Fetal malnutrition and its impacts on neonatal outcome in preterm infants

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Fetal malnutrition is an important risk factor for both early and late neonatal outcome and adult diseases. In this study, we aimed to investigate the incidence and characteristics of fetal malnutrition and its impacts on early neonatal morbidity and mortality in preterm infants by using the clinical assessment of nutritional status score (CANSCORE). Preterm infants whose gestational ages were between 28-34 weeks were included in the study. Detailed prenatal and natal history, anthropometric measurements, and intrauterine growth status were defined, and CANSCORE was applied to all infants. Infants were separated into two groups according to total score as malnourished (total score <25) and well nourished (total score ≥25). Early and late neonatal morbidities, which were observed during the clinical progress, were noted in all infants. A total of 93 preterm infants were enrolled in the study. The incidence of fetal malnutrition was 54.8% (n=51) in all infants. The incidences of maternal hypertension and preeclampsia, oligohydramnios and disturbed umbilical artery Doppler flow in the prenatal period and the incidences of neonatal hypoglycemia, polycythemia, feeding intolerance, and necrotizing enterocolitis in the postnatal period were significantly higher in preterm infants with fetal malnutrition. Fetal malnutrition contributes significantly to many early and late neonatal morbidities in preterm infants, and it should be identified in every preterm infant in the first days of life for predicting neonatal outcome, even though they are appropriately grown.

Key words: clinical assessment of nutritional status score, fetal malnutrition, preterm infant.

The term "fetal malnutrition" differs from the terms "intrauterine growth restriction" or "small-for-gestational age (SGA)", and represents a situation that may exist with or without these conditions in any newborn. Chronic placental insufficiency is the leading cause of fetal malnutrition, and fetal malnutrition can lead to intrauterine growth restriction and preterm labor. In fetal malnutrition, tissue structure and composition, metabolic reactions and enzyme functions in many systems are affected. In the newborn, the features of fetal malnutrition can be clinically recognized by the observation of several morphological changes in the subcutaneous fat and muscle tissues, skin and hair. Thinner hair, reduced buccal and gluteal fat pads, neck with loose, wrinkled skin, and accordion skin folds in extremities are some examples of these morphologic changes. In fetal malnutrition, the birth weight may be in normal ranges for that gestational age in specific intrauterine growth charts, so that the newborn is defined as appropriate-for-gestational age (AGA), or it may be under the lowest percentile, eventually leading to the diagnosis of a SGA infant[1-4].

Fetal malnutrition is associated with an increased risk of poor early and late neonatal outcome. There is also strong evidence that it has long-term consequences in adulthood characterized by increased risk of cardiovascular diseases

and insulin resistance by the mechanism of "fetal programming". The incidences of perinatal hypoxia and related morbidities and late neurodevelopmental problems have been reported to be higher in term infants with fetal malnutrition[5-10].

Prematurity is also a major risk factor for many early and late neonatal morbidities and mortality[11-14]. The coexistence of prematurity and fetal malnutrition may have further effects on neonatal outcome. However, the incidence and characteristics of fetal malnutrition in preterm infants have not been investigated before.

Clinical assessment of nutritional status score (CANSCORE) has been developed for the assessment of fetal malnutrition in term newborn infants. The method enables a relatively quantitative analysis of neonatal nutritional status at birth and is based on the systematic observation of nine superficial physical parameters, which include hair and buccal fat in the cheeks, chin and neck, arms, back inter or subscapular skin, buttocks, legs, chest, and abdominal wall skin[1]. Although CANSCORE has not been applied to preterm infants before, we aimed to use it in this population, as the main principle of the method depends not on gestational age but on morphological changes that occur due to the intrauterine loss of normal subcutaneous fat and muscle tissues. Thus, theoretically, CANSCORE could be applied to all newborn infants irrespective of gestational age.

In this study, we therefore aimed to investigate the incidence and characteristics of fetal malnutrition by using CANSCORE together with the risks of related morbidities in preterm infants.

