

Peer Review File

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Reviewer 1

Comments 1.....An escape from extrauterine growth restriction (the percentile of body weight > 10% at term period) is influenced by the degree of fetal growth restriction and actual feeding volume, and others.....

Reply: Yes, our study demonstrated that the occurrence of EUG was affected by many factors such as the use of antibiotics and ventilator, breastfeeding and so on. The latest literature also mentioned this point.

Xingli Zhao, Li Ding, Xiaoqian Chen, et al. Characteristics and risk factors for extrauterine growth retardation in very-low-birth-weight infants. *Medicine* 2020;99:47(e23104)

Comments 2... In table 1, the degree of intrauterine growth restriction in EUGR group appeared to be stronger than in non-EUGR group, which may undermine the validity of present study. The authors should add the z score of body weight at birth and at discharge, respectively.

Reply: Yes, birth weight is different, but there is no statistical difference. In the design of this study, only the data of children with EUGR after discharge were collected, therefore, there is no specific grouping of birth conditions, such as AGA or SGA. In the follow-up study, we will further expand the sample size, grouping at birth, grouping again after discharge, and collecting stool at birth and discharge to further obtain clinical related information. This is also an important direction for us to improve the experiment.

Comments 3...In addition, daily actual feeding volume during NICU should be added as independent variables. It seems to be better to adopt the amount of weight gain rate from birth to term as dependent variable instead of the presence of EUGR, because the hospitalization days of both groups are absent.....

Reply: There is a difference in the length of stay between two groups. Because the condition of EUGR children was more serious, the length of stay was also prolonged. We will supplement this in Table1. In addition, the daily feeding amount was adjusted at any time according to different conditions, which was not included in the statistical range. According to the commonly used EUGR diagnostic criteria, as long as the discharge indication was reached, we bring the case into experimental group. According to the concept of EUGR, we will include the children whose weight is less than 10% when they are discharged from the hospital. If the difference of discharge weight was counted, difference will be founded.

Table 1. Characteristics of infants with and without EUGR

Variable	EUGR	HC	P VALUE
Hospitalization days	65 ±7	51 ±8	P<0.05

Reviewer 2

Comments 1...The premise and the analyses in this paper about very and moderate preterm infants are based on the concept that EUGR is a major problem. However several neonatal researchers recently pointed out five reasons why EUGR is not a useful growth metric for preterm infants, primarily that it is not associated with adverse neurodevelopment (Extrauterine growth restriction and postnatal growth failure are misnomers for preterm infants. J Perinatol 2020. doi:10.1038/s41372-020-0658-5) so it is unclear whether this work provides any value.....

Reply: The concept of EUGR is not perfect, but it provides clinicians with the basis and content of follow-up, It is difficult to raise children with EUGR after discharge if they are not given active diet or disease guidance. Although it is controversial, there are also many studies on its later development.

Martínez-Jiménez, Gómez-García, Gil-Campos. Comorbidities in childhood associated with extrauterine growth restriction in preterm infants: a scoping review .European Journal of Pediatrics, Accepted: 12 February 2020.

Han-Chun Chien, Chao-Huei Chen, Teh-Ming Wang, et al. Neurodevelopmental outcomes of infants with very low birth weights are associated with the severity of their extra-uterine growth retardation. Pediatrics and Neonatology (2018) 59, 168e175.

In addition, as more and more premature babies are born, the incidence rate of premature delivery and EUGR is also increasing. Therefore we should pay more attention to the growth and development of these children in the later stage.

Comments 2.....Regarding their reference 4: The Chien paper they cited as evidence for EUGR as being predictive of adverse neurodevelopment is a study that does not agree with the rest of the body of literature on this topic. It does not make sense to cite an outlier study as evidence of an important relationship.

