Original Article

Intrauterine growth retardation (IUGR) as determinant and environment as modulator of infant mortality and morbidity: the Tanjungsari Cohort Study in Indonesia

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Background and Objectives: Intrauterine growth retardation (IUGR) is related to mortality and morbidity. However, defining IUGR by suitable field methods remains a challenge. A maternal-child Risk-Approach-Strategy (during 1988-1989) and follow-on Tanjungsari Cohort Study (TCS) (1989-1990), aimed to generate a practical classification of IUGR and explore its usage in predicting growth, mortality and morbidity of infants in the cohort. **Study Design:** Some 3892 singleton live-birth infants were followed. IUGR was defined by birth weight (BW) and length (BL) classified as: acute, chronic, non-IUGR or 'probably preterm'. Growth, mortality, and survival curve were calculated to prove that the classification identified the most vulnerable infants. Fever >3 days and diarrhoea were assessed based on IUGR classification, sex, exclusive breastfeeding, and environmental factors. **Results:** IUGR infant weight and length did not catch-up with the non-IUGR in the first year. Infant mortality rate was 44.7 per 1000 where some 61% died within 90 days. Using age specific mortality by BW, 23.6% of all deaths occurred when it was <2500 g compared to 66.2% from IUGR and preterm groups. Fever and diarrhoea rates increased over 12 months. Diarrhoea was associated with poor source-of-drinking-water and latrine. **Conclusion:** The IUGR classification predicted one-year growth curves and survival, besides age and sex. IUGR based on BW and BL identified a larger group of at-risk infants than did low BW. High morbidity rates were partly explained by poor environmental conditions. IUGR inclusive of BL has value in optimizing nutritional status in the first 1000 days of life.

Key Words: birth weight, birth length, water supply, latrines, fever, diarrhoea, first-1000-days-of -life

INTRODUCTION

Approximately 3 million children under the age of five die each year with the highest rate in the first year of life.[1] Preterm birth complications include Intrauterine Growth Retardation (IUGR), which is reflected in low birth weight (LBW) is the most crucial factor affecting neonatal mortality and a significant determinant of post-neonatal mortality.[2–11] IUGR and LBW are healthcare problems, numerous in developing countries,[12] hampering healthy growth and development during the first 1,000 days of a child's life and increasing morbidity.[5,8,11,13] In addition LBW and IUGR may affect child development and intellectual potential.[14]

In developing countries, the overall prevalence of LBW is 16% (range: 9-35%).[15] Globally, the number of babies born with LBW is almost 22 million, with the highest incidence in Asia.[16] While birth weight is known to be a critical determinant of infant survival,[3,4,6-10] birth-weight-specific infant mortality rate (IMR) is scarce, and, when available, usually from hospitals or national demographic and health surveys. This is particularly true for developing countries,[9,11,17] such as Indonesia[18-23] LBW is a concept traditionally used by epidemiologists for public health purposes, is defined as a birth weight <2500 g, but weight ≥2500 g did not exclude intrauterine growth

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retardation (IUGR) and preterm newborn who did not have LBW.[24] In spite of its limitations, LBW is more often used than an IUGR classification, because IUGR determination is not easy.

Standardized clinical methods (using the Ballard score or ultrasonographic examination) for identifying IUGR newborns are recognised,[25,26] but cannot be employed in many rural areas with limited resources.

IUGR has become an important indicator so far as its relation with child growth and development, and its consequences in later life. IUGR contributes significantly to the development of non-communicable disorders such as obesity, type 2 diabetes, hypertension and heart disease in adult life.[27] In line with this in utero programming of disease, Chatrath et al,[28] among others,[29,30] demonstrated that IUGR led to the development of less potent cellular immunity, posing children a greater risk of severe infectious disease. Thus far, research in this topic has demonstrated that IUGR contributes to decreased growth in infancy and childhood;[31] distorted lipid metabolism;[32] the development of type 2 diabetes mellitus,[33] cardiovascular diseases,[34] microalbuminuria;[35] delayed menarche;[36] and an intergenerational cycle of LBW.[37,38]

Besides IUGR, many external factors contribute to the morbidity and mortality of infants. Amongst others are unhygienic and unsafe environments like low access to sanitation and shortage of water availability; diarrheal disease caused by contaminated water and food.[13,20,39] Unsafe water sources, low access to sanitation and shortage of water availability contribute to around 1.5 million child deaths each year, with 88% of these deaths specifically due to diarrhoea caused by contaminated water and food.[40,41] During the 1990s, acute respiratory tract infections, mostly pneumonia, and diarrhoea were the leading causes of deaths of infant in the developing world, accounting for 25% and 20%–25% of total deaths, respectively.[42,43] But besides these deleterious exposures, breastfeeding is a factor that helps prevent morbidity in early life. Breast milk is a complete and ideal food for the first 4–6 months of life.[44-50] Exclusive breastfeeding promotes development of the infant's immunity and protects the infant from gastrointestinal and respiratory tract infections, probably atopic/allergic diseases and diarrhoea.[45,51–62]

To understand the complex interplay between IUGR and LBW, and their potential health outcomes in both early and later life, was one objective for the Tanjungsari Cohort Study. The Tanjungsari birth cohort is unique in several aspects. It covered population-based registration of all births and deaths over a period of more than 2 years, and infants were followed longitudinally for a year and more. The collected data allowed us to define IUGR using anthropometric indicators, and explore to what extent IUGR and LBW, including exclusivity breastfeeding, predict morbidity and mortality of infants. These favourable conditions allowed for the identification of peak mortality by age. Our data on IUGR in a cohort of children living in a rural area were also collected within limited means. In limited resource settings, it becomes necessary to identify children with retarded growth solely from anthropometric indicators.

Against this background, we set out to establish the prevalence of LBW and IUGR classified by birth weight and length and assess the effect of LBW and IUGR on infant morbidity and mortality in an infant cohort born in the Tanjungsari Subdistrict. Additionally, we have explored what postnatal factors might affect the growth and health trajectories in the first year of life. The follow-on studies are reported elsewhere.[39,63-68]

The 1988 Tanjung Sari perinatal health initiative

Perinatal and maternal mortalities in West Java became of concern in the late 1970s to Dr Anna Alisjahbana and colleagues in public health and health services, and were confirmed by their systematic provincial and national documentation.[63] Since some 90% of births took place at home, the Tanjungsari district of West Java was identified as a locality where a community-based risk management strategy might reduce the maternal-child health burden (Figure 1). In 1987, traditional birth attendants (TBA) were trained with a view to their ability and effectiveness to identify risk factors for unfavourable birth outcomes in community setting. From January 1st, 1988 to December 31st, 1989, some 4694 pregnant women in Tanjungsari were followed and assigned either a trained or untrained TBA. In the first year, early neonatal and maternal mortality rates (32.9 per 1000 and 170 per 100,000 deliveries respectively). Although possible to improve health worker performance, and community engagement, the ultimate benefit of this approach has probably been less in evidence and limited through remoteness and both the people and material resource restraints 'downstream' of the TBA services. Three decades later, Indonesian neonatal and maternal mortality rates are 14 per 1000 and 126 per 100,000 live births in 2015 (globally 16.2 in 2009 and 216 in 2015), respectively. They still demand improvement, despite more births being hospital-based and many in birthing homes known as 'polindes' or at the 'puskesmas' (community health centre).

