Original Article

Levels of insulin-like growth factors and their receptors in placenta in relation to macrosomia

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Objective: To investigate the associations between mRNA levels that encodes for insulin-like growth factors (IGF_S) and their receptors in term placenta, and the risk of macrosomia. Methods: Term placentas were collected from 37 neonates with macrosomia and 37 neonates with normal birth weight in Changzhou Women and Children Health Hospital from March 1 to June 30, 2008. The IGF mRNA levels and their receptors in those placentas were measured by Real-time PCR. Results: The placental weight was positively correlated with the birth weight both in the macrosomia group (r=0.550, p=0.004) and the control group (r=0.678, p=0.000). After adjusting for potential confounders, multivariable adjusted ORs of neonates with macrosomia for those in the increasing two tertiles were 17.3 (95%CI: 2.50-19.2) and 5.94 (95%CI: 0.96, 36.8), respectively, compared with those in the lowest tertile in terms of IGF-Ⅱ mRNA level. Similarly, multivariable adjusted ORs of neonates with macrosomia for those in the increasing two tertiles of IGF-Ⅰ R mRNA were 25.3 (95%CI: 3.43-187) and 43.0 (95%CI: 4.89, 378), respectively. Conclusion: These results indicate that the levels of placental IGF-Ⅱ and IGF-Ⅰ R mRNA may be involved in the development of macrosomia.

Key Words: macrosomia, placenta, insulin-like growth factor, receptor, case-control study

INTRODUCTION

In recent years, many studies have highlighted that abnormal birth weight relates to abdominal obesity and insulin resistance in adults and can lead to the development of other diseases and medical conditions.[1-3] Rogers I reviewed literature on Medline since 1966 with regard to the association between birth weight (BW) and body mass index (BMI) and obesity in later life and found an association between BW and subsequent BMI and overweight in young adults and children.[4] This association was found to be linear and positive in some studies and J- or U-shaped in others. Therefore, it is very important for the neonates to have a normal birth weight. With the advances in socioeconomic and health conditions and the improvement in women's living standards, the incidence of low BW infants decreased gradually and that of macrosomia increased. The morbidity of macrosomia had reached 7-10%.[5] In 2006, the morbidity of macrosomia was 6.5% in China.[6] Furthermore, high BW leads to adult obesity and chronic disease, and increasing macrosomia in newborns raises the risk for birth-related problems. Increased cancer risk is also tied to higher BW,[7-10] which suggest that increased BW has dangerous implications in terms of human health and survival. To study the risk factors that are closely related to macrosomia is of particular importance to reduce the incidence of macrosomia.

Nutrition during pregnancy may contribute to macrosomia directly. Overweight or obesity before pregnancy, weight gain during pregnancy, rapid weight gain during middle and late pregnancy are all risk factors of macrosomia.[11] As all the nutrients for the fetus comes from the maternal placenta, the size, shape, blood supply and nutrients transported by the mammal's placenta play a critical role in the fetal growth and development.[12]

Over the last decade it has been recognized that the insulin-like growth factor axis has a critical role in mediating fetal and postnatal growth.[13] The insulin-like growth factors (IGFs), IGF-Ⅰ and IGF-Ⅱ are two small, highly homologous single chain polypeptides with similarities to pro-insulin. Their actions are mediated by binding to the type-1 IGF receptor (IGF-Ⅰ R). A large body of data have suggested that the insulin-like growth factor (IGF) system, and IGF-Ⅰ and IGF-Ⅱ in particular, plays a critical role in fetal and placental growth throughout gestation.[14] IGF-Ⅰ stimulates fetal growth and IGF-Ⅰ

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deficiency in humans have a phenotype of severe intrauterine growth restriction (IUGR).[15] IGF-Ⅱ plays a key role in placental growth and nutrient transfer.[16,17] Deletion of either the IGF gene or the IGF-ⅠR gene retards fetal growth while over-expression of IGF-Ⅱ leads to fetal overgrowth.[18] The importance of the study of how the IGF axis regulates placental development and function is apparent. However, most to date studies were conducted in animals and focused on investigating the relationship between IGFs and Placental restriction that lead to fetal growth restriction (FGR). Few have even looked at the potential relationship between IGFs with theirs receptors in placenta and macrosomia. In this study we will investigated the association between the expression of IGFs/IGFs receptors in the placenta and the occurrence of macrosomia, controlling for some potential risk factors of macrosomia.

