ORIGINAL ARTICLE

Effect of intrauterine infection and perinatal risk factors on serum concentrations of insulin like growth factor (IGF-I) in full-term and preterm newborns

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Abstract

OBJECTIVES: IGF-I is believed to be a key factor in fetal growth dynamics It is widely known, that serious early-onset infection in the newborn is a risk factor for further developmental disturbances in a child. However, effect of congenital infection as well as an influence of infectious and non-infectious perinatal risk factors on circulating IGF-I concentrations in newborns has not been examined, yet.
DESIGN: Thus, the aim of this study was: 1) evaluation of IGF-I venous blood serum concentration in full-term and premature infants considering their sex, occurrence of intrauterine infection and perinatal risk factors; 2) establishing the relationship between IGF-I serum concentrations and choosen anthropometric parameters values in infected and healthy newborns. **SETTING:** The study involved 112 newborns appropriate for gestational age. Taking into consideration occurrence of early onset infection and gestational age we divided examined children into 4 groups: I group – infected, full-term newborns; II group – infected premature newborns; III group – healthy full-term newborns; IV group – healthy premature newborns. In all infants immediately after birth anthropometric measurements were performed (birth weight, body length, circumference of head and circumference of chest) and serum IGF-I concentration was determined. **RESULTS:** We demonstrated that full-term infants with intrauterine infection have statistically significantly higher concentration of IGF-I in blood serum than infected premature infiants and healthy full-term infants. Analysis of correlation revealed a significant positive linear correlations between IGF-I serum concentration and gestational age and anthropometric parameters values. **CONCLUSIONS:** We conclude that intrauterine infection increases serum IGF-I concentration in full-term infants, but not in preterm infants, that may be a result of immaturity. We suggest serum IGF-I concentration may be considered an additional element of developmental and nutritional state assessment in infected newborn.

Abbreviations:
CNS – central nervous system
IGF-I – insulin like growth factor I
IGFs – insuline like growth factors
IUGR – intrauterine growth retardation
NEC – necrotizing enterocolitis
OFC – occipital-frontal circumference
pc – percentile
SGA – small for gestational age
WBC – white blood cell count

INTRODUCTION

Recently, a role of endocrine and paracrine factors in fetal development has been intensively studied. It has been demonstrated that the insulin-like growth factors (IGFs) I and II are implicated in fetal growth and development. IGFs are expressed abundantly in almost all tissues [8,42,45]. The major source of circulating of IGFs is liver, but it may be produced also by all tissues of mesenchymal origin [20,49]. IGFs exert important metabolic insuline-like effects influencing intracellular transport of glucose and aminoacids. They are also strong mitogenic factors, stimulating cellular proliferation and differentiation, production of proteins and nucleic acids [8,15,20,27,30,33,52].

IGF-I is detected in fetal tissues from 9th week of gestation and in fetal circulation from 13th week of gestation, that suggests the involvement of fetal membranes in fetus development via local secretion of IGF-I. During late gestation, significant amounts of IGF-I and IGF-II were found in intestine and kidney tubules, columnar epithelia of the pulmonary airways, hepatocytes, adrenal cortical cells, dermal cells, skeletal and cardiac muscle fibers, pancreatic islet and acinar cells [19]. Additionally, mRNA for IGF-I expression in fetal tissues has been reported [20]. Arterial and venous umbilical cord blood IGF-I concentrations does not vary significantly, that suggests its *in situ* production in fetal tissues [36]. It has been demonstrated that IGF-I does not cross placenta and its circulatory concentrations depend on gestational age. Values of IGF-I blood concentrations in perinatal period are low, they increase in postnatal period, reaching maximal levels (2–3-fold higher than in adults) during puberty and then gradually decrease in adults [4,8,25,27,32,49].

