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RESEARCH ARTICLE

INSULIN AND LEPTIN STATUS IN APPROPRIATE- FOR -GESTATIONAL-AGE INFANTS OF DIABETIC AND NON -DIABETIC MOTHERS

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ABSTRACT

Adequate glycemic control before and during pregnancy is crucial to improving outcome of gestational and pre-gestational diabetes mellitus and may normalize birth weight (Waldemar, 2016). However, it is still a controversy whether intra-uterine exposure to maternal diabetes is a risk factor for changing hormone levels involved in the development of insulin resistance in these infants. This cross sectional study was conducted on 60 terms appropriate of gestational age (AGA) neonates (30 Infants of diabetic mothers and 30 infants of non diabetic mothers) delivered in Obstetrics and Gynecology Departments, at El Menofiya University Hospital and Shebin- Elkom Teaching Hospital, from September 2014 to Marsh 2015. This study revealed that serum Insulin, Leptin & Insulin resistance were higher in average birth weight IDM compared with controls with statistically highly significant differences ($p \leq 0.001$). Infants with bad maternal diabetic control showed higher serum Insulin and Leptin levels than infants with fair maternal diabetic control. Thus interventions during pregnancy, aimed at a close monitoring of maternal blood glucose concentrations, are likely to have an impact not only on maternal and neonatal health, but also on the epidemic of T2DM and childhood obesity. Breast feeding and postnatal follow up of IDM weight gain may be essential to protect infants of diabetic mothers from these complications. We found that appropriate for gestational age (AGA) infants of diabetic mothers had higher cord serum insulin, leptin and insulin resistance index than those of non diabetic mothers which were directly correlated to maternal diabetic control as regard Hba1c levels.

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INTRODUCTION

The incidence of diabetes in pregnancy reflects that of T2DM in the population and is as high as 5–8% of pregnancies in the USA and in Europe, and reaches 15–20% in parts of the developing world. Impaired glucose–insulin metabolism programmed during the critical window of perinatal development may be passed to the next generation, possibly through epigenetic changes in gene expression **(**Umberto & David, 2009). The subsequent incidence of diabetes mellitus in infants of diabetic mothers is higher than that in the general population (Waldemar, 2016). Thus even in normal birth weight offspring from diabetic pregnancies, the risk for obesity during childhood was increased (Umberto and David, 2009). Leptin, the product of the obesity (ob) gene, is a hormone of 16 kDa comprising 167 amino acids (Delia-Marina Alexe *et al*., 2006). It plays an essential role in the regulation of energy homeostasis, food intake and body composition beginning in the early life, when the hormone also controls overall fetal growth and development (Umberto Simeoni & David J. Barker, 2009). Thus, factors that influence fetal leptin levels may alter the programming of the appetite behavior by modifying the normal set-points, as well as the energy metabolism and adiposity. These changes further lead to an increased risk of developing cardiovascular and metabolic diseases in later life (Bunt *et al*., 2005). Insulin is an anabolic hormone that promotes glucose uptake, glycogenesis, lipogenesis, and protein synthesis of skeletal muscle and fat tissue through the tyrosine kinase receptor pathway. In addition, insulin is the most important factor in the regulation of plasma glucose homeostasis, as it counteracts glucagon and other catabolic hormones (The global diabetes community, 2014; Alzira Martins *et al*., 2004). Insulin, whose action leads to increased adiposity, and leptin, which is

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involved in the down regulation of appetite, are linked through the adipo-insular axis, which connects the brain and the pancreas with leptin-and insulin-sensitive peripheral tissues.

Elevated insulin levels have been shown to be related to the later development of obesity. An interesting hypothesis is thus that pregnancy diabetes may lead to an increased secretion of insulin, which is insufficiently balanced by raised leptin concentrations, and the development of obesity (Dabelea, 2007; Umberto Simeoni, David J. Barker, 2009).

Subjects and Methods

This cross sectional study was conducted on 60 terms neonates (35 females and 25 males) delivered in Obstetrics and Gynecology Departments, at El Menofiya University Hospital and Shebin- Elkom Teaching Hospital.The study was carried out from September 2014 to Marsh 2015.

