

# Effect of Insulin and Insulin-Like Growth Factor I on Fetal Macrosomia in Healthy Women

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## ABSTRACT

*The aim of the study was to determine the values of insulin, insulin-like growth factor I (IGF- I) and glucose in the umbilical cord blood of macrosomic ( $\geq 4000$  g) and control (3,000–3,500 g) infants born to healthy mothers, and to assess their possible correlation with the newborns' birth weight and maternal anthropometric parameters. A series of 207 macrosomic term infants, and 200 control term infants, born to healthy mothers with normal oral glucose tolerance test throughout gestation, were studied. The glucose concentration did not differ between the macrosomic and control group while macrosomic infants had significantly higher values of insulin and IGF-I. Female macrosomic infants had significantly higher levels of insulin and IGF-I than male macrosomic infants. The levels of insulin and IGF-I, but not levels of glucose, differed between the macrosomic and control group according to the maternal weight, height, pregestational body mass index, weight gain during gestation, and maternal birth weight. The maternal anthropometric parameters were significantly greater in the macrosomic infants. Accordingly, macrosomia was concluded to be a multifactorial condition.*

## Introduction

Fetal growth and development are a complex and, as differentiated from the postnatal growth, as yet inadequately clarified process that involves the inter-

relationship among the mother, placenta and fetus. Any deviation from the normal growth, be it intrauterine growth retardation or excessive fetal growth, increases the morbidity and mortality rate. The effects of maternal and fetal genetic

factors on birth weight account for 38%, while environmental factors including maternal ones (age, parity, weight, weight gain during gestation, and birth weight) account for the remaining 62%<sup>1</sup>. Endocrine regulation of the fetal growth differs from the postnatal one. Insulin has long been known to influence fetal growth, either directly or indirectly *via* insulin-like growth factor I (IGF-I)<sup>2</sup>. IGF-I has a marked lipogenic effect manifesting as an excessive fatty tissue increase in the children born to diabetic mothers. Insulin-like growth factors I and II (IGF-I and IGF-II), that exert an autocrine/paracrine action in early pregnancy, and endocrine action in late pregnancy, are known to play the main endocrine role in the fetal growth<sup>3</sup>. Thus, the primary fetal axis involved in the fetal growth regulation is the glucose – insulin – IGF-I axis<sup>4</sup>. Recent clinical studies have pointed to a correlation between birth weight, and values of insulin and IGF-I in umbilical cord blood.

The aim of the study was to determine the values of insulin, IGF-I and glucose in the umbilical cord blood of macrosomic and control group newborns born to healthy mothers, and to correlate them with maternal birth weight and anthropometric factors.

### Patients and Methods

A total of 407 autochthonous mothers and their infants were prospectively studied from January 1, 1995 until December 31, 1996. All infants were normal (Apgar score 8–10), born from single pregnancies and at term. The mothers had normal oral glucose tolerance test (OGTT) performed between 24<sup>th</sup> and 32<sup>nd</sup> week of gestation, and were free from any intra- or postpartal complications.

The mothers and their infants were divided into two groups. A study group included 207 infants with birth weight

4000 g (macrosomic newborns) and their healthy mothers who had normal reproduction history, normal (no symptoms of EPH gestosis) and controlled (6 control examinations) course of pregnancy, and normal OGTT during pregnancy, as well as normal family history concerning diabetes. A control group consisted of 200 newborns with birth weight 3,000–3,500 g and their mothers (matched by inclusion criteria with the study group). The control group of infants was obtained by including, following the birth of a macrosomic infant, the first mother matching the study group mother by age, parity and gestational age, who gave birth to a newborn weighing 3,000–3,500 g.

Gestational age was determined according to the onset of the last menstruation, by ultrasonic assessment, and by postnatal evaluation of infants according to Farr. OGTT with 75 g glucose was performed in all women between 24<sup>th</sup> and 32<sup>nd</sup> week of gestation. A finding of < 6.7 mmol/L glucose in fasting capillary blood and 7.8 mmol/L at 2 h after loading was considered normal. Maternal body weight was measured at initial examination (within the first 8 weeks of gestation). Pregestational body mass index (BMI) was calculated according to the formula  $BMI = W/H^2$ , where W = weight in kg and H = height in m. Maternal birth weight was determined from the present and past history data. Neonatal ponderal index was calculated according to the formula  $PI = W/H^3 \cdot 100$  where W = weight in g and H = height in cm. Macrosomic infants were divided into two categories according to ponderal index: 1. PI 2.2–2.8 (proportionate macrosomia), 2. PI > 2.8 (disproportionate macrosomia)<sup>5</sup>. The 1- and 5-min Apgar score was determined in all newborns.

