases, pH determination with a calculation of base excess was

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**Table 1. Neonatal studies related to the ischemia-modified albumin and hypoxia**

| Study         | Group | No. | Biological sample | Time of sample collection | Mean IMA level | Unit of assay | P value |
|---------------|-------|-----|-------------------|---------------------------|---------------|--------------|---------|
| Gugliucci et al. | ND    | 12  | Cord blood        | Delivery                  | 0.64±0.24     | Absorbance values at 470 nm | 0.037   |
|               | CD    | 14  |                    |                           | 0.96±0.5      |              |         |
| Iacovidou et al. | AGA  | 110 | Cord blood        | Delivery                  | 112.44        | U/mL         | >0.05   |
|               | IUGR  | 57  |                    |                           | 115.54        |              |         |
| Kumral et al.  | ND    | 153 | Cord blood        | Delivery                  | 153.3         | pmol/mL      | 0.015   |
|               | CD    | 16  |                    |                           | 332.0         |              |         |
| Biswas et al.  | ND    | 40  | Cord blood        | Delivery                  | 32.44         | U/mL         | <0.01   |
|               | CD    | 40  |                    |                           | 55.7          |              |         |
| Kar et al.     | NHP   | 40  | Cord blood        | Delivery                  | 31.55         | U/mL         | <0.0001 |
|               | NPE   | 45  |                    |                           | 45.66         |              |         |

IMA, ischemia modified albumin; ND, noncomplicated deliveries; CD, complicated deliveries; AGA, appropriate for gestational age; IUGR, intrauterine growth retardation; NHP, newborn of healthy pregnant women; NCP, newborn of complicated pregnancy; NPE, newborn of pre-eclamptic pregnant. Boldface indicates a statistically significant difference with P<0.05.
analyzed on Roche OMNI L (Roche Diagnostics GmbH, Mannheim, Germany).

IMA assay, 5 mL of cord blood was collected, kept in ice-filled containers and brought to the clinical pathology laboratory of Zagazig University Hospital within 30 minutes hours then serum is separated and stored at -20°C for IMA estimation. IMA levels were detected in patients and control groups by double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) using a commercially available ELISA (Cat. No: 201-12-1137; Sun Red Biotechnology, Shanghai, China).

2. Statistical analysis

Data were checked, entered, and statistically analyzed by IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA). Data were expressed as a mean±standard deviation for quantitative variables or number and percentage for categorical variables.

Student t test for continuous variables and chi-square test for categorical variables were used to compare mean values between the 2 independent groups. Data were compared using analysis of variance test for more than 2 groups. For nonparametric data, Mann-Whitney U test was used to compare quantitative variables between the 2 groups and Kruskal-Wallis for more than 2 groups. Correlations between continuous variables were calculated by Pearson coefficient. IMA’s role in predicting HIE was calculated using:

- Sensitivity (percent of positives detected correctly identified) = true positives/(true positive + false negative)
- Specificity (percent of negatives detected correctly identified) = true negatives/(true negative + false positives)
- PV+ = true positive/(true positive + false positive), PV- = true negatives/(true negatives + false negatives). The area under the curve (AUC) was derived from the receiver operating characteristic curve.
- P value of >0.05 was insignificant, P<0.05 was significant and P<0.001 was highly significant.

Results

Our study included 60 patients with asphyxia (male:female, 36:24), delivered by elective cesarean section (n=10) or vaginally (n=50) and 60 healthy subjects as a control group (male:female, 21:39), delivered by elective cesarean section (n=15) or vaginally (n=45), the history, demographic data and laboratory investigations of the study population are shown in Table 2. The cord blood serum IMA levels were also higher in newborns with perinatal asphyxia than the healthy controls with P<0.001.

There was no statistically significant difference between asphyxiated and control groups regarding the mode of delivery as shown in Table 2. In both groups, the mean cord blood IMA levels were slightly elevated in neonates from cesarean sections compared to those from vaginal deliveries but it was not statistically significant as shown in Table 3.