Material and Methods

This study was performed at the Neonatal Intensive Care Unit of Hacettepe University İhsan Doğramacı Children's Hospital, Ankara, Turkey between June 2006 and December 2007. All preterm infants with gestational ages between 28-34 weeks were included in the study. Infants with congenital anomalies and chromosomal disorders were excluded. Prenatal history, which consisted of maternal age, chronic or gestational diseases that complicated the pregnancy, and the last obstetric or Doppler ultrasonography findings before delivery were recorded for each patient. Intrauterine growth restriction was defined as an estimated fetal weight of <10 p for that gestational age in the intrauterine growth nomogram determined by measuring biparietal diameter and abdominal circumference of the fetus by obstetric ultrasonography. Disturbed umbilical artery Doppler flow velocimetry was defined as diminished, absent or reversed end diastolic blood flow in the umbilical artery defined by Doppler ultrasonography. Oligohydramnios was defined as an amniotic fluid index of ≤5 cm[15-17]. Mode of birth, Apgar score at the 5th minute, delivery room resuscitation by endotracheal intubation, chest compression or medication, and cord pH were noted for each infant.

In the first day of life, birth weight and length of each infant were measured. Head circumferences were measured on the second day of life in order to eliminate the effect of scalp edema on the first day. Gestational ages of the infants were assessed by New Ballard Score and intrauterine growth of all infants was assessed by Lubchenco intrauterine growth curves[18,19]. On the same day, CANSCORE was applied to all preterm infants for the assessment of fetal malnutrition by a single experienced observer in order to exclude interobserver error. CANSCORE is a systematized observation of the characteristics of nine superficial physical parameters including hair and buccal fat in the cheeks, chin and neck, arms, back inter or subscapular skin, buttocks, legs, chest, and abdominal wall skin. These signs were rated from 1 (worst, severe fetal malnutrition) to 4 (best, well nourished), and the highest and lowest total scores are 36 and 9, respectively. A total score of <25 was taken as clinical evidence of fetal malnutrition that occurred *in utero*[1]. All preterm infants were separated into two groups according to total score as malnourished (total score <25) or well nourished (total score ≥25).

In the evaluation of early and late neonatal clinical outcomes, SGA and large-for-gestational-age (LGA) infants were excluded in order to eliminate the effects of restricted or excessive intrauterine growth on neonatal outcome and only AGA infants were included in this part of the study. The clinical diagnoses and problems

in the neonatal period, durations of mechanical ventilation, supplemental oxygen therapy, time to full enteral nutrition, total parenteral nutrition, and hospitalization durations were recorded for each infant. Hypoglycemia was defined as a blood glucose level of <50 mg/dl detected at least two times and requiring treatment with an increased intravenous glucose infusion in the first 24 hours of life whether the infant was symptomatic or not[20]. Polycythemia was defined as a central venous hematocrit of >65% at the sixth hour of life[21]. Respiratory distress syndrome was confirmed with the presence of typical clinical, radiological and arterial blood gas analysis findings[22]. Criteria of feeding intolerance were defined as: (1) abdominal distension with prominent intestinal loops, (2) gastric residue of ≥3 ml/kg before a single feeding noted at least two times in a 24-hour period, and (3) absence of occult blood in stools and pneumatosis intestinalis in abdominal X-ray. Necrotizing enterocolitis (NEC) was diagnosed according to modified Bell's staging[23]. Intraventricular hemorrhage was confirmed with cranial ultrasonographic examination in the first week of life and classified according to the system of Papile[24]. Bronchopulmonary dysplasia was defined according to the criteria of the National Institutes of Child Health and Diseases[25]. Retinopathy of prematurity (ROP) was examined in every preterm infant whose gestational age was <32 weeks and birth weight was <1500 g by a senior ophthalmologist and was staged according to the International Classification of ROP[26].