Umbilical cord blood samples for determination of glucose, insulin and IGF-I concentrations were obtained upon cord ligation. The mothers received non-glu-

**TABLE 1**  
MATERNAL AND NEONATAL CHARACTERISTICS

Parameter	Macrosomic group		Control group		P
	X	SD (N)	X	SD (N)	
<i>Maternal</i>					
Height (cm)	171.2	6.1 (207)	167.1	6.1 (200)	< 0.00001
Weight (kg)	67.8	10.3 (207)	61.4	7.9 (200)	< 0.00001
BMI (kg/m <sup>2</sup> )	23.1	3.2 (207)	22.0	2.6 (200)	< 0.0001
Weight gain (kg)	16.0	4.5 (207)	13.9	4.2 (200)	< 0.00001
Birth weight (g)	4051.0	437.7 (140)	3171.0	399.9 (116)	< 0.00001
Age (yrs)	28.3	5.4 (207)	27.2	5.4 (200)	> 0.05
Parity	2.02	0.9 (207)	2.1	0.9 (200)	> 0.05
<i>Neonatal</i>					
Gestational age (wk)	39.6	1.3 (207)	39.5	1.2 (200)	> 0.05
Birth weight (g)	4291.0	283.9 (207)	3272.4	137.5 (200)	< 0.00001
Male	4326.0	298.8 (127)	3282.3	136.2 (99)	< 0.00001
Female	4235.6	246.5 (80)	3263.4	137.0 (101)	< 0.00001
Ponderal index (g/cm <sup>3</sup> )	2.87	0.2 (207)	2.75	1.3 (200)	> 0.05

cose containing intravenous infusion during labor and delivery. After centrifugation, serum was stored at  $-20^{\circ}\text{C}$  until insulin and IGF-I determination. The concentration of glucose in umbilical cord blood was determined by the glucose para-amino antipyrine (glucose-PAP) color enzymatic method. The concentration of insulin in umbilical cord blood was determined by radioimmunoassay (RIA) using Insulin-CT kits (Cis BioInternational, France). The intra- and interassay coefficient of variation (CV) was 8.2% and 8.8%, respectively. The concentration of IGF-I in umbilical cord blood was determined by the immunoradiometric method (IRMA) using kits for quantitative determination of serum IGF-I (Diagnostic Products Corporation – DPC, Los Angeles, USA). Before IGF-I determination, IGF-I was separated from the binding proteins in serum by acid-ethanol extraction. The intra- and interassay CV was 3.0% and 1.5%, respectively.

The study was approved by the regional Ethics Committee for Medical Research, and an informed consent was obtained from all mothers participating in the study.

Mann-Whitney test, a non-parametric statistical test for independent samples, was used to compare numerical data and results of ordinal scale measurement between the two groups. Non-parametric Kruskal-Wallis test was used to analyze more than two independent groups of data.

## Results

Characteristics of the mothers and their infants are presented in Table 1. The values of maternal height, pregestational body weight, pregestational BMI, weight gain during gestation, and birth weight were higher in the macrosomic than in the control group ( $p < 0.00001$ ),

whereas no differences were recorded for maternal age, parity and gestational age ( $p > 0.05$ ).

Table 2 shows mean values of glucose, insulin and IGF-I concentrations in the umbilical cord blood of macrosomic and control infants according to sex. There was no difference in the cord blood concentration of glucose between the macrosomic and control group ( $p > 0.05$ ). No sex related difference was recorded ( $p > 0.05$ ). The macrosomic group had significantly higher insulin and IGF-I concentrations in cord blood compared with the control group ( $p < 0.00001$ ). Also, the con-

centrations of insulin and IGF-I in cord blood from female macrosomic infants were statistically significantly higher than those measured in male macrosomic infants ( $p < 0.001$  and  $p < 0.00001$ , respectively). In the control group, a statistically significant sex difference was only observed for cord blood values of IGF-I, which were higher in female infants ( $p < 0.001$ ).

