REVIEW

Fetal growth restriction and post natal growth failure : Improving prevention in resource-constrained settings, a narrative review.

Sandrine Kengne Kamga [1], Julienne Louise Ngo Likeng, Anne Esther Njom Nlend [,2]

[1]Ecole des Sciences de la Santé de l'Université Catholique d'Afrique Centrale [ESS/ UCAC] 2 Higher Institute of Medical Technology.

Cooresponding Author : Anne Esther Njom Nlend, MD, Associate Professor of Pediatrics.
Higher Institute of Medical Technology - Yaoundé Nkolondom, Université de Douala.
anne.njom@gmail.com

ABSTRACT : Postnatal growth failure (PGF) is a common problem in low birth weight (LBW) children. It is estimated that fetal growth restriction (FGR) can concern less than 10% of pregnancies in high resource settings while almost 25% are affected in low- and middle-income countries (LMICs). In order to reach the target of ending low birth weight by 2025, notably in low resource settings where prevalence is still high, we conducted a narrative review around the main factors affecting PGF. The aim of this study was to describe risk factors of postnatal growth failure after FGR and to extract solutions for the field in our context. We found that prenatal risk factors particularly (factors related to infections, exposure to toxins, chronic diseases of the mother, nutritional deficiencies of the mother) influence the occurrence of postnatal growth failure or its prognosis in newborn. After birth, inappropriate uptake of both energy and protein compromise extrauterine growth. It is therefore essential in LMICs to start this prevention early, through nutrition programmes, fighting against malaria in pregnancy. At birth, nutritional support is a key element for prevention of post-natal growth failure. It should emphasize breastfeeding with own mother milk (OMM) rather than donor bank human milk. In addition, hybrid feeding or fortification of OMM using preterm formula powder might be indicated to ensure appropriate protein and caloric uptake. Basically, putting to scale Kangaroo mother care is a must. At last, routine monitoring of height and head circumference, should be added to weight, as indicator of lean body mass in all neonatal units.

INTRODUCTION

Fetal growth is a complex process conditioned by many factors including genetics and environment. Disturbance of fetal growth can result in fetal growth restriction (FGR) or small for gestational age (SGA) usually depending on maternal health status, fetal factors usually genetic and placental function impairment. Low birth Weight (LBW) includes all babies born with a birth weight below 2500g. In 2015, the World Health Organizations (WHO) estimated that 20.5 million children were born each year in the world with a LBW, i.e. 14.6% of all live births, 91% of them in developing countries, three-quarters of them in South Asia and sub-Saharan Africa [1]. In developed countries, we note an average of about 7% corresponding to less than half of that observed in developing countries, i.e. 19%. Asia ranks first, followed by Africa. South Asia is the region with the highest incidence with 27.8% in Bangladesh [2]. In data poor countries, though Demographic health surveys usually record rate of LBW every 5 years in low resource settings, scarcity of data on SGA remains common [3]. It is estimated that FGR can concern less than 10% of pregnancies in high resource settings while almost 25% are affected in low- and middle-income countries. Following FGR, post-natal growth failure (PGF) can occur among both babies with FGR or not including those with weight appropriate for gestational age (AGA) or those large for gestational age [4-7]. In the context of achieving target of ending low birth weight by 2025, notably in low resource settings where prevalence is still high, we conducted a short narrative review around the main conditions factors affecting eextrauterine growth retardation (EUGR) after FGR in order to increase prevention. Specifically, we went through the following points 1/definition of key terms 2 / main causes of FGR, 3/ Post natal growth failure after LBW and FGR 4/ factors associated to Post Natal Growth Failure and 5/ Ways to prevention in resource-constrained settings.

1. DEFINITION

Newborn babies with inappropriate weight at birth can fall upon the following groups and definition. Low birthweight [LBW] is defined as a birthweight below 2500 g regardless of gestational age and is usually applied to live births only [1]. LBW is an important marker of maternal and fetal health, predicting mortality [60-80% of neonatal deaths], stunting, and adult-onset chronic conditions [1,4,5]. Small for gestational age usually used as similar to FGR, which consider any baby with birth anthropometric parameters (usually for weight and or length or head circumference) falling below the 10th percentile on the antenatal

charts in regard to the gestational term. Both SGA and LBW are fragile at increased risk of harmful conditions and deaths [6,7]. In addition, they can be exposed to extrauterine growth retardation [EUGR]. At last, a category of babies with FGR according to the charts, can be constitutionally small without any explaining disease and the proportion of this late categories can reach 40% according to the parameters and the charts used [7,8]. In many low resource settings due to limitations to record appropriate gestational age, using early obstetrical echography, LBW is commonly used and may include SGA, premature infants appropriate for gestational age plus genetically small babies free of any disease.

