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Preterm feeding recommendations are achievable in large-scale research studies

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Abstract

Background: The INTERGROWTH-21st Project aimed to produce international, prescriptive, postnatal growth standards for preterm infants born to healthy, well-nourished mothers receiving adequate antenatal care. There is little information available regarding optimal postnatal growth among uncomplicated preterm newborns. We describe how the preterm infants contributing to the standards followed evidence-based feeding recommendations.

Methods: In the Fetal Growth Longitudinal Study (FGLS), a component of the INTERGROWTH-21st Project, fetal growth was monitored by ultrasound from <14 weeks' gestation until birth in pregnancies at low risk of adverse outcomes. All preterms ($\geq 26^{+0}$ and <37⁺⁰ weeks' gestation) were followed up during infancy. Internationally-accepted feeding recommendations for preterms, agreed by the INTERGROWTH-21st Neonatal Group, were implemented at each study site. Standardised questionnaires served to record information on their feeding practices.

Results: Feeding data were collected from 201 eligible preterms. The median (interquartile range, IQR) gestational age at birth was 36.0 (35.0 – 36.6) weeks. The prevalence of *any breastfeeding* was 82 % within 72 h of birth, 96 % at 2 weeks, 82 % at 4 months and 70 % at 8 months postnatal age. The figures for *exclusive breastfeeding* were 51 % within 72 h of birth, 72 % at hospital discharge, 49 % at 4 months, 38 % at 5 months and 12 % at 6 months. Complementary foods were introduced at a median (IQR) postnatal age of 6.0 (5.1 – 6.8) months.

Conclusion: Most preterms were exclusively breastfed upon hospital discharge, and breastfeeding remained a substantial source of nutrition throughout the study. Recommendations, centred on breastfeeding, were adequately followed within the expected variation of such diverse settings.

Keywords: Preterm infants, Nutrition, Breastfeeding, Postnatal growth and development

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Background

INTERGROWTH-21st is a multi-country project to develop international, prescriptive standards for fetal growth, newborn size and preterm postnatal growth [1], to complement the existing WHO Child Growth Standards [2, 3]. Such standards describe how individuals *should* grow, as opposed to reference charts that describe how individuals *have* grown at particular times and locations [4]. The aim of the *Postnatal Preterm Follow-up Study* (PPFS), a component of the INTERGROWTH-21st Project was to construct prescriptive standards to monitor the postnatal growth of preterm infants following our *a priori* conceptual framework [4]. Using a similar approach to the WHO Multicentre Growth Reference Study (MGRS) [2, 3], we studied a cohort of uncomplicated, preterm infants born to healthy, well-nourished women from geographically diverse populations, who received adequate antenatal care and were at low risk of adverse maternal and perinatal outcomes, and who were not exposed to any known non-microbiological contamination or toxic substances [5].

Preterm infants are a heterogeneous group, varying by gestational age at birth and the severity of their comorbidities, many of which are associated with being born at a very early gestational age and growth restricted [6]. Some of the comorbidities are also probably associated with immature gastrointestinal function, resulting in an imbalance between rapid growth, nutrient supply and the adequacy of the metabolic response, occurring during the unplanned transition from trans-placental nutrition to oral feeding [7, 8].

There is controversy, both conceptually and at a practical level, about how best to feed preterms; hence, feeding practices vary among and within countries [9]. Some practices have been proposed, which should support a tissue accretion rate matching that of normal intrauterine growth. This approach assumes that the growth rate of a fetus of a comparable gestational age is desirable for the postnatal growth, development and long-term health of a preterm. However, such a pattern is seldom attained in preterm neonates, who almost always show a postnatal cumulative nutritional deficit and so-called 'extrauterine growth restriction' [10]. Feeding guidelines for term infants are based on the substantial benefits of breast milk, e.g. decreased rates of infection and mortality, and better long-term outcomes, including improved neurocognitive and cardiovascular development. There is increasing evidence that there are also important benefits to be gained from giving the mother's milk to sick and preterm infants in neonatal intensive care units [11]. However, their nutritional needs are different from those of term infants and should be evaluated carefully, especially bearing in mind the need to fortify human milk [11].