Parenteral nutrition was initiated on the first day of life in very-low-birth weight (VLBW) infants (<1500 g) and in infants who could not be fed enterally because of concurrent illness. Parenteral glucose was started at 6-8 mg/kg/min on the first day of life and increased daily as tolerated to 12 mg/kg/min. All patients received 80-100 kcal/kg/day at the end of the first week. Minimal enteral nutrition with breast milk or preterm formula was initiated at the end of 24 hours in VLBW infants. Infants without severe concurrent illness were fed enterally by breast milk or preterm formula as was tolerated according to the nursery protocol. Full enteral feedings were defined as 150 ml/kg/day.

Statistical data were analyzed using SPSS for Windows 10.0 program. Parameters with nominal values were compared with χ^2 test or Fisher's exact test. The independent sample *t* test was used to compare differences in normally distributed parameters while Mann-Whitney U test was used for non-parametric variables. A p value of <0.05 was considered statistically significant. Relative risks (RR) with 95% confidence intervals (CI) of various neonatal morbidities in the presence of fetal malnutrition were analyzed by non-test based RR-CI for cumulative data.

Results

A total of 93 preterm infants were enrolled in the study. The incidence of fetal malnutrition was 54.8% (n=51) in all preterm infants, while it was 44.0% (n=33) in AGA infants (n=75) and 100.0% (n=18) in SGA infants (n=18). The incidences of fetal malnutrition and its distribution in different weight-for-gestational age groups are shown in Table I.

After excluding SGA infants (n=18), the demographic, anthropometric and perinatal characteristics of AGA preterm infants with and without fetal malnutrition are given in Table II. Although the mean gestational ages were similar in both groups, the mean birth weight, length and head circumference of preterm infants with fetal malnutrition were significantly lower than in well-nourished

Table I. The Incidences of Fetal Malnutrition in Different Weight-for-Gestational Age Groups in Preterm Infants

Intrauterine growth	Well-nourished infants n (%)	Infants with fetal malnutrition n (%)	Total
Appropriate for gestational age	42 (56)	33 (44)	75
Small for gestational age	-	18 (100)	18
Large for gestational age	-	-	-
Total	42 (45.2)	51 (54.8)	93

Table II. Demographic, Anthropometric and Perinatal Characteristics of Preterm Infants With and Without Fetal Malnutrition (after excluding SGA infants)

Demographic, anthropometric and perinatal characteristics	Well-nourished infants (n=42)	Infants with fetal malnutrition (n=33)	p
Gender (M/F), n	23/19	15/18	
Gestational age (wk), mean ± SD	32.6 ± 1.7	31.8 ± 2.1	0.065
Birth weight (g), mean ± SD	1891 ± 355	1624 ± 357	0.002
Length (cm), mean ± SD	43.2 ± 2.9	41.2 ± 2.9	0.004
Head circumference (cm), mean ± SD	30.7 ± 2.6	29.3 ± 2.1	0.018
Disturbed umbilical artery Doppler flow velocimetry (diminution/absence/ reversal of blood flow), n (%)	2 (4.8)	8 (24.2)	0.018
Oligohydramnios, n (%)	1 (2.4)	6 (18.2)	0.039
Maternal hypertension and preeclampsia, n (%)	3 (7.2)	10 (30.3)	0.013
Abruptio placentae, n (%)	-	4 (12.1)	0.034
Rupture of membranes >24 h, n (%)	6 (14.3)	4 (12.1)	1.000
Chorioamnionitis, n (%)	4 (9.5)	2 (6.0)	1.000
Mode of delivery (V/CS), n (%)	19/23 (45.2/54.8)	12/21 (36.4/63.6)	0.082
Delivery room resuscitation, n (%)	4 (9.5)	6 (18.2)	0.320
Apgar at 5 min, mean ± SD	8.4 ± 1.2	7.5 ± 1.0	0.000
Cord pH , mean ± SD	7.32 ± 0.02 (n=15)	7.30 ± 0.03 (n=16)	0.037

preterm infants ($p<0.01$, $p<0.01$ and $p<0.05$, respectively). In the examination of perinatal characteristics, the incidences of maternal hypertensive disorders (chronic hypertension and preeclampsia), abruptio placentae, disturbed umbilical artery Doppler flow velocimetry, and oligohydramnios were significantly higher in preterm infants with fetal malnutrition than in well-nourished preterm infants ($p<0.05$ in all). Mean Apgar score at the 5th minute and cord blood pH were lower in preterm infants with fetal malnutrition ($p<0.001$ and $p<0.05$, respectively).