According to ponderal index there were 73 (35.3%) proportionate macrosomic infants, and 134 (64.7%) disproportionate macrosomic infants. Table 3 shows mean values of glucose, insulin

**TABLE 2**  
VALUES OF GLUCOSE, INSULIN AND IGF-I IN THE UMBILICAL CORD BLOOD OF MACROSOMIC AND CONTROL INFANTS ACCORDING TO SEX

Sex	Glucose (mmol/l)				Insulin ( IU/ml)				IGF-I (ng/ml)			
	I		II		I		II		I		II	
	118		93		127		99		127		99	
Male	4.0	1.4	4.3	1.1	12.4	5.6	10.1	4.8**	60.9	34.4	33.9	28.4***
	78		95		80		101		80		101	
Female	4.1	1.2	4.3	1.1	15.1	7.1	10.2	4.0***	81.6	42.7	41.2	24.5***
M/F diff.					*				***			
	196		188		207		200		207		200	
Total	4.1	1.3	4.3	1.2	13.4	6.3	10.1	4.4***	69.0	39.3	34.7	22.5***

I – macrosomic group; II – control group; \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$

**TABLE 3**  
VALUES OF GLUCOSE, INSULIN AND IGF-I IN THE UMBILICAL CORD BLOOD OF MACROSOMIC INFANTS ACCORDING TO PONDERAL INDEX (PI)

PI (g/m <sup>3</sup> )	Glucose (mmol/l)		Insulin ( IU/ml)		IGF-I (ng/ml)	
	68		73		73	
2.2–2.8	4.2	1.5	12.9	5.7	61.1	36.6
	128		134		134	
> 2.8	4.0	1.2	13.8	6.6	73.4	40.1
PI diff.	*					
	196		207		207	
Total	4.1	1.3	13.4	6.3	69.0	39.3

\* $p < 0.05$

**TABLE 4**  
 MATERNAL CHARACTERISTICS AND CORD BLOOD VALUES OF GLUCOSE, INSULIN  
 AND IGF-I IN MACROSOMIC AND CONTROL INFANTS

	N		Glucose (mmol/l)				Insulin ( IU/ml)				IGF-I (ng/ml)			
	I	II	I	II	I	II	I	II	I	II	I	II		
Height (cm)														
< 155	1	2												
155–164	29	74	4.4	1.6	4.5	1.1	3.2	4.0	9.4	3.7****	76.9	50.7	34.7	22.7****
165–174	115	94	3.9	1.3	4.2	1.2	13.4	6.7	10.4	4.9****	70.2	38.5	34.1	22.5****
175	62	30	4.2	1.2	4.2	1.1	13.8	6.5	11.1	4.2*	64.4	34.7	38.3	22.3****
Weight (kg)														
< 55	13	34	5.0	1.2	4.4	1.2	10.7	5.2	9.9	3.9	47.0	19.2	33.8	21.6
55–64	73	105	4.0	1.4	4.3	1.1	13.3	5.7	10.1	4.7****	68.0	40.7	33.5	31.8****
65–74	82	48	3.9	1.2	4.1	1.2	13.9	6.3	10.0	4.1****	72.4	40.6	37.2	21.7****
75	39	13	4.2	1.3	4.4	1.2	13.6	7.3	10.4	4.7*	72.8	36.3	37.2	18.4****
Pregravid BMI (kg/m <sup>2</sup> )														
19.9	24	4	4.0	1.2	4.4	1.1	11.5	5.0	11.3	3.8	54.5	30.5	34.6	21.3**
20.0–24.9	140	139	4.1	1.4	4.3	1.2	13.8	6.8	9.8	4.6****	70.8	40.8	39.5	51.8****
25.0–29.9	36	19	4.2	1.4	4.2	1.1	12.8	4.4	10.0	3.6**	70.6	39.3	30.8	21.8****
30.0	7	2	3.5	0.8	4.7	0.1	15.4	9.3	13.6	7.0	80.6	24.5	28.0	21.2
Weight gain (kg)														
13.0	59	104	4.3	1.2	4.3	1.1	15.0	6.6	9.8	3.9****	73.9	46.4	34.6	23.0****
14.0–17.0	80	57	4.0	1.4	4.3	1.2	13.6	6.8	10.2	3.9****	69.9	38.5	47.2	35.6****
18.0	68	39	4.0	1.4	4.4	1.3	14.0	5.3	11.3	6.1**	64.3	32.8	31.2	17.9****
Birth weight (g)														
< 2500	0	5	/		4.5	0.8	/		12.9	2.3	/		55.2	24.3
2500–3999	40	104	4.5	1.4	4.3	1.3	11.9	4.3	10.4	4.1*	67.9	40.2	40.0	22.8****
4000–4499	78	6	4.1	1.4	4.7	0.9	13.7	6.9	8.4	2.1**	72.3	35.9	43.8	21.9*
4500	22	1	4.2	1.3			13.4	4.6			68.4	38.3		

I – macrosomic group; II – control group; \*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.01; \*\*\*\*p < 0.01

and IGF-I concentrations in the umbilical cord blood of macrosomic infants according to ponderal index. There was no difference in the cord blood concentrations of glucose and insulin between proportionate and disproportionated macrosomic infants ( $p > 0.05$ ). Disproportionated macrosomic infants had significantly higher IGF-I concentration in cord blood compared with proportionated macrosomic infants ( $p < 0.05$ ).