The original 1988 cohort of women, their children and grandchildren are now providing opportunities to examine the medium to long term outcomes of risk factors for health, including those which are nutritional, such as birth weight and growth.[63] These studies are increasingly available from this cohort study as health and nutrition intermediates rather than simply as endpoints.[39,63-68]

MATERIALS AND METHODS

Tanjungsari Cohort Study (TCS) 1988–89

In 1987, Alisjahbana et al began a population-based cohort study in Tanjungsari, a rural subdistrict of West Java, Indonesia (Figure 1).[44,71] Its policy focus was a maternal-child Risk Approach Strategy (RAS). Pregnant women who agreed to join were enrolled in the study. Infants born in the period from 1 January 1988 through 31 March 1990 were followed up. Infants were excluded when infants were aborted, still-birth, or twin. Trained research interviewers visited the respondents at 7, 28, and 42 days and at 3, 6, 9, and 12 months. Thereafter, as reported elsewhere, a visit was made every 6 months until age 3 years and annually until age 5 years or until they died or were lost to follow-up (out-migration).[64-68] The National Research and Development Board of the Ministry of

Health of Indonesia approved this study and gave ethical clearance.

Anthropometric measurements

The data of birth weight (BW), birth length (BL), and head circumference were collected within 48 hours of birth (except for stillbirths) according to standardised procedures and with the use of local-made spring scales, length boards, and flexible measuring tape.[69,70] LBW is defined as birth weight <2500 g while normal birth weight (NBW) is categorized for birth weight ≥2500 g.[71] Length, weight, and head circumference were also measured in every follow-up until age 12 months. Length and head circumference were recorded to the nearest 0.1 cm. Babies were weighed without clothes, and the recorded weight was rounded to the nearest 100 g.

Interview

Information on the socioeconomic and demographic condition of families was collected during the first visit at pregnancy, including parental age, education, and occupation; and presence of siblings. Environmental data collected were source of drinking and type of latrines. The interview was conducted in the local language (Sundanese). Data on sex and gestational age were collected after delivery.

Each mother was asked whether her baby had suffered any of the following: fever lasting more than 3 days (by mother's evaluation of infant's body temperature above normal); and diarrhoea (abnormal frequency and consistency of stools) since the time of previous interviews. Morbidity questions focused on symptoms in the period between the previous and present visit. Thus, the time intervals for disease recall were different (unequal) between home visits. Shorter intervals at the 7th, 28th, 42nd days and 3 months of interviews and equally 3 months intervals at 6, 9 and 12th months visits. The mother was also asked whether their infant was still breastfeeding and if the infant received other liquid or solid foods.

Population size and number of respondents in study area

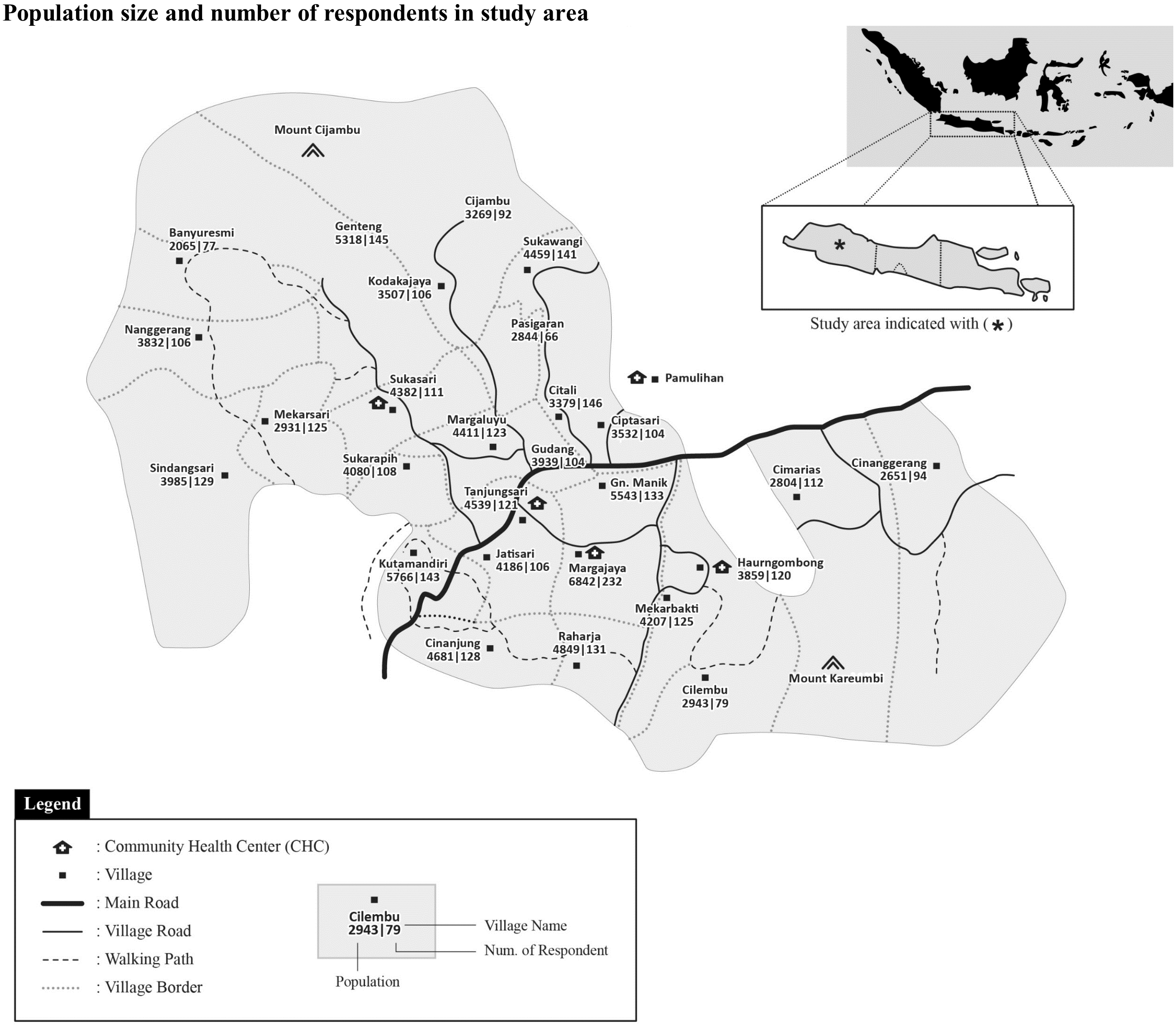

Figure 1. Map of Tanjungsari subdistrict, Community Health Centers and population size and the child cohort in year 2002.