In the investigation of neonatal morbidities and mortality, the incidences of hypoglycemia, polycythemia, feeding intolerance, and NEC were significantly higher in preterm infants with fetal malnutrition than in well-nourished preterm infants ($p<0.01$, $p<0.05$, $p<0.01$ and $p<0.05$, respectively). The incidences of various early and late neonatal morbidities and mortality in both groups are shown in Table III.

The RRs of various neonatal morbidities and mortality with 95% CIs in the presence of fetal malnutrition in preterm infants are shown in Fig. 1. The highest RR was for feeding intolerance (1.46, 95%CI: 1.11-1.91), while the lowest RR was for mortality (0.94, 95%CI: 0.81-1.08).

Discussion

This is the first study in the literature that has used CANSCORE in preterm infants and investigated the incidence and characteristics of fetal malnutrition together with its consequences on neonatal morbidity and mortality. Physical characteristics of preterm infants are very different from those of term infants. The skin is thinner and there is less subcutaneous fat and muscle tissue. In addition, they show an advancing maturation with advancing gestational age. However, the main principal of CANSCORE, which has been used in the clinical assessment of fetal malnutrition in term newborns, depends not on gestational age but on the physical changes that occur with the loss of *normal* subcutaneous fat and muscle tissues[1]. Thus, theoretically, the CANSCORE method can also possibly be used for the determination of fetal malnutrition in preterm infants.

In our study, the incidence of fetal malnutrition in preterm infants was found to be 54.8%, which was much greater than the incidences that have been reported for term infants. In the

Table III. Clinical Characteristics of Preterm Infants With and Without Fetal Malnutrition (after excluding SGA infants)

Early and late neonatal morbidities	Well-nourished infants (n=42)	Infants with fetal malnutrition (n=33)	p
Hypoglycemia, n (%)	5 (11.9)	13 (39.4)	0.006
Polycythemia, n (%)	-	4 (12.1)	0.034
Respiratory distress syndrome, n (%)	6 (14.3)	8 (24.2)	0.272
Patent ductus arteriosus, n (%)	8 (19)	8 (24.2)	0.586
Intraventricular hemorrhage (grade III-IV), n (%)	3 (7.1)	1 (3)	0.626
Feeding intolerance, n (%)	3 (7.1)	12 (36.4)	0.003
Necrotizing enterocolitis (≥ Stage II), n (%)	1 (2.4)	6 (18.2)	0.039
Sepsis (culture-proven), n (%)	2 (4.8)	4 (12.1)	0.395
Bronchopulmonary dysplasia, n (%)	2 (4.8)	3 (9.1)	0.649
Retinopathy of prematurity (grade III-IV), n (%)	2 (4.8)	5 (15.2)	0.229
Time to full enteral feeding (d), median (min-max)	5 (3-34)	15 (5-32)	0.000
Total duration of total parenteral nutrition (d), median (min-max)	1 (0-28)	12 (0-25)	0.000
Total duration of mechanical ventilation, (d), median (min-max)	0 (0-21)	0 (0-16)	0.387
Days on oxygen, median (min-max)	2 (0-36)	3 (0-28)	0.192
Length of hospital stay (d), mean ± SD	21.2 + 16.7	36.3 + 16.6	0.000
Mortality, n (%)	5 (11.9)	2 (6.1)	0.456

literature, the incidence of fetal malnutrition in term infants has ranged from 10.9% to 40%[1,2,4,27,28]. This could be explained by the high incidence of prenatal risk factors such as maternal or obstetric diseases and placental disorders, leading to both prematurity and fetal malnutrition in preterm infants. Thus, the underlying etiological factors of both fetal malnutrition and preterm labor or iatrogenic preterm delivery, which is performed for the optimal survival of the preterm infant, appear to be common.

