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Brief report

Earlier appearance of the ossification center of the femoral head in breast-fed versus formula-fed infants

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ABSTRACT

Objective: The aim of this study was to evaluate possible differences in the rate of appearance of the femoral head ossification center (FHOC) in infants according to the type of feeding (exclusive breast-feeding, formula, mixed feeding).
Methods: A retrospective study was conducted in a population of 285 healthy infants who consecutively underwent echographic evaluation of the hip as a screening for hip dysplasia from April 1 through October 31, 2008. For each infant, type of feeding, sex, gestational age, weight at birth, and age at the time of echographic examination were recorded. Data analysis was performed in the entire sample population and in a subpopulation of 143 infants after exclusion of preterm or low-birth-weight infants and those who underwent echographic examination outside the scheduled age range. Data were analyzed by chi-square test, Kruskal–Wallis test, and multiple logistic regression analysis.
Results: An FHOC was present in 48.3% of breast-fed infants, 25.7% of formula-fed infants, and 28% of the mixed feeding group ($P = 0.001$). In multiple logistic regression analysis, the best regression model included the following variables: age at test ($P = 2.23 \times 10^{-7}$), gestational age ($P = 0.0017$), and exclusive breast-feeding ($P = 0.0003$). Similar results were obtained in the selected subpopulation of 143 infants (FHOC in 54.2% of breast-fed group, 28.2% of formula-fed group, and 33.3% of mixed-feeding group, $P = 0.01$).
Conclusion: Exclusive breast-feeding may be associated to an earlier appearance of FHOC in a population of normal infants compared with formula feeding.

Introduction

Breast milk is considered the gold standard in infant feeding: it is species-specific and it is believed to ensure ideal nutritional support to newborns and infants in the first months of life. Although artificial formulas have been improved to be more similar to breast milk, it is generally assumed that breast-feeding has many known and unknown advantages compared with formula-feeding [1].

Appearance of the femoral head ossification center (FHOC) is an important landmark in the development of the hip in the first months of life [2]. A delay in its appearance is an indication of congenital hip dysplasia, but it can also occur when a pathologic condition involving bone growth or mineralization, such as hypothyroidism, is present [3].

The presence of FHOC is routinely assessed in echographic screening for hip dysplasia [4]. An appropriate timing for this echographic examination can be set at about 3 mo of age according to the observation that the FHOC can be seen on x-ray starting at 3 to 4 mo of age, although it usually can be identified sooner echographically.

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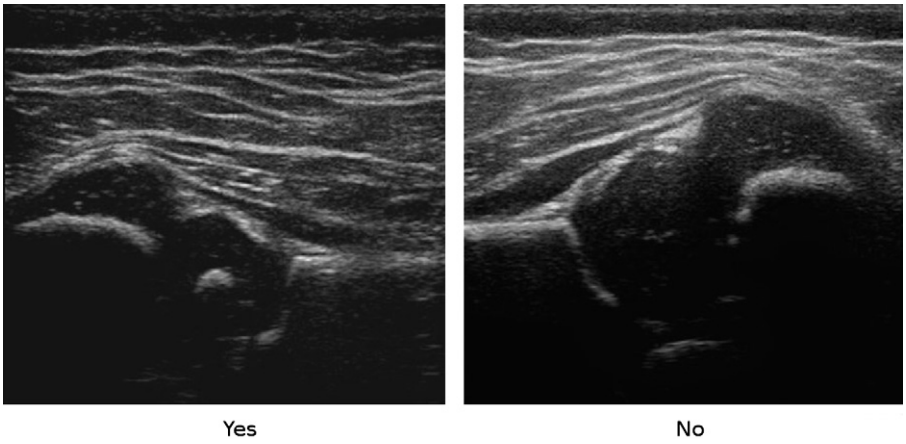

Fig. 1. Echographic evaluation of the femoral head ossification center. (Left) The femoral head ossification center was considered present if a hyperechogenic image with evidence of a posterior shadow cone in the context of the cartilaginous femoral head was detected. (Right) Absent femoral head ossification center.

The aim of this study was to evaluate if data gathered at the time of a routine echographic screening for hip dysplasia in infants show any differences in the rate of appearance of the FHOC according to the type of feeding received in the first months of life (exclusive breast-feeding versus formula or mixed feeding).

Materials and methods

This retrospective, unblinded study was conducted in a population of 285 healthy infants who consecutively underwent an echographic evaluation of the hip as a systematic screening for hip dysplasia, from April 1 through October 10, 2008, at the pediatric operative unit of the Azienda Ospedaliera S. Elia in Caltanissetta, Italy. The sample consisted of infants with no specific risk factors for hip dysplasia. The echographic examination is usually scheduled at 11 to 15 wk of age, but the actual age range was 5 to 21 wk (mean 12.39 wk, median 13 wk).