Reply: For the nervous system and endocrine sequelae of EUGR, you can also refer to this article

Martínez-Jiménez, Gómez-García, Gil-Campos. Comorbidities in childhood associated with extrauterine growth restriction in preterm infants: a scoping review. *European Journal of Pediatrics*, Accepted: 12 February 2020

Comments 3...Their claim about metabolic syndromes supported by the 2013 reference [5] is also a controversial area and not one that is established. In fact, there is doubt being raised about the reported associations between small size in early life and adverse metabolic outcomes in later life since many of the studies that purport this association adjusted for later weight, which is a questionable practice as it distorts regression analysis results

Reply: This article on endocrine sequelae can be referred to.

Prematurity With Extrauterine Growth Restriction Increases the Risk of Higher Levels of Glucose, Low-Grade of Inflammation and Hypertension in Prepubertal Children, *Front. Pediatr.* 8:180. doi: 10.3389/fped.2020.00180

Comments4 The researchers did not report the rates of small for gestational age at birth or any of the social determinants of health (income, education etc) in the two groups. There are important differences between their 2 groups that suggest that there may be a higher rate of small for gestational age infant in the EUGR group (higher rates of ventilation, higher rates of caesarean section). Small weight for gestational age at birth is associated with the social determinants of health, which could actually be the

causal factor behind the associations that they reported. In other words, they have likely identified the incorrect causal pathway.

Reply: The problem of SGA in EUGR children does exist, but this design only compares the children who come up to the EUGR standard after discharge. There was a study that analyzed the correlation between EUGR children and SGA. According to the corrected OR value, there is no statistical significance. EUGR is more able to evaluate the growth and sequelae in the later stage.

Comments5 Another important concern is multiple comparisons, with 59 p-values in the results section. With so many p-values, several comparisons will be statistically significant from chance alone.

Reply: Multiple statistics is certainly better, but based on the data of this study, *P* value is enough to show the results.

Reviewer 3

Comments1 What weight curves (length and cranial perimeter?) were used to define the 10th Percentile below which the EUGR would exist?

Reply: We still define EUGR according to the standard of less than 10% of discharged body weight.

Comments2 At what point was the existence of EUGR defined? At discharge? At 36 weeks postmenstrual age? ...?

Reply: We used discharge define EUGR.

Comments3 The fourth criterion of exclusion ("severe digestive tract malformation") is included in the first.

Reply: The fourth criterion of exclusion has been included in the first in the manuscript.

(1) born with severe abnormalities, congenital heart or pulmonary disease, severe digestive tract malformation, metabolic disease or chromosomal disorders; (2) dead during hospitalization or with poor comorbid disease control; (3) mandatory discharge from the hospital without meeting

the standard required. Our study was performed in accordance with the Declaration of Helsinki with regard to ethical principles for research involving human subjects.

Comments4 Table 1 lacks the "p" to see if there is a significant difference between each variable in the two groups, which would make them difficult to compare. Other neonatal pathologies, especially necrotizing enterocolitis, also need to be reported.

Reply: We will supplement this information.

Comments5 The diet of newborns with EUGR was clearly different from that of normal newborns ($p = 0.017$). Could it have influenced the differences in the microbiome?

Reply: Yes, diet is an important factor, which is also one of the important factors affecting the occurrence of EUGR.

Comments6 SGA (weight less than the 10th percentile at birth) should have been differentiated from non-SGA newborns. In EUGRs that are also SGA, the intrauterine involvement will not be due to the intestinal microbiota as the contributions are only placental. These infants with SGA are born already “marked” and, as Figueras-Aloy J indicates in Eur J Pediatr 2020, they are not “true EUGR” (without SGA).

Reply: The opinion of experts is very right. Because our study did not distinguish SGA, there must be children with SGA in our group. This is a limitation of our study. We will distinguish SGA and AGA children from the beginning of grouping, and then follow up their incidence of EUGR, as well as the difference of bacterial flora.

Comments7 At the end of the Discussion, a paragraph with the “weaknesses” of the work is missing, in which everything indicated above should be cited.

Reply: Yes, thanks you suggestions. The limitation of our study is that the ratio of SGA and AGA is not distinguished. It will be better if we can follow up for more one or two months. The lack of detection of

short chain fatty acids in stool is also one of the defects. If we can detect the metabolic level of short chain fatty acids, it may be more able to explain the subsequent development problems.