The incidences of fetal malnutrition in different weight-for-gestational age groups of term newborn infants have been reported in a few studies. In the original article of Metcoff [1], the incidence of fetal malnutrition was 5.5% in AGA infants and 54.0% in SGA infants. Deodhar et al.[4] reported an incidence of 12.9% in AGA infants and 84.2% in SGA infants, while Sankhyan et al.[28] found that 3.8% of AGA and 57.1% of SGA infants were malnourished. However, in our study, the incidences of fetal malnutrition in preterm AGA and SGA infants were much higher (44.0% and 100%, respectively) than those of term infants as shown in Table I. These results indicate that preterm infants, who have reached their normal weight-for-gestational age and are classified as "AGA" postnatally, might have an important incidence of fetal malnutrition. It also strongly emphasizes the importance of the nutritional status of preterm infants rather than anthropometric measures, which lead to the underestimation of fetal malnutrition. The results also indicated that almost all of the SGA infants have lost their normal growth potential and normal subcutaneous tissues due to severely decreased or inhibited intrauterine nutrient supply because of several maternal and/or placental factors that had their onset long before signs of preterm labor developed or elective operative delivery was planned. Chronic placental insufficiency seems to be a reasonable cause of fetal malnutrition and growth restriction in these infants. The duration and severity of chronic placental insufficiency probably determines whether the fetus would have only fetal malnutrition or both fetal malnutrition and intrauterine

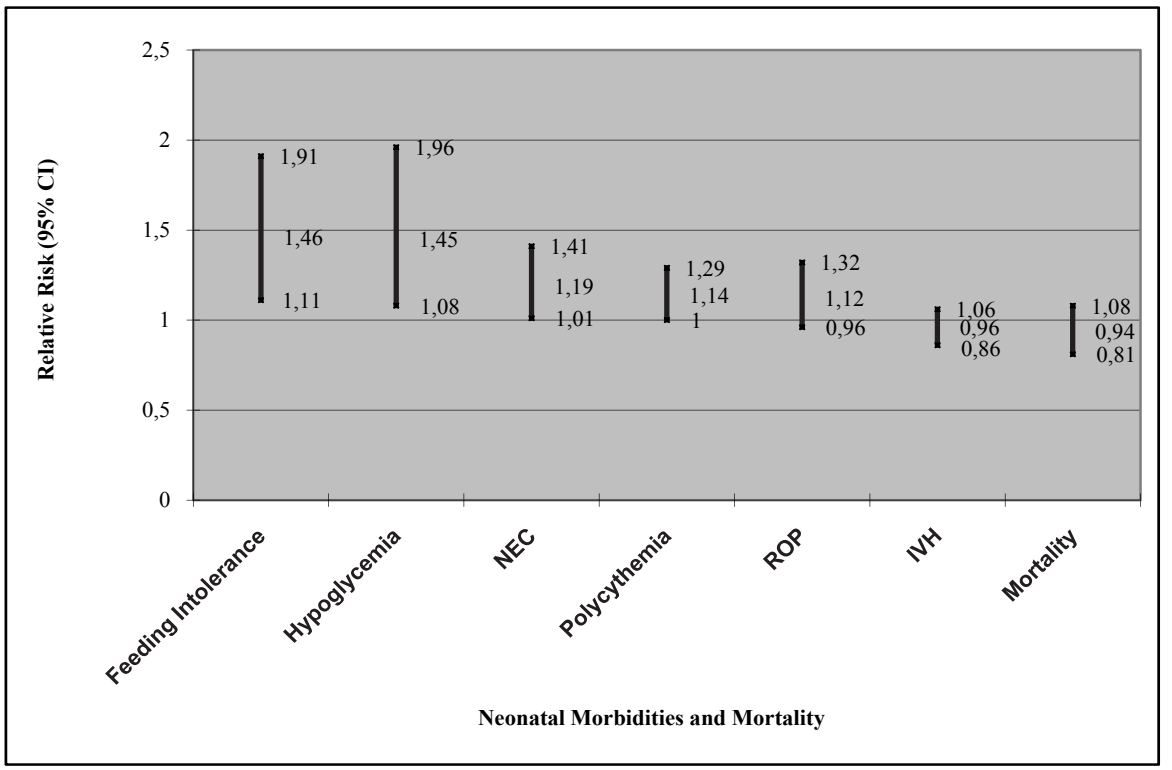

Fig. 1. The relative risks of various neonatal morbidities (95% CI) in the presence of fetal malnutrition in preterm infants.