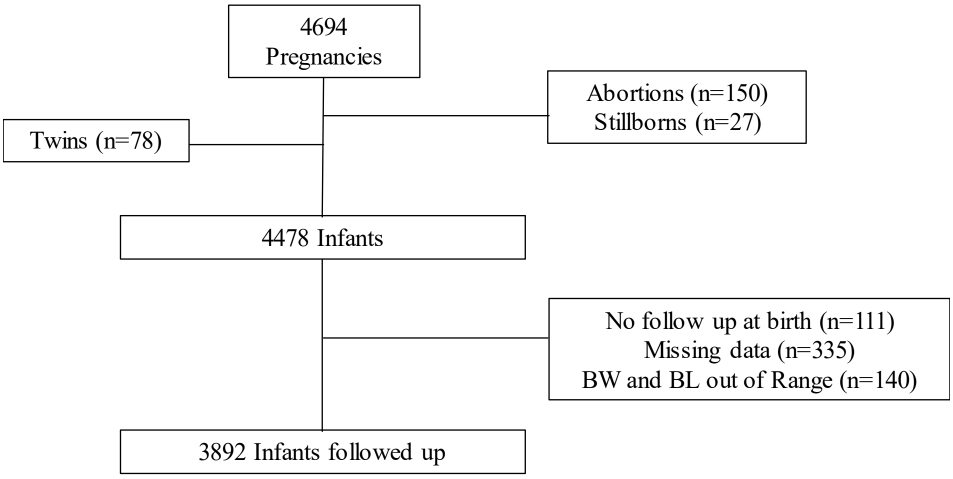

Figure 2. Inclusion and exclusion of infant in the cohort.

Table 1. Classification of children for intrauterine growth in Tanjungsari cohort study

Birth weight (g)	Birth length (cm), N				
	> 50	48 – 50	45–47	<45	Total (N)
≥3000	Non-IUGR 445	Non-IUGR 656	Gestational diabetes 417	Rare† 60	1578
2700–2999	Non-IUGR 69	Non-IUGR 407	IUGR Chronic 619	Rare 68	1163
2500–2699	IUGR Late, acute 17	IUGR Late, acute 119	IUGR Chronic 436	Pre-term 137	709
<2500	Rare 1	IUGR Late, acute 27	IUGR Chronic 229	Pre-term 185	442
Total	532	1209	1701	450	3892

†Infant born with birth weight ≥3000 grams very seldom have birth length of <45 cm.

Participants

To define acceptable ranges, we based categorisation on the distributions of BL and BW in a reference population described as essentially Gaussian but slightly peaked.[72] The distribution of weight and length in the Tanjungsari growth cohort was also Gaussian (data not shown) but with additional births in the two tails. We therefore selected wide ranges of mean ±3 standard deviations (SD) for weight and for length. This resulted in ranges of 2000–3800 g for BW and 40–54 cm for BL. Infants with measurements outside these ranges were excluded (BW <2000 g; BW >3800 g; BL <40 cm; BL >54 cm (overall total n=140).[63]

Classification for IUGR

Infants were considered as non-IUGR, IUGR, or 'probably preterm'. In the literature, preterm is defined as birth occurring earlier than 37 weeks gestational age. The classic definition of IUGR is birth weight below the 10th percentile of sex-specific birth weight in the gestational age reference curve.[73] According to this definition, gestational age and BW are required to define infants as IUGR. We assessed the validity of using gestational age in our cohort in two ways: by the range, which should be narrow, and by comparing mean BW and BL at different gestational ages with the intrauterine growth curves of Tanner.[74]

In our cohort, the range of gestational ages was excessively wide. We expected the infants of our cohort to be mainly full term, indicated by a range of gestational ages for 95% of the infants of 37–42 weeks; however, the actual range was 29–49 weeks. In addition, the infants did not exhibit the expected growth spurts at typical gestational ages as described by Tanner. The variation in weight and length at particular gestational ages was unacceptably large.

We therefore developed another means of classifying infants as non-IUGR or IUGR using only BW and BL and without employing gestational age (Table 1). Newborns were considered to have an acceptable fetal growth rate (non-IUGR) if their BW and BL were not less than the local mean minus one SD (i.e. non-IUGR = BW ≥2700 g and BL ≥48 cm). Newborns were considered to have impaired fetal growth (IUGR) in two circumstances. A combination of BW <2700 g with a normal BL of ≥48 cm was considered to imply acute IUGR; this form of IUGR commonly consists of growth retardation in the latter weeks of gestation, with impaired fat deposition, but does not affect birth length, which is already almost at its maximum at the end of the second trimester. A combination of BW <3000 g and BL <48 cm implies chronic IUGR, which results in slow linear growth in the first half of pregnancy and/or cessation of linear growth in the final weeks of pregnancy. The deficit in weight is proportional to that in length, because the fetus has not yet acquired body fat before 32–35 weeks of gestation and thus cannot lose this contributor to weight. Although the concept of acute and chronic IUGR may affect the consequences of IUGR in childhood and adulthood, we do not distinguish between these two types in this report and consider them both as IUGR. Newborns with BW ≤2500 g and BL <45 cm were most likely to have been born premature. The classification of non-IUGR, IUGR, and preterm infants is shown in Table 1. The numbers of infants classified as non-IUGR, IUGR, or preterm were 1577, 1447, and 322, respectively.

Assessing the validity of IUGR classification by infant growth

To validate that the classification identified the most vulnerable infants, we examined growth in the first year of life. Growth was chosen because it reflects the total well-being of the child, the growth of a child is expected to continue in the growth channel determined at birth. Implicitly, a child with IUGR may never reach the weight and length of normal peers, but remain smaller and lighter. To detect growth retardation, weight and length were expressed as z-scores, calculated using 'WHO AnthroPlus 3.2.2'[75] as the distributions for the reference population. We calculated weight-for-age z-score (WAZ) and height-for-age z-score (HAZ).

Survival curves and mortality

Within the first week of death, a physician visited the home to perform a verbal autopsy using a checklist of causes of death. The verbal autopsy did not differentiate between direct and indirect causes. All infants were followed from birth to 12 months or until they died or were lost to follow-up. Incomplete follow-ups (moved or not retraceable) were coded as censored in the life table analysis. The lost to follow-up infants were still included in the analysis and coded as having censored follow-up times. The subjects that neither died nor were lost to follow-up were considered as censored after 365 days. Survival times were analysed using the life table approach[76] and survival curves were developed using the Kaplan–Meier method. The differences between curves were estimated by hazard ratios (HRs).[77]

Age-specific infant mortality by birth weight and IUGR categories

Age-specific (age at scheduled home visits) infant mortality was calculated as the number deceased by age as a percentage of all deaths in specified birth weight and IUGR categories. Mortality probabilities were determined for: (1) non-IUGR; (2) late, acute IUGR; (3) chronic IUGR, and (4) preterm. Sample size constraints applied where number of deaths were only 5 of the 71 infant deaths which occurred in the late-acute IUGR group, for instance. The three most contrasting categories were retained: IUGR, non-IUGR, and preterm.

Morbidity

Morbidity at age 0, 7, 28, 42 days and 3–12 months was described as the proportion of infants having at least one event of fever of more than 3 days or diarrhoea. The proportion of infants so affected was expressed were per time between interviews. The total occurrence of fever of more than 3 days or diarrhoea over the first year were cumulated. Categorisation was ≤1 or >1 fever of more than 3 days in one year. Diarrhoea was categorized as ≤2 diarrhoea or >2 events in one year.

