

The Correlation of Maternal and Fetal Blood Irisin with Fetal Growth Pattern and Birth Weight

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ABSTRACT

Background: A novel myokine, named Irisin, was identified in human that secreted by skeletal muscle after exercise. Irisin increases energy expenditure by turning white adipose tissue into brown adipose tissue. Irisin is considered as a potential biomarker for obesity and metabolic syndrome.

Objectives: To investigate the maternal/fetal concentrations of the myokine irisin in intrauterine growth restricted (IUGR) fetuses versus large for gestational age (LGA) and appropriate for gestational age (AGA) and the correlation of irisin with fetal growth pattern birth weight.

Methods: A case – control study conducted at Al-Yarmouk teaching hospital from the 1st of January, 2017 to the 1st of January 2018. Ninety six pregnant women between (20_40)years old all with singleton pregnancies, gestational age from 37⁰ – 40⁶ weeks were involved in the study and were divided into three groups: (Group 1) 32 cases with their fetal weight for gestational age between 10th_90th percentile AGA the case group, the control group, (Group 2) 32 cases with their fetal weight for gestational age<10th percentile IUGR and (Group 3) 32 cases with their fetal weight for gestational age>90th percentile LGA, the case group. In all groups, we measured maternal blood irisin & umbilical cord blood irisin, by using ELIZA kits.

Results:

The study involved 32 cases for each control AGA, IUGR and LGA groups. GA was significantly lower in IUGR compared to both LGA and control, ponderal index (PI) was lower in IUGR compared to both LGA (p-value <0.001), and control (p-value <0.001). Fetal irisin was significantly lower in IUGR (0.08 ± 0.05 µg/ml) compared to control (2.17 ± 0.79 µg/ml) and LGA (2.25 ± 0.80 µg/ml), no significant difference between LGA and control. Maternal irisin was significantly lower in IUGR (0.29 ± 0.11 µg/ml) compared to control (2.35 ± 0.76 µg/ml) and LGA (2.44 ± 0.78 µg/ml). In LGA and IUGR there was direct significant correlation between fetal and maternal irisin, Maternal irisin had excellent ability to predict IUGR with cut points ≤ 0.43 , sensitivity 99% and specificity 99%.

Conclusions: maternal blood irisin level directly correlated with fetal blood irisin level. Both maternal & fetal Irisin blood level directly correlated with fetal growth pattern & birth weight. Maternal irisin level best to use as an indirect biomarker for IUGR.

Keywords: Irisin, fetal growth, Appropriate for gestational age AGA, Intrauterine growth restriction IUGR, Large for gestational age LGA.

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INTRODUCTION

Fetal Growth:

Fetal growth regulation is complex and is dependent on maternal, placental and fetal interactions. The primary determinants of fetal growth are adequate delivery of both nutrient and oxygen through the placenta⁽¹⁾.

Phases of Fetal growth: 1- Hyperplasia: occur in the first 16 weeks and is characterized by a rapid increase in cell number with fetal-growth rate 5 g/day. 2_ Cellular hyperplasia and hypertrophy. From 17 to 32 weeks of gestation with fetal growth rate 15_ 20 g/day. 3_ Cellular hypertrophy: occur after 32 weeks of gestation, in this phase most fetal fat and glycogen are accumulated, with fetal-growth rate 30 to 35 g/day⁽²⁾.

DISORDERS OF FETAL GROWTH: Fetal growth disorder is defined as the failure of a fetus to grow according to its genetic potential. fetal growth is defined depending on the expected dimensions of the infant in relation to its gestational age⁽³⁾, fetal size is described in terms of its size for gestational age and is presented on percentile charts⁽⁴⁾, depending on both the gestational age as well as on the birth weight fetal which as illustrated in figure (1), growth pattern classified as : Appropriate for Gestational

Age (AGA): Birth weight lies between the 10th and 90th percentiles⁽⁵⁾, Small for gestational age (SGA): Birth weight <10th centile is small for gestational age which may be constitutionally small or intrauterine growth restricted (IUGR)⁽¹⁾, Large for gestational age (LGA) : Birth weight above the 90th percentile for gestational age⁽⁵⁾.