growth restriction. Mild or moderate chronic placental insufficiency could lead only to fetal malnutrition while a severe or prolonged form could lead to both fetal malnutrition and intrauterine growth restriction. Consistent with this argument, as shown in Table II, the incidence of prenatal hemodynamic disturbances as diminished, absent or reversed umbilical artery Doppler flow velocimetry and the incidence of maternal chronic hypertension and preeclampsia were higher in malnourished preterm infants.

Fetal malnutrition is associated with an increased risk of neonatal morbidity and mortality. In term newborn infants, fetal malnutrition and intrauterine growth restriction have been found to be associated with increased risk of early and late (motor and developmental delay) neonatal problems[5,29,30].

Prematurity and fetal malnutrition are strongly associated with increased morbidity and mortality[11,12]. In the management of these infants, complications of preterm birth can be amplified by the effect of suboptimal fetal nutrition and growth. The provision of full support for resuscitation and subsequent intensive care and treatment of these infants are crucial to the short- and long-term health of these infants. In the literature, the risk and incidence of neonatal morbidities and mortality have been extensively studied in intrauterine growth-restricted infants. Intrauterine growth restriction is associated with increased risks of hypoglycemia, polycythemia, NEC, respiratory distress syndrome, bronchopulmonary dysplasia, ROP, mortality, and late neurodevelopmental problems among preterm infants[31-34]. However, the impact of fetal malnutrition on early and late neonatal outcome has not been investigated in appropriately grown preterm infants. In our study, as shown in Table III, the incidences of early neonatal hypoglycemia, polycythemia, feeding intolerance, and NEC were higher in AGA infants with fetal malnutrition than well-nourished AGA infants. Neonatal hypoglycemia and polycythemia are the results of altered glucose metabolism in the presence of intrauterine substrate deficiency and increased erythropoiesis due to intrauterine chronic hypoxia, respectively[7]. Furthermore, the time

to full enteral nutrition, the mean duration of total parenteral nutrition and length of hospital stay were longer in infants with fetal malnutrition. NEC is a multifactorial disease, in which intestinal ischemia is a major risk factor in the pathogenesis, and this is especially important for infants with fetal malnutrition[35]. Furthermore, in infants with prenatal abnormal fetal Doppler velocimetry, the "existence" of "intestinal ischemia" has been proven by the demonstration of postnatal disturbed superior mesenteric artery hemodynamics, indicating persistent redistribution of regional blood flow. These infants have been shown to have an increased risk of gastrointestinal problems and "NEC-like" clinical picture very early, even before the initiation of enteral feedings in the first few days of life[36]. In our study, the incidence of disturbed prenatal umbilical artery Doppler flow velocimetry was significantly higher in infants with fetal malnutrition, and this finding strongly explains the increased incidence of gastrointestinal problems like feeding intolerance and NEC in these infants. Therefore, not only "intrauterine growth-restricted or SGA" preterm infants but also "intrauterine malnourished" preterm infants should be considered as "high-risk infants", even though they are appropriately grown. These infants should also be followed for long-term complications and "fetal programming" effects such as growth failure, hypertension, insulin resistance, and disorders of glucose metabolism and hyperlipidemia.

In conclusion, identification of the incidence and characteristics of fetal malnutrition in preterm infants carries great importance from the points of short- and long-term neonatal morbidity and mortality. Fetal malnutrition in preterm infants can be detected with the CANSCORE method, but the suitability of this method for preterm infants should be investigated with future studies, and this may lead to modification of CANSCORE by adding more appropriate morphological parameters for this population.

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