They were divided into two groups

Group1 (The cases group):30 Infants of diabetic mothers (IDM) with weight appropriate for gestational age (AGA), 23 were gestational and 7 were pre-gestational based on history & laboratory data of their mothers. Group2 (The control group):30 apparently healthy neonates with appropriate weight for gestational age of non diabetic mothers (INDM).

Exclusion criteria

Any apparent congenital anomalies.
Clear chromosomal abnormalities e.g. Down syndrome.
Any major systemic disease or severe brain damage.

All cases and controls were subjected to the following

Age, mode of delivery, detailed medical history including: for diabetic mothers, diabetic history-including type of diabetes, types of diabetic medication if used, diabetic control if known and any recent investigations for Diabetes. Complete clinical examination of the newborns.

Table 1. Comparison between the mothers of the two studied groups according to R.B.S (mmol/L) and HbA1c

	Group1 (n =30)		Group 2 (n =30)		T	P
R.B.S (mmol/L)	4.22 – 12.22		3.67 – 5.11			
Range	5.51 ± 1.90		4.32 ± 0.37		3.346*	0.002*
Mean ± SD	5.25		4.33			
Median						
HbA1c	7.15 – 17.0		4.50 – 6.0			
Range	9.70 ± 3.28		5.41 ± 0.56		7.072*	<0.001*
Mean ± SD	8.30		5.65			
Median						
HbA1c	No.	%	No.	%	□□	P
•6-7% good control	0	0.0	30	100.0	60.00*	<0.001*
•7.1-8.4 % fair control	19	63.3	0	0.0		
•≥8.5% bad control	11	36.7	0	0.0		

Table 2. Comparison between the two studied groups according to Babies' data

	Group 1 (n =30)		Group 2 (n =30)		Test of sig.	P
	No.	%		%		
Gestational age (weeks)						
Range	37.0 – 37.0		38.0 – 40.0		t=14.966*	<0.001*
Mean ± SD	37.0 ± 0.0		38.10 ± 0.40			
Median	37.0		38.0			
Sex	37.0					
Male	13	43.3	11	36.7	t=14.966*	0.598
Female	17	56.7	19	63.3		
Weight (kg)						
Range	2.50 – 3.50		2.40 - 3.50			0.087
Mean ± SD	3.04 ± 0.28		2.91 ± 0.29		χ^2= 0.278	
Median	3.0		2.90			
Length (cm)						
Range	45.0 – 48.0		46.0 – 50.50		t=6.536*	<0.001*
Mean ± SD	46.32 ± 0.65		48.13 ± 1.38			
Median	46.0		48.0			
B.M.I						
Range	11.81 – 16.54		10.0 – 16.54		t=6.536*	<0.001*
Mean ± SD	14.17 ± 1.32		12.64 ± 1.82			
Median	13.88		12.43			
Pallard score(Age)						
Range	35 – 38.0		38.0 – 40.0		t=3.744*	<0.001*
Mean ± SD	36.70 ± 2.26		38.60 ± 1.75			
Median	37.50		39.0			
Apgar score (1min)						
Range	6.0 – 9.0		7.0 – 9.0		t=7.464*	<0.001*
Mean ± SD	7.07 ± 0.64		8.20 ± 0.71			
Median	7.0		8.0			
Apgar score (5min)						
Range	8.0 – 10.0		8.0 – 10.0		t=6.473*	0.011*
Mean ± SD	9.03 ± 0.61		9.43 ± 0.57			
Median	9.0		9.0			
R.B.S (mmol/L)						
Range	4.44 – 7.78		2.61 – 3.89		t= 2.616*	<0.001*
Mean ± SD	5.49 ± 0.86		3.18 ± 0.37			
Median	5.53		3.19			