MATERIALS AND METHODS

This is a cross-sectional study of the association between the insulin-like growth factors and their receptors in the placenta of neonates with macrosomia and those with a normal birth weight. The study was approved by the Human Research Ethics Committees of the Changzhou Women and Children's Health Hospital. Informed consent was obtained from a parent prior to any study related procedure.

Subjects

37 neonates with macrosomia were chosen randomly from 116 cases that were born in Changzhou Women and Children Health Hospital from March 1 to June 30, 2008. The Macrosomic neonates in this study was defined as those neonates whose BW were equal to or greater than 4000 g. 37 neonates with normal BW in the corresponding period were chosen as the controls. Mothers of both groups had no diabetes and other complications during pregnancy, confirmed by negative results of oral glucose tolerance test of 75 g in 24^{th} -28^{th} week of pregnancy.

Biomarkers detection

A piece of villus tissue of 1×1×1cm size was collected from the center of the placenta under aseptic conditions within 5 minutes after the delivery of the placenta. Then the specimen was cleansed by Normal Saline (NS) and preserved in liquid nitrogen.

The Primer and Probe of GAPDH, IGF-Ⅰ, IGF-ⅠR, IGF-Ⅱ and IGF-ⅡR were designed by Primer Primier 5.0 according to the sequence offered by Gene NIU Primer (NM_002046, AK312231, NM_000875, HUMGFIL2 and NM_000876) and produced by Shanghai Sangon Biological Engineering Technology and Services Co., LTD. The standard samples of each gene were ordered from Shanghai Shenyou Biological Technology Co., LTD. The Sequence of Primer and Probe are displayed in table 1.

Tissue general RNA was gathered according to steps described in the manual of the general RNA extraction kit. 2μg general RNA was gathered from every tissue. Reverse transcription reaction was done in the qualitative PCR device. All Rea1 Time PCR reaction was done on the ABI 7300 Real-time PCR device. Complex control was done on every specimen. Standard sample was involved in every reaction. The PCR reaction system is composed of: 10×PBS2.5 μl, 25mmol/L $MgC1_2$ 1.5 μl, 10 mmol/L 4×dNTPs 0.5 μl, 100μmol/L Justice primer

Table 1. Sequences of PCR primers and specific probes (5′- 3′) for the detection of GAPDH, insulin-like growth factor (IGF) I, IGF-IR, IGF-II, and IGF II R by real time PCR

	Primer	Sequence
GAPDH	sense primer	GGA AGG TGA AGG TCG GAG TC
	Antisense primer	CGT TCT CAG CCT TGA CGG T
	Probe	FAM-TTT GGT CGT ATT GGG CGC CTG-TAMRA
IGF-Ⅰ	sense primer	TGT CCT CCT CGC ATC TCT TCT AC
	Antisense primer	ATA CCC TGT GGG CTT GTT GAA ATA
	Probe	FAM-TGC CAC GGC TGG ACC GGA GAC GCT C-TAMRA
IGF-ⅠR	sense primer	TTT CCC ACA GCA GTC CAC CTC
	Antisense primer	AGC ATC CTA GCC TTC TCA CCC
	Probe	FAM-CCG AAT GGC TTG CCA GTG GCT CTG T-TAMRA
IGF-Ⅱ	sense primer	CGG CTT CTA CTT CAG CAG GC
	Antisense primer	TGG CGG GGG TAG CAC AGT
	Probe	FAM-CAA GCC GTG TGA GCC GTC GCA-TAMRA
IGF-ⅡR	sense primer	GCA ATA AAA CCG CAG GTA ACG
	Antisense primer	AGG CGT ATT CCG TGT CCC AT
	Probe	FAM-CTG TAT TCA CAG GGG AGG TTG ACT GCA-TAMRA

0.1 μl, 100μmol/L anti-sense primer 0.1 μl, 100μmol/L probe 0.1 μl, 5 U/μl Taq enzyme 0.25 μl, specimen 2 μl. PCR Water Level was kept at 25μl. The reaction went through several steps: predegenerationg at 95 c for 1 min, then degeneration at 95 c for 5 s, extension of the annealing at 60 c for 30 s (collection of fluorescent signal at this step) and enlargement to 40 cycles. The standard sample was diluted by 10 times of the concentration gradient (10^8-10^3), a threshold cycle （CT） value Standard curve was drawn on the concentration logs of all standard samples. CT value was defined as the cycle number when a fluorescent signal was registered in the reaction tube when a set threshold was reached. Then the start copy number was calculated from the Standard curve in accordance to the CT value of the unknown specimen.