Maternal height, weight, pregestational BMI, weight gain and birth weight, and cord blood concentrations of glucose, insulin and IGF-I in macrosomic and control infants are presented in Table 4. The concentration of glucose in cord blood did not differ between the macrosomic and control group of infants in any of the categories. The concentrations of insulin and IGF-I in cord blood were significantly higher in the macrosomic infants in all

maternal weight categories of  $\geq 55$  kg while no such difference was recorded in the maternal weight category of  $< 55$  kg. The values of insulin and IGF-I in cord blood of macrosomic infants significantly exceeded those measured in control infants in all maternal height categories. The level of insulin in cord blood was significantly greater in macrosomic infants born to mothers with pregestational BMI ranging from 20.0 to 29.9 kg/m<sup>2</sup>, whereas no difference was observed in those born to mothers with pregestational BMI  $< 20.0$  kg/m<sup>2</sup>.

A significantly higher cord blood concentration of IGF-I was found in macrosomic infants in all categories of maternal pregestational BMI. The maternal pregestational BMI category of 30.0 kg/m<sup>2</sup> was too small for statistical analysis. The concentrations of insulin and IGF-I in cord blood were higher in macrosomic infants in all categories of maternal weight gain during pregnancy. With maternal birth weight of 2,500–4,500 g, the concentrations of insulin and IGF-I in cord blood were significantly higher in the macrosomic group of infants, while the birth weight categories of  $< 2,500$  g and  $> 4,500$  g were too small for statistical analysis. There was no significant difference in the cord blood concentrations of glucose, insulin and IGF-I according to maternal height, pregestational weight, pregestational BMI, weight gain and birth weight in either macrosomic or control group of infants.

## Discussion

The regulation of fetal growth differs from the postnatal growth regulation. In the physiologic conditions, postnatal growth is exclusively limited by genetic factors. Fetal growth, especially in late gestation, is limited by maternal and placental factors. The development of macrosomia is related to a number of factors,

most of them of the maternal origin. The effects of maternal weight, height, BMI, weight gain during pregnancy, birth weight, age and parity on fetal birth weight have been demonstrated<sup>6–11</sup>.

The effect of maternal factors on fetal birth weight was also demonstrated in this study. The probability of giving birth to a macrosomic newborn increased with the maternal birth weight increase, and was 27.8%, 92.9% and 95.6% in the categories respectively (Table 4).

A correlation has also been reported between the sex of the neonate and birth weight<sup>7,8,11</sup>. In the present study, macrosomia showed a male predominance.

Along with adequate nutritional supply, the endocrine system is involved in the regulation of fetal growth. Glucose has been shown to be an important but not exclusive source of energy for fetal growth. Also, IGF and insulin have been accepted as the key hormones in the fetal growth regulation<sup>2,12</sup>. The transplacental transport of glucose influences insulin secretion, and insulin in turn influences the secretion of IGF-I<sup>12</sup>. A positive correlation between the umbilical cord insulin level and neonatal birth weight has been reported from numerous studies of pregnancies with and without diabetes<sup>13–15</sup>. Most studies have shown the macrosomic infants born to healthy mothers (normal OGTT during gestation) to have a higher umbilical cord insulin concentration than those of an average birth weight for gestational age<sup>16–19</sup>. In the study of Wiznitzer et al.<sup>20</sup>, the cord blood insulin level in macrosomic infants did not significantly exceed the level found in the control group. In our study, however, the mean cord blood insulin level was significantly higher in the macrosomic than in the control group of infants. Insulin level in cord blood did not differ significantly in macrosomic infants according to their ponderal index. In the studies of Hoegsberg et al.<sup>17</sup> and Krew et al.<sup>15</sup>, sex had no sig-

nificant effect on the cord blood insulin level, although the latter<sup>14</sup> report on a higher mean cord blood insulin level in female than in male neonates. In this study, however, the insulin concentration showed a sex difference in the macrosomic group. Although the male macrosomic infants were heavier, the female macrosomic infants had higher insulin levels. This may influence the high risk of developing Type 2 diabetes in females.