According to the criteria of Sarnat and Sarnat, we classify the asphyxiated group into 3 stages and the percentages of the 3 stages are (stage I, 30%; stage II, 50%; and stage III, 20%). The history, demographic data, and laboratory investigations of the 3 stages are shown in Table 4.

There was a statistically significant difference between asphyxiated and control groups regarding the mortality, where 12 cases (20%) were dead in the asphyxiated group in comparison to zero among the control group as shown in Table 2. The percentage of mortality at different stages of HIE are 0%, 13.3%, 67.7% in stage I, II, III respectively.

The cord blood IMA levels were also higher in the dead newborns with perinatal asphyxia as compared to survived newborns with perinatal asphyxia (293.22±7.65 pmol/mL vs. 240.23±32.21 pmol/mL, respectively with P=0.001). Also, there was a highly significant difference between the 3 stages of the HIE group regarding the cord blood IMA levels (207.3±26.65, 259.28±11.68, 294.99±4.41 in mild, moderate, severe stages, respectively) as shown in Table 4.

The degree of correlation between the different parameters of the cases and controls are shown in Table 5. In this study, at a cutoff level of IMA 197.6 pmol/mL, the sensitivity was 84.3%, the specificity was 86%, positive predictive value (PPV) was 83.8%, negative predictive value (NPV) was 86.8%, and the positive and negative likelihood ratios were 2.25 and 0.23, respectively.

### Table 2. Comparison of patient history, demographic data and laboratory results

| Variables                      | Asphyxiated (n=60) | Control (n=60) | P value |
|--------------------------------|--------------------|---------------|---------|
| Sex                            |                    |               |         |
| Male                           | 36 (60)            | 21 (35)       | 0.12    |
| Female                         | 24 (40)            | 39 (65)       |         |
| Mode of delivery               |                    |               |         |
| Vaginal                        | 50 (83.3)          | 45 (75)       | 0.1     |
| Cesarean                       | 10 (16.7)          | 15 (25)       |         |
| Mortality                      |                    |               |         |
| Survived                       | 48 (80)            | 60 (100)      | 0.035   |
| Dead                           | 12 (20)            | 0 (0)         |         |
| Gestational age (wk)           | 40.15±1.18         | 39.8±0.69     | <0.001  |
| Birth weight (kg)              | 3.64±0.38          | 3.10±0.21     | <0.001  |
| Apgar score, 1 min             | 2.40±0.50          | 7.35±0.98     | <0.001  |
| Apgar score, 5 min             | 4.55±0.88          | 8.7±1.16      | <0.001  |
| pH                             | 7.22±0.11          | 7.38±0.03     | <0.001  |
| PO2 (mmHg)                     | 76.16±12.64        | 94.85±9.20    | <0.001  |
| PCO2 (mmHg)                    | 47.72±8.05         | 39.3±3.61     | <0.001  |
| Hb (g/dL)                      | 14.82±1.83         | 16.05±1.87    | 0.032   |
| IMA (pmol/mL)                  | 250.83±36.07       | 120.24±38.9   | <0.001  |
| CRP (mg/L)                     | 4.80±2.90          | 3.0±1.9       | 0.002   |

Values are presented as number (%) or mean±standard deviation. Boldface indicates a statistically significant difference with P<0.05.

### Table 3. Ischemia-modified albumin levels by mode of delivery

| Variable | Vaginal | Cesarean | P value |
|----------|---------|----------|---------|
| Asphyxiated (n=60) | 238.53±34.60 | 254.53±35.40 | 0.13    |
| Control (n=60)     | 154.86±10.85 | 178.45±20.30 | 0.105   |

Values are presented as mean±standard deviation.
82.8%, negative predictive value (NPV) was 88.3%, and the AUC was 0.963 (95% confidence interval, 0.913–0.99; P < 0.001) as shown in Fig. 1.