Therefore, in developing the preterm prescriptive growth standards, it was essential to ensure that the recommended feeding practices for optimal postnatal growth in preterms were implemented, including the provision of supplements and complementary foods when necessary. In this paper, we describe the breastfeeding and complementary feeding practices of the infants enrolled in PPFS.

Methods

Study design

INTERGROWTH-21st was a population-based project conducted between 2009 and 2014, in eight urban areas: the cities of Pelotas, Brazil; Turin, Italy; Muscat, Oman; Oxford, UK; Seattle, USA; Shunyi County, a suburban district of the Beijing municipality, China; the central area of the city of Nagpur (Central Nagpur), Maharashtra, India; and the Parklands suburb of Nairobi, Kenya [1].

All singleton, preterm newborns ($\geq 26^{+0}$ to $< 37^{+0}$ weeks' gestation) in the *Fetal Growth Longitudinal Study* (FGLS) component of INTERGROWTH-21st, whose intrauterine growth was monitored by ultrasound, were eligible for PPFS. The detailed methodology has been published elsewhere [1]. Briefly, infants contributing to the standards must have: a) been free of major congenital malformations and severe neonatal conditions associated with impaired postnatal growth; b) received standardised, evidence-based care [12], and c) been exclusively or predominantly breastfed according to current recommendations. To achieve this goal, the INTERGROWTH-21st Neonatal Group developed, before the study commenced, a set of minimum recommendations for neonatal and postnatal care, based on current practice and recent publications (Table 1) [12–15]. Their feeding recommendations promoted exclusive breastfeeding by the time of hospital discharge and up to 6 months of age, consistent with the recommendations of WHO that have been adopted widely. Food source recommendations were, in order of preference, breastfeeding or expressed breast milk, donor human milk, and preterm formula. Guidelines for the initiation of milk feeding and progression volumes, and the use of nutritional supplements and fortifiers were provided [12, 15].

Data collection

Follow-up visits were scheduled 48–72 h after birth, every 2 weeks (i.e. 2 weeks \pm 2 days, 4 \pm 3, 6 \pm 4, and 8 weeks \pm 5 days from birth) during the first 8 weeks after birth, then every 4 weeks (i.e. 3 months \pm 9 days, 4 \pm 12, 5 \pm 15, 6 \pm 18, 7 \pm 21, and 8 months \pm 24 days after birth) until 8 months of postnatal age. Standardised questionnaires, used at each visit, recorded feeding practices and morbidity (available from www.intergrowth21.org.uk). Mothers were asked to recall the food

Table 1 Evidence-based recommendations used in Preterm Postnatal Follow-up Study of the INTERGROWTH-21st Project

The overall goal of this guideline is to promote exclusive breastfeeding of the preterm infant by the time of hospital discharge.	
What to feed, in order of preference	1. Mother's own milk from the breast. 2. Mother's expressed breast milk. 3. Donor human milk, if available. 4. Preterm formula.
How to feed	Orogastric feeding is preferred over a nasogastric tube, especially if the infant has increased work of breathing. Continuous, over-bolus feeds not recommended, no strong evidence for this. Infants should be encouraged to suck at the breast once sucking behavior is observed.
Feed volume	Start with approximately 80 ml/kg per day. Increase by 10–20 ml/kg per day to a maximum of approximately 160–180 ml/kg per day by the end of the first week of life.
Feed progression	Most infants >32 weeks' gestation will tolerate maintenance enteral feeds from the first day of life. Infants <32 weeks' gestation should be introduced to small amounts of trophic feeds (10–24 ml/kg per day) on first day of life. Infants >32 weeks' gestation are likely to tolerate faster increases in volume.
Human milk supplementation	Vitamin D: 400 IU per day. Phosphorus & calcium: some evidence for reducing metabolic bone disease in infants weighing <1,500 g. Iron: 2 mg/kg per day, start by 8 weeks of age. Multi-component fortifiers: Associated with short-term increases in weight gain, linear growth and head growth. No evidence for long-term benefits or adverse effects.
Duration of exclusive breastfeeding	6 months in low birth weight infants accompanied by iron supplementation.

types consumed, methods of feeding, use of vitamin and mineral supplements, and dietary intake of their infant in the 24-h period preceding the visit, using an Infant Food Recall (IFR) questionnaire. If their diet on that day was atypical (e.g. due to illness or travelling), mothers were asked to recall the last typical day. Anthropometric measurements (weight, length and head circumference) were taken as in WHO MGRS [16].