Covariates

Information about the pregnant women's age, height, education, weight before pregnancy, weight gain during pregnancy, time of pregnancy and time of delivery were collected using a self-defined questionnaire.

Statistical Analysis

Group comparisons of basic characteristics were performed using the Student-t test or the Wilcoxon rank sum test, as appropriate. Pearson or Spearman rank correlation coefficients between indicators were calculated depending on the distributions of the variables related. The significance of the coefficients was tested with the t-test and the comparison between two groups was conducted with the z test. IGFs and receptor expression levels were divided into three groups according to theirs tertiles, with the lowest tertile as the reference. Simple and multiple logistic regression models with a stepwise forward strategy were used to explore the risk factors in the development of macrosomia.

All analyses were performed with Stata 10.0 (StataCorp, College Station, Texas, USA). A p value of< 0.05 was considered statistically significant.

RESULTS

General information from pregnant women in the two groups

The average BW of neonates with macrosomia was 4176 ± 179g while those in the control group was 3230 ± 304g. The mothers in the macrosomia group had a higher BMI before pregnancy and higher weight gain during pregnancy. There were no significant differences in maternal age, pregnant duration and gestational weeks between the two groups (table 2). No significant differences were found in education (p = 0.246), income of the family (p = 0.445), and pregnant times (p = 0.853), either.

The level of IGF_S and their receptors in the placenta

Data representing the level of IGF_S and theirs receptors was positively skewed; therefore, median and interquartile ranges (Q1-Q3) were used to describe the data. The level of IGF_S and their receptor expression in the placenta of neonates with macrosomia and control was displayed in Table 3. Based on the result of Wilcoxon test, no statistical significance differences were found with regard to placental IGF-ⅠmRNA level between the macrosomia group and the control, while there were significant differences in IGF-ⅡmRNA, IGF-ⅠR mRNA，

Table 2. Basic characteristics of pregnant women*

	Macrosomia†	Normal birth weight	p values‡
No. of participants	37	37	
Age (yr)	28.0 ± 3.30	27.2 ± 3.04	0.330
BMI before pregnancy§	21.2 ± 2.36	20.2± 1.58	0.026
Weight gain during pregnancy (kg）	20.5 ± 4.34	17.2 ± 4.78	0.003
Pregnant days	279 ± 6.36	276 ± 4.79	0.059
Gestational weeks	39.7 ± 0.90	39.4± 0.72	0.080

* Plus-minus values are mean ± SD.
† Macrosomia is defined as those neonates with a birth weight ≥ 4000 g.
‡ Difference between groups was tested by Student-t test.
§ BMI = body-mass index, which is the weight in kilograms divided by the square of the height in meters.

Tablet 3. Levels of insulin growth factors (IGFs) and their receptors in maternal placenta between groups

Group	No. of participants	IGF-ⅠmRNA		IGF-ⅡmRNA		IGF-ⅠR mRNA		IGF-ⅡR mRNA	
		Median	Q1-Q3*	Median	Q1-Q3	Median	Q1-Q3	Median	Q1-Q3
Macrosomia†	37	0.65	0.34-1.04	2.53	2.18-4.30	0.002	0.001-0.003	0.003	0.002-0.006
Normal birth weight	37	0.45	0.38-0.72	1.70	0.87-3.55	0.001	0.001-0.002	0.002	0.001-0.003
p values‡		0.254		0.025		0.000		0.005	

* Q1-Q3 denotes inter-quartile range.
† Macrosomia is defined as those neonates with a birth weight ≥ 4000 g.
‡ Difference between groups was tested by Wilcoxon rank sum test.