Investigations

- Fasting blood glucose and HbA1c was measured for all mothers.
- Baby's blood Glucose was measured during the first hour of life using glucometer.
- A 5 ml cord venous blood sample was taken immediately after the separation of the placenta. Blood was left to clot then centrifuged for 10 minutes at 5000 rpm. The sera were separated and stored at -20 ºC until the time of the assay (time no longer than 6 months).
- Serum Insulin and Leptin were measured from cord blood sample by ELISA.
- Insulin resistance was calculated according to the following formula:
- Glucose (mmol/L) × insulin (µUI /mL)/22.5 (Haffner, *et al*., 1997).
- Data were analysed by SPSS (Statistical Program for Social Solution) V.20 (Kirkpatrick, Feeney, 2013)

RESULTS

Diabetic mothers showed no statistically significant difference between them and non diabetic ones regarding their age, modes of their delivery and hypertension, but there is statistically highly significant difference between the cases and control groups regarding maternal fasting blood sugar (R.B.S) and HbA1c.(Table 1)

NB: In blood glucose measurement, 1 mmol / L is equal 18 mg / dl, and 1 mg / dl is equal 0.0556 mmol / L. In spite of being all term, average body weight and no statistical sex difference, IDM showed lower gestational age, Pallard score, Apgar score at 1 &5 minutes than INDM.

Despite all babies were of average length for gestational age at birth, IDM babies were significantly shorter. On the other hand IDM group had higher babies BMI & RBS at birth in comparison to control group where the differences were statistically highly significant (Table 2). Serum Insulin, Leptin & Insulin resistance were higher in IDM group when compared with controls. The differences were statistically highly significant ($p \leq 0.001$) (Table 3). In this study infants with maternal bad diabetic control showed higher serum Insulin and Leptin levels than infants with fair maternal diabetic control where cord serum leptin was statistically highly significant (Table 4).

DISCUSSION

At the central nervous system (CNS) level, leptin exerts neurotrophic actions that control feeding during the critical period of development of the hypothalamus. Unlike what happens in later life, some findings from animal studies indicate that leptin does not inhibit the appetite during intrauterine and early postnatal life. On the contrary, it seems that leptin promotes swallowing activity and hyperphagia, therefore contributing to the rapid growth and weight gain of the newborn, but this evidence is still inconclusive (Plagemann *et al*., 1997; Meigs *et al*., 2000). Thus, factors that influence fetal leptin levels may alter the programming of the appetite behavior by modifying the normal set-points, as well as the energy metabolism and adiposity. These changes further lead to an increased risk of developing cardiovascular and metabolic diseases in later life (Bunt *et al*., 2005). Induction of leptin resistance in utero may therefore be hypothesized as potential mechanisms for later development of obesity in offspring exposed to diabetes in utero as part of the phenomenon of hypothalamic obesity (Dana Dabelea and Tessa Crume, 2011). Despite of appropriate weight of gestational age of the studied infants, and being all terms IDM had less gestational age than control group (mean gestational ages were 37 &38 weeks respectively). This was also observed by Ma Martha *et al*., 2012.

Table 3. Comparison between the two studied groups according to cord venous blood laboratory results

	Group (n =30)	Group 2 (n =30)	Z	P
Serum Insulin (µIU/mL)				
Range	2.22 – 101.80	0.52 – 11.56	3.918*	<0.001*
Mean ± SD	17.81 ± 28.83	3.86 ± 2.72		
Median	7.57	3.10		
Serum Leptin (ng/mL)				
Range	10.47 – 77.10	0.56 – 24.61	5.914*	<0.001*
Mean ± SD	26.60 ± 19.12	6.86 ± 5.78		
Median	19.95	6.03		
Insulin resistance				
Range	0.46 – 35.06	0.06 – 1.71	5.278*	<0.001*
Mean ± SD	4.93 ± 8.87	0.54 ± 0.39		
Median	1.66	0.42		

Z: Z for Mann Whitney test

Table 4. Relation between HbA1c level with insulin and leptin in IDMs group

	HbA1c level		Z	P
	7.1-8.4 % fair control (n =19)	≥8.5% bad control (n =11)		
Insulin				
Range	2.22- 8.85	3.49-101.80	3.723*	<0.001*
Mean ± SD	5.50±2.29	39.07±40.20		
Median	5.91	20.07		
Leptin				
Range	10.47-36.91	11.76-77.10	2.044*	0.041*
Mean ± SD	19.25±6.75	39.31±26.43		
Median	17.22	25.32		