### Discussion

Perinatal asphyxia is one of the most critical birth complications and a leading cause of permanent disability and death in full-term neonates.

Our study revealed a significant difference between the 2 studied groups regarding the birth weight and this was attributed to increasing incidence of obstructed labor and hypoxic insult in high birth weight neonates as well as large for gestational age which is matched with other studies which found a strong association of perinatal asphyxia with prolonged labor due to macrosomia.15 On the other hand, our results disagreed with Lee et al.16 who found that lower birth weight in cases of HIE than the control group due to respiratory distress syndrome, sepsis, and pneumonia in those babies. However, other studies found no significant relationship between HIE and birth weight.17

Apgar score is still the most achievable and practical to do in the delivery room. The 5-minute Apgar score is still a valid and fast index for estimating the efficacy of resuscitative efforts to the infant. Trevisanuto et al.18 found that 5 minutes Apgar score<5 was a significant risk factor for severe HIE. In our study, there was a highly significant difference in Apgar score at 1 and 5 minutes between the 2 studied groups. Other studies consistently showed that low Apgar scores at 5 minutes are associated with greater risk of occurrence of HIE.15,17,18

Our study demonstrates no significant association between gender and brain insult, this is in matching with previous studies.19 However, male sex predominance among newborns with perinatal asphyxia was evident in many studies.20 This finding was explained by Greenough et al.21 who found that male fetuses have lower catecholamine levels than their female peers and so are less protected against intrapartum hypoxia and its consequences. Furthermore, Lang and McCullough22 reported that females are more protected from hypoxia and ischemic neuronal cell death than males due to the neuroprotective effects of estrogen (17β estradiol or E2) against ischemic insults. In both groups, there was no statistically significant difference between the mean cord blood IMA levels in neonates from cesarean sections compared to those from vaginal deliveries. This has helped to remove the effect of different modes of deliveries on oxidative stress.

The mortality rate in this study was 12 cases (4 cases in stage II, 8 cases in stage III) from 60 asphyxiated neonates with a percent equal to 20% which is near to the results of Campbell et al.23

### Table 4. Comparison of different stages of hypoxic-ischemic encephalopathy in terms of history, demographic data, and laboratory results

| Variable                  | I (mild) (n=18) | II (moderate) (n=30) | III (severe) (n=12) | P value |
|---------------------------|----------------|---------------------|---------------------|---------|
| Gestational age (yr)      | 39.66±0.81     | 40.3±1.05           | 40.1±1.7            | 0.239   |
| Apgar, 1 min              | 2.83±0.40      | 2.30±0.48           | 2.0±0.0             | 0.015   |
| Apgar, 5 min              | 5.83±0.4       | 4.9±0.56            | 2.75±0.5            | 0.001   |
| Hospital stay (day)       | 12.3±4.17      | 25.0±7.9            | 37.25±6.18          | <0.001  |
| pH                        | 7.29±0.09      | 7.22±0.10           | 7.11±1.1            | 0.044   |
| PO2                       | 83.08±9.87     | 77.08±13.06         | 63.5±5.01           | 0.043   |
| PCO2                      | 41.83±8.6     | 49.35±5.80          | 52.47±8.70          | 0.074   |
| Hb (g/dL)                 | 14.66±1.5      | 14.22±1.7           | 16.55±2.79          | 0.089   |
| IMA (pmol/mL)             | 207.3±25.65    | 259.28±11.68        | 294.99±4.41         | <0.001  |
| CRP (mg/L)                | 4.0±3.09       | 5.4±3.2             | 4.5±3.7             | 0.84    |

Values are presented as mean±standard deviation.

Hb, hemoglobin; IMA, ischemia modified albumin; CRP, C-reactive protein. Boldface indicates a statistically significant difference with P<0.05.