Macrosomic infants had a significantly higher insulin concentration than control infants regardless of the maternal weight gain during pregnancy, which is consistent with the observations of Hoegsberg et al.<sup>17</sup> and Modesto Caballero et al.<sup>18</sup>, and a higher insulin concentration in all categories of maternal height and weight, in contrast to literature reports<sup>17,18</sup>. Macrosomic infants also had a higher insulin concentration according to maternal pregestational BMI and birth weight.

Macrosomic newborns, especially those from diabetic pregnancies, are susceptible to hypoglycemia. Akinbi and Gerdes<sup>19</sup> found 20% of macrosomic infants born to non-diabetic mothers to have experienced hypoglycemia within the first 24 hours of life. In our study the glucose levels in macrosomic infants were slightly lower, although the insulin concentration was significantly higher. Similar observations have also been reported elsewhere<sup>16,20</sup>. This may indicate that the macrosomic fetuses had degree of insulin resistance. It appears that macrosomia in infants born to healthy mothers, i.e. those with normal OGTT during gestation, need not necessarily be associated with hypoglycemia. The risk of hypoglycemia in macrosomic newborns increases with the maternal history of gestational diabetes or diabetes mellitus. The maternal anthropometric parameters of body height,

body weight, pregestational BMI, weight gain during pregnancy, and birth weight did not influence the values of umbilical cord blood glucose in either macrosomic or control group.

Most clinical studies point to a relationship between birth weight and cord blood IGF-I concentration<sup>12,20–27</sup>, however, some studies failed to demonstrate it<sup>28,29</sup>. The more so, deletion of the IGF-I gene has recently been shown to cause intrauterine growth retardation and postnatal growth failure<sup>30</sup>. Studies in macrosomic infants born to healthy (non-diabetic) mothers have also pointed to a correlation between cord blood IGF-I levels and birth weight<sup>20,24,25</sup>. In our study, macrosomic infants had significantly higher cord blood levels of IGF-I. Disproportionate macrosomic infants had significantly higher cord blood concentration of IGF-I compared to proportionate macrosomic infants. In contrast to some other reports<sup>22–24</sup>, the level of IGF-I showed a significant sex difference, i.e. it was significantly higher in female than in male infants. Daughaday and Rotwein<sup>31</sup>, however, found the values of IGF-I in serum to be slightly higher in females than in males in all age groups.

The possible effect of maternal factors on IGF-I was demonstrated by Simmons<sup>14</sup>. The concentration of IGF-I correlated positively with maternal height and pregestational BMI. In our study, a significantly greater concentration of IGF-I was found in macrosomic infants in all categories of maternal weight, height, pregestational BMI, weight gain and birth weight.

In conclusion, the concentrations of insulin and IGF-I in cord blood were higher in the macrosomic compared with the control group of infants, while no difference was found for glucose concentrations. Fetal macrosomia was found to po-



sitively correlate with maternal height, weight, pregestational BMI, weight gain during pregnancy and birth weight, as well as with the male sex of the newborn.

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## **UTJECAJ INZULINA I INZULINU SLIČNOG ČIMBENIKA RASTA I (IGF-I) NA FETALNU MAKROSOMIJU U ZDRAVIH TRUDNICA**

### **S A Ž E T A K**

Cilj istraživanja je bio odrediti vrijednosti inzulina, inzulinu sličnog čimbenika rasta I (IGF-I) i glukoze u krvi iz pupkovine makrosomne ( > 4000 g) i kontrolne (3000–3500 g) novorođenčadi zdravih trudnica te utvrditi jesu li one povezane s porodnom težinom novorođenčadi i antropometrijskim parametrima majke. Ispitano je 207 donesene makrosomne novorođenčadi i 200 kontrolne novorođenčadi, čije su majke bile zdrave i imale uredan OGT-test tijekom trudnoće. Koncentracija glukoze u krvi iz pupkovine nije se razlikovala u makrosoma i kontrolnoj skupini, dok su makrosomi imali značajno veće vrijednosti inzulina i IGF-I. Ženska makrosomna novorođenčad imala je značajno veće vrijednosti inzulina i IGF-I od muške makrosomne novorođenčadi. Vrijednosti inzulina i IGF-I, ali ne i vrijednosti glukoze, razlikovale su se između makrosoma i kontrolne skupine prema majčinoj težini, visini, pregravidnom indeksu tjelesne mase, dobitku u težini tijekom trudnoće i majčinoj porodnoj težini. Majčini antropometrijski parametri bili su značajno veći u makrosomne novorođenčadi. Iz dobivenih rezultata može se zaključiti da je makrosomija multifaktorijalno uvjetovana.