IRISIN: Irisin is an adipokine/ myokine, discovered by Boström and co-workers in 2012, identified as a cleaved and secreted product of the fibronectin type III domain containing protein 5 (FNDC5) protein⁽⁶⁾.

Irisin is a novel polypeptide hormone including 112 amino acids and is derived from the carboxy terminus of a membrane-spanning protein with 196 amino acids known as fibronectin type III domain containing protein 5 (FNDC5)⁽⁷⁾.

Synthesis and Secretion of Irisin are induced by exercise⁽⁷⁾, the peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1-α), a transcriptional coactivator released by the muscle that induces mitochondrial biogenesis and thus thermogenesis as well as glucose, lipid, and energy homeostasis, PGC1-α induces the expression of the fibronectin type III domain

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containing 5 (FNDC5) gene which is cleaved and secretes irisin from the skeletal muscle⁽⁸⁾.

Still there is some controversy about the exact mechanism of irisin activity. Many recent studies show that irisin is molecules released by skeletal muscle and heart in response to exercise and act as messengers to tissues, including skeleton, heart, liver, fat and the brain. Recent studies show that irisin acts by stimulating browning of white adipose tissue, promoting glucose uptake in skeletal muscle and heart, improving hepatic glucose and lipid metabolism, and pancreatic β cell function, these physiological functions of irisin accomplished through the activation of p38 mitogen activated protein kinase (p38 MAPK) and extracellular regulated protein kinase⁽⁷⁾.

Irisin concentrations are present at ~3.6 ng/ml in sedentary individuals and are significantly increased to ~4.4 ng/ml in individuals undergoing aerobic interval training. Irisin being regulated by endurance exercise, the muscle mass is the main predictor of circulating irisin levels in humans⁽⁹⁾. These findings suggest that irisin release could be a function of muscle energy demand⁽¹⁰⁾. Bariatric surgery-induced weight loss therefor associated with decrease in irisin levels, independent of BMI⁽¹¹⁾.

METHODS

This is a prospective case - control study conducted at AL-Yarmouk teaching hospital (department of obstetrics and gynecology) in Baghdad city during the period from 1st of January 2017 to 1st of January 2018. Informed consent was obtained from all participants women enrolled in this study.

A total of 96 pregnant women between (20_40)years old all with singleton pregnancies, their gestational age ranged from 37⁺⁰ to 40⁺⁶ weeks were involved in this study and were divided into 3 groups according to growth pattern of their fetuses& identified risk factors for fetal growth disorders Group 1: includes 32 cases with no risk factors and their fetuses weight for gestational age between 10th_90th percentile as control group, Group 2: includes 32 cases with risk factors of IUGR and their fetal weight_ for gestational age<10th percentile and Group 3: includes 32 cases with risk factors for LGA and their fetal weight _for gestational age>90th percentile, a s case group.

Exclusion criteria: Unknown pre pregnancy BMI, Symmetrical IUGR fetuses, Fetal Congenital anomaly, Constitutionally small fetuses, Multiple pregnancy, Pregnant women with PROM& preterm labour. Detailed history was taken, Physical examination and investigations looking for risk factors for IUGR and LGA (pre_eclampsia, hypertension with superimposed pre_eclampsia, diabetes whether gestational or pre_gestational diabetes , history of thrombophilia). Prenatal diagnosis of IUGR fetuses was based on: Positive history of risk factors for IUGR, Clinical examination (small for date uterus), Ultrasound examination(increase HC/AC ratio ,the EFW <10th percentile , abnormal Doppler indices).

Prenatal diagnosis of LGA fetuses was based on: Positive history of risk factors for LGA, obstetrical examination (Leopold s maneuver), Sonography features (EFW>90th percentile).

A five milliliter of venous blood was taken from each participant after the initial assessment for sampling and irisin assay.