Determinants of mortality and morbidity

Determinants considered for mortality and morbidity included IUGR; sex; maternal age (21-35 years regarded as 'normal', ≤20 as 'high risk young', and >35 regard as 'high risk old'), pregnancy (primipara or multipara); maternal education (≥6 years and <6 years) and whether breast feeding was exclusive, or with any liquid or solid by infant age or interview.[78] Exclusivity breastfeeding at 3 months was considered as a determinant for mortality. Environmental determinants assessed were the type of drinking water source (categorized as 'improved' if tap water, closed well, or electric pump from a closed well), and family latrine usage (categorized as 'improved' if water sealed latrine, or closed pit latrine).

Statistical analysis

For infant mortality, censoring for still births, Cox proportional hazards regression was used to estimate the HRs and their associated 95% confidence intervals by birthweight or IUGR. Models quantified differences in survival rates with and without adjustments for relevant covariates. The proportional hazards assumption for the birthweight groups was tested in each model by the addition of an appropriate time-dependent covariates age at death) - a product of the system time variable T (SPSS notation) and the variable age. All covariates were categorical to permit possible non-linearity.

The associations of morbidity (diarrhoea and fever more than 3 days) against all of the determinants for each time of interview as well to the total event in one year were assessed using descriptive statistics (frequency distribution and chi square). Determinants that were identified as statistically significant were analyzed using stratification method. The data set was analysed using SPSS (Statistical Package for the Social Science) version 22.

RESULTS

A total of 4694 pregnant women enrolled in the study giving live birth to 4478 singleton infants due to abortion (n=150), stillbirth (n=27) and 78 twins. From this group, we excluded those with no follow up visit at birth (n=111), and incomplete information on BW and BL (n=335). We also excluded outlying measurements to obtain a dataset of infant without pathological growth patterns (n=140) (Figure 2). Finally, 3892 singleton live-born infants (85.2%) were eligible for analysis. Descriptive values of the cohort and anthropometrical parameters at birth are summarised in Table 2.

Birthweight and IUGR classification

The mean BW and BL of the non-IUGR infant were less than the reference means at 3116 g and 49.1 cm, respectively; the WAZ was −0.40 compared with an HAZ of −0.22, indicating that foetal weight deviated to a greater

Table 2. Infant characteristics, their mother and environmental factors

	Total cohort n=3892	Non-IUGR n=1577	IUGR n=1447
Infant characteristics			
Gender (Freq (%))*			
Girls	1910 (49.1)	691 (43.8)	754 (52.1)
Birth weight (mean (SD)) (g)*	2825.1 (416.5)	3115.9 (263.8)	2614.7 (197.3)
Girls	2785.6 (418.1)	3087 (254.6)	2614.7 (201.4)
Boys	2902.5 (363.8)	3137.8 (268.8)	2620.1 (192.9)
WAZ at birth (mean (SD))*	-0.97 (0.83)	-0.40 (0.57)	-1.53 (0.50)
Girls	-0.95 (0.67)	-0.33 (0.57)	-1.45 (0.51)
Boys	-0.98 (0.82)	-0.45 (0.57)	-1.62 (0.47)
Birth length (mean (SD)) (cm]*	47.1 (2.2)	49.1 (1.2)	46.4 (1.1)
Girls	46.9 (2.2)	49.0 (1.2)	46.4 (1.1)
Boys	47.4 (2.2)	49.3 (1.3)	46.4 (1.1)
HAZ at birth (mean (SD))*	-1.28 (1.19)	-0.22 (0.67)	-1.67 (0.62)
Girls	-1.22 (1.19)	-0.08 (0.63)	-1.50 (0.59)
Boys	-1.34 (1.18)	-0.34 (0.67)	-1.86 (0.60)
Ponderal index at birth (g/cm^3)**	27.5 (3.6)	26.3 (2.4)	26.4 (2.7)
Head circumference at birth (cm]	33.5 (1.3)	34.1 (1.2)	32.9 (1.1)
Mother's factors			
Mother's education (freq (%))**			
Not elementary school	1141 (29.3)	461 (29.2)	429 (29.7)
Elementary school	2300 (59.1)	886 (56.2)	871 (60.2)
Secondary school and above	448 (11.5)	229 (14.5)	146 (10.1)
Mother age group (freq (%))			
Normal (21-35)	2565 (65.9)	1039 (65.9)	951 (65.7)
High risk young (≤20 yrs)	1120 (28.8)	442 (28.0)	419 (29.0)
High risk old (>35)	206 (6.1)	96 (6.1)	76 (5.3)
First pregnancy (freq (%))			
First	3815 (98.0)	1546 (98.0)	1415 (97.8)
Second or more	77 (2.0)	31 (2.0)	32 (2.2)
Exclusive breast feeding (freq (%))			
Up to 3 months	228 (5.9)	83 (5.3)	93 (6.4)
Up to 6 months	22 (0.6)	8 (0.5)	9 (0.6)
Environmental factors (Freq (%))			
Improved source of drinking water* (tap water, closed well)	1752 (45.0)	796 (50.5)	593 (41.0)
Use of improved latrine in the house* (water sealed, closed pit)	1871 (48.1)	833 (52.8)	655 (45.3)

WAZ: weight-for-age z-score; HAZ: height-for-age z-score; PI: ponderal index; HC: head circumference.
Data are mean (SD) or number (%).
*p<0.01, ** p< 0.05.

degree than foetal length. The WAZ of the IUGR infant was −1.53 and HAZ was −1.67. The ponderal index was comparable to that of the non-IUGR infant, but the mean head circumference of the IUGR infant was 1.2 cm smaller, indicating that brain growth was affected during the gestational period.

In the non-IUGR and IUGR groups, the HAZ was different between genders. The mean BL of the girls was closer to the reference mean than that of the boys, the difference being larger in the non-IUGR group. Growth in infancy (0–12 months) was assessed for the non-IUGR and IUGR groups separately by gender by plotting the mean WAZ and HAZ (Figures 3a & b).

The Tanjungsari cohort infants were lighter and smaller than the reference population, as demonstrated by the negative Z-scores. In the first 3 months, the cohort grew faster and gained more weight compared with the reference population, as illustrated by the upward trend in WAZ and HAZ in Figure 3 as well as in Table 3. After 3 months, however, growth began to falter, as shown by the deviation from the reference mean (i.e. away from Z-score=0) for both groups. This growth faltering was progressive until the age of 12 months.

We compared the growth of IUGR with that non-IUGR infants (Table 3). Throughout the entire year, the mean HAZ deviated from the reference by a larger extent than did the WAZ. 0.47. The growth curves for the IUGR infants were consistently below those of the non-IUGR infants.