IGF-I is believed to be a key factor in fetal growth dynamics Infants with intrauterine growth retardation (IUGR) have significantly lower umbilical cord blood IGF-I concentrations in comparison with eutrophic newborns [8,14,16,30,31,38]. Also appropriate for gestational age, but premature infants reveal lower umbilical cord blood IGF-I concentrations than infants born at term [10,16]. Low IGF-I concentrations may contribute such complications as: retinopathy of prematurity, bronchopulmonary dysplasia, intracranial haemorrhage and NEC development [21,46]. Perinatal asphyxia is an additional factor decreasing IGF-I concentration in infants [6,35,43].

Serious early onset infection in the newborn is a risk factor for further developmental disturbances in a child.

IGF-I has profound effects on the immune system. In some studies performed in adults, a link between changes in IGF-I concentrations and chronic inflammatory diseases (reumatoid arthritis and autoimmunological hepatits) has been suggested [17,37]. IGF-I promotes cord blood naive T-cell and monocyte–derived dendritic cells maturation and inhibits their apoptosis. It increases also the production of tumor necrosis factor (TNF-alpha). This may have a great influence on vulnerability and course of intrauterine infection [34].

Effect of intrauterine infection as well as an influence of infectious and non-infectious perinatal risk factors on circulating IGF-I concentrations in newborns has not been examined, yet. Thus, the aim of this study was: 1) evaluation of IGF-I venous blood serum concentration in full-term and premature infants considering their sex, occurrence of intrauterine infection and other perinatal risk factors; 2) establishing the relationship between IGF-I serum concentrations and choosen anthropometric parameters values in infected and healthy newborns.

MATERIAL AND METHODS

Subjects

The study involved 112 newborns aged from 2 to 4 days appropriate for gestational age including 61 newborns born at full term and 51 infants born prematurely. All newborns were treated in Neonatal Intensive Care Unit in Zabrze, Silesian University of Medicine in Katowice, Poland in 2001–2005 years. Healthy newborns were delivered in Obstetric Department, Silesian University of Medicine in Zabrze, Poland. Newborns small for gestational age (SGA), delivered by mothers with diabetes or endocrine disorders were not included to the study. Sixty three of examined newborns (56.25%) were male and 49 (43.75%) were female. Fifty five of newborns (49.11%) were delivered through natural passages and 57 (50.89%) by Caesarean section.

Taking into consideration occurrence of intrauterine infection and gestational age we divided examined children into 4 groups:

I group – infected, full-term newborns
II group – infected premature newborns
III group – healthy full-term newborns (control group for group I)
IV group – healthy premature newborns (control group for group II)

Clinical characteristics of studied grups is shown in Table 1.

Early onset infection involved: sepsis (11 newborns from group I and 15 newborns from group II), pneu-

Table 1. Clinical charcteristics of examined groups of newborns (m-male, f-female).

Group	n	*mean ± SD (minimum-maximum)*					*median ± interquartile range (minimum-maximum)*	
		Fetal age (weeks)	Body weight (g)	Length (cm)	Head circumference (cm)	Chest circumference (cm)	Apgar score (points)	
							1 min	5 min
I	27 m=17 f=10	39.6±0.91 (38.0–42.0)	3284.07±387.64 (2600.00–3950.00)	54.29±2.18# (51.00–58.00)	34.11±1.50# (32.00–37.00)	33.18±1.44# (31.00–36.00)	9±3 (2–10)	10±2# (4–10)
II	34 m=21 f=13	32.7±3.01 (26.0–37.0)	1999.85±654.11 (870.00–3150.00)	46.35±5.73 (34.00–55.00)	30.38±2.94 (24.00–35.00)	27.82±3.47 (21.00–34.00)	7±3 (2–10)	7±2 (2–10)
III	34 m=16 f=18	39.29±0.94 (38.00–41.00)	3401.76±318.51 (2800.00–4100.00)	53.62±2.11 (33.00–55.00)	35.18±2.94 (31.00–37.00)	33.88±1.34 (31.00–36.00)	10±2 (7–10)	10±0 (8–10)
IV	17 m=9 f=8	34.06±0.90 (33.00–36.00)	2086.47±178.50 (1850.00–2400.00)	47.00±1.27 (45.00–50.00)$	31.88±0.78 (31.00–33.00)$	30.06±0.97 (29.00–32.00)*$	8±1 (7–9)	9±1 (7–10)

# p<0.001 in comparison to II group
* p<0.05 in comparison to II group
$ p<0.0005 in comparison with III group

monia (7 and 14 newborns, respectively), pneumonia and meningitis (1 and 2 newborns, respectively) and urinary tract infection (8 and 3 newborns, respectively). Concomitant non-infectious pathologies in infected newborns were: respiratory distress syndrome in 8 (23,53%) newborns from group II and intracranial haemorrhage in 1(3.70%) newborn from group I and 9 (26.47%) newborns from group II.