Variable definitions and classifications

Feeding practices were defined according to WHO indicators [17]. *Exclusive breastfeeding* refers to exclusive human breast milk with no other foods or liquids (including water), except oral rehydration solution and drops/syrups of vitamins, minerals or medicines. *Predominantly breastfed* refers to breast milk as the main source of nourishment but additional water or water-based drinks, such as teas or infusions, fruit juice or ritual fluids, were offered. *Partial breastfeeding* refers to some breast milk as well as other foods or food-based fluids, such as formula milk or weaning foods. *Formula*

and other liquids refer to predominantly received standard-, preterm-, high-energy-, soy-based-, hydrolysed-, or other special- formulas for preterm and low-birth-weight infants, plus water, fruit or vegetable juice, tea or sweetened drinks.

Complementary foods included all semi-solid or solid foods besides milk or formula, except water, fruit or vegetable juice, tea and sweetened drinks and were categorised into seven groups: *grains, roots and tubers; legumes and nuts; dairy products; flesh foods; eggs; vitamin A-rich fruits and vegetables; and other fruits and vegetables.*

Data analysis

The mean and standard deviation (SD), or median and interquartile range (IQR), were used to describe continuous variables, and percentages for categorical variables. Where appropriate, the infants were categorised according to gestational age into early (<34⁺⁰ weeks' gestation) and late (≥34⁺⁰ to <37⁺⁰ weeks' gestation) preterms.

Ethical approval and consent

The INTERGROWTH-21st Project was approved by the Oxfordshire Research Ethics Committee "C" (reference 08/H0606/139), the research ethics committees of the individual participating institutions, and the corresponding regional or national health authorities where the project was carried out. We obtained institutional consent to use routinely collected data and women gave oral consent.

Results

In total, 224 preterms were born in FGLS. Of these, 201 (99 boys and 102 girls) were alive, free of congenital malformations and enrolled in PPFS. The distribution of the 201 preterm newborns across sites was: Brazil = 18 %; China = 9 %; India = 15 %; Italy = 12 %; Kenya = 15 %; Oman = 15 %; UK = 11 %, and USA = 5 %. We documented feeding practices of these infants during their first 8 months after birth.

Most mothers (45.3 %) were aged 25–30 years and 72.6 % were nulliparous; 30.4 % had pregnancy-related and 19.9 % non-pregnancy-related complications (Table 2). Of those with pregnancy-related complications, the most common were pregnancy-induced hypertension (8.5 %), vaginal bleeding >27 weeks' gestation (5.5 %), gestational diabetes (5.0 %), and pre-eclampsia (3.0 %) (data not shown). At birth, the mean (SD) birthweight was 2,452 (519) g, length 45.6 (2.7) cm, and head circumference 31.7 (1.8) cm (Table 2). The population was mostly composed of late preterm infants, as the median gestational age (GA) was 36 weeks (IQR 35.0 - 36.6).

Forty-seven percent of newborns were admitted to an intensive or special care unit after birth for respiratory support (10.1 %), surfactant treatment (2.4 %) or tube

