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Original Research Article

Cord serum leptin in infants born to diabetic mothers

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ABSTRACT

Objective: In genetically diabetes-prone populations, maternal diabetes during pregnancy increases the risk of their children developing diabetes and obesity (the vicious cycle of type 2 diabetes). Fetal hyperinsulinemia at birth acts as a marker of this risk. The objective of this study is to find out whether cord blood leptin concentrations are increased in offspring of mothers with type 2 and gestational diabetes mellitus (GDM) and to evaluate gender differences if any, in their levels.

Materials and Methods: Cord Serum Leptin measured by ELISA: 1. Cord Blood from 40 babies (20M, 20F) born to GDM Mothers. 2: Cord Blood from 20 babies (9M, 11F) born to Type 2 DM Mothers. 3. Cord Blood from 30 babies (15M, 15F) born to Non Diabetic Mothers.

Results: Babies born to mothers with both type 2 diabetes and GDM had higher birth weight. They also had higher Leptin concentrations [ng/ml] compared to Controls; Leptin concentrations in Type 2 Diabetes -Mean [42.32+24.09], in GDM – Mean [40.31+22.71] & in Control subjects – Mean [23.87+15.48]. Birth weight of the female babies were also higher than that of male babies.

Leptin concentrations were not significantly higher in the female babies in comparison to the male babies.

Conclusion: High cord leptin, birth weight and ponderal index (kilograms per cm^3), in babies born to Type 2 diabetes and GDM mothers.

1. Introduction

Gestational diabetes is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy". It is said to affect 3-10% of pregnancies and is believed to be due to the hormones produced during pregnancy that increase a woman's insulin resistance.

The precise mechanisms underlying gestational diabetes remain unknown. The hallmark of GDM is increased insulin resistance. Pregnancy hormones and other factors are thought to interfere with the action of insulin as it binds to the insulin receptor. The interference probably occurs at the level of the cell signalling pathway behind the insulin receptor. Since insulin promotes the entry of glucose into most cells, insulin resistance prevents glucose from entering the cells properly. As a result, glucose remains in the bloodstream, where glucose levels rise. More insulin is needed to overcome this resistance; about 1.5-2.5 times more insulin is produced than in a normal pregnancy.

Gestational diabetes mellitus (GDM) is associated with increases in maternal and perinatal morbidity, including caesarean section, neonatal hypoglycaemia, and macrosomia.[1,2] Moreover, human epidemiological and animal studies suggest that the intrauterine diabetic environment increases risk for hypertension, obesity, and type II diabetes in adulthood. These findings suggest that measurement of cord serum leptin and c peptide levels is of considerable interest.

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In humans and animals, plasma leptin increases early during gestation, derived primarily from the placenta.[3–5] Although leptin and its receptor messenger RNA (mRNA) are expressed by the placenta,[5–7] the role of increased leptin during pregnancy in maternal-fetal metabolism and intrauterine growth remains unclear. The leptin gene has a placenta-specific upstream enhancer,[8] implying that placental leptin is differentially regulated from leptin of adipose origin. In the mouse, leptin protein and mRNA are colocalized to the trophoblast giant cells at the maternal interface of the placenta and to the cytotrophoblasts in close proximity to the developing fetus.[5,9] There is no correlation between maternal leptin levels and fetal weight; however, several studies have reported that umbilical cord blood leptin levels are positively correlated with fetal insulin, birth weight, ponderal index(kilograms per cm^3), and length and head circumference,[10–12] suggesting a potential relationship between placental leptin and fetal growth. The higher leptin levels in umbilical veins than umbilical arteries and the marked fall after placental delivery indicate that the placenta is one of the major sources of leptin in the fetal circulation.[13]

Leptin is a protein hormone that plays a key role in regulating energy intake and energy expenditure, acting through the hypothalamus. It is one of the most important adipose derived hormones. It is manufactured primarily in the adipocytes of white adipose tissue, and the level of circulating leptin is directly proportional to the total amount of fat in the body. In addition to white adipose tissue—the major source of leptin—it can also be produced by placenta (syncytiotrophoblasts) during pregnancy. Leptin normally reduces appetite and increases energy expenditure, acting through the hypothalamus.[14,15] Leptin also has direct metabolic effects on several tissues, resulting in increased glucose utilization and lipolysis.[16–19] Although the effect of leptin on insulin secretion is controversial, some investigators report that leptin inhibits insulin secretion.[20–22]

The marked increase in maternal leptin, an appetite suppressant, suggests there is some form of maternal leptin resistance, or perhaps there is an alternative role for maternal leptin. Leptin also serves as a mitogen for a growing number of cell types, including endothelial cells, hemopoietic cells, lung epithelial cells, and pancreatic ß-cells in vitro.[23–26] Leptin could therefore be acting as a mitogen for the placenta in addition to stimulating growth of tissues in the developing fetus.