Perinatal asphyxia was stated in 2 (7.41%) newborns from group I and 8 (16.39%) newborns from group II.

Among 4 newborns who died, 1 was full-term with congenital CNS defect and 3 preterm with severe asphyxia and sepsis complicated with NEC.

Methods

Clinical data of examined subjects were collected from case records. The degree of maturity was assessed basing on duration of pregnancy according to Naegele formula verified with ultrasound assessment. Normal birth weight (range: 10–90 pc.) was evaluated according to birth weight percentile charts for Silesian newborns population [1].

Birth weight was established with neonatal scales. Anthropometric measurements were performed in all examined subjects immediately after delivery using measuring tape. Birth length was measured along physiological curvatures from vortex to plantar plane of feet positioned perpendicularly to shanks; circumference of head (occipital-frontal circumference, OFC) – through the point on forehead located between frontal tubers and the point located the furthest to the back on occiput; chest circumference – on the height of the sternum body and xyphoid process junction.

Early onset infection was diagnosed basing on clinical and laboratory parameters such as: pathological jaundice, respiratory failure, increased serum C-reactive protein concentration, increased (≥20.0 G/l) or decreased <4.0G/l WBC, disturbed leucocytic formula, thrombocytopenia (<100 G/l), hyper- (>7.8 mmol/l) or hypoglycaemia (<.34 mmol/l), hypoproteinaemia <45 g/l, metabolic acidosis, changes in chest X-ray, pleocytosis over 30/μm^3 with predominance of pMNs in CSF, positive blood, CSF and urine cultures. Diagnosis of RDS was established basing on clinical symptoms of respiratory failure and chest X-ray. Intracranial haemorrhage was detected using transfontanel ultrasound scan of brain and perinatal asphyxia according to low Apgar score at 1 and 5 minute of life and low pH value (<7.16) of venous cord or capillary blood in first hour of life.

In all infants immediately after birth IGF-I serum concentration was determined using commercial ELISA test (IBL-America, USA) characterized by cross-reactivity to IGF-II <0.05%, sensitivity of 0.156 ng/ml and inter-assay variance < 8%. Peripheral venous blood samples were collected from 2nd to 4th day of life between 8.00 and 10.00 AM, centrifuged and stored in -22^0C until measured. None of studied newborns received blood or hematogenous preparation beforehand.

Local ethics committee of Silesian Medical School in Katowice gave their consent to the study.

Statistics

Distribution of data was tested with Kolmogorow-Smirnow test. Comparisons between groups were performed using ANOVA with post-hoc Tukey`s test, when distribution of data was normal and non-parametric Friedman's ANOVA test, if distribution of data was different than normal. Pearson's linear correlations (for normal data distribution) or Spearman correlations

