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Effect of Early Breast Milk Nutrition on Serum Insulin-Like Growth Factor-1 in Preterm Infants

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Abstract

BACKGROUND: Insulin-like growth factor 1 (IGF-1) is one of the essential intrauterine hormonal mediators of growth, and its serum values are often low after preterm delivery.

AIM: To evaluate the influence of immediate breast milk feeding on serum IGF-1 in preterm newborns.

SUBJECTS AND METHODS: This prospective, observational cohort study included 60 premature infants born < 32 weeks of gestation, divided into group A and B regarding breastfeeding or formula feeding. Growth measurements were taken at birth. The standard deviation of each measurement was calculated. Serum IGF-I was measured one day postnatal and at a time equivalent to 40 weeks of gestation.

RESULTS: Significant higher level of mean serum IGF-1 was detected in group A than B at postnatal age equivalent to 40 weeks of gestation. In group A, the higher significant level was detected in mean serum IGF-1 at an age equivalent to 40 weeks of gestation than at birth (25.21 ± 6.69 and 20.13 ± 5.46 $p < 0.05$). Multiple linear regression analysis showed that high birth weight, increased age of gestation and breastfeeding were correlated to the elevated serum level of IGF-1 at a postnatal age corresponding to 40 weeks gestational age.

CONCLUSION: Immediate breast milk feeding was accompanied by elevated IGF-1 in the serum of preterm infants.

Introduction

IGF-1 is an anabolic hormone with mitogenic, differentiating, antiapoptotic and metabolic effects [1]. A plethora of genetic and experimental researches suggest that IGF-1 is an essential factor of intrauterine growth of the fetus and after birth [2]. The placenta secretes IGF-1 throughout gestation which encourages the transmission of important nutrients from the mother to the fetus via the placenta [3]. During gestation, fetal circulating IGF-1 increases and at term birth, levels of cord serum IGF-1are positively related to the size of fetus and fat mass [4]. Fetal serum IGF-I constantly increases during last trimester, which coincides with the interval of the most rapid increase in fetal weight [5]. Late in gestation, circulating IGF-1 is mainly derived from the liver, although all fetal tissues express IGF-1 from an early stage of development [6]. The amniotic fluid contains higher IGF-1 concentrations than cord blood during gestation and at delivery and is swallowed by the fetus, and this source is missing after premature delivery [7]. Insulin is the main determinant of fetal and neonatal hepatic IGF-1 secretion, and via insulin, IGF-1 is magnified by the direct and indirect influences of nutrients like glucose and protein. Also, insulin reciprocally regulates hepatic production of insulin-like growth factor binding protein (IGFBP-1),

which in turn inhibits IGF-1 bioactivity [8]. There is 6 binding proteins (IGFBP) control IGF-1 action. About 80% of IGF-1 is combined with IGFBP-3 which together with an acid-labile subunit maintains a reservoir of circulatory IGF-1 [9]. After fasting and during hypoxia serum levels of IGFBP-1 increase, which restrict growth through lowering the IGF-1 bioavailability [10]. Mothers' milk should be advised for preterm infants by direct breastfeeding and/or by mother's own expressed milk [11]. Some studies on Holder pasteurisation have demonstrated partial or total inhibition of bioactive components as immunological, growth and antioxidant factors. These constituents are available in huge quantities in preterm infants' mothers' milk and are significantly essential immediately after delivery [12]. In particular, the premature breast milk contains high levels of IGF-1which are lowered by approximately 40% upon Holder pasteurisation [13]. Milk-borne IGF-1 acts as a growth factor for intestinal maturation; while, some animal researches have demonstrated possible absorption into circulation with a dose-dependent elevation in orally administered IGF-1 and protective action of milk proteins on IGF-1 degradation [14].

The current study aimed to evaluate the influence of immediate breast milk feeding either expressed breast milk (EBM) or direct breastfeeding on levels of serum IGF-1in preterm newborns.

Subjects and Methods

This is a prospective, longitudinal, observational cohort study; included all preterm infants of < 32 weeks gestational age admitted into neonatal intensive care unit of Children Hospital, Faculty of Medicine, Ain Shams University between December 2016 and January 2018. The study was approved by the medical ethical committee of National Research Center, Cairo, Egypt by the code of ethics of the world medical association (Declaration of Helsinki) for experiments in humans, 1975. Approval No. (18113).