Z: Z for Mann Whitney test

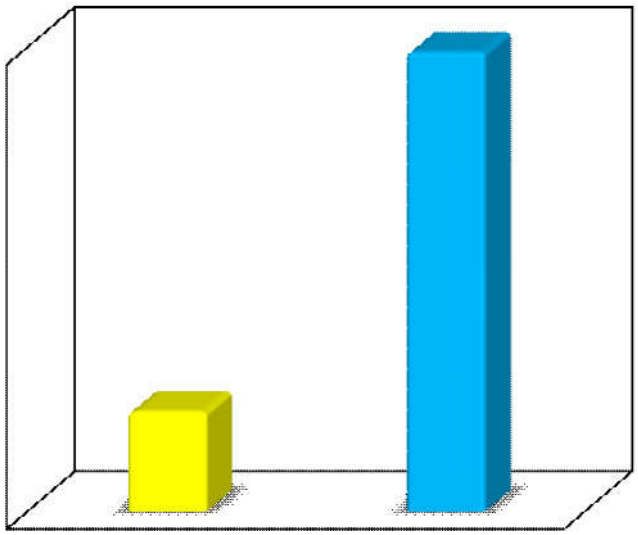

Figure 11. Comparison between the two studied groups according to Insulin

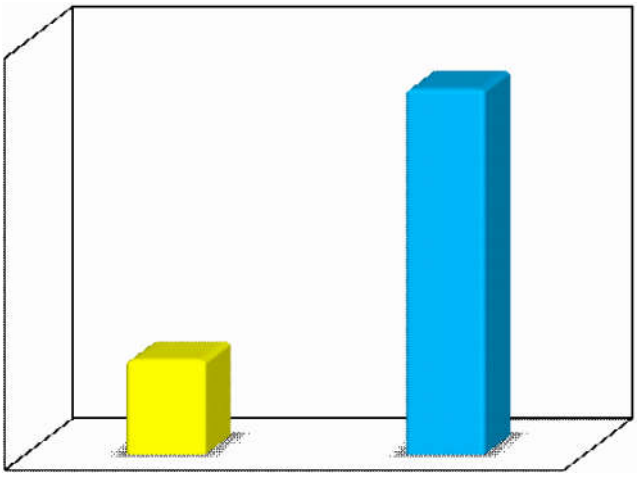

Figure 12. Comparison between the two studied groups according to Leptin

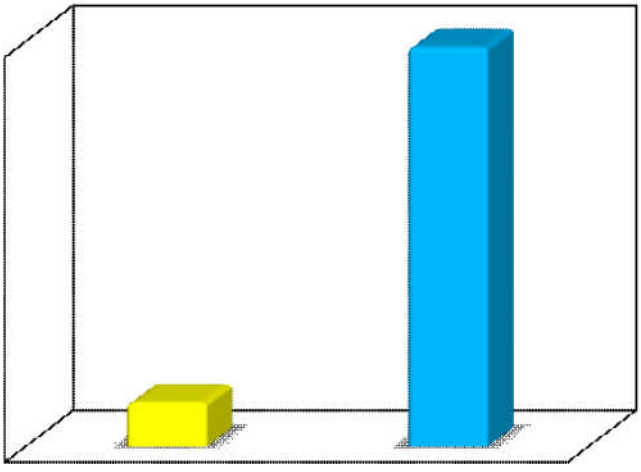

Figure 13. Comparison between the two studied groups according to Insulin resistance

The risk of advancing fetal macrosomia, birth injury, and in utero demise increases as the due date approaches (Zurawin, 2015).