2. Materials and Methods

2.1. Study population

2.1.1. Cases

The study sample comprised 40 babies (20M,20F) born to GDM mothers and 20 babies(9M,11F) born to type 2 DM). Inclusion criteria was mothers aged between 25-35 years and without any other medical complications of pregnancy. Mothers with complications like preeclampsia, preterm deliveries, twin pregnancies and other complications during labour were excluded.

2.1.2. Controls

Controls consists of 30 babies(15M,15F) born to non-diabetic mothers with no medical complication of pregnancy aged between 25 to 35 years.

1. Gestational age: Calculated with LMP and USG findings in first trimester.
2. Birth weight and placental weight measured in kilograms.
3. Ponderal index(kilograms per cm^3) of babies measured using birth weight and length of the babies.
4. Head circumference of babies measured in cm.
5. Venous cord blood was obtained from the fetal side and the serum separated immediately and stored in the deep freezer.
6. Cord serum leptin(ng/ml) and Cpeptide (ng/ml)measured by ELISA.

2.2. Statistical analysis

1. One way ANOVA and bonferroni test were used to compare the parameters like birth weight, placental weight, gestational age, head circumference, serum leptin, in all 3 populations.
2. Pearson correlation coefficient was used to compare ponderal index, leptin levels in the population.
3. Gender differences were compared using students independent t test and one way ANOVA.
4. Parity of mothers in all 3 groups compared using one way ANOVA.

3. Results

Table 1 shows that leptin levels are significantly elevated in GDM and type 2 DM than in controls. Ponderal index, again is higher in cases than in controls. One way ANOVA has been done to find the significance. Birth weight and Placental weight have also been significantly elevated in cases than in controls.

Table 2 shows significant correlation has been found between leptin, c peptide levels and ponderal index in GDM, Type 2 DM and controls.

Table 3 shows significant correlation between gestational age of mothers and leptin, C Peptide in babies.

Table 4 shows significant correlation between leptin and anthropometric measures of babies.

Table 5 shows there is difference between leptin levels in males and females in each population, but the difference is not very significant

Table 1: Neonatal anthropometric measures in GDM, Type 2 DM and Control

Parameters	Group						Oneway ANOVA	Bonferroni t-test
	GDM		TYPE 2 DM		Control			
	Mean	Std Deviation	Mean	Std Deviation	Mean	Std Deviation		
Leptin	40.31	22.71	42.32	24.09	23.87	15.48	F=6.74 P=0.002**	Control Vs GDM, Type2
Ponderal Index	27.38	3.57	27.85	3.63	25.92	2.69	F=2.51 P=0.09	Control Vs GDM, Type2
C peptide	2.00	0.88	2.17	0.76	1.12	0.34	F=17.89 P=0.001***	Control Vs GDM, type2
Gestational Age	38.08	0.53	37.40	2.23	39.10	0.96	F=12.29 P=0.001***	Control Vs GDM, Type2
Head Circumference	34.80	0.84	35.12	0.71	34.41	0.69	F=5.40 P=0.006**	Control Vs Type2
Mothers Age	30.83	3.08	31.60	1.43	30.60	2.69	F=0.89 P=0.41	-
Birth Weight	3.21	.64	3.28	.71	2.82	.52	F=4.47 P=0.01**	Control Vs GDM, Type 2
Placental Weight	513.67	38.47	516.95	41.08	485.80	40.42	F=5.36 P=0.006***	Control Vs GDM, Type 2
Length	48.80	1.40	48.80z	1.61	47.60	1.40	F=6.85 P=0.002**	Control Vs GDM, Type2

* Significant at P<0.05 ** highly significant at P<0.01 ** Very High significant at P<0.001

Table 6 shows significant difference within male and female populations across all 3 groups. But no significant difference between males and females in each individual group

Table 7 shows no significance in parity between the 3 groups

4. Discussion

The fact that all pregnancies, especially diabetic pregnancies are associated with maternal leptin resistance suggests that fetal macrosomia would more likely be associated with changes in placental or fetal leptin expression. The factors that increase fetal leptin levels in macrosomia are not known. In the rodent there is very little or no fetal adipose tissue; thus, the macrosomia may be a function of increased placental production, whereas in other animal models, fetal leptin correlates with adipose tissue mass.