Exclusion criteria were conditions that influence IGF-1 plasma levels: intrauterine growth retardation, small for gestational age, insulin or steroid therapy; also, infants with cerebral lesions or any gestational congenital anomaly were excluded. The study design and clinical and laboratory assessments were explained, and informed consent was obtained from parents and/or legal guardians of infants before enrolment in the study.

Subjects of the study were divided into 2 groups regarding breast milk intake (direct or expressed breast milk) shortly after birth: Group A, 30 newborns fed on breast milk ≥ 50 mL/Kg/day and glucose infusion (10%), without any parenteral supplementation with fat or amino acids from the first days of life; Group B, 30 infants received glucose infusion (10%), plus milk formula without any parenteral supplementation with fat or amino acids due to insufficient mother's breast milk or the illness of the mother by any condition that prevents normal breastfeeding as infection of the mother by HIV or Hepatitis B. Parenteral feeding was started on the first day of life in all infants with a birth weight < 1250 g. Fluid intake was started with 60 mL/Kg/day to guarantee sufficient intake of calories (120-130 Kg/day) [15]. Before administration, the milk bottles were shaken to integrate any remains, and the needed amount was aseptically separated. Fresh breast milk was not given to infants of mothers with HIV, HBV, HCV, CMV, typhoid, paratyphoid, brucellosis, pertussis, active pulmonary tuberculosis, or syphilis, or under medications unsuitable for breastfeeding. Also, breastfeeding was interrupted temporarily in the case of mastitis, nipple mycosis, breast or chest herpes simplex or varicella zoster infections. To estimate feeding tolerance, the daily gastric residual volume (GRV) and episodes of daily emesis were recorded. The criteria for decreasing enteral feeding were GRV > 4 mL/Kg after one meal or > 2 mL/Kg after 3 consecutive meals, or > 3 consecutive episodes of vomiting. For a total withdrawal of enteral feeding were GRV > 5 mL/Kg after one meal, abdominal distension with an increase in abdominal circumference > 2 cm in 24 hours, metabolic acidosis with pH < 7.20 for > 2 hours, hypoxia with paO2 < 50 mm/Hg for > 2 hours, or hypotension. Full enteral feeding was defined by an intake of 150 mL/kg/day. Total parenteral and enteral caloric and protein intakes were calculated. Despite the diversity of macronutrients, with breast milk given over the first two weeks of life, it was assumed that the raw milk energy and protein contents were 78 kcal/100 mL and 2.2 g/100 mL, respectively [16].

IGF-I in serum was measured by chemiluminescence immunoassay (Liaison, DiaSorin, Saluggia, Italy) at 1-2 days postnatal and 40 weeks gestational age. The intra-assay coefficient of variation is 8% at both 10.3 nmol/l and 17.5 nmol/l and 9% at 23.8 nmol/l. Inter-assay coefficient of variation is 10% at 6.9 nmol/l, 7.4% at 30.8 nmol/l and 16% at 59.4 nmol/l.

Standardised measurements of weight, length, and head circumference (HC) were recorded within the first 24 h after birth and then weekly on the same weekday as blood sampling for IGF-I and continued until discharge. Most of the growth measurements were performed by one examiner. Weight was measured on a digital scale (Tanita TL-150MA, Tanita Corporation, Tokyo, Japan). Crown to heel length was measured using a portable length scale instrument with increments in millimetres developed at the NICU enabling measurements within the incubator as on the nursing table. HC was measured in the maximum front-occipital plane using

an individual non-extensible plastic-coated tape with increments in millimetres. Z-score (Standard deviation score, SDS) was calculated for all measurements of each respective growth parameter. SDS signifies how many SD is > or < the mean of a reference population. SDS length and SDS HC were computed from a gender-specific growth reference in the Egyptian population, whereas SDS weight was calculated from an intrauterine growth curve based on ultrasonically estimated fetal weights in Egypt (17).

It was done by statistical package for social sciences (SPSS) version 21 for Windows (IBM Corp., Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation and were compared by using student's t-test and paired t-test. Categorical data were expressed as numbers and analysed with the two-tailed chi-square test. Multiple linear regression analysis was done to find predictors of serum IGF-1 at birth and at age correspond to 40 weeks gestational age. P < 0.05 was accepted as statistically significant.

Results

A group of 70 preterm newborns were included in the study. We excluded 6 neonates small for gestational age and 4 with cerebral lesions. The remaining 60 were divided into 2 groups: group A (N = 30) fed breast milk either direct or expressed and group B (N = 30) receiving formula till the age corresponding to 40 weeks of gestation. Table 1 shows the baseline features of both groups.