Mortality in infancy by age, sex, and cause of death

Among the 3892 singleton live births, 174 infant deaths were recorded, resulting in an IMR of 44.7 per 1000 live births. Almost twice as many boys as girls died (110 vs 64). However, the pattern of mortality was comparable for both sexes (Table 4a). The first week after birth appeared to be the most critical period (accounting for approximately 15% of deaths, compared with some 7% at 8–28 days). Relatively few infants died between 29–42 days (12.6%), but there was another peak at 43–90 days (25.3%). Of all infant deaths, 61% occurred at age 0–90 days. The proportion dying fell to approximately 5% per month at age 91–270 days, and few died in late infancy

Table 3. Mean WAZ and HAZ in the first year, difference between non-IUGR and IUGR

	Non-IUGR n=1577	IUGR n=1447	Difference Non-IUGR / IUGR
WAZ (age in months)			
0	-0.40 (0.57)	-1.51 (0.50)	1.11
3	-0.28 (0.95)	-1.04 (1.01)	0.76
6	-0.21 (1.00)	-0.85 (1.05)	0.64
9	-0.38 (0.95)	-0.93 (1.01)	0.55
12	-0.52 (0.94)	-1.04 (0.99)	0.52
Difference 0- 12 months	-0.12 (1.09)	0.47 (1.02)	-0.59
HAZ (age in months)			
0	-0.22 (0.66)	-1.67 (0.61)	1.45
3	-0.58 (1.29)	-1.54 (1.20)	0.96
6	-1.14 (1.34)	-1.93 (1.41)	0.79
9	-1.46 (1.24)	-2.14 (1.21)	0.68
12	-1.68 (1.27)	-2.28 (1.22)	0.60
Difference 0-12 months	-1.46 (1.28)	- 0.62 (1.30)	0.84

WAZ: weight-for-age z-score; HAZ: height-for-age z-score.
Data are mean (SD).

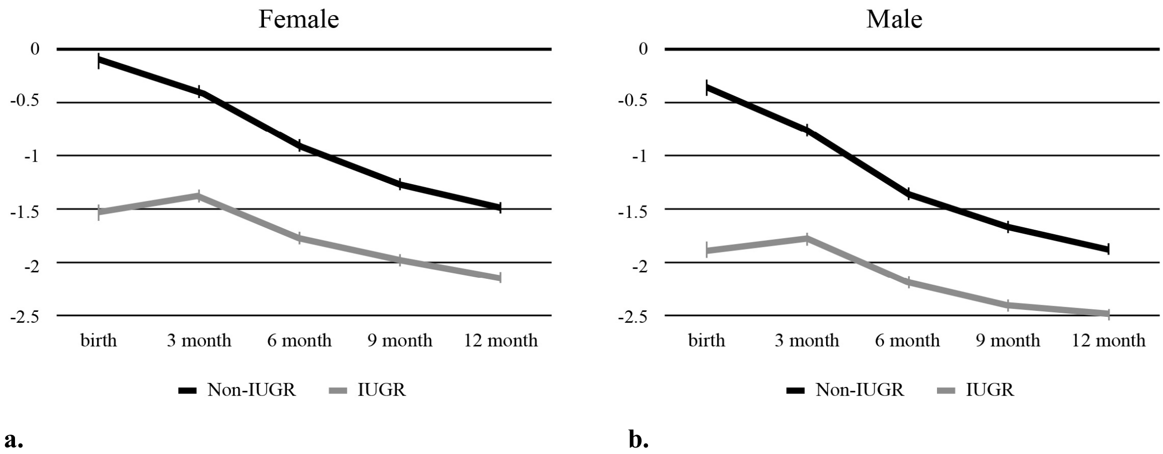

Figure 3. HAZ in infancy for girls (a) and boys (b) in the non-IUGR (n=691; 886) and IUGR (n=754; 693) groups.

(Table 4). Pneumonia and bronchopneumonia were the most common causes of death (51%) followed by non-infectious causes (26%), which included asphyxia in association with congenital malformation along with undernutrition (data not shown).

Mortality in infancy by birth weight& IUGR category

In the neonatal period, the proportion of deaths in LBW infants and in the next birth weight class (2500–2699 g) was comparable, namely approximately 30% (Table 4a). The percentage was much lower in the birth weight classes 2700–2999 g and ≥3000 g (17% and 13%, respectively). At ages 29–42 days ad 43–90 days, the expected gradient in mortality by birth weight was observed. Over-all, babies tended to die in the first 90 days: 73% of the LBW babies and 51% of those with a birth weight of ≥3000 g. However, due to the distribution of birth weight, the deaths in each birth weight class as a percentage of the total infant deaths were almost equally distributed among the birth weight classes. Contrary to expectation, 24% of all deaths occurred among LBW infants and 30% in birth weight class ≥3000 g.

Infant mortality by age in the selected intrauterine growth categories did trend in the expected direction (Table 4b). First-week deaths were particularly confined to preterm babies (26% vs. 14% in the other two categories, not shown in Table 4b), and there was a downward gradient across preterm, IUGR, and non-IUGR categories in first-42-days deaths (More than 45% in preterm and IUGR babies vs 22% in non-IUGR babies). After 3 months of age, the mortality pattern was comparable across the three IUGR categories. With respect to the category of IUGR, the proportion that died was 1.5 to 2 times higher among the preterm babies (9%) than among the term babies (IUGR 4% and non-IUGR 4%). However, albeit uncertainty with a small sample of preterm babies, 48% of all infant deaths occurred among IUGR babies and 35% among non-IUGR babies.

Survival curves and risk ratios

The cumulative survival at 1 year was approximately 95%, and the probability of dying was highest in the first 3 months (Figure 4a). Disaggregated by birth weight, a distinct difference was found between the LBW and birth weight ≥3000 g groups (p<0.0001), but the difference between the intermediate birth weight and largest birth weight groups was nonsignificant (Figure 4b). As previously mentioned, birth weight is a crude indicator of

Table 4a. Age specific mortality by sex

Age at death	Male (n=1982)		Female (n=1910)		Total	
	n	%	n	%	n	%
0-28	25	22.7	39	22.4	14	21.9
29-42	14	12.7	22	12.6	8	12.5
43-90	25	22.7	44	25.3	19	29.7
91-180	19	17.3	32	18.4	13	20.3
181-270	20	18.2	27	15.5	7	10.9
271-365	7	6.4	10	5.7	3	4.7
Total	110		174		64	
% died per class	5.5		4.5		3.3	
% of all death	63.2		100		36.8	

Table 4b. Age specific mortality by birth weight group, sexes combined

Age at death, days	<2500 (N=442)		2500-2699 (N=709)		2700-2999 (N=1163)		≥3000 (N=1578)		Total	
	n	%	n	%	n	%	n	%	n	%
0-28	14	34.1	9	32.1	9	17.3	7	13.2	39	22.4
29-42	8	19.5	3	10.7	8	15.4	3	5.7	22	12.6
43-90	8	19.5	6	21.4	14	26.9	16	30.2	44	25.3
91-180	5	12.2	2	7.1	8	15.4	17	32.1	32	18.4
181-270	4	9.8	6	21.4	10	19.2	7	13.2	27	15.5
271-365	2	4.9	2	7.1	3	5.8	3	5.7	10	5.7
Total	41	100	28	100	52	100	53	100	174	
% died per class	9.3		6.3		11.8		12		4.5	
% of all deaths	23.6		16.1		29.9		30.5		100	

