Introduction
Since the improvement in neonatal intensive care, newborns with an increasingly small gestational age (GA) and very or extremely low birth weight have survived with less complications and sequela. Appropriate nutritional support during early life is essential to ensure the proper growth and development of the infants. Unfortunately, despite efforts of improving nutrition management, especially feeding strategies, many preterm infants still do not receive adequate nutritional support due to various factors, which might result in extrauterine growth retardation (EUGR). In this study, the feeding practice and weight gain of preterm infants were evaluated during hospitalization and 3 months after discharge.
Methods

Subjects

Preterm newborns were sampled from neonates admitted to NICU of the First Affiliated Hospital of Shantou University Medical College from January 2014 to January 2016. In total, 141 preterm infants who were born before 37 weeks, hospitalized within 24 hours after birth, and participated in follow-up clinics until 3 months after discharge, were included. Infants with congenital malformations or metabolic diseases were excluded. Seventy-eight males and 63 females were enrolled, among whom 3 (2.13%) were extremely low birth weight infants (ELBWI), 43 (30.50%) were very low birth weight infants (VLBWI), 85 (60.28%) were low birth weight infants (LBWI), and 10 (7.09%) were normal birth weight infants (NBWI). The GAs varied from 27 to 36 weeks with a median of 31 \( +6 \) weeks. Hospitalization days ranged from 4 to 66 days with a median of 21.5 \( (10.1, 44.8) \) days. Weights at discharge varied from 1,400 to 4,220 g with a median of 2,463.7 \( (1,809.7, 2,201.4) \) g. As it relates to the primary diseases, there were 78 cases of neonatal respiratory distress syndrome, 25 cases of infectious pneumonia, 10 cases of aspiration pneumonia, 10 cases of asphyxia, 9 cases of intrauterine infection, and 9 cases of pathological jaundice. As this was a retrospective study, informed consent was exempt from approval by the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College.

Nutrition practices

Nutritional strategies mainly followed “Guide for feeding preterm/low-birth-weight infants” recommended by the Chinese Society of Pediatrics (1). Enteral feeding should be started as soon as possible for the infants without congenital digestive tract malformations or critical medical conditions. The trophic feeds were started within 12 hours after birth to those infants whose birth weight was larger than 1,000 g with relatively stable vital signs, and it was delayed to 24–48 hours after birth in those who had severe perinatal asphyxia and extremely low birth weight. Breast milk was the first choice of feeding regimen. As the volume of breast milk was more than 100 mL/kg, human milk fortifier (HMF) was initially added semi-enhanced and then fully-enhanced if tolerated. If there was no or not enough breast milk, preterm formula milk was used. Trophic feeds started from 12 mL/(kg-d). If the infants could tolerate it, nutritional feeds were gradually introduced from 15–20 to 150–180 mL/(kg-d). The total or partial parenteral nutrition strategy was based on the “Guide for clinical application of nutrition support in critical neonates in China” (2). The types of milk after discharge included pure breast milk, breast milk with HMF, post-discharge formula (PDF), and term formula milk.

Data collection

The clinical data, including daily weight gain, initiation time of enteral nutrition, the period of returning to birth weight, the period of achieving the reference dietary intakes (RDIs) of 120 kcal/(kg-d), etc., were collected. The weight, length, and head circumference (HC) were recorded weekly during hospitalization and at the 1st week, 1st month, 2nd month, and 3rd month after discharge during follow-up. The evaluation of growth was based on Fenton Growth Chart 2013 (3) or the Child Growth Chart of Nine Cities in China 2005 (4) before or after corrected GA of 40 weeks. IUGR was defined as any anthropometric value, including weight, length or HC, below the 10th percentile at birth while EUGR was defined as an anthropometric value below the 10th percentile of corrected age. The definition of pathological weight loss was the following: the weight loss was more than 10% of birth weight, or body weight did not return to birth weight within 10 days after birth.

Statistical analysis

SPSS for Windows 13.0 statistical analysis software was used for statistical analysis, \( t \) test was used for comparison of quantitative data, \( \chi^2 \) test was used to compare rate, and nonparametric rank-sum test was used to analyze the skew distribution data. P<0.05 was considered as statistically significant.