Immediately after delivery along with assessment of Apgar score at t first and fifth minute and weighted the

newborns, divided them in to three groups based on: birth weight for gestational age, ponderal index calculation ($PI = \text{birth weight} \times 100 / (\text{Crown head length})^3$), clinical examination by pediatrician: 1_AGA: infants with birth weight between 10th_90th percentile. 2_A symmetrical IUGR confirmed by: Birth weight <10th percentile for gestational age and clinical examination with characteristics features. 3_LGA/ macrosomic confirmed by: Birth weight >90th percentile for gestational age and Birth weight>4000g.

Few milliliters of mixed arteriovenous cord blood were taken from doubly clamped fetal umbilical cord at birth for each infant

After sampling, both maternal and neonatal samples were collected separately into tubes containing EDTA (Ethylene Diamine Tetra-acidic Acid) for irisin assay each sample mixed separately for 10-20 minutes then placed in centrifuge at 2000-3000 RPM for approximately 20 minutes, then collect the supernatant plasma and stored at deep freezer -20C° until analysis.

Plasma irisin was measured for neonates& mothers by using enzyme linked immunoassay (ELIZA) by using human irisin ELIZA Kit, (SHANGHAI YEHUA Biological technology co., Ltd. Cat. NO: YHB176Hu) according to manufactures

instruction, With assay range : 0.05 μ g/ml→15 μ g/ml and Sensitivity :

0.024 μ g/ml. Discrete variables presented using their number and percentage, chi square test used to analyze the discrete variable. Two samples t test used to analyze the differences in means between two groups (if both follow normal distribution with no significant outlier), while one-way ANOVA used to analyze the differences between more than two groups (if they follow normal distribution with no significant outlier) after that in the results is significant post Hoc Tukey test will be used to find which pair is significant.

Linear regression analysis performed to assess the relationship between different variables, if one or both of them follow normal distribution person regression used but if both did not follow normal distribution spearman correlation will used. Scatter plot used to present the regression analysis (correlation coefficient or standardized beta is a representative of magnitude and direction of the relationship), 0.00-0.29 = little or no correlation; 0.30-0.49 = weak; 0.50-0.69 = moderate; 0.70-0.89 = strong; and 0.90-1.00 = very strong. Negative signs indicate inverse relationship, but positive sign represent direct relationship.

Receiver operator curve used to see the validity of different parameters in separating active cases from control (negative cases) and area under the curve i.e., AUC and its p value prescribe this validity (if AUC \geq 0.9 mean excellent test, 0.8 – 0.89 means good test, 0.7 – 0.79 fair test otherwise unacceptable). Trapezoidal method used for calculating the curve.

In a ROC curve the true positive rate (Sensitivity) is plotted in function of the false positive rate (100-Specificity) for different cut-off points. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold.

RESULTS

In our study, ninety-six pregnant women with gestational age from 37⁺⁰- 40⁺⁶ weeks were involved and divided in to three groups {IUGR, LGA, AGA (control)}, we observed

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plasma level of both maternal & fetal blood irisin in these groups and its correlation with fetal growth status.

Mean age, BMI and parity were not statistically different between different groups. The frequency of DM, pre_gestational DM and GDM in LGA was statistically higher than in IUGR and control (AGA), pre_eclampsia, thrombophilia, was significantly higher in IUGR compared to LGA and control, (table1).

Gestational age was significantly lower in IUGR compared to control (p-value = 0.001) and LGA (p-value <0.001). PI was significantly lower in IUGR compared to control (p-value <0.001) and LGA (p-value <0.001). APGAR 1 min and 5 minutes was not significantly different between the groups. (Table 2 & Figure 1).

Fetal and maternal irisin was significantly lower in IUGR compared to both control and LGA, no significant difference between LGA and control, (Table 3 and Figure 2&3).

Maternal irisin had excellent ability as predictor of IUGR, at cut point ≤ 0.43 had 99% sensitivity and 99% NPV; best indicate that this maternal irisin can be used as screening tool to predict IUGR, maternal irisin can act as both confirmatory test and screening test since both PPV and NPV are high for IUGR from control, (table 4 and figure 4). There was direct significant correlation between fetal irisin with Ponderal index in IUGR and LGA patients (stronger in LGA), there was non-significant correlation between fetal irisin and gestational age and baby weight in both IUGR and LGA, except the correlation between baby weight with fetal irisin was direct and significant in LGA, (Table 5 & Figure 5).