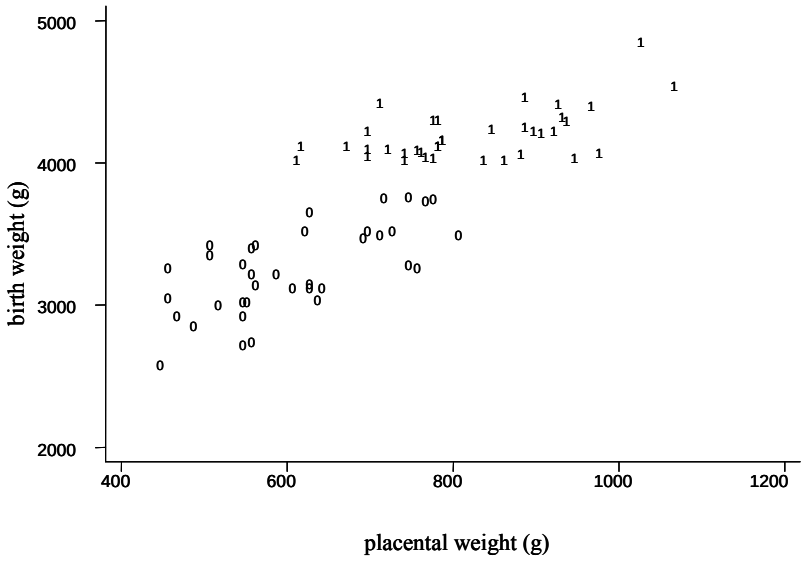

Figure 1. Correlation between the placental weight and birth weight**,** * 0: normal birth weight, 1: macrosomia. †Pearson coefficient of correlation between placental weight and birth weight is 0.550 (p = 0.004) in macrosomia and 0.678 (p = 0.000) in the control group.

Table 4. Effects of insulin growth factors (IGFs) and their receptors' on macrosomia*

Risk factors	macrosomia† (n=37)	Normal birth weight (n=37)	OR (95%CI)		p values‡
IGF-Ⅰ mRNA					
Tertile 1	10	15	1.00		
Tertile 2	12	13	1.38	(0.45-4.25)	0.569
Tertile 3	15	9	2.50	(0.79-7.90)	0.118
IGF-Ⅱ mRNA					
Tertile 1	4	21	1.00		
Tertile 2	20	5	21.0	(4.92-89.6)	<0.001
Tertile 3	13	11	6.20	(1.63-23.6)	0.007
IGF-Ⅰ RmRNA					
Tertile 1	3	22	1.00		
Tertile 2	17	8	15.6	(3.58-67.8)	<0.001
Tertile 3	17	7	17.8	(4.00-79.3)	<0.001
IGF-Ⅱ RmRNA					
Tertile 1	7	18	1.00		
Tertile 2	15	10	3.86	(1.18-12.6)	0.025
Tertile 3	15	9	4.29	(1.29-14.3)	0.018
BMI before pregnancy§			1.32	(1.02-1.71)	0.033
Weight gain in pregnant term (kg)			1.19	(1.05-1.34)	0.006

* All the models were constructed by using simple logistic regression with the IGFs or their receptors as three tertile groups and T1 as the reference.
† Macrosomia is defined as those neonates with a birth weight ≥4000g.
‡ p values were obtained by using Wald's Z test.
§ BMI = body-mass index, as denoted under table 2.

IGF-Ⅱ R mRNA.

Correlation between placental weight and BW

Placental weights of neonates in the macrosomia group was significantly higher than those in the control group (824 ± 112g vs. 611 ± 102 g, p<0.001, Student-t test). The scattered plot (Figure 1) showed that BW had a linear upward trend along with the increase of placental weight in both macrosomic (r = 0.550, p = 0.004) and control groups (r = 0.678, p = 0.000). There was no statistical significance difference in the correlation coefficients between the two groups (z = 0.859, p = 0.390)

Spearman rank correlation analysis suggested that the level of IGF-Ⅰ mRNA, IGF-Ⅱ mRNA, IGF-Ⅰ RmRNA and IGF-Ⅱ RmRNA in placenta have no correlation with the placental weight in either the macrosomic or the control group. Similarly, there was no correlation between the levels of IGFs with theirs receptors and the birth weight in both groups.

Risk factors in macrosomia

The levels of IGF-Ⅰ mRNA, IGF-Ⅱ mRNA, IGF-Ⅰ RmRNA and IGF-Ⅱ RmRNA in placenta of both the macrosomic and control groups were divided into three groups based on their tertiles. Simple logistic regression

Tablet 5. Multivariable-adjusted odds ratios (ORs) and 95% CIs on macrosomia*

Risk factors	Regression coefficient	Standard error	OR (95%CI)		*p* values†
Weight gain during pregnancy	0.297	0.093	1.35	(1.12-1.62)	0.001
BMI before pregnancy‡	0.519	0.265	1.68	(1.00-2.82)	0.050
IGF-Ⅱ Tertile2	2.85	0.986	17.3	(2.50-19.2)	0.004
IGF-Ⅱ Tertile3	1.78	0.930	5.94	(0.96-36.8)	0.056
IGF-ⅠR Tertile2	3.23	1.02	25.3	(3.43-187)	0.002
IGF-ⅠR Tertile3	3.76	1.11	43.0	(4.89-378)	0.001