All babies showed average length for gestational age, but IDM babies were significantly shorter than INDM. This could be explained by their maternal metabolic control as Ma. Martha *et al*.,2012 recorded that IDM with HbA1c >6 % in the third trimester showed lower height when they were compared with those infants whose mothers showed better metabolic control. Higher Leptin levels represent a mechanism for enlarging bone size, and thus bone resistance, to cope with increased body weight (Hamrick *et al*., 2008) but no significant correlation between cord leptin and birth length (Ali Awsat Mellati,*et al*., 2009). IDM showed higher BMI & RBS at birth than INDM. Numerous studies support the results of this study (Alexe *et al*., 2006; Matsuda *et al*., 1997; Schubring *et al*., 1997; Collinson *et al*., 2005).

Neonatal glucose level at 1 hour of age correlated significantly with venous cord leptin levels in the diabetic group only (John G. Manderson *et al*., 2003). This goes with our results.

Why AGA infants?

Birth weight correlated significantly with venous cord leptin levels in both groups (John G. Manderson *et al.,* 2003), *so we standardized birth weight in both case & control groups*. Exposure to GDM was associated with both hyperleptinemia and hyperinsulinemia in large-for-gestational age (LGA) infants (Simmons, Brejer, 2002; Wolf *et al*., 2000), but AGA IDM were not included. In this study, serum Insulin, Leptin & Insulin resistance were higher in IDM group when compared with controls. The differences were statistically highly significant ($p \leq 0.001$) despite of average birth weight in both groups. These results also agreed by Ma. Martha *et al*., 2012. Wolf *et al*., 2000 recorded that fetal leptin and insulin levels only correlate in large-for-gestational age infants and did not differ between appropriate-for-gestational age and SGA neonates. These results did not go with our results because the included AGA newborns in that study were not infants of diabetic mothers. In this study infants with bad maternal diabetic control showed higher serum Insulin and Leptin levels than infants with fair maternal diabetic control where cord serum leptin was statistically highly significant, these results were agreed by (John G. Manderson *et al*., 2003) who recorded that cord leptin level is influenced by glycemic control in the diabetic group; levels are higher across the birth weight spectrum.

Conclusion

AGA infants of diabetic mothers - both pre gestational and gestational diabetes- showed higher cord serum Leptin, Insulin readings and Insulin resistance index than those of non -diabetic mother s which were directly correlated to maternal diabetic control as regard Hba1c levels. These results suggest IDM babies are still more susceptible to childhood obesity and early onset type 2 DM than INDM even in AGA infants.

Recommendations

1. Interventions during pregnancy, aimed at a close monitoring of maternal blood glucose concentrations, are thus likely to have an impact not only on maternal and neonatal health, but also on the epidemic of T2DM.

2. The importance of childhood nutrition and weight gain on lifelong health, follow-up of neonates and infants born to mothers who had GDM should receive enhanced attention. Breastfeeding and avoidance of overfeeding in early childhood may be key first steps in this approach (Umberto and David, 2009).
3. A large, well-designed prospective multi-centers study with long term follow up of IDM should be done to confirm the association between high serum leptin levels in AGA IDM babies and the incidence of childhood obesity and early onset type 2DM.

REFERENCES

Alexe, D.M., Syndou, G. and Petridou, E.T. 2006. Determinants of early life leptin levels and later life degenerative outcomes. *Clin. Med Res.,* 4: 326e 335.

Ali Awsat Mellati, Seideh Mazloomzadeh, Afagh Anjomshoaa,Mohsen Alipour,Fatemeh Karimi,Sahar Mazloomi,and Seyed Ali Naghi Kazemi, 2009. Multiple Correlations Between Cord Blood Leptin Concentration and Indices of Neonatal Growth, Iran., *Archives of Medical Research*, 41 (2010) 26e32.

Alzira Martins Ferreira de Souza, Jorge A. López 2004. Insulin or insulin-like studies on unicellular organisms: a review. Braz. arch. biol. technol. Vol.47 no.6 Curitiba Nov. 2004. The global diabetes community, Diabetes.co.uk, 2014.