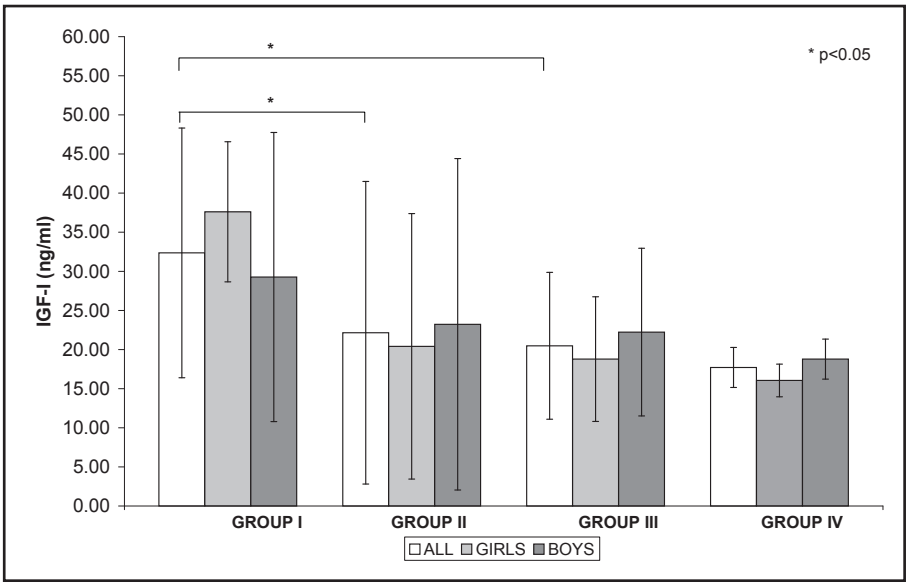

Figure 1. Serum IGF-I concentration in examined groups of newborns

(for data distribution different than normal) and multiple regression analysis with IGF-I as dependent variable were also performed. The level of significance at $p<0.05$ was accepted for all the performed comparisons and calculated statistics.

RESULTS

Results of IGF-I venous blood serum concentrations assessment are shown on Figure 1.

We demonstrated that full-term infants with intrauterine infection have statistically significantly higher concentration of IGF-I in blood serum than infected premature infiants and healthy full-term infants. We did not observe statistically significant differences between male and female newborns.

Analysis of correlations revealed a significant positive linear correlation between IGF-I serum concentration (r=0.22; $p<0.05$) and gestational age of all examined infants. When taking into consideration only infected infants (group I and II), also the same correlation was noted (r=0.32; $p<0.05$). Serum IGF-I concentration correlated significantly (r=0.21; $p<0.05$) with birth weight in all infants, in all infected infants (group I and II) (r= 0.32; $p<0.05$) and in all prematurely born infants (r=0.35; $p<0.05$). When correlated with anthropometric measurements values, in all infants IGF-I showed significant positive correlation with body length (r=0.21; $p<0.05$), head circumference (r=0.20; $p<0.05$) and chest circumference (r=0.26; $p<0.05$). In infected newborns (groups I and II) IGF-I serum concentrations correlated well with body length (r=0.26; $p<0.05$), head circumference (r= 0.34; $p<0.05$) and chest circumference (r=0.41, $p<0.05$). A positive linear correlation between serum IGF-I concentration and head circumference (r=0.29; $p<0.05$) as well chest circumference (r=0.38; $p<0.05$) was found in premature infants (group II and IV).

We also found a positive correlation of Apgar score in 1 minute of life with IGF-I concentration in healthy infants (group III and IV) r=0.12; $p<0.000$, but such relation was not observed in infected newborns.

On the basis of multilple regression analysis we confirm the relation between IGF-I concentration and intrauterine infection both in full-term and premature infants. There is also a correlation between serum IGF-I concentration, chest circumference and the length of body. The higher IGF-I serum concentration, the bigger chest circumference and smaller body length. These results are presented in Table 2.

DISCUSSION

In our study serum IGF-I concentrations in full-term born infants with intrauterine infection were significantly higher than in healthy full-term born infants.

This suggests, that early (congenital) infection stimulates production od IGF-I. A few authors hypothesized, that IGF-I plays and important role in inflammatory response to intrauterine infection. Liu et al. demonstrated profound effects of IGF-I on the human immune system. It promotes cord blood naive T-cell and monocyte–derived dendritic cells maturation and inhibits their apoptosis. It also increases the production of tumor necrosis factor (TNF-alpha) [34]. The study by Scheet et al. showed, that proinflammatory cytokines as Il-11 beta, Il-6, or TNF alfa may inhibit the function of GH-IGF-I axis [44].

On the other hand, there is also some data suggesting the lack of influence of inflammatory processes on IGF-I serum concentrations. In very small prematurely born infants with bronchopulmonary dysplasia, which

Table 2. Results of multiple-regression analysis.