* The model was constructed with multiple logistic regression under a stepwise forward variable selection strategy with 0.05 as the significance level. The height (continuous), BMI (continuous) and weight gain of the mother during pregnancy (continuous), two IGFs and their receptors were candidate factors in the analysis (dummy variables of tertiles with the first tertile as reference).
† *p* values were obtained by using Wald's Z test.
‡ BMI = body-mass index, as denoted under table 2.

with each factor entered into the model as dummy variables with the first tertile as the reference showed that the level of IGF-ⅡmRNA was associated with the occurrence of macrosomia, so was that of IGF-ⅠRmRNA, IGF-ⅡRmRNA, BMI before pregnancy and weight gain during pregnancy (Table 4).

Statistical significant variables in single analysis were considered in the multiple logistic regression model as potential risk factors. The levels of IGFs with their receptors were introduced into the model as dummy variables, with the first tertile as the reference. With 0.05 as the significance level, four variables, i.e. IGF-ⅡmRNA, IGF-ⅠRmRNA, weight gain during pregnancy and BMI before pregnancy, were found to be statistically significant.
As compared with those in the lowest tertile of IGF-ⅡmRNA levels, multivariable adjusted ORs of macrosomia for those in the increasing two tertiles were 17.3 (95%CI: 2.50-19.2) and 5.94 (95%CI: 0.96, 36.8), respectively. Similarly, multivariable adjusted ORs of macrosomia for those in the increasing two IGF-ⅠRmRNA tertiles were 25.3 (95%CI: 3.43-187) and 43.0 (95%CI: 4.89, 378), respectively (Table 5).

DISCUSSION

Our research showed that the placental weight of neonates with macrosomia was significantly greater than that of the control group. The placental weight of both the macrosomic and control groups had a positive correlation with BW. Our study also revealed the potential association between the development of macrosomia and the IGF_S with their receptors on placenta and fetus. Our data generally agreed with those found in previous studies.[16,17] However, our study did point out several important differences.

The relationship between IGF-Ⅰ in the placenta and the growth of the placenta and macrosomia

At physiological levels, IGF-Ⅰ may promote cellular mitosis and differentiation, as well as suppressing cellular apoptosis. But according to our observation, there was no statistical difference with regard to the expression of IGF-ⅠmRNA in the placenta between the macrosomic group and the control group. IGF-Ⅰ or IGF-Ⅱ null mice result in a 40% decrease in BW compared to their wild-type littermates, though only IGF-Ⅱ null mice exhibited smaller placentas.[19] It would be suggested that IGF-Ⅰ in the placenta could not contribute to the change in size and function of the placenta and the consequence of macrosomia. Other regulation mechanisms to keep IGF-Ⅰ in the placenta on a steady status can not be excluded. However, one can not rule out that this is the result of a lack of power based on a null association from 37 cases and 37 controls and further studies with large sample sizes are warranted.

The relationship between IGF-Ⅱ in the placenta, the growth of the placenta and macrosomia

It was reported that reduced foetal size in IGF-Ⅱ knockout mice was accompanied by changes in the morphological features and also the size of the placentas in these animals.[16,20] Sibley illustrated further that IGF-Ⅱ affected not only the placental development but also the placental transportation ability using Knockout Mice.[17] Hereby, it is reasonable to speculate that over-expression of IGF-ⅡmRNA contribute to macrosomia. Although we did not find a positive correlation between IGF-ⅡmRNA levels and the fetal BWs, we did find that the placental weights of macrosomics were much heavier than those in the control group and placental IGF-ⅡmRNA levels in macrosomics were significantly higher than those in the control group (p=0.025). The over-expression of IGF-Ⅱ mRNA in the placenta was confirmed as an independent risk factor, indicated by both single and multiple logistic regression analysis. Single logistic regression analysis revealed that the risk of macrosomia were 21 times in the second tertile group and 6.20 times in the highest tertile group, as compared with the lowest tertile group in terms of the level of IGF-ⅡmRNA. Multiple logistic regression analysis revealed that the risk of macrosomia was 17.27 times and 5.93 times in two high tertile groups. The fact that the risk of macrosomia of the highest group was lower than the middle group suggested a possible tiptop risk value of the IGF-Ⅱ. Other regulation mechanisms will be initiated to prevent the overdevelopment of the placenta and fetus when the level of IGF-ⅡmRNA exceeds the tiptop.