The examination was performed by a well-trained ultrasonographer and a pediatrician. For each infant, type of feeding and other variables, including type of feeding, sex, gestational age at birth in weeks (GA), weight at birth in grams (BW), and age at the time of echographic examination in weeks (AE), were recorded.

Type of feeding was categorized as exclusive breast-feeding (infants who had been receiving exclusively breast milk since birth), exclusive formula (infants who had had been receiving exclusively formula, except for possible attempts at breast-feeding during the first week of life) or mixed (all other infants).

Data analysis was performed in the entire sample population or, to avoid possible bias, in a subpopulation of 143 infants after exclusion of preterm or low-birth-weight infants and those who underwent the echographic examination outside the scheduled age range.

Statistical methods

Distributions of variables in different groups were analyzed by non-parametric methods: Kruskal–Wallis test for continuous variables and chi-square test for independence for categorical variables. To further analyze the relation between the type of feeding and FHOC, a logistic multiple regression analysis was performed. All statistical analyses were performed using the free open-source software R 2.9.0 [5].

Results

In none of the 285 screened infants was hip dysplasia or any other pathologic condition involving bone mineralization documented. The presence of FHOC was demonstrated by a hyperechogenic image with evidence of a posterior shadow cone in the context of the cartilaginous femoral head (Fig. 1) [6]. Table 1 presents the population characteristics (sex, GA, and BW) according to the type of feeding.

More than half of participating subjects were fed exclusively with formula (51.9%). The sample population showed a good homogeneity for sex distribution ($P = 0.33$). GA was slightly older in the breast-fed group ($P = 0.055$), and BW was slightly but significantly greater in the breast-fed group ($P = 0.005$). AE was not significantly different among the three groups ($P = 0.37$).

The FHOC was present in 48.3% of the breast-fed group (95% confidence interval [CI] 38.1–58.6), 25.7% of the formula-fed group (95% CI 19.3–33.3), and 28% of the mixed group (95% CI 17.5–41.7). This difference was statistically significant ($P = 0.001$, chi-square test).

Unfortunately, the three groups were not comparable for many important parameters, which can potentially affect the presence of FHOC at the time of examination, particularly BW and GA. Moreover, the time of examination, although not significantly different among the three groups, can greatly

Table 1
Population characteristics according to type of feeding

Type of feeding	*n* (%)	Sex (%)		GA (wk)			BW (g)		
		Female	Male	Range	Mean	Median	Range	Mean	Median
BF	87 (30.5)	47 (54%)	40 (46%)	35–42	39.3	40	1980–4350	3286	3300
Fa	148 (51.9)	67 (45.3%)	81 (54.7%)	29–42	38.7	39	1180–4850	3091	3050
Mx	50 (17.6)	27 (54%)	23 (46%)	35–42	38.7	39	2200–4500	3095	3000
Total	285	141 (49.5%)	144 (50.5%)	29–42	38.8	39	1180–4850	3151	3150

BF, breast-fed; BW, birth weight; Fa, formula-fed; GA, gestational age; Mx, mixed feeding Distribution of the main variables in the different feeding groups

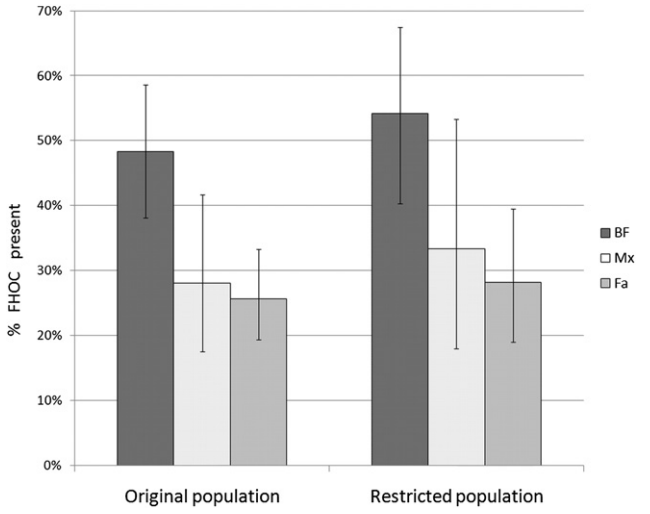

Fig. 2. Percentage of FHOC presence at the time of examination in the three feeding groups, with 95% confidence intervals. Results in the original population and the restricted subpopulation were compared. BF, breast-fed group; Fa, formula-fed group; FHOC, femoral head ossification center; Mx, mixed feeding group.

influence the results. Therefore, a multiple logistic regression analysis was performed, including sex, BW, AE, GA, and type of feeding as explanatory variables.