Table 1: Neonatal characteristics of preterm infants in both groups

	Group A (N = 30)	Group B (N = 30)	
	Mean ± SD	Mean ± SD	P
Gestational age (weeks)	30.13 ± 1.07	30.17 ± 1.02	0.902
Weight (kg)	1.45 ± 0.25	1.44 ± 0.24	0.813
Length (cm)	37.43 ± 1.49	37.87 ± 1.55	0.274
Head circumference (cm)	27.47 ± 1.61	27.22 ± 1.31	0.518
Weight SDS	0.26 ± 0.55	0.21 ± 0.41	0.700
Length SDS	-0.59 ± 0.47	0.42 ± 0.37	0.122
Head circumference SDS	0.10 ± 0.65	-0.01 ± 0.50	0.335
Apgar score (1 minute)	5.04 ± 1.43	5.07 ± 1.36	0.929
Apgar score (5 minutes)	7.46 ± 0.95	7.46 ± 0.92	0.991
	No	No	
Sex (Male/Female)	10/20	10/20	1.000
Mode of delivery (CS/SVD)	24/6	25/5	0.739

P < 0.05 is significant; SDS = Standard deviation score; CS = Cesarean section; SVD = Spontaneous vaginal delivery.

No apparent differences were seen in both groups as regards gestational age, weight, height, head circumference and SDS of height, weight and head circumference (p > 0.05). Both groups included 10 males and 20 females. In group A, 24 were delivered by section and 6 by normal labour, while in group B, 25 were delivered by section and 5 by normal labor with no marked difference among both groups (p > 0.05).

However, mean plasma level of IGF-1in group A was not significantly different from that in group B at birth (p > 0.05), a significantly higher level of mean serum IGF-1 was detected in group A than in Group B at age equivalent to 40 weeks of gestation measurement (p < 0.05) (Table 2).

Table 2: IGF-1 in the studied groups at birth and at 40 weeks gestational age

	Group A (n = 30)	Group B (n = 30)	p
	Mean ± SD	Mean ± SD	
IGF-1 at birth	20.13 ± 5.46	20.19 ± 6.21	0.970
IGF-1 at 40 weeks GA	25.21 ± 6.69	21.11 ± 4.59	0.008*

*p < 0.05 is significant; GA = Gestational age.

In Table 3, mean serum IGF-1 in each separate group was compared at birth and 40 weeks GA using a paired t-test. In group A, a higher significance level was detected in mean serum IGF-1 at equivalent 40 weeks of gestation than that at birth (p < 0.001) while in group B, no evident difference was shown (p > 0.05).

Table 3: IGF-1 at birth and 40 weeks gestational age in each group

	IGF-1 at birth	IGF-1 at 40 weeks GA	p
	Mean ± SD	Mean ± SD	
Group A (n = 30)	20.13 ± 5.46	25.21 ± 6.69	0.000*
Group B (n = 30)	20.19 ± 6.21	21.11 ± 4.59	0.111

*p < 0.05 is significant; GA = Gestational age.

Table 4, and 5 shows the predictors of IGF-1 as the dependent variable at birth and equivalent 40 weeks of gestation respectively. At birth, birth weight and gestational age were the main predictors of serum IGF-1. High birth weight and high gestational age were associated with high serum IGF-1 at birth.

Table 4: Multiple linear regression analysis for the predictors of serum IGF-1 at birth

	Unstandardized Coefficients		Standardised Coefficients	t	P
	B	Std. Error	Beta		
Gestational age (weeks)	3.585	1.663	.645	2.156	0.036*
Weight (kg)	11.557	5.287	0.467	2.186	0.034*
Length	-1.511	0.810	-0.406	-1.867	0.068
Apgar score 1 min	0.342	0.630	0.078	0.542	0.590
Apgar score 5 min	1.760	0.956	0.278	1.841	0.072

*P < 0.05 is significant.

At the age equivalent to 40 weeks of gestation, predictors of serum IGF-1 were birth weight, gestational age and breastfeeding during the early months of postnatal life. Increased birth weight, high GA and breastfeeding were accompanied by high serum level of IGF-1 at a postnatal age corresponding to 40 weeks GA.

Table 5: Multiple linear regression analysis for the predictors of serum IGF-1 at 40 weeks gestational age

	Unstandardized Coefficients		Standardised Coefficients	t	Sig.
	B	Std. Error	Beta		
Gestational age (weeks)	3.560	1.630	0.603	2.184	0.034*
Weight (kg)	11.396	5.173	0.433	2.203	0.033*
Length	-0.200	0.802	-0.051	-0.249	0.804
Apgar score 1 min	0.890	0.617	0.191	1.442	0.156
Apgar score 5 min	0.253	0.936	0.038	0.270	0.788
Group	-4.822	1.501	-0.391	-3.213	0.002*

*P < 0.05 is significant.