The relationship between IGF-ⅠR in the placenta, the growth of the placenta and macrosomia

IGF-ⅠR has two kinds of ligands: IGF-Ⅰ and IGF-Ⅱ. IGF-ⅠR is widely expressed in all tissue types in the human. It plays an important role in cellular growth, mitosis and differentiation. Our data did not find a positive correlation between placental IGF-ⅠRmRNA levels and placental weight, as well as fetal weight. But over-expression of placental IGF-ⅠRmRNA have been regarded to be associated with macrosomia, as indicated by both single and multiple logistic regression analysis. Moreover, IGF-ⅠRmRNA presented a linear trend risk during the development of macrosomia. (p for trend = 0.001). This was consistent with findings from several recent reports: Faivre reported on four children from two unrelated families presenting with overgrowth, their parents showed a balanced translocation involving 15q26.1-qter. Molecular and cytogenetic studies showed three copies of the IGF-ⅠR gene. These finding suggests that overgrowth observed in the patients might be related to a dosage effect of the IGF-ⅠR gene.[21] Besides this, Abuzzahab found that mutations in the IGF-ⅠR gene might underlie some cases of prenatal and postnatal growth failure because mutations lead to abnormalities in the function or number of IGF-Ⅰ receptors.[22] Similarly, placental growth may have a close relationship with IGF-ⅠR. Studies of transgenic mice lacking the IGF-ⅠR led to the hypothesis that a reduction in the number of placental IGF-ⅠR might be a contributing factor in pregnancies complicated by IUGR.[23] Therefore, it is reasonable for us to speculate that over-expression of IGF-ⅠR mRNA in placenta contributes to macrosomia.

The relationship between IGF-ⅡR in theplacenta, the growth of the placenta and macrosomia

IGF-ⅡR has a high affinity for IGF-Ⅱ and can trigger the degradation of IGF-Ⅱ and the inhibition of its mitogenic actions. Absence or mutation of the IGF-ⅡR gene would weaken the function of degradation to IGF-Ⅱ followed by increments of IGF-Ⅱ levels in the serum and tissue.[24] We found that there was a significant difference in placental IGF-ⅡR mRNA levels between the macrosomic group and the control group. But this difference disappeared after “BMI before pregnancy” and “weight gain during pregnancy” were adjusted. This suggested that the degradation ability in relation to IGF-Ⅱ levels is similar between the two groups or the degradation of IGF-ⅡR was not enough to produce a difference in terms of IGF-ⅡmRNA levels. It seemed that IGF-ⅡR was not related to the development of the placental and fetal.

In conclusion, the significantly positive associations between the level of placental IGF-Ⅱ and IGF-ⅠR and macrosomia were observed. Our findings suggest that a potential risk effect with regard to the expression of IGF-Ⅱ mRNA and IGF-ⅠR mRNA in the placenta may exist during the development of macrosomia.

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AUTHOR DISCLOSURES

There is no conflict of interest.

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胎盘中的 IGFs 及其受体的表达水平与巨大儿关系的研究

目的：研究足月胎盘中胰岛素样生长因子及其受体的 mRNA 的表达水平，與巨大儿发生风险的關聯。方法：从 2008 年 3 月 1 日至 6 月 30 日，在常州市妇幼保健院，收集足月分娩的 37 例巨大儿和 37 例正常体重儿的胎盘组织，采用 Real Time PCR 技术对胎盘中的胰岛素样生长因子及其受体的 mRNA 的表达水平进行检测。结果：在巨大儿组与对照组，胎盘的重量与新生儿出生体重均成正相关(r=0.550, *p*=0.004 及 r=0.678, *p*=0.000)。采用多因素非条件羅吉斯回归分析，在控制了混杂因素后，与最低 IGF-II mRNA 水平组相比，IGF-II mRNA 中等水平组和高水平组发生巨大儿的 OR 值分别为 17.3 (95%CI: 2.50, 19.2) 和 5.94 (95%CI: 0.96, 36.8)；而与最低 IGF-IR mRNA 水平组相比，中等水平组和高水平组 IGF-IR mRNA 发生巨大儿的 OR 值分别为 25.3 (95%CI: 3.43, 187) 和 43.0 (95%CI: 4.89, 378)。结论：本研究显示胎盘中的 IGF-II mRNA 和 IGF-IR mRNA 的表达水平与巨大儿的发生可能有关。

关键词： 巨大儿、胎盘、胰岛素样生长因子、受体、病例对照研究