Table 4c. Age specific mortality by intrauterine growth categories, sexes combined

Age at death, days	Probably preterm (N=322)		IUGR (N=1447)		Non IUGR (N=1577)		Total	
	n	%	n	%	n	%	n	%
8-28	9	18	19	26.8	9	33.3	37	25.0
29-42	4	4	14	19.7	2	14.8	20	13.5
43-90	5	38	15	21.1	19	18.5	39	26.4
91-180	3	20	9	12.7	10	11.1	22	14.9
181-270	5	16	9	12.7	8	18.5	22	14.0
271-365	1	4	5	7	2	3.7	8	5.4
Total	27	100	71	100	52	100	148	
% died per class	15.5		4.9		1.7		4.4	
% of all deaths	18.2		48.0		35.1		100	

IUGR; likewise, the date of last menstruation of the mother does not usually lead to accurate measures of gestational age,[64] as in the Tanjungsari population. The combination of weight and length at birth is likely the next-best indicator of IUGR in field conditions. Throughout infancy, the survival curve of non-IUGR infants was better than that of IUGR infants, whereas the preterm infants (which can also include infants with birth weights of 2500–2700 g) had the highest probability of death. Within the IUGR and preterm categories, significant differences in the survival curve were identified (p<0.001, Figure 4c).

At 3 months of age, the risk of death for the LBW babies was 3.1 times higher than that for the normal birth weight (≥2500 g) babies and was comparable to that of the preterm versus non-IUGR babies (2.9 times higher in preterm). The risk for IUGR babies was 1.7 times higher than that for non-IUGR babies. The same gradient was observed at 12 months (data not shown). The relative risk of dying was, however, only significant in the age period 0–90 days, for LBW versus normal birth weight infants (risk ratio [RR] 3.1; 95% CI 2.04–4.64), for IUGR versus non-IUGR infants (RR 1.7; 95% CI 1.1–2.73), and for pre-term versus non-IUGR infants (RR 2.9; 95% CI 1.66–5.20). However, the risk was not significantly different between the preterm and IUGR infants (RR 1.7; 95% CI 0.99–2.85).

The risk of IUGR and other determinants to infant mortality were calculated using hazard ratio and adjusted hazard ratio (aHR) for all of the factors in Table 5. Besides IUGR, which had aHR 1.6 (95% CI; 1.14-2.36) we found that sex was significantly affecting mortality with aHR 2.1 (95% CI: 1.44-3.11). Maternal education of less than 6 years and latrine usage type were significantly associated with mortality in the crude HRs, but not when adjusted for sex and IUGR. Other determinants like maternal age, number of pregnancies, source of water and improved latrine did not correlate with mortality (Table 5).

Infant feeding

Infant feeding practices are described in Figure 5. This graph shows that exclusive breastfeeding in the first sev-

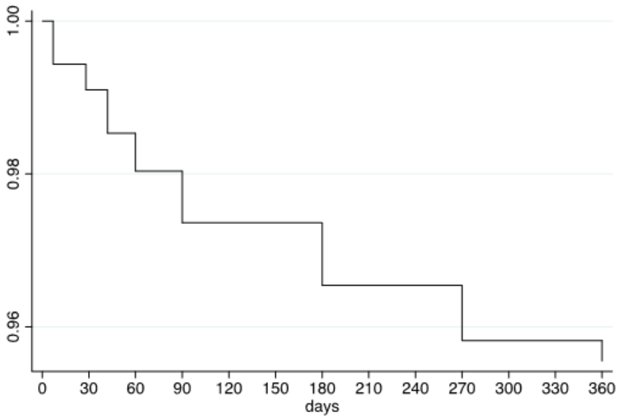

Figure 4a. Kaplan–Meier survival curve of all infants in the first year of life.

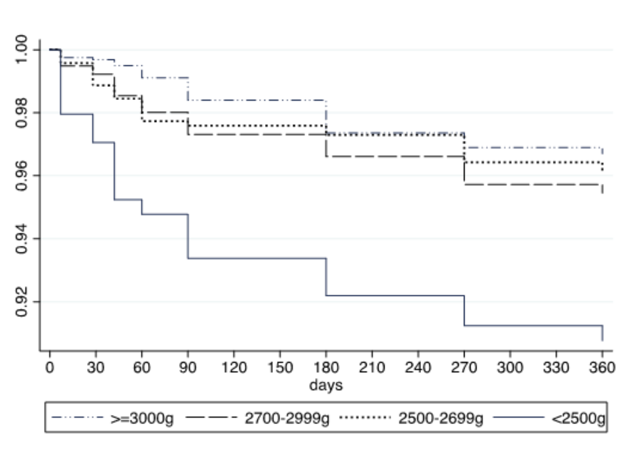

Figure 4b. Kaplan–Meier survival curve of infants in the first year of life by birth weight category.

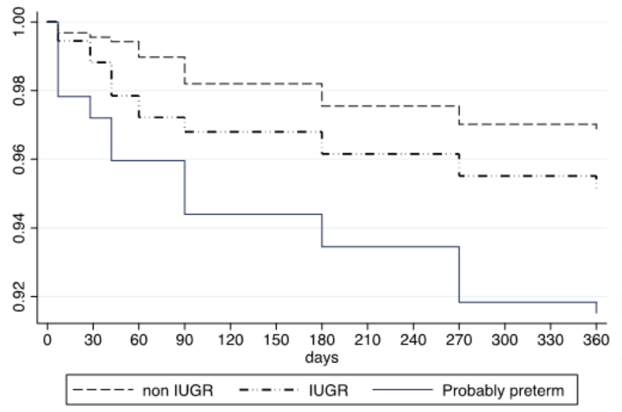

Figure 4c. Kaplan–Meier survival curve of infants in the first year of life by IUGR category.

en days of life was practiced by 24.5% mothers during the first week after delivery, decreased to 6.2% in the third month, and 0.6% at 6 months of infant's age. This graph shows that 61.4% of infants received some form of liquid other than breast feeding and 7.8% solid food right after birth. Nonexclusive breast feeding was practiced by most of the mothers, starting at 80.9% right after birth, and continued high, above 95%, of mother until the 12th month (Figure 5).

Morbidity pattern

Figure 6 depicts the proportion of infants with fever more than 3 days or diarrhoea in the period since the previous visit at ages 7 days–12 months. In general, older infant (3-12 months) had higher morbidity proportion than infant at age 0-3 months.

Determinants of morbidity

The proportion of infants with morbidity symptoms in the BW and IUGR classification at any given time of interview were similar, except for the proportion with diarrhoea which was higher in the IUGR group compared with the non-IUGR group. 36.8% vs 33.5% (p<0.05) at the 3 month of age.