Table 2 Neonatal and maternal characteristics

Variables	N (N = 201)	Value
Maternal		
Mother's age at delivery (%)		
19–24	38	18.9
25–30	91	45.3
31–36	72	35.8
Parity (%)		
0	146	72.6
1	41	20.4
2 or more	14	7.0
Pregnancy-related complications (%)	61	30.4
Non-pregnancy-related complications (%)	40	19.9
Neonatal		
Girls (%)	102	50.7
Gestational age at birth (weeks) (median, IQR)	201	36.0 (35.0 – 36.6)
Early preterm, <34 weeks (%)	28	13.9
Late preterm, ≥34 weeks and <37 weeks (%)	173	86.1
Birthweight (g) ^a (mean ± SD) ^a	200	2452 (±519)
Head circumference (cm) ^a (mean ± SD) ^a	193	31.7 (±1.8)
Length (cm) ^a (mean ± SD) ^a	191	45.6 (±2.7)
Apgar at 5 min (mean ± SD) ^a	200	9.2 (±0.9)
Days until hospital discharge (median, IQR)	201	4.0 (2.0 – 8.0)
Intensive/special care unit admission > 1 day (%)	82	40.7
Tube feeding or parenteral nutrition (%)	44	21.9
Hyperbilirubinemia (%)	46	22.9
Respiratory distress syndrome (%)	21	10.4
No oral feeds for >24 h but <7 days (%)	24	11.9
Transient tachypnea of the newborn (%)	30	14.9
Hypoglycemia (%)	16	8.0
Apnea of prematurity (%)	14	7.0
Anaemia requiring transfusion (%)	2	1.0
Patent ductus arteriosus requiring pharmacological treatment (%)	4	2.0
Hypotension requiring inotropic treatment or steroids (%)	3	1.5
Bronchopulmonary dysplasia (%) ^b	1	0.5
Other infection (%)	2	1.0
Meconium aspiration with respiratory distress (%)	1	0.5
Intraventricular hemorrhage grade I-II (%)	2	1.0
Retinopathy of prematurity (%)	1	0.5
Pneumonia/Bronchiolitis (%)	5	2.5
Stoppage of enteral feeding for >3 consecutive days (%)	2	1.0

^a Missing data^b With normal growth and development

feeding/parenteral nutrition (34.3 %). The most common neonatal problems were hyperbilirubinemia (22.9 %), respiratory distress (10.4 %), lack of oral feeding for >24 h (11.9 %), and transient tachypnea (14.9 %). The median

(IQR) length of stay at special care units was 4.0 (2–8) days; three (1.5 %) preterms stayed in hospital for ≥60 days (data not shown). As expected, most of the postnatal morbidities known to be related to severe

prematurity (e.g. bronchopulmonary dysplasia, apnea of prematurity, retinopathy of prematurity) were observed in the very preterm infants (GA <32 weeks)

Within the first 72 h after birth, oral feeding was initiated in 94 % of the infants. The percentage of infants who received any breastfeeding was 81.8 % within 72 h of birth, 96.4 % at 2 weeks of age, 93.5 % at 8 weeks and 82 % at 4 months (Fig. 1). Exclusive breastfeeding increased from 51.1 % at 72 h after birth (Fig. 1) to 72.1 % by hospital discharge, (late preterms = 75.7 % and early preterms = 50.0 %, data not shown), with a further 16.9 % partially breastfed at hospital discharge (late preterms = 15.0 % and early preterms = 28.6 %, data not shown) (Fig. 2). The rate of exclusive breastfeeding continued to increase to 64.1 % at 2 weeks, and was sustained until 3 months of postnatal age in 55.5 % of the cohort (57.6 and 44.0 % of late and early preterms, respectively; data not shown). At 4 weeks, 31.1 % of infants were fed with breast milk and other milk/formula only, decreasing to 26.0 % at 8 weeks, 31.7 % at 3 months, 26.7 % at 4 months and 10.3 % at 6 months (Fig. 1). Exclusive breastfeeding gradually diminished between 5 and 8 months from 36.8 to 0.8 % and 41.7 to 4.6 %, in late and early preterms, respectively (data not shown), while the consumption of semi-solid and solid foods increased from 32.3 % at 5 months to 96.5 % at 8 months (37.2 to 97.5 %, and 4.17 to 90.9 %, in late and early preterms, respectively) (Fig. 2). High rates of any breastfeeding continued with 73.7 % still being breastfed at 6 months, and 70.4 % (early preterms = 70.8 % and late preterms = 68.2 %, data not shown) still receiving breast milk at 8 months of age (Fig. 2).