Discussion

It is known that fetus ingests significant amounts of amniotic fluid during the intrauterine third trimester, which contains higher values of IGF-1 than cord blood during pregnancy or at delivery. Human milk also, particularly colostrum, contains IGF-1. Although preterm infants may be fed on maternal milk/colostrum, the amounts are often very scanty, and maternal expression of colostrum could be inconvenient after birth immediately. Therefore, in preterm newborns, lack of IGF-1 resources in amniotic fluid and colostrum/milk may lead to less IGF-1 levels [18]. After very premature delivery, IGF-1 serum values decrease significantly to about 10 ng/ml while it is about > 50 ng/ml intrauterine at 23 to 30 weeks GA. Continuous low levels of IGF-1 after premature delivery are shown to be accompanied by a poor general and brain development as well as neonatal complications as intraventricular haemorrhage, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD)and necrotising enterocolitis (NEC) [19]. Levels of IGF-1were shown to be scanty at time of delivery of low birth weight babies, but increased gradually over the first 8 weeks of life and were positively associated with body weight, body length and body mass index at all time points. Also, IGF-I was shown to be accompanied by satisfactory growth at early postnatal age than by feeding and influence of nutrition on values of IGF-I may be limited to the period of settled catch-up growth [20]. In the current study, mean serum IGF-1 in preterm infants feeding breast milk (from birth till age corresponding to 40 weeks of gestation) was markedly more than that in preterm newborns feeding formula milk. Early breastfeeding was associated with increased serum value of IGF-1in preterm newborns.

In 2013, de Zegher et al. compared the influence of breastfeeding vs formula feeding after birth (small for gestational age) on weight and endocrine markers in late infancy (at birth, 4 and 12 months) [22]. In contrast to the results of our study, they found that formula-fed infants had increased adiposity and higher IGF-I values than breastfed babies. That can be explained by the difference in the age at which IGF-1 was measured, and type of infants included in the study at birth at an age corresponding to 40 weeks of gestation and premature infants in the present study [21], [22]. Hansen-Pupp et al., 2011 studied the interaction between feeding, IGF-I, and growth in 64 of premature infants. They concluded that IGF-I is related to growth at an earlier postnatal age more than feeding and influence of feeding on IGF-I levels may be limited to the phase of settled catch up growth [23]. Giapros et al., 2012 investigated in a prospective study the 1st year of life's IGF serum levels in 112 premature babies born equivalent to 32-36 weeks of gestation and their correlation with weight at birth and early neonatal growth. The average values of IGF-I at 2 and 6 weeks, was shown to be 82 ± 44, 100 ± 31 ng/ml, respectively [24]. In the current study, mean serum IGF-1, at the start and end point was 20.13 ± 5.46 and 25.21 ± 6.69 in group A respectively which were below than that in Giapros et al. 's results. That can be explained by the difference in GA of preterm babies enrolled at the start point of both studies [24].

Serrao et al., 2016 studied 52 premature newborns with GA < 31 weeks. They were divided into two groups as regards intake of expressed breast milk (< or ≥ 50 mL/Kg/day) till 32 weeks of gestation when sampling of blood for IGF-1 analysis was performed. In contrast to our study, they found that early expressed breast milk did not influence IGF-1 plasma values in preterm newborns [25]. The difference in results could be explained by the end point of measurement of IGF-1 which was 32 weeks of gestation in their study and 40 weeks of gestation in our study.

In conclusion, early breast milk nutrition, either expressed or direct feeding was correlated with a high serum IGF-1 in premature babies who may act to diminish general growth abnormalities, metabolic disorders, lung and retinal immaturity and brain developmental abnormalities which results in abnormalities in cognitive function. This study encourages maximum efforts to support immediate breast milk nutrition in the neonatal intensive care unit.

Further clinical trials are needed to study pitfalls and advantages of IGF-1 replacement in very premature newborns to keep postnatal IGF-1 to near fetal levels.

The essential restriction of this study is a small number of infants. The results have to be confirmed in larger groups of preterm infants to ensure high statistical power. Second, the study recruited subjects born in one hospital, and this limited sample makes it hard to be generalised on other populations. Finally, residual confounding factors not measured in our study may have affected the correlation between breastfeeding and IGF-1.

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