There was direct significant correlation between maternal irisin with Ponderal index in LGA and IUGR patients (however it was stronger in LGA), there was non-significant correlation between maternal irisin gestational age and baby weight in both IUGR and LGA, (Table 6).

Table 1: maternal characteristics

Variables	Control	IUGR	LGA	p-value
Number	32	32	32	-
Age (years), mean \pm SD	30.4 \pm 6.6	32.6 \pm 7.0	30.0 \pm 6.8	0.270 ^a
BMI (kg/m ²), mean \pm SD	22.1 \pm 2.8	23.6 \pm 4.6	23.8 \pm 4.0	0.174 ^a
Parity, mean \pm SD	3.8 \pm 2.1	3.8 \pm 2.3	2.8 \pm 2.6	0.156 ^a
DM, no. (%)	0 (0%)	4 (12.5%)	28 (87.5%)	<0.001 ^b
GDM, no. (%)	0 (0%)	0 (0%)	22 (68.8%)	<0.001 ^b
Pre-gestational DM, no. (%)	0 (0%)	4 (12.5%)	6 (18.8%)	0.034 ^c
Pre_eclampsia, no. (%)	0 (0%)	11 (34.4 %)	4 (12.5%)	<0.001 ^c
Thrombophilia, no. (%)	0 (0%)	5 (15.6%)	0 (0%)	0.009 ^c
C/S delivery, no. (%)	6 (18.8%)	22 (68.8%)	28 (87.5%)	<0.001 ^b

IUGR: intrauterine growth restriction, LGA: large for gestational age, C/S: Caesarean section

a One-way ANOVA, b chi-square test, c Fisher-Freeman-Halton exact test

Table 2: neonatal characteristics

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Variables	Control	IUGR	LGA	p-value
Number	32	32	32	-
Gestational age (weeks), mean \pm SD	38.3 \pm 1.1	37.4 \pm 0.5	38.3 \pm 0.9	<0.001 ^a
Ponderal index (kg/m ³), mean \pm SD	42.46 \pm 1.04	27.60 \pm 4.76	53.63 \pm 6.79	<0.001 ^a
APGA 1 min, mean \pm SD	7.2 \pm 0.9	7.1 \pm 0.8	6.9 \pm 0.9	0.420 ^a
≥ 7 (normal), no. (%)	23 (71.9%)	23 (71.9%)	18 (56.3%)	0.310 ^b
APGAR 5 min, mean \pm SD	8.4 \pm 1.0	8.4 \pm 1.2	7.9 \pm 1.1	0.162 ^a
≥ 7 (normal), no. (%)	32 (100%)	30 (93.8%)	32 (96.9%)	0.130 ^c
Gender, no. (%)				
Female	15 (46.9%)	13 (40.6%)	13 (40.6%)	0.843 ^b
Male	17 (53.1%)	19 (59.4%)	19 (59.4%)	

IUGR: intrauterine growth restriction, LGA: large for gestational age, a One-way ANOVA, b chi-square test, c Fisher-Freeman-Halton exact test

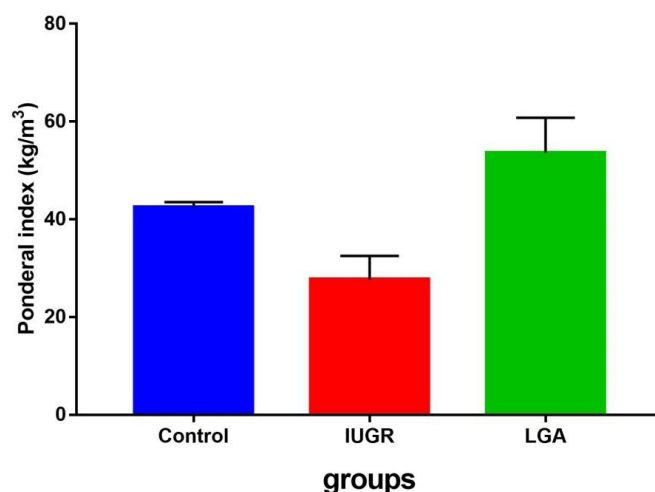


Figure 1: Ponderal index of different groups

Table 3: comparison of fetal and maternal irisin in different groups

Variables	Control	IUGR	LGA	p-value
Number	32	32	32	-
Fetal irisin (μ g/ml)	2.17 \pm 0.79	0.08 \pm 0.05	2.25 \pm 0.80	<0.001
Maternal irisin (μ IU/ml)	2.35 \pm 0.76	0.29 \pm 0.11	2.44 \pm 0.78	<0.001