2. MAIN CAUSES OF FETAL GROWTH RESTRICTION

Fetal growth restriction generally can be caused by three main groups of causes: maternal, foetal and placental impairment and dysfunction

Maternal conditions

Many maternal conditions can hamper the normal growth velocity of the fetus. Maternal poor nutrition, notably iron deficiency and anemia, malaria, maternal hypertension, and late-stage diabetes; other conditions are drug consumption such as tobacco, alcohol and any maternal chronic disease and or infectious diseases including HIV. In addition, other environment factors included lack of physical activity and domestic violence can affect fetal growth.

Factors Related to Maternal Chronic Diseases

Many maternal chronic diseases are known to be risk factors for EUGR by increasing small for gestational age (SGA) and LBW, which are major factors in altering adaptation and extrauterine growth. Thus, hypertensive disorders increase the frequency of SGA : chronic arterial hypertension (by a factor 2), preeclampsia (by a factor 5 to 12 depending on the severity of the condition and studies), pregnancy diabetes with vascular involvement is associated with SGA (6-fold risk) [6,9].

Factors related to exposure to toxic substances

The consumption of psychoactive substances during notably opiates, such as heroin, opium, morphine, and codeine during pregnancy increases the risk of obstetric and pediatric complications (prematurity, intrauterine growth retardation, and developmental defects) [10]. In this paper Lejeune shows that the perinatal and pediatric prognosis depends on the nature and number of products consumed, but also on the overall medico-psychosocial context. In addition, it has been proven that active smoking

during pregnancy increases the risk of FGR by a factor of two for a consumption of 10 cigarettes per day with a dose effect [11]. Not only active, passive smoking is also associated to side effects and can lead to FGR. Alcohol consumption doubles this risk and drug use during pregnancy is associated with a three fold increased frequency of LBW during pregnancy [10,12].In addition, great caution and education should be emphasized on the use of antiepileptic drugs during pregnancy, with possible birth defects and anomalies, notably with valproic acid[10].

Factors related to maternal nutritional deficiencies and socio economic risk factors

As far as poor nutrition is considered, pre-pregnancy low birth weight and or low weight gain during pregnancy can result in FGR and LBW. It has been considered that a poor caloric daily intake below 1500-1600 Kcal per day will damage normal fetal growth [13]. In addition, anemia and iron-deficiency are statistically associated with an increased frequency of FGR[6,13]. Similarly, maternal vitamin D deficiency during pregnancy has been shown to increase the risk of LBW and SGA [14]. Among the maternal and socio-economic risk factors, there is a strong tendency at the limit of significance for underage mothers, low maternal school enrolment [15]. The father's occupation also influences the weight of the mother and child at birth [16].

Fetal conditions

Genetic disorders

Many genetic disorders can alter the normal growth of the fetus leading to FGR. Chromosomal disorders, autosomal abnormalities and sex chromosome impairment can hamper fetal growth including growth restrictions associated to congenital polygenic malformations [17].Genetic disorders will resulted in harmonious and symmetric FGR, with low ponderal index, due to restriction of cell hyperplasia started early during pregnancy.

Factors related to fetal infections

Infections during pregnancy recorded as embryotoxic or teratogenic were initially gathered under the acronyms TORCH (TOxoplasmosis, Rubella infection, Cytomegalovirus, Herpes simplex 1 and 2) ; the O later transformed as Other infections as led to add to this growing list Treponema Pallidum, varicella zoster, parvovirus and recently the virus Zika. Infections such as syphilis, rubella, cytomegalovirus infection and Zika virus infection are generally responsible for spontaneous abortion, premature delivery, microcephaly, low birth weight, and other complications of pregnancy [18-20]. The embryopathy of rubella with the classic triad of Gregg

consists of deafness, cataract and congenital cardiac abnormalities, is being phased-out due to immunization coverage [19,21]. In addition, other diseases can affect fetal growth without inducing major malformations as HIV, malaria.and periapical dental infections[18,22,23]. The HIV effect on anthropometric parameters is affected by the patient's status under ART or not including the kind of protocols [with or without protease inhibitors]. Some teams have reported SGA and/LBW and or preterm births. Of note, Njom Nlend et *al* showed that antiretroviral treatment initiated during pregnancy was an independent factor of LBW [24].

Placental dysfunction

In most cases, FGR will be the results of the many modifications of the placental anatomy : vascular, attrition, thrombotic modifications and reduction of the effective surface of exchange [25]. All these modifications will create a reduction of oxygen transfer, creating disturbance of fetal growth through chronic stress and anoxia. According to the level and duration of chronic hypoxemia the FGR will be harmonious or disharmonious.

3. POST NATAL GROWTH FAILURE /EUGR - Definition and epidemiology

After birth, all infants having suffered of LBW or FGR are likely to pursue their growth. For preterm births, there are increasing evidences that intrauterine growth charts may not be appropriate to monitor extrauterine growth. For SGA, rapid catch-up of growth restriction is better known to be damageable, with high later risk of metabolic syndrome. Growth velocity can be measured in variation of Z scores for weight and height from birth to term corrected age (> 0.67,< -0.67 or between -0.67;+0.67) [26] but also by daily weight gain in g/kg/day. this may varies from 14- 20/kg/day according to the baseline, weight, gestational age [27].

EUGR has commonly been considered as a growth parameters(weight, height or head circumference) being below the 10th percentile or a growth z-score at discharge <–1.28 of expected intrauterine growth or standard postnatal growth [28,29]. EUGR used as a continuous variable outlines differences between z-scores at birth and 36 weeks or 40 weeks postmenstrual age (PMA; near-term corrected age) or at hospital discharge [30,31]. The measure of growth parameters at hospital discharge; 36 weeks or 40 weeks postmenstrual age (term equivalent age) are often used to compare the incidence of EUGR in neonatal intensive care units [8,32,33].In the majority of cases, EUGR

also named post natal growth failure primarily concern preterm infants with LBW or Very low Birth Weigth (VLBW).

However, it is more appropriate to consider the EUGR as the reduction in z-weight score between birth and discharge > 1 standard deviation (SD) [30,31,34,35]. Because, EUGR can be present in both small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) infants [36].

The prevalence of post-natal growth restriction varies from study to study around the world depending on context, regional setting, pregnancy features, genetics, gestational age, disease, nutrition, and the interaction between these factors [8,29,37]. EUGRs are still common in neonatal units [38] and occur in the majority of extremely preterm infants [39]. In the study in Rhône Alpes (France), the prevalence of EUGR was 34% [40]; in China among premature newborns it was 36,4 % [41] and 72.1% in very low birth weight infants [42]. Takayanagi found 47.5% in Japan[5]and Lee found 50.3% in Korea in very low birth weight preterm infants [43]. The United States has the lowest rates with 26% [8]. In Africa, very little data are available on the subject, but the incidence is expected to be higher there, given that of the 20.5 million low birth weight children identified in 2015 by WHO, 91% were in low-middle-income countries [1]. However, a study in Senegal on postnatal weight growth of LBW infants showed that the incidence of EUGR at 40 post-conception week was 85.7% [44].

4. FACTORS ASSOCIATED WITH POST NATAL GROWTH FAILURE

There are three types of factors that can affect the growth of a low-birth-weight newborn during the period between birth and discharge at home:

— those related to the child's initial status:

— those related to the postnatal pathology of the child

— those directly related to the nutritional protocol used during the post-natal period.

Initial status of children with postnatal failure at discharge

In general, LBW and low initial term are independent variables related to postnatal failure. This is shown by the Lima longitudinal study carried out in four neonatal units, which included 570 very low birth weight infants, 33% of whom were small for gestational age (SGA). In this study, EUGR was high in the population

(149/570 or 26%), especially among infants who were SGA. SGA was the variable with the greatest impact on stunting for weight (OR = 4.33) and head circumference (OR = 2.11) in the adjusted analyses[45]. In several studies, incidence of EUGR for infants with FGR was significantly higher than for infants without FGR (p <0.01) [8,41,44,46]. Cao has shown that very low birth weight infants (VLBW) have a higher incidence of EUGR than infants without this problem (p < 0.01). Incidence of EUGR increases with decreasing gestational age (P <0,01) [43,43,46–49]. Finally, with respect to gender, EUGR is more common among girls [45] while other studies show the opposite [8,50]. In summary, the lower the weight, GA or both variables at birth, the higher the risk of occurrence of EUGR.

Pathologies occurring during hospitalization associated with the occurrence of postnatal growth failure

PGF is influenced by several factors such as morbidities, during the period of delivery and hospitalization and during the period following hospital discharge[49]. The need for assisted ventilation on the first day of life and the prolonged need for respiratory support (42) the length of hospital stay, and the development of neonatal morbidities such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and delayed sepsis are factors independently related to post natal growth failure [8,41,42,46,48]. In addition, metabolic bone disease and retinopathy of prematurity during the first period of life, as well as hospital readmissions during follow-up, increased the probability of a Z score < -2 SD in Rover's study [49].

Nutritional Characteristics of the Population with Postnatal growth failure

Probably the most important factor of PGF is the accumulation of significant protein and energy deficits in the first few weeks of life that are difficult to reverse [8]. For example, in 2015, in Cao's study of 694 premature newborns with a gestational age of less than 34 weeks, 217 developed a postnatal growth failure. After analysis, the values of variables such as the fasting time, the duration of parenteral nutrition, the time that the child begins to feed, and the age required for complete enteral feeding were significantly higher in the group of infants who developed postnatal growth failure (P <0.01). Cumulative protein deficit and cumulative caloric deficit in the first week of life were also higher (p <0.05) [46]. Similarly, Faye's study shows that postnatal growth failure is linked to deficient caloric and nutrient intakes in the first few days of life [44]. Indeed, early initiation and aggressive progression of enteral feeding contribute to a decrease in the incidence of EUGR. The delay to reach 100 ml/kg of enteral feeding is critical in determining

whether or not growth retardation occurs [43]. Also, long duration of parenteral care, late onset of enteral nutrition (EN), timing of complete EN, and longer duration of hospitalization are the independent risk factors of EUGR [50]. In addition, with respect to the quantity, but also the quality, of nutrient intakes, inadequate nutrient intakes may increase the risk of EUGR in children with very low birth weight, especially energy intakes [51]. Cumulative energy and protein deficits were significantly higher during the first eight weeks and the third to seventh weeks in the EUGR group, respectively. Logistic regression showed that there was a significant negative correlation between cumulative energy deficits and changes in weight z-score ($r = -0.001$, $P < 0.05$): when energy deficit increased by 100 kcal, weight z-score decreased by 0.1 SD. Thus, nutritional or fortifying preparations of breast milk ("Human Milk Fortifier", HMF), made up of whole or hydrolysed proteins, minerals and electrolytes are being developed to cover these nutritional requirements.

5. WAYS TO PREVENTION IN RESOURCE CONSTRAINED SETTINGS

At this point, there are many evidences that post-natal growth failure is not only due to nutritional deficits after birth. Prenatal risk factors measured by child status at birth, play a key role in its occurrence. Following LBW or FGR, it happens difficult in many cases to join a normal growth curve[[8,41,44–46]].In addition, some problems in terms of definitions are still pending with fallacies around definition of EUGR for SGA. As stated, EUGR in small-for-gestational-age (SGA) infants cannot be considered a true EUGR but a postnatal pursuit of their in utero FGR [52]. After having acknowledged, the birth status of the newborn, few can be done at birth. FGR factors must be addressed earlier through safe motherhood and nutrition programs. In this concern and in line with WHO 2025, for a reduction by 30% of LBW, the following preventive strategies should be emphasized : 1/fighting against malaria during pregnancy by ensuring a high uptake of preventive intermittent treatment for at least 80% of pregnant women in endemic areas [19], 2/ensuring at least 8 antenatal visits for appropriate follow-up of pregnancy and detecting of hypertension and others comorbidities susceptible to alleviate normal growth, monitoring of fetal growth and vitality of the fetus 3/ ensuring appropriate maternal nutrition including iron and calcium uptake with a minimal daily caloric uptake above 1800 Kcal during pregnancy, including appropriate preconceptional diet, 4/fighting against any consumptions of drugs including alcohol, tobacco, cocaine, heroin, including some medications. [10,12,13 53-54].

The main modifiable risk factor after birth, is nutritional support and appropriate management of any comorbidity. In fact, despite

the implementation of aggressive and early nutrient interventions described in numerous studies, the PGF is still observed in this vulnerable category of children (SGA, preterm infants). These deficiencies can be more important in low resource settings where standards of enteral and parenteral nutrition in neonatology are usually lacking. So far, prenatal risk factors and enteral nutritional support are the key elements to act on, with a very advantageous cost/effectiveness ratio, especially in low-incomes countries (LICs), compared to the entire therapeutic arsenal necessary for the prevention of the direct causes of EUGR (energy and protein deficiency) [43,51].

The optimal nutritional support at birth, must ensure appropriate weight gain through caloric uptake, while height and head circumference are depending of protein intake [51,55]. In regards to quantity, requirements in energy, macro and micronutrient need both parenteral nutrition (PN) and enteral nutrition (EN). In LICS, PN is often restricted to intravenous infusion of glucose plus electrolytes in many cases, with evidence of shortage in protein and fat requirements [55,56,57]. In addition, lack of protein can favor EUGR through epigenetic factors, while excess of amino-acids can be harmful [55, 58]. After the starting of early parenteral nutrition, enteral nutrition may follow without extended delay. No differing enteral nutrition has both advantage in trophicity and maturation of the gastrointestinal track including prevention of necrotizing enterocolitis (NEC) [59, 60]. To cover the needs of the baby, breastfeeding with the own milk of the mother is still the best option for appropriate protein uptake and prevention of accumulation of aberrant fat. This is based on the protein composition of the breastmilk which varies with gestational age. Apart from protein profile, the osmolality of breastmilk may also prevent necrotizing enterocolitis (NEC) [61,62]. Altogether, own milk of the mother should be the first-choice prior donor bank milk and any formula [63]. However, breastmilk may need to be fortified in order to ensure correct protein and energy intake resulting in appropriate growth. Methods of fortification can be different standard versus target fortification. However, all methods of fortification will increase the osmolality of the breastmilk thus raising the risk of NEC [62,64-65]. In restricted constrained settings, access to both standard or target fortification is limited due to cost. In this context, alternatives have advocated the use of hybrid feeding (mother's milk supplemented with formula) and fortification with preterm powder milk [66, 67]. Studies' results are laudable as regard to weight gain and feed intolerance. Methods to fortify breastmilk using these alternatives should therefore be identified, assessed and come to scale, to respect the osmolality upper limit to reduce the risk of NEC [61-68]. The place of special preterm

babies' formula should be indicated in absence of breastmilk ensuring access to potable water in rural areas; even if catch up of growth is better under preterm formula, the risk of necrotizing enterocolitis is real [69]. The main issue in this catching-up period is to ensure a normal growth velocity, as rapid catch-up growth may be harm, and a leading cause of metabolic syndrome with later negative consequences on cardiovascular health [70, 71].

In most situations, the Kangaroo mother care programme will be helpful to prevent EUGR [69,72] and ensure a normal post-natal growth, including in communities. KMC has proven to provide many advantages in terms of growth, reduction of duration of hospital stay, duration of exclusive breastfeeding period [73-74]; lower rates of infections and better temperature control [75,76]. In addition, more evidences are documented on post discharge and communities KMC [77]. Finally, as the measure of growth using body s compartments are not yet common in low resources setting of Sub Sahara Africa [SSA], we did not extend our review on under this chapter. However, it is widely reported than, after FGR, body compartments are affected (inflation of water and salt, lower attrition of protein, higher fat mass [78]; it is advisable to institute the measure of height to monitor lean body mass of all the preterm and SGA babies.

CONCLUSION

In LICS, postnatal growth failure remains frequent and usually follows the FGR present at birth. For prevention, the main modifiable factors both pre- and post-natal are nutrition and fighting against infections especially malaria in pregnancy, within integrated antenatal care. The post-partum intervention to prevent PGF is the nutritional support based on maternal own's milk plus fortifiers, KMC and breastfeeding. It is therefore important to put all these programmes to scale in order to achieve the 2025 global objective of nutrition.

CONFLICT OF INTEREST: None

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