The best regression model in terms of goodness of fit (expressed as the lowest value of the Akaike information criterion) was obtained by including the explanatory variables AE, GA, and exclusive breast-feeding. Table 2 lists the regression coefficients for each variable (95% CI, standard error, *z* value, *P*, and estimated odds ratio with 95% CI). The category of exclusive breast-feeding in the model had a regression coefficient of 1.15529 (95% CI 0.54–1.79, $P = 0.000287$) and an estimated odds ratio (versus formula-feeding) of having FHOC present at the examination of 3.17 (95% CI 1.71–5.99).

To eliminate any other possible bias, an additional analysis was performed in a restricted subpopulation excluding from the general sample all infants who presented one of the following exclusion criteria: 1) preterm birth, 2) BW lower than 2500 g, or 3) echographic examination performed before 11 or after 15 wk of age.

The resulting restricted subpopulation of 143 infants was divided into three subgroups according to the type of feeding. There were no statistically significant differences among the subgroups for GA, BW, and AE.

The distribution of the presence of FHOC was very similar to what was observed in the original population: 54.2% in the breast-fed group (95% CI 40.3–67.4), 28.2% in the formula-fed group (95% CI 19.0–39.5), and 33.3% in the mixed feeding group (95% CI 18.0–53.3). The difference among the subgroups was statistically significant ($P = 0.01$, chi-square test).

Figure 2 presents the results, showing the percentage of the presence of FHOC in the feeding groups for the original population and for the restricted subpopulation (and corresponding 95% CIs). It can be observed that 95% CIs of the breast-fed and formula-fed groups do not overlap.

Discussion

The present results showed a significantly higher percentage of FHOC presence at the time of examination in the exclusive breast-feeding group versus the exclusive formula-feeding group, whereas the mixed feeding group is somewhere in between, although more similar to the formula-feeding than to the breast-feeding group.

However, the three groups were not completely comparable for GA and BW, which were slightly lower in the formula-fed group, with a statistically significant difference for BW. This could be explained by the observation that preterm and small-for-GA infants are more likely to be artificially fed for several reasons, including longer separation from the mother at birth. Because preterm and smaller infants may require longer times to achieve good bone growth and mineralization, the observed difference is a potential cause of bias. Moreover, the examination, usually scheduled from 11 to 15 wk of age, was actually performed in a wider age range, from 5 to 21 wk. Such a wide range, even if not significantly different among the three groups, is a reason for concern, because this variable is potentially related to the observed results.

To better eliminate any possible bias, two additional analyses were performed: 1) multiple logistic regression analysis on the entire sample population using the presence or absence of the FHOC as a binary dependent variable and 2) univariate analysis in a selected, more homogeneous subpopulation of 143 infants from the entire sample population (restricted subpopulation). The regression model and the subpopulation univariate analysis were in agreement, showing that, although AE was certainly the most significant explanatory variable, the type of feeding seemed to show a significant independent role, even more significant than GA.

The design of the study certainly has many limitations. In all studies on breast-feeding, no randomization can be performed, and therefore various forms of selection bias can be present. Moreover, this study was retrospective and unblinded. We had to rely on existing data, and unfortunately these did not include important anthropometric parameters, such as length at birth and weight and length at the time of examination, which could better explain the possible causes of the observed difference. Therefore, our results should be considered with caution.

However, the observed effect seems strong enough, and interesting enough, to warrant further investigation in view of its potential meaning for understanding how different feeding methods in the first few months of life could significantly affect the growth process.

Table 2
Logistic regression parameters

	Coefficient estimate	95% CI	SE	z	*P*	OR estimate	95% CI
AE (wk)	0.26537	0.17–0.37	0.05124	5.179	2.23×10^{-7}	1.3	1.18–1.44
GA (wk)	0.26566	0.11–0.44	0.08451	3.144	0.001668	1.3	1.11–1.55
Exclusive breast–feeding	1.15529	0.54–1.79	0.31851	3.627	0.000287	3.17	1.71–5.99

AE, age at time of examination; CI, confidence interval; GA, gestational age; OR, odds ratio

Conclusions

According to the present results, it is possible to hypothesize that exclusive breast-feeding is associated to an earlier appearance of the FHOC in a population of normal infants compared with formula-feeding. Further controlled studies are warranted to confirm this hypothesis.

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