One-way ANOVA

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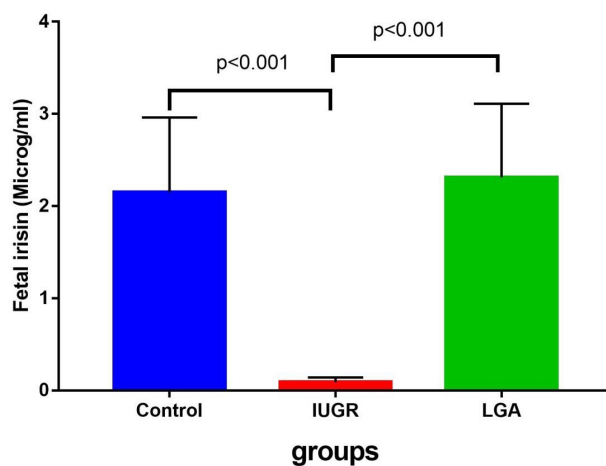


Figure 2: Fetal irisin in different groups

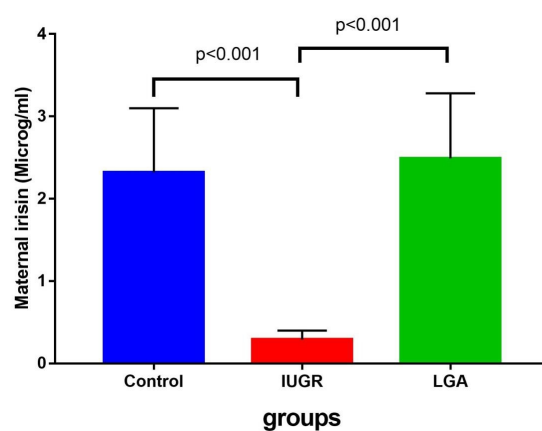
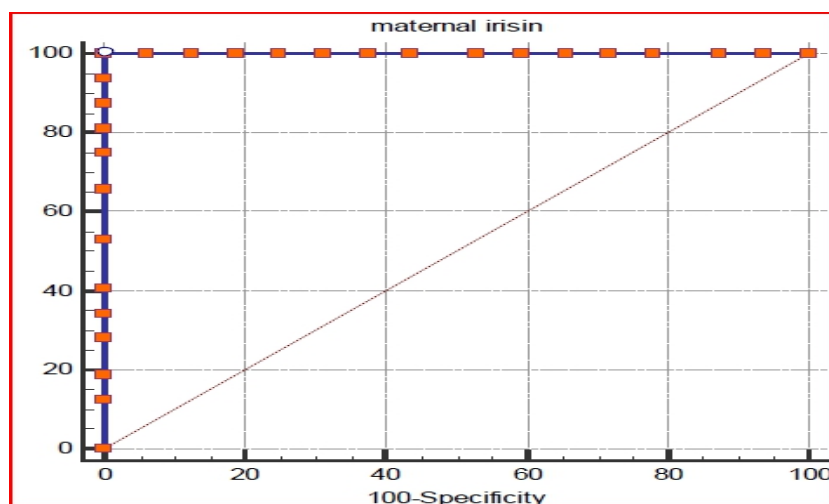


Figure 3: Maternal irisin in different groups

Table 4: Predictive value of maternal Irisin as predictor of IUGR from AGA

AUC	p-value	Cut point	SN	SP	PPV	NPV
0.999	<0.001	≤0.43	99%	99%	99%	99%

AUC: area under the curve, SN: sensitivity, SP: specificity, PPV: positive predictive value, NPV: negative predictive value, ROC: receiver operator characteristics