Grains, roots and tubers were consumed by 19.3 % of preterms at 5 months, 51.1 % at 6 months and 90.1 % at

8 months of age (Fig. 3). By 5 months, *vitamin A-rich fruits and vegetables* and *other fruits and vegetables* were being consumed by 12.4 and 16.8 %, respectively. These two food groups were not offered as frequently as *grains, roots and tubers*, but were given to 61.3 and 72.5 % of infants, respectively, by 8 months. *Flesh foods, eggs*, and *legumes and nuts* were offered to 36.8, 7.9, and 13.2 % of infants at 7 months of age, respectively. By 8 months, flesh foods were given to 51.4 % of preterms, while the consumption of *eggs*, and *legumes and nuts* remained low (14.1 and 19.7 %, respectively).

Iron supplements were routinely given to preterm infants at most sites in hospital and after discharge, except Oxford where, typically, only infants <35 weeks' gestation received supplements. Most sites provided Vitamin D supplements for infants after discharge but in the participating Nairobi hospitals, vitamin D was only given to selected preterms, and the practice was not standard in Oman. Vitamin K was given at birth to preterm babies at all sites, and most gave multivitamins during and after the hospital stay. Participating hospitals in Brazil gave multivitamins to selected preterms only; standard practice in China was Vitamin A supplementation in hospital and after discharge.

The patterns of longitudinal growth in this cohort for length were very similar to those of the WHO Child Growth Standards for term neonates [2] during the first months of life, but weight and head circumference differed from the WHO standards until 64 weeks' post-menstrual age [18].

Discussion

One of the aims of the INTERGROWTH-21st Project was to produce, for the first time, international standards for

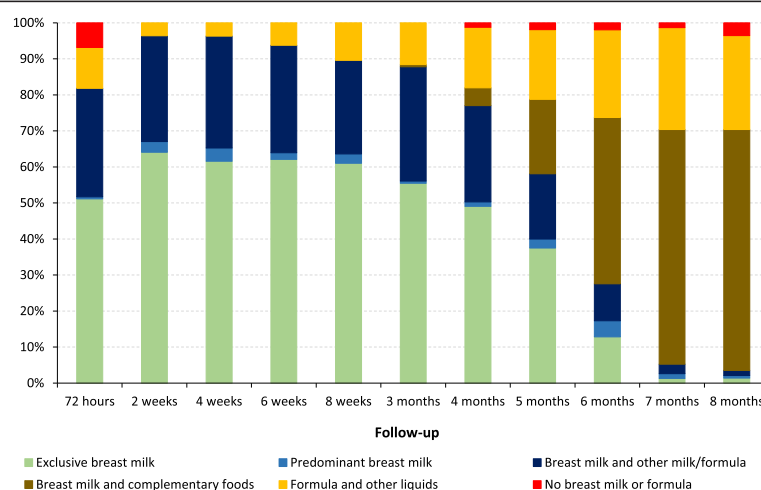
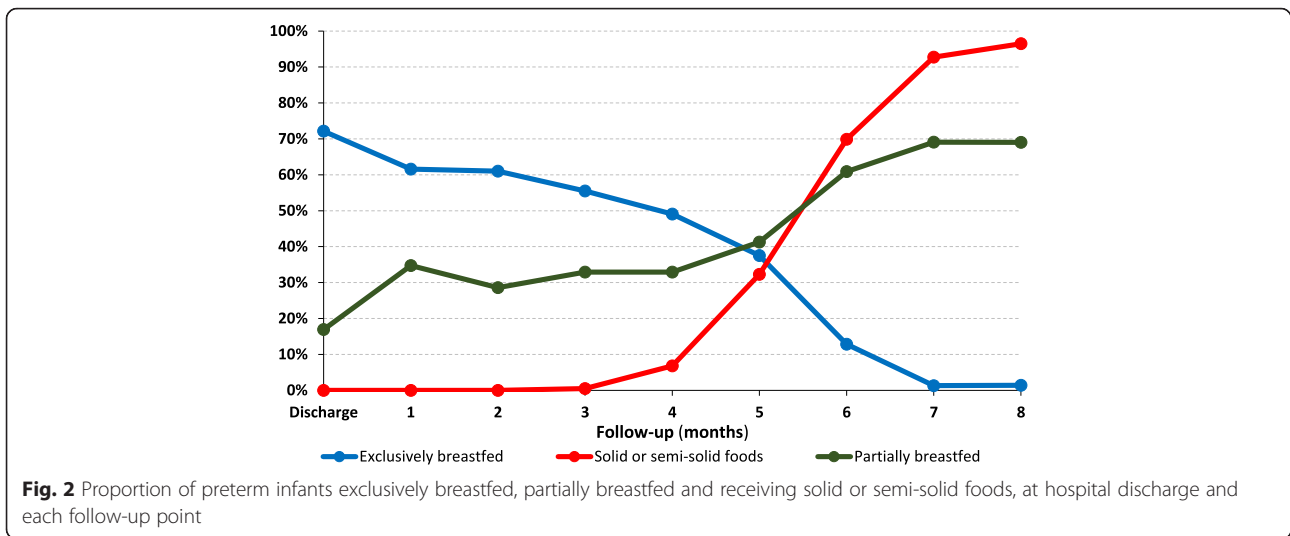