Results

Feeding and growth during hospitalization

The initiation time of nutritional feeds ranged from 1 to 20 d after birth with a median of 4.3 d. The period of achieving RDIs was 3 to 30 d with a median of 10.6 d. The underlying reasons for feeding delay might involve gastric retention (46.10%), abdominal distention (25.53%), coffee-ground like (19.15%) or biliary (9.22%) vomiting, or gastric aspiration. Among the 141 preterm infants, 103 had physiological weight loss and 38 had pathological weight loss.
loss. A total of 124 infants had achieved birth weight before discharge. The period of returning to the birth weight was 11–20 d with a median of 13.2 d. The velocity of weight gain after achieving birth weight was 2–38 g/(kg·d), with a median of 16.7 g/(kg·d). The growth velocity of the length and head circumference were 0.2–1.7 and 0–1.4 cm/week, with a median of 1.0 and 0.8 cm/week, respectively. There were 25 cases (17.7%) of IUGR. However, there were 65 cases (46.1%) of EUGR at discharge. The incidence of EUGR was significantly higher than that of IUGR (χ²=6.68, P<0.01). There were differences in feeding regimen and weight gain between preterm infants born before or after 34 weeks of gestation. The comparison is shown in Table 1. The velocity of weight gain and incidence of IUGR were similar between the two groups. Feeding delay was more serious and the incidence of EUGR was higher in preterm infants born before 34 weeks of gestation than those born after 34 weeks of gestation.

**Feeding and growth after discharge**

After discharge, the preterm infants were fed by different kinds of milk according to the parents’ choice and doctors’ recommendation. At the 3rd month after discharge, the incidence of EUGR was 44.7% (63/141), which was similar to that at discharge (P>0.05). The incidence of EUGR and the growth velocity were not significantly different between the preterm infants born before and after 34 weeks of gestation (P>0.05) (Table 2). The differences of incidence of EUGR and growth velocity among infants under different feeding regimens were statistically significant (P<0.05). Infants fed by fortified breast milk or breast milk with PDF had less EUGR and better weight gain compared with those fed by pure breast milk or term formula milk (Table 3).

### Discussion

Optimal nutrition support for preterm infants especially ELBW/VLBW is essential to promote neonatal overall survival and a better long-term outcome. Evidence from randomized controlled clinical trials showed that enhanced nutrient intakes within the first few weeks in preterm infants benefited cognitive function in adolescence by changing brain structure (5,6). Therefore, preterm infants have been reasonably proposed to achieve a growth velocity as close as possible to the normal intrauterine growth of the same

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of feeding and growth between preterm infants with different GA during hospitalization</th>
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<tbody>
<tr>
<td>Variable</td>
<td>GA (weeks)</td>
</tr>
<tr>
<td>Initiation time of nutritional feeds (d)</td>
<td>7.43±4.11</td>
</tr>
<tr>
<td>Period of achieving BW (d)</td>
<td>15.50±6.23</td>
</tr>
<tr>
<td>Period of achieving RDIs (d)</td>
<td>15.69±8.83</td>
</tr>
<tr>
<td>Weight gain [g/(kg·d)]</td>
<td>18.92±6.55</td>
</tr>
<tr>
<td>Cases of IUGR (%)</td>
<td>7 (14.6)</td>
</tr>
<tr>
<td>Cases of EUGR (%)</td>
<td>31 (64.6)</td>
</tr>
</tbody>
</table>

The data are presented as mean ± SD or n (%). GA, gestational age; BW, birth weight; RDIs, reference dietary intakes; IUGR, intrauterine growth retardation; EUGR, extrauterine growth retardation.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison of growth status between preterm infants with different GA 3 months after discharge</th>
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</thead>
<tbody>
<tr>
<td>Variable</td>
<td>GA (weeks)</td>
</tr>
<tr>
<td>Cases</td>
<td>48</td>
</tr>
<tr>
<td>Cases of EUGR at the 3rd month after discharge, n (%)</td>
<td>25 (52.1%)</td>
</tr>
<tr>
<td>Average weight gain (g/mon)</td>
<td>539.7</td>
</tr>
</tbody>
</table>

GA, gestational age; EUGR, extrauterine growth retardation.
Breast milk + HMF and breast milk + PDF group $P < 0.05$; *, compared with breast milk + term formula group $P < 0.05$; $\#$, compared with PDF group $P < 0.05$; $\#$, compared with breast milk + PDF group $P < 0.05$; $\&$, compared with breast milk group $P < 0.05$; $\&\&$, compared with term formula group $P < 0.05$.