Proportion of infant having fever of more than 3 days was not associated with any of the determinant tested. However diarrhoea was strongly associated with the use of unimproved water source at 7 days, 42 days, 3, 6, 9

Table 5. Hazard ratio of risk factors for infant mortality

Risk factor	Crude HR (CI 95%)	Adjusted HR (CI 95%)
IUGR		
Non IUGR	1.00	1.00
IUGR	1.6 (1.1–2.2)*	1.6 (1.14–2.36)**
Sex		
Girl	1.00	1.00
Boy	1.7 (1.2–2.3)**	2.1 (1.44–3.11)**
Age of mother		
21–35	1.00	1.00
≤20	1.2 (0.84–1.59)	1.3 (0.85–1.85)
>35	0.7 (0.36–1.67)	1.1 (0.5–2.36)
Number of pregnancies		
2 or more		
First	0.68 (0.28–1.66)	0.5 (0.20–1.21)
Education		
≥6 year	1.00	1.00
<6 year	1.51 (1.1–2.04)**	1.4 (0.97–2.05)
Exclusive breast feeding 3 month		
Exclusive	1.00	1.00
Not exclusive	1.1 (0.58–2.25)	1.4 (0.58–3.45)
Source of water		
Improved	1.00	1.00
Unimproved	1.3 (0.98–1.81)	1.1 (0.75–1.66)
Latrine		
Improved	1.00	1.00
Unimproved	1.44 (1.1–1.96)*	1.1 (0.76–1.68)

*Significant $p<0.05$; **$p<0.01$.

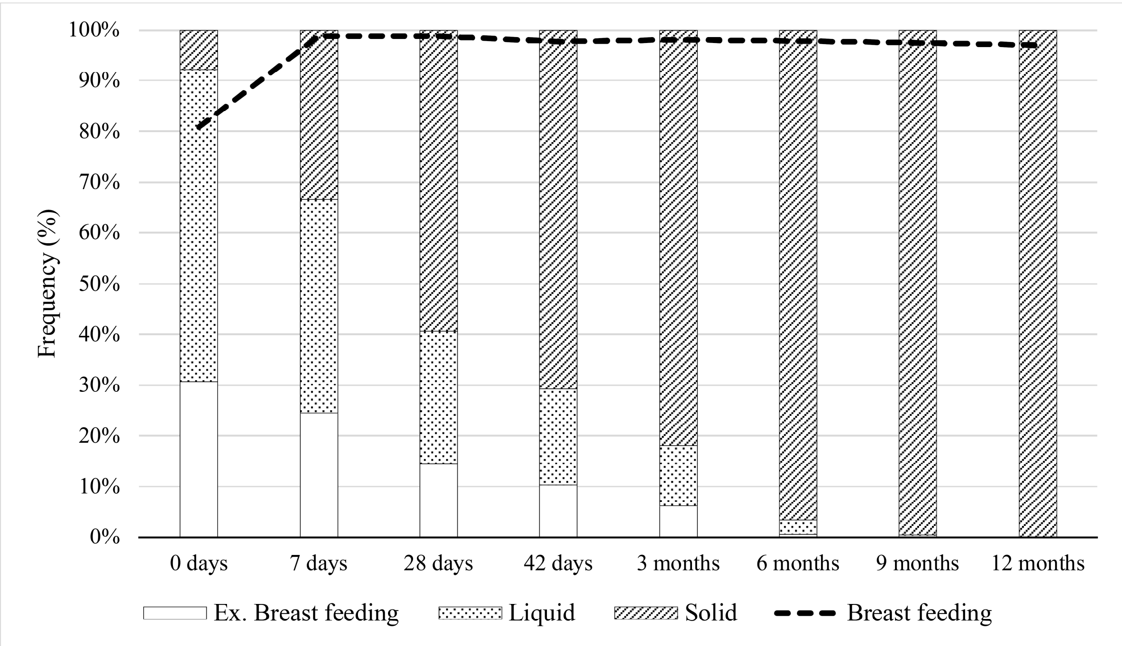

Figure 5. Breast feeding and weaning practice during 0-12 months of age.

and 12 months ($p<0.01$). Cumulative frequencies for diarrhoea more than two times in the year, were significantly higher among infants living with an unimproved versus improved water source (45.2 vs 39.8% respectively; $p<0.01$). Diarrhoea was also more common in infants whose family used unimproved latrine (open pit, river, gully, anywhere) at the age of 9 and 12 months. Cumulatively, infants with diarrhoea more than two times in a year was more common in the group with unimproved versus improved latrine (44.5 vs 40.9%), $p<0.05$. Stratification of these findings by IUGR classification, sex, or other determinants did not show any effect.

DISCUSSION

A novel classification for IUGR without reference to gestational age was assessed using growth in infancy and proved to be valid. A combination of weight and length at birth for classifying IUGR refined the identification of babies at risk of death in infancy compared with LBW as the sole indicator.

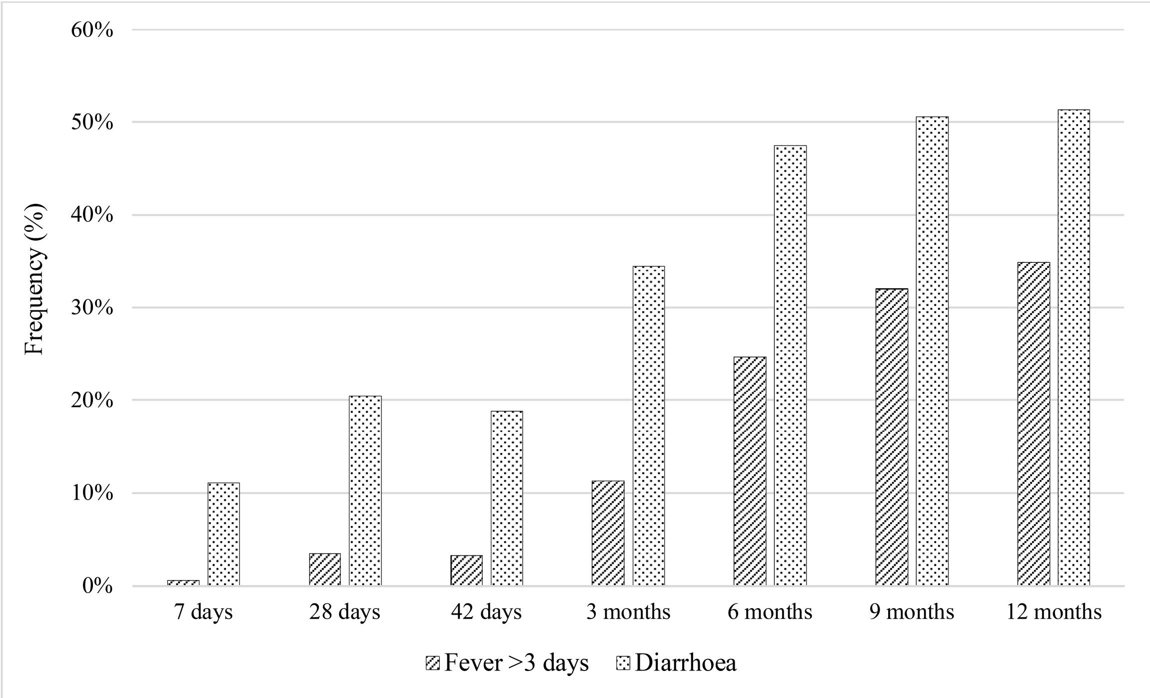

Figure 6. Proportion of infants having fever of more than 3 days and diarrhoea since the previous interview.