### Table 5. Correlation between ischemia-modified albumin levels and gestational age, birth weight, Apgar score, laboratory results, and arterial blood gas levels of the 2 studied groups

| Variable                  | Asphyxia (n=60) | Control (n=60) |
|---------------------------|----------------|---------------|
| **IMA**                   |                |               |
| r                         | P value        | r             | P value |
| Gestational age           | 0.326          | 0.21          | -0.407  | 0.075   |
| Birth weight              | 0.582          | <0.001        | -0.349  | 0.132   |
| Apgar score, 1 min        | -0.831         | <0.001        | 0.118   | 0.621   |
| Apgar score, 5 min        | -0.831         | <0.001        | 0.117   | 0.622   |
| Hospital stay             | 0.834          | <0.001        | -       | -       |
| Hb                        | 0.164          | 0.312         | 0.284   | 0.226   |
| CRP                       | 0.449          | 0.004         | 0.130   | 0.586   |
| pH                        | -0.720         | <0.001        | -0.259  | 0.270   |
| PO2                       | -0.641         | <0.001        | 0.002   | 0.994   |
| PCO2                      | 0.581          | <0.001        | -0.003  | 0.990   |

IMA, ischemia modified albumin; Hb, hemoglobin; CRP, C-reactive protein. Boldface indicates a statistically significant difference with P<0.05.
who reported that asphyxia as a secondary cause of neonatal mortality in Egypt (18%) after prematurity as a primary cause.

Our result revealed a highly significant relation between prolonged hospital stay and severity of HIE in asphyxiated neonates, which runs with a previous study. However, our findings were not consistent with other studies which determined that the short-term outcomes of infants depend on perinatal academia, 5-minute Apgar score < 4, cord arterial pH < 7.1, and base deficit > 20 and did not depend on the duration of hospital stay.

We found that the hemoglobin level was significantly lower in the asphyxiated group than controls. It agrees with Caliskan et al. and Brucknerová et al. Who assumed that anemia was caused by increase of oxidative stress during prenatal and direct postnatal period, as well as by hemorrhage or by blood redistribution (adaptive mechanisms which assist keep up ideal blood supply to the most sensitive organs such as central nervous system, heart). In the present study, CRP was higher in the asphyxiated group than controls. This agrees with Shang et al. indicating the presence of an acute inflammatory response in the patients. We did not find a significant difference in the CRP level between the 3 stages of the asphyxiated group but Shang et al. found a correlation between the elevation of CRP and the severity of the disease. Thus, patients with greater inflammatory responses suffered from a severe progression of the disease.

Regarding arterial blood gases (ABG) values, the mean pH values and PO2 were significantly lower in HIE infants than the control group while the mean pCO2 was significantly elevated in the asphyxiated group than controls. This agrees with Shang et al. who reported in previous studies.

Khan et al. who did not find a significant difference between the asphyxiated group and the control group. In comparison to the control group, where there was no significant correlation between IMA and all variables.

Our study found that the cord blood IMA levels were significantly elevated (nearly double elevation) in hypoxic than healthy full-term neonates, this runs with other studies that found a significant increase in IMA levels in perinatal asphyxia than the control subjects. Firstly, Gugliucci et al. who found that the cord blood IMA levels in neonates from complicated deliveries are 50% higher than in neonates from uneventful deliveries (P < 0.05) while their albumin values are not significantly different and hypothesized that decreased blood flow in complicated deliveries results in insufficient oxygenation, anaerobic metabolism, localized acidosis and may increase IMA and concluded that cord blood IMA levels could be used as a marker for fetal ischemia in complicated pregnancies. Also, Kar et al. found a significant elevation of IMA in cord blood of babies born to preeclamptic mothers. Secondly, Iacovidou et al. who found that the reactive oxygen species, produced during ischemia/reperfusion, can create the highly reactive hydroxyl radical caus-
Conflicts of interest
No potential conflict of interest relevant to this article was reported.

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