Parameter	beta	Statistical error beta	B	Statistical error B	t	p
All examined newborns (group I-IV)						
					(108)	
Chest circumference	0.89	0.22	3.93	0.97	4.05	0.0000
Infection	–0.48	0.10	–14.55	2.99	–4.86	0.0000
Lenght	–0.52	0.21	–1.53	0.61	–2.50	0.014
Newborns at term (group I and III)						
					(58)	
Infection	–041	0.12	–11.37	3.32	–3.42	0.001
Body weight	–0.12	0.12	–0.004	0.005	–1.05	0.30
Preterm newborns (group II and IV)						
					(47)	
Chest circumference	1.16	0.26	6.02	1.34	4.50	0.0000
Infection	–0.50	0.14	–16.83	4.76	–3.54	0.0009
Lenght	–0.72	0.24	–2.43	0.81	–2.99	0.004
Infected newborns (group I and II)						
Chest circumference	0.97	0.28	4.68	1.34	3.47	0.0009
Lenght	–0.61	0.28	–1.89	0.86	–2.19	0.03
Healthy newborns (group III and IV)						
					(48)	
Head circumeference	0.38	0.15	1.63	0.64	2.55	0.01
Apgar score	–0.33	0.15	–2.18	0.99	–2.20	0.03

pathogenesis is strictly concerned with inflammatory factors there were no significant changes in IGF-I concentrations during therapy with dexamethasone, although they revealed severe developmental disturbances, predominantly affecting linear growth [24].

We also confirmed a strong positive correlation of IGF-I concentration and gestational age, both in all examined subjects and infants with early infection demonstrated by others. Klauwer et al. [27] showed a dependent on fetal age linear growth of umbilical cord blood serum IGF-I concentration until 270th day of gestation. After a short period of stable values, IGF-I serum concentration decreased since 275 day of gestation, suggesting restriction of nutritional supplementation concerned with longer duration of pregnancy. A positive correlation between umbilical blood serum IGF-I concentration and gestational age has been also reported by Lewitt et al. [33]. Giudice et al. observed almost 4-fold increase of IGF-I concentrations between 25–31 and 38–40 week of gestation. On the contrary, other authors suggested that fetal circulatory IGF-I concentration remains almost unchanged until 34 week of gestation, and then it doubles between 32 week of gestation and term of labor [22,41].

It should be also considered that IGF-I serum concentration in an infant may depend on feeding. Diaz-Gomez et al. [10] determined IGF-I serum concentrations in preterm newborns in first and third week of their life and demonstrated the highest values in brest-feeded infants. The lowest IGF-I concentrations were found in parenetrally fed newborns. Human IGF-I is present in breast milk [10,11,13]. Experimental studies showed that IGF-I from breast-milk is not digested in gastrointestinal tract of newborn and may interact with IGFs receptors in intestine mucous membrane, promoting vinfectedus cells proliferation and sealing up blood- intestine barrier [29]. Baumrucker and Blum [2] demonstrated that recombinant human IGF-I in newborn calves is absorbed from gastrointestinal tract and was detected in circulation.

We did not find relation between gestational age of preterm born newborns (either infected or healthy). Moreover, serum IGF-I concentration was significantly lower in prematurely born infected newborns in comparison with full–term born group. This may point to insufficient ability of immature infant to increase IGF-I production in response to infection. Immaturity and/or dysfunction of liver may contribute to lower IGF-I serum concentration in premature infants, as hepatocytes are believed to be the main source of circulating IGF-I [1,22,23,49]. It should be noted, that jaundice was present in more than 93% of premature and 36% fully-term infants examined.

Engerström et al. demonstrated very slow increase of IGF-I concentrations in infants born between 23 and 32 week of gestation [12]. Studies by Pawlus et al. [40] and Walczak et al. [51] showed that significantly lower IGF-I concentrations in preterm infants after intrauterine infection may disturb further development of a child [21,51]. Low IGF-I concentrations seem to be related with neonatal period complications such as: respiratory distress syndrome, intrauterine infections, intra-

cranial haemorrhage, anaemia nad chronic diseases as bronchopulmonary dysplasia, NEC and retinopathy of premature [5,21,28]. In the latter pathology, Smith et al. [46] reported a cessation of the normal vascular growth of retina as a result of inhibition of the normal function of vascular endothelial growth factor by low IGF-I concentration in retinopathy of premature.