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Figure 4: ROC curve of maternal irisin as predictor IUGR

Table 5: Correlation between fetal irisin and various parameters in IUGR and LGA

Variables	Fetal irisin			
	IUGR		LGA	
	R	p-value	r	p-value
Gestational age	-0.067	0.717	0.261	0.149
Ponderal index	0.397	0.024 [Sig.]	0.623	<0.001 [Sig.]
Baby weight	0.246	0.063	0.498	0.004 [Sig.]

r: Linear correlation coefficient

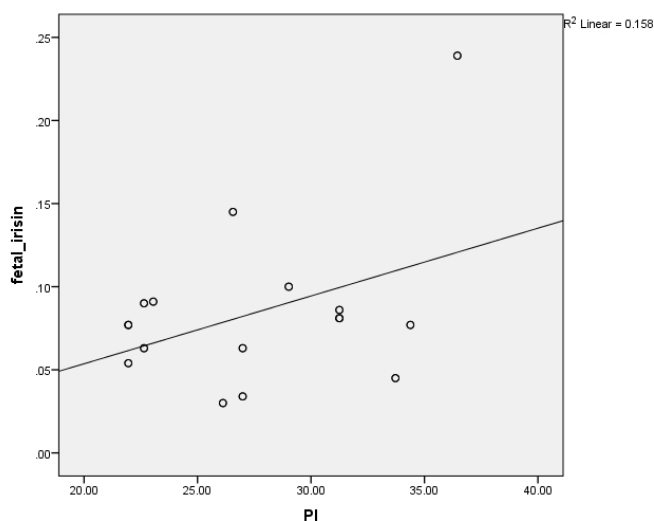


Figure 5: Correlation between PI and fetal irisin in IUGR baby.

Table 6: Correlation between maternal irisin and various parameters in IUGR and LGA

Variables	Maternal irisin			
	IUGR		LGA	
	r	p-value	r	p-value
Gestational age	0.162	0.375	0.156	0.393
Ponderal index	0.361	0.043 [S.]	0.436	0.013 [Sig.]
Baby weight	0.076	0.851	0.250	0.168

r: Linear correlation coefficient

DISCUSSION

Irisin is a newly discovered marker with effect to enhance the conversion of white adipose tissue to brown adipose tissue which subsequently causes positive energy balance toward enhancing tissue metabolic homeostasis⁽¹²⁾. In the current study we found both fetal and maternal irisin are correlated with growth status of fetus, indicating its possible association with fetal growth pattern and birth weight.

The mean maternal age in this study was early thirty, there was no significant difference in age between the study groups, which was in agreement with Yuksel *et al*

2014⁽¹³⁾, no significant difference between control, IUGR and LGA groups, also in agreement with Keleş and Turan 2016., also there was no significant difference in parity between the different groups, with was in agreement with previous study⁽¹⁴⁾. In our study the frequency of diabetic was significantly higher in LGA patients compared to both control and IUGR, same result was reported by other study showing the association between LGA with DM (especially gestational DM)⁽¹⁵⁾.

fetal irisin was significantly lower in IUGR in this study compared to both LGA and control (p-value < 0.001), despite that fetal irisin was higher in LGA compared to

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control there was no statistically significant difference between them, this study is in agreement with Baka et al 2015⁽¹⁶⁾. An impairment of glucose homeostasis is associated with early BAT reduction since it will lead to suppression of energy expenditure and possibly obesity⁽¹⁷⁾, **irisin** down-regulation in IUGR fetuses may suggest a reduction of early BAT depots, predisposing to the later emergence of insulin resistance. Irisin levels did not vary significantly between subjects of normal BMI and overweight-obese subjects, also fetal irisin did not correlate with maternal age ($r = -0.225$), BMI ($r = -0.084$) this was found in Caglar et al study (2014)⁽¹¹⁾. In Caglar et al study (2014), fetal irisin was significantly lower in IUGR compared to control (0.253 vs. 0.361 $\mu\text{g/ml}$, p -value = 0.003)⁽¹¹⁾, in Keleş et al study (2016) which compared fetal irisin between 34 AGA and 34 small gestational age (SGA) fetal irisin was significantly lower in SGA than control p -value < 0.001⁽¹⁴⁾. In Baka et al study (2015) which involved 30 LGA, 30 IUGR and 20 AGA they reported that fetal irisin were significantly lower in IUGR compared to AGA and LGA (p -value = 0.002 and 0.003, respectively), and no significant difference between LGA and AGA⁽¹⁶⁾. These studies appear to agree with our findings in this regard.