Bunt JC, Tataranni PA, Salbe AD.2005: Intrauterine exposure to diabetes is a deter-minant of hemoglobin A(1)c and systolic blood pressure in pima Indian chil-dren. *J Clin Endocrinol Metab*., 90:3225–9.

Catalano, P.M., Thomas, A., Huston-Presley, L. and Amini, S.B. 2003; Increased fetal adiposity: a very sensitive marker of abnormal in utero development. *Am. J. Obstet. Gynecol.,* 189:1698–704.

Catov, J.M., Patrick, T.E. and Powers, R.W. 2007. Maternal leptin across preg-nancy in women with small for gestational infants. *Am. J. Obstet. Gynecol.,*

Dana Dabelea and Tessa Crume, 2011: Maternal Environment and the Transgenerational Cycle of Obesity and Diabetes, the American Diabetes Association. Diabetes, Vol. 60 no. 7, 1849-1855.

Freedman, D.S., Dietz, W.H. and Srinivasan, S.R., 1999. The relation of over-weightto cardiovascular risk factors among children and adolescents: The Bogalusa Heart Study. *Pediatrics*, 103:1175e1182.

Geary, M., Pringle, P., Persaud, M., Wilshin, J., Hindmarsh, P., Rodeck, C., *et al.* 1999. Leptin concentrations in maternal serum and cord blood: relationship to maternal anthropometry and fetal growth. *Br. J. Obstet. Gynaecol.,* 106:1054-60.)

Hauguel-de Mouzon, S., Lepercq, J. and Catalano, P. The known and unknown of leptin in pregnancy. *Am. J. Obstet. Gynecol.,* 194:1537e1546.

Helland, I., Reseland, J., Saugstad, O. and Drevon, C. 1998. Leptin levels in pregnant women and newborn infants: gender differences and reduction during the neonatal period. Pediatrics; 101:E12.

Highman, T., Friedman, J., Huston, L., Wong, W. and Catalano, P. 1998. Longitudinal changes in maternal serum leptin concentrations, body composition, and resting metabolic rate in pregnancy. *Am. J. Ob-stet. Gynecol.,* 178:1010-5.

John G. Manderson, Christopher C. Patterson, David R. Hadden, Anthony I. Traub, Hilary Leslie and David R. McCance, 2003. Leptin concentrations in maternal serum and cord blood in diabetic and nondiabetic pregnancy, Belfast, United Kingdom, *Am J Obstet Gynecol*., 2003;188:1326-32.

Keshavarz, M. *et al.* 2005, Gestational diabetes in Iran: incidence risk factors and pregnancy outcomes. *Diabetes Res Clin Pract*., 69(3):279-86.

Ma. Martha, Vela-Huerta, Norma Amador-Licona, and Blanca Murillo-Ort iz:2012 Insulin and Leptin Levels in Appropriate- f or -Gestational-Age Infants of Diabetic Mother, Mexico, *Iran J Pediatr*., Dec 2012; 22(4): 475–480.

National Institute for health and Clinical Excellence NICE, 2008. Ante-natal care- diabetes in pregnancy –costing report-implementing NICE guidance March 2008- page 10.

Schubring, C., Kiess, W., Englaro, P., Rascher, W., Dotch, J., Hanitsch, S., *et al.* 1997. Levels of leptin in maternal serum, amniotic fluid and ar-terial and venous cord blood: relation to neonatal and placental weight. *J. Clin. Endocrinol. Metab.,* 82:480-3.

Tamura, T., Goldenberg, R., Johnston, K. and Cliver, S. 1998. Serum Leptin concentrations during pregnancy and their relationship to fetal growth. *Obstet. Gynecol.,* 91:389-95

The Global Diabetic Community, Diabetes.com.uk, 2014.

Umberto Umberto Simeoni & David J. Barker, 2009: Seminars in Fetal & Neonatal Medicine, *Elsevier*, 14 (2009) 119–124.

Waldemar A. Carlo, 2016, Nelson text book of pediatric 20th edition,Chapter107 Infant of diabetic mother.

Wild, S. *et al.* 2004. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030 Diabetes Care, 27(5):1047-53.

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