IGF-I is also involved in gastrointestinal tract development. Corticosteroids have been shown to accelerate intestinal epithelial cell migration up the vinfectedus in late fetal development and IGF-I is a mediator of dexamethasone effect upon ileal epithelial cells [18,48]. Ozen et al. demonstrated that IGF-I protects intestinal mucosa from necrosis and apoptosis after hypoxia/reoxygenation [39].

In our study IGF-I concentration values were comparable in both studied groups of prematurely born infants (group II and IV). These findings are contradictory to values reported by others [21,40], who showed significantly lower IGF-I concentrations in infected premature infants in comparison to healthy premature newborns. This discrepancy may be a result of different study protocol. Pawlus et al. [40] examined all infected premature subjects without taking into consideration particular type of observed pathology, while Hellström et al. excluded subjects with congenital infection [21]. However, it cannot be undoubtedly determined if low IGF-I concentration in umbilical cord blood may be a reliable index of its diminished production. Apart from endocrine effects, IGF acts also auto- or paracrinely [22,23,49]. Than more immature fetus is, than markedly local IGF-I effects are exerted. The study on mRNA for IGF-I expression in fetal tissues between 10 and 16 week of gestation showed abundant distribution of IGF-I and its receptor [20].

Results of a few experimental studies suggest that changes in IGF-I serum concentrations in newborns may be also concerned with perinatal asphyxia. Wang et al. [53] examined serum IGF-I concentrations in newborn piglets with experimentally evoked hypoxic-ischemic changes in the brain. IGF-I serum concentration 72 hours after brain hypoxia correlated with severity of these changes. In an *in vitro* study IGF-I increased tolerance of cortical and hippocampal rat cells to hypoxia [54]. In our study we examined also relation between serum IGF-I concentration and Apgar score in 1st and 5th minute of life. We demonstrated that in all healthy newborns (both fully-term and prematurely born) than less Apgar score in 1st minute of life was, than higher IGF-I concentration detected. This observation is confirmed also by others. Cooley et al. [6] found significant correlation between umblical cord blood serum IGF-I concentration and fetal acidosis at delivery. As IGF-I takes part in myelinization of nervous tissue and synaptic connections formation it cannot be excluded, that IGF-I plays an important neuroprotective role in hypoxia and its potential beneficial effect against hypoxia-ischaemia may be clinically applied [3,47,55].

Our observations showed positive linear correlations between IGF-I serum concentration and birth weight in all examined subjects, as well as in newborns with early infections and preterm infants. Similar relation was stated for IGF-I serum concentration and body length, circumference of head and circumference of chest. Multiple regression analysis showed the higher IGF-I concentration, the bigger circumference of chest and smaller body length. Vatten et al. [50] demonstrated positive correlation between IGF-I and birth weight and body length in full-term born newborns. Our findings confirm the hypothesis that such postnatal parameters of development as body weight and body length as well as circumference of head and circumference of chest are related to the values of IGF-I concentrations in serum of infected infants. Thus, we suggest an assay of serum IGF-I concentration is an additional element of developmental and nutritional state assessment in infected newborn and also a prognostic factor for future. Studies on IGF-I concentrations in first years of life demonstrated its lower values in prematurely born children, independently on IUGR occurrence. On the other hand children born at term, but with low birth weight reveal increased serum IGF-I concentrations [7]. According to these findings it has been postulated that prematurity has greater influence on IGF-I concentration in first years of life than low birth weight alone.

We conclude that intrauterine infection increases serum IGF-I concentration in full-term infants, but not in preterm infants, that may be a result of immaturity. As serum IGF-I concentrations correlate with anthropometric measurements values, we suggest serum IGF-I concentration may be considered an additional element of developmental and nutritional state assessment in infected newborn.

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