IUGR classification and child growth

In the non-IUGR infant, head circumference was close to the reference mean, although weight and length were inadequate. This indicates that the fetus adjusted to the available energy and nutrients to develop an adequate weight-for-length ratio and to preserve the supply of energy to the brain.[79] In the IUGR infant, this brain-sparing effect was insufficient, as demonstrated by their head circumference being 1 cm lower compared with the non-IUGR infant. At the first 3 months, the infants showed catch-up growth as a reaction to malnutrition during gestation. Subsequently, however, their growth faltered,[80] probably due to the synergism of infectious morbidity and malnutrition.[81]

We compared growth in the first 12 months of non-IUGR and IUGR infant to assess the validity of our IUGR classification. During infancy, the gap between the non-IUGR and IUGR infant persisted. Growth-retarded infant never reach their growth potential and remain smaller and lighter than their peers.[59,82,83] This finding in our study was consistent with general observations and even the clinical assessment of IUGR by Shrimpton et al.[80] Our study, in agreement with others,[25,84] determined that use of the last menstrual period as an indicator of gestational age was unreliable. Incorrect recording of gestational age could have been caused by recollection bias, misinterpretation of the interview questions by the mother, undetected miscarriages, or inappropriate contraceptive use. We concluded that gestational age could not be used in the classification of IUGR in this study.

Infant mortality

The first week, first month and first 90 days after birth (in this sequence) were the most vulnerable age periods regarding infant mortality. The IMR of the Tanjungsari study population of 1988–89 was 44.7 per 1000 live births, much lower than the contemporaneous IMR of 122 per 1000 live births in the East Java Pregnancy Study in Madura and the national average IMR of 77 per 1000 live births in the 1980s reported by the Indonesian Central Bureau of Statistics and UNICEF.[85] The difference between the two Indonesian study populations can likely be attributed to postnatal environmental factors and the availability and quality of health services, because the average birth weight and length in the Tanjungsari and Madura studies were comparable. In both studies, and in another study conducted in other developing countries,[11] the first 3 months after birth were the most critical to infant survival.

Although growth monitoring of young infants is common practice in almost all developing countries, little effort is put into identifying infants at risk at birth from the actual death. From all indicators, LBW (<2500 g) is commonly used as the cut-off for identifying risk of infant mortality.[30-32] However, if health programmes concentrate on the LBW infants, only 23.6% of all infant deaths may be avoided (Table 4a) while targeting interventions to preterm and IUGR newborns could potentially prevent more than 60.2% of infant death (Table 4b)

Morbidity and prenatal factors (BW and IUGR)

The proportion of infants reported as having fever of more than three days and diarrhoea was lowest in the first 42 days of life and increased as the infant grew. Analysis of morbidity by BW classification and IUGR was not instructive. There were slight differences among the BW and IUGR groups but not of statistical significance. A study by Black, Chen, and Kalanda showed that at age less than 6 months, LBW infants had a higher prevalence of diarrhoea (adjusted by socioeconomic differences), but no difference was found in the prevalence of fever or cough.[20,39,40]

Morbidity and its determinants

Although it is a universally accepted notion that exclusively breastfed infants receive more antibodies and other essential nutrients,[46,86] our study did not find lower risk of morbidity in exclusively breast fed infants. Despite the known function of breast milk, Raisler, Alexander, and O'Campo claimed that minimal breastfeeding does not give significant protective effect against common infant illnesses as exclusive and regular breastfeeding.[87] However, in the present study, information on how frequent and how much breast milk or food was given in the partially breastfed group was unavailable; therefore, we could not relate the amount of feeding and type of nourishment to any protective effect against morbidity.

In addition, other factors, such us unhygienic and unsafe environments like limited access to sanitation, shortage of water, and diarrhoeal disease caused by contaminated water and food[5,82,88] have been well documented as major contributors to infant morbidity. Unsafe water sources, low access to sanitation and shortage of water availability contribute to around 1.5 million child deaths each year, while 88% of these deaths are specifically due to diarrhoea caused by contaminated water and food.[40,41] In this study, we also discovered that diarrhoea was related to unimproved drinking water sources and the use of unimproved latrines. This finding shows the effect of environmental exposures on infant morbidity, more than other early life situations, including exclusive breastfeeding practice. The importance of distinguishing infants by LBW or IUGR was not evident in the morbidity analysis.

Strengths and limitations

Different recall periods make difficulty for comparison between the present observations and other studies. Most morbidity studies use a constant and short 1-2-week recall period to minimize recall bias and to avoid misinterpretation of the reference period of morbidity. One study even recommended inquiry about diarrhoea and fever event only in the previous one or two days to prevent underreporting.[89] The present report employed secondary data from the RAS Tanjungsari study conducted in 1988–1990, the objectives of which were related to safe motherhood and the role of traditional birth attendants in maternal–child healthcare.[63] The information collected was not specifically designed for the investigation of morbidity and breastfeeding in the birth cohort. The interview data reflected the mother's own perceptions of morbidity and their infant's health between home visits rather than the number of sickness episodes recorded as recommended in the WHO guidelines.[49] Similarly, feeding habits and practices were inquired in general terms rather than according to WHO/UNICEF definitions of exclusive or partial breastfeeding and complementary foods.[44] However, the use of health interviews or self-perceived morbidity interviews in developing countries has been supported by a study by Rousham et al who discovered strong associations between maternal reports of their infant's illness and the biochemical profiles of the infant, even when the mothers were illiterate.[90]

The strengths of this study were the longitudinal nature of data collection, and the use of the same, well-trained village health workers throughout the entire study period. The Tanjungsari cohort is one of the few cohorts, particularly in developing countries, for which a large amount of anthropometric data has been collected. Birth weight and length were measured under standardised conditions. It is a unique dataset for answering questions that require longitudinal data—in our case, data on IUGR and its effect on child growth and health. The data collected can thus be reasonably expected to reflect the morbidity picture and general child feeding habits among the study population. These favourable conditions allowed for the identification of peak mortality by age.

Our classification of IUGR resulted in a clear difference between the growth curves of non-IUGR and IUGR infant. Our data on IUGR in a cohort of infants living in a rural area were also collected within limited means. It sets an example that collecting high quality data within limited means is possible. In limited resource settings, it becomes necessary to identify infants with retarded growth solely from anthropometric indicators, but it can only be done when data are reliable and accurate. The combination of weight and length at birth is likely the next-best indicator of IUGR in field conditions. IUGR classification based on a combination of BW and BL identified a larger group of infants at health risk compared with LBW. The developed IUGR classifications, therefore, are recommended for application in health policy development to optimize nutritional status in the first 1000 days of life.

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AUTHOR DISCLOSURES

The authors declare that they have no competing interests. The 1988 Tanjung Sari perinatal health initiative was funded by the Ford Foundation Project no. 840 417 and the Sophia Stichting, Rotterdam, the Netherlands. Additional and intensive data analysis efforts were supported by NMCP project Nr.25112MIA, Japan International Cooperation Agency, and the Neys van Hoogstraten Foundation, the Netherlands.

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