In our study, similar fetal irisin level between LGA and AGA suggest that irisin are not directly implicated in the metabolic disturbances associated with fetal macrosomia^(18,19), Yuksel et al study they suggest no differences in cord blood irisin levels between patients with GDM and healthy pregnant women⁽¹³⁾.

In the current study maternal irisin was significantly lower in IUGR compared to both LGA and control (p -value < 0.001), despite that maternal irisin was higher in LGA compared to control there

was no significant difference between them, this disagreement with Briana et al study (2016) which involved studying the difference between three group IUGR (30 infant), LGA (30 infant) and appropriate for gestational age infant (AGA, 20 infants) maternal irisin showed no statistically significant difference among the three groups with no correlation with insulin in each ones, indicating that irisin may not be directly play a role in the maternal metabolic disturbances associated with abnormal fetal growth⁽²⁰⁾. In Caglar et al study (2014), maternal irisin show no significant difference between control and women with fetal growth restriction (1.695 vs. 1.171 $\mu\text{g/ml}$, p -value = 0.806)⁽¹¹⁾.

In our study there was direct significant correlation between maternal and fetal irisin with Ponderal index ($r = 0.623$, $r = 0.436$, respectively), fetal irisin was significantly and directly correlated with both Ponderal index and birth weight; however, this correlation was stronger in LGA compared to IUGR, which could be attributed to pathology of IUGR and lower growth status. In Caglar et al study (2014) there was direct significant correlation between fetal irisin with birth weight ($r = 0.462$), birth height ($r = 0.434$), gestational age at delivery ($r = 0.462$)⁽¹¹⁾, in Baka et al (2015) study there was direct correlation between fetal irisin with birth weight and customized centiles ($r = 0.245$, $p = 0.029$ and $r = 0.247$, $p = 0.027$, respectively).

This positive correlation between fetal irisin with infant growth parameters (weight, Ponderal and index customized centile) may contribute to a slower fat gain in heavier neonates during early infancy, by promoting higher total energy expenditure^(12, 18). Previous studies suggest that newborns with higher birthweight have a

slower weight and fat gain than newborns with lower birthweight during early infancy, probably due to higher total energy expenditure in the LGA^(19, 21).

Irisin release is associated with exercise and cold exposure (through shivering)⁽¹²⁾, after delivery; since extra uterine environment are cooler than intrauterine environment the neonate cools down, to maintain neonatal temperature via brown adipose tissue (BAT) in non-shivering process⁽²²⁾, this illustrate the role of BAT as a source of postnatal temperature homeostasis and maintenance of neonatal growth during pregnancy is sustained by glucose supply through the mother⁽²³⁾.

In Caglar et al study (2014) maternal irisin did not correlate with birth weight, birth height, gestational age at delivery, maternal age, and BMI⁽¹¹⁾, in Briana et al study (2016) maternal irisin, show no significant correlation with maternal age, BMI before and after pregnancy, delivery mode, fetal gender, or maternal diabetes⁽²⁰⁾, these findings were also in agreement with Hernandez-Trejo study (2016)⁽²⁴⁾.

In Conclusion, fetal blood irisin level was directly correlated with maternal blood irisin level,

both maternal and fetal irisin directly correlated with fetal growth pattern, &confirmatory tool for IUGR. Maternal irisin had ability to predict of fetal growth disorders, specifically to use as a screening & confirmatory tool.

We recommend using maternal irisin as a biomarker for screening of fetal growth disorders, specifically as a screening biomarker for prediction of IUGR in combination with standard screening protocols for fetal growth disorders.

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