Studies have shown that environmental factors, including weight gain during pregnancy, maternal glucose levels, and fetal hyperinsulinemia, can contribute to fetal macrosomia.[27–29] In our study, Table 2 shows significant correlation has been found between leptin, c peptide levels and ponderal index in GDM, Type 2 DM and controls.

Pregnant women with GDM have more severe insulin resistance and abnormal insulin secretion (impaired glucose tolerance) compared with weight-matched pregnant control subjects.[30–32] The mechanisms for insulin resistance in GDM include a 30–40% decrease in insulin receptor tyrosine kinase activity in skeletal muscle compared with obese pregnant controls[33] and is exacerbated by decreased insulin receptor substrate-1 (IRS-1) tyrosine phosphorylation, due in part to decreased IRS 1 expression.[33] Given these abnormalities, there are animal studies that exogenous leptin treatment during late gestation might reduce insulin resistance, thereby lowering maternal glucose and preventing fetal over growth. Table 4 shows significant correlation between leptin and anthropometric measures of babies

These findings will be of help in humans as well.

There is evidence that leptin treatment in mice reduces adiposity and improves insulin sensitivity, suggesting it may potentially be an effective means of reducing the abnormal glucose tolerance associated with GDM. There is a role for fetal and placental leptin expression in the regulation of fetal growth, independent of maternal glucose. Placental leptin levels are increased in human diabetic pregnancies[34] and decreased in pregnancies complicated by fetal growth retardation.[35] Leptin's ability to influence fetal growth could have important implications for susceptibility to adult disease with higher concentrations of leptin in cord blood and placenta. A role for leptin in stimulating fetal pancreatic

Table 2: Comparison of Leptin, c peptide levels and ponderal index in all the three populations

Group			Ponderal Index	Leptin	C Peptide
GDM	Ponderal Index	Pearson Correlation	1	0.951**	0.961**
		Sig. (2-tailed)	.	.000	.000
		N	40	40	40
	Leptin	Pearson Correlation	0.951**	1	.952
		Sig. (2-tailed)	.000	.	.000
		N	40	40	40
	C Peptide	Pearson Correlation	0.961**	0.952**	1
		Sig. (2-tailed)	0.000	.000	.
		N	40	40	40
Type 2 DM	Ponderal Index	Pearson Correlation	1	.962**	.927**
		Sig. (2-tailed)	.	.000	.000
		N	20	20	20
	Leptin	Pearson Correlation	.962**	1	1
		Sig. (2-tailed)	.000	.	.
		N	20	20	20
	C Peptide	Pearson Correlation	0.927**	.904**	.906**
		Sig. (2-tailed)	.000	.000	.000
		N	20	20	
Control	Ponderal Index	Pearson Correlation	1	.956**	.906**
		Sig. (2-tailed)	.	.000	.00
		N	30	30	30
	Leptin	Pearson Correlation	0.956**	1	.883**
		Sig. (2-tailed)	0.000	.	.000
		N	30	30	30
	C Peptide	Pearson Correlation	.906**	.883**	1
		Sig. (2-tailed)	.000	.000	.
		N	30	30	30

* Significant at P<0.05 ** highly significant at P<0.01 ** Very High significant at P<0.001

development has been suggested,[26,36] which could result in early insulin production and stimulate an increase in fetal growth. Alternatively, fetal hyperinsulinemia could stimulate increased fetal and placental leptin, which, in turn, could contribute to increased fetal growth in tissues expressing the leptin receptor. Studies are currently underway to determine whether maternal leptin administration alters insulin and the b-cell gene expression profile in neonatal mice.

However, in our study, Table 1 