### Table 3 Comparison of development status among preterm infants fed by different kinds of formula

<table>
<thead>
<tr>
<th>Variable</th>
<th>Breast milk</th>
<th>Breast milk + HMF and breast milk + PDF</th>
<th>Breast milk + term formula</th>
<th>PDF</th>
<th>Term formula</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>17</td>
<td>16 (4 and 12)</td>
<td>23</td>
<td>31</td>
<td>54</td>
<td>-</td>
</tr>
<tr>
<td>Cases of EUGR at the 3rd month after discharge</td>
<td>5 (29.4%)$^&amp;&amp;$</td>
<td>4 (1 and 3) (25%)$^{&amp;&amp;}$</td>
<td>10 (43.5%)$^&amp;&amp;$,</td>
<td>11</td>
<td>22 (40.7%)$^&amp;$</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>Average weight gain (g/mon)</td>
<td>553.6$^&amp;&amp;$</td>
<td>626.6$^&amp;&amp;$</td>
<td>581.7$^&amp;$,</td>
<td>600</td>
<td>541.6$^&amp;&amp;$</td>
<td>$&lt;0.05$</td>
</tr>
</tbody>
</table>

* Universally, EUGR in preterm infants is not rare. Clark et al. conducted a retrospective study on 24,371 preterm infants with GAs of 23–34 weeks and evaluated the incidence of growth restriction at discharge by weight, length, and head circumference, which were 28%, 34%, and 16% respectively (11). The pediatric collaboration group of the Chinese Society of Parenteral and Enteral Nutrition analyzed the data of preterm infants from 10 hospitals and found that the incidence of IUGR and EUGR at discharge was 27.3% and 60.1% respectively (12). The incidences of IUGR and EUGR at discharge in our study were 17.7% and 46.1% respectively. The EUGR incidence in infants born before 34 weeks of gestation was significantly higher than those born after 34 weeks of gestation, which indicated that infants with smaller GA were more prone to get EUGR. IUGR is associated with gene expression and hereditary factors. A number of EUGR cases were a continuation of IUGR. Nutritional factors could regulate gene expression through epigenetic modification regarding the correlation between methylation and the protein and lipid intake. Imprinting Centre 1 (IC1) is the popularly studied gene region. A pilot study found that a reduction of nutritional intake was negatively feedbacked to increase IC1 methylation, causing an increase of insulin-like growth factor (IGF)-2 expression in order to promote a catch-up growth and to prevent EUGR (13). Even though these gene expressions were reversible with abundant nutrition supplementation (14), there were still a proportion of infants with IUGR that persisted to EUGR. On the other hand, the smaller the GA was, the more immature the gastrointestinal function was, the longer the gastric emptying time and poorer the intestinal peristalsis they had, and the greater the likelihood was of developing feeding intolerance. As indicated by our study, feeding intolerance presenting as gastric retention and abdominal distension was the main reason for postponing nutritional feeds. Inadequate enteral feeds rarely met increasing metabolic demands and nutritional needs of preterm infants, which resulted in malnutrition and failure to thrive. Other intricate factors, including regional, ethical, and traditional factors may also contribute to EUGR, perhaps through interactions with genetics and epigenetics. However, the molecular mechanisms need further investigations.

* The growth velocity was ideally 10–20 g/(kg·d). Bloom et al. analyzed the weight growth of 1,995 preterm infants with birth weight of 401–1,500 g within 28 days after birth and found that the mean weight gain velocity was only 8.7±5.0 g/d in the slow-growth group (834 cases) and 12.7±6.0 g/d in the fast-growth group (1,161 cases) (15). In our study, preterm infants had a weight gain velocity of 2–38 g/(kg·d) after returning to birth weight, with an average growth gain of 16.7 g/(kg·d). The preterm infants with GA <34 weeks had delayed nutritional feeds due to various medical conditions and the period of returning to birth weight and achieving RDIs was prolonged. However, after returning to birth weight, they had a similar weight gain velocity to the preterm infants with GA ≥34 weeks, perhaps due to more aggressive parenteral nutrition support. These results should be scrutinized under light of the study’s small sample size, which might lead to the bias.

* The incidence of EUGR in the 3rd month after discharge was not significantly improved compared with that at discharge, which may be related to inappropriate feeding
strategy after discharge. Several clinical randomized controlled trials suggested that the premature infants fed with nutritionally enhanced formula, including PDF and HMF, after discharge, were more conducive to achieving catch-up growth than those fed by breast milk (16,17). Milk fortifier was recommended for preterm infants to enhance the nutrient supplement. However, the fortifier introducing rate was low in this study. A vast number of premature infants after discharge were still fed by pure breast milk or term formula milk, leading to high incidence of EUGR.

**Conclusions**

EUGR is not rare in preterm infants, especially those with small GA during the early stages of life, which is difficult to be improved within a short period of time. After discharge, feeding with fortified breast milk or PDF is more suitable to prevent EUGR in preterm infants than feeding with the pure breast milk or term formula milk.

**Acknowledgements**

None.

**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The study was approved by the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College. As this was a retrospective study, informed consent was exempt.

**References**


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