Fig. 1 Feeding practices of the preterm infants at each follow-up point. *Parenteral nutrition or complementary foods* refers to preterm infants receiving parenteral nutrition support during their first 72 h, and infants receiving complementary foods only thereafter. *Formula and other liquids* refers to exclusive formula feeding during their first 72 h and formula with other liquids thereafter

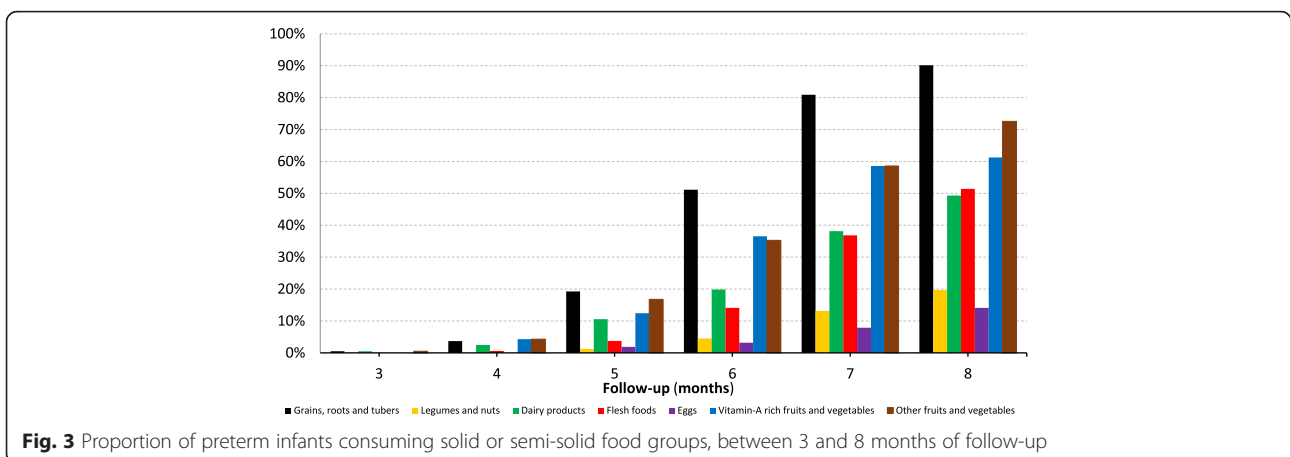


postnatal growth of preterm infants by gestational age, conforming to the prescriptive approach used in WHO MGRS. Healthy, well-nourished women with minimal constraints on fetal growth were studied prospectively, resulting in a relatively homogenous and ‘healthy’ population (according to gestational age) of preterm infants. To support the development of the standards, descriptive data were collected to document the degree to which feeding guidelines for adequate postnatal growth were followed.

The participating neonatal teams agreed to follow a set of recommended feeding practices based on the increasing evidence of the short- and long-term benefits of breastfeeding for preterm infants. This included guidelines on supplementation and the introduction of complementary foods.

In this cohort, nearly half the preterm infants were exclusively or predominantly breastfed until 4 months of age, and over two-thirds were still being breastfed at

8 months of age. The rates of exclusive or predominant breastfeeding were lower in this study than in WHO MGRS (MGRS – approximately 80 and 63 %; PPFS – 65.3 and 56.5 % at 4 weeks and 3 months, respectively) [19]. These results are not unexpected as breastfeeding rates are generally lower in preterm compared to term infants [9, 20–22], and establishing and maintaining breastfeeding in preterms requires considerable support. Factors that may impact upon the ability of preterms to breastfeed are clinical conditions related to prematurity, extended hospitalization, increased sleepiness and maternal illness. Other obstacles may include reduced muscular strength affecting latching, suckling and swallowing. The infant may also be discharged before lactation is fully established, so breastfeeding difficulties cannot be addressed by healthcare professionals. We emphasised these issues across the study sites, suggesting strategies to help mothers overcome these barriers.



However, moving from the context of a research project to general practice will, realistically, be far more challenging.

It has been suggested that, wherever possible, preterm infants should be introduced to solid foods between 5 and 8 months of age to ensure that the appropriate transition period is not missed, and to encourage the development of feeding skills [23]. Healthy, late preterms, born ≥ 34 weeks' gestation, may be introduced to solid foods using the same guidelines as term infants. The mean age at which complementary foods were introduced in PPFS was 6 months; not much later than reported for term infants (5.4 months) enrolled in a similar context, who achieved the recommended feeding criteria in WHO MGRS [24]. Of the complementary food groups, the *grains, roots and tubers* group was the most consistently offered, also similar to WHO MGRS.

Both the American Academy of Pediatrics and European Society of Paediatric Gastroenterology, Hepatology and Nutrition recommend preterm infants receive an iron supplement after hospital discharge [25, 26]. Unlike exclusively breastfed term infants, who can usually maintain their iron levels until approximately 6 months of age, breastfed preterm infants should receive regular iron supplementation, 2–4 mg/kg/day, from hospital discharge until approximately 6 to 12 months of age [25–27]. Such recommendations were fully implemented at all INTERGROWTH-21st sites. There is some evidence to suggest that low birth weight infants and preterms <32 weeks' gestation may benefit from multivitamins and vitamin D supplementation [14]; nearly all our sites provided these supplements after hospital discharge, and vitamin K was given as standard at birth.

PPFS was designed to construct prescriptive standards from a population of preterm infants with the best potential for healthy growth and development, if supported by adequate nutrition and clinical care. Exclusive breastfeeding was established in most PPFS infants by hospital discharge and breastfeeding remained an important source of nutrition for these infants throughout the study. This was consistent with the main goal of the INTERGROWTH-21st Neonatal Group feeding guidelines [12], which were based on the most current evidence to promote optimal growth at the population level for uncomplicated preterm infants [14].

By 64 weeks' postmenstrual age, the 50th centiles of our cohort's weights, lengths and head circumferences merged with those of the WHO Child Growth Standards [2], which indicates that preterm infants without severe postnatal complications, who are predominantly breastfed and receiving adequate postnatal care, progressively recuperate in early postnatal life [18].

Conclusions

There is little high-quality information available regarding the most appropriate patterns of postnatal growth for the optimal development and long-term health of preterm infants. Current evidence advocates breastfeeding with appropriate supplementation as the best way to support the growth and development of healthy preterm infants. When conducting postnatal growth research, it is essential to document feeding practices and the extent to which they adhered to the best available evidence.

Uncomplicated, preterm infants can follow evidence-based feeding recommendations centered on breastfeeding. When assessed against the WHO Child Growth Standards for 6 month old infants, adequate growth is achievable for babies born preterm with appropriate nutrition and clinical care.

Appendix

Members of the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) and its Committees

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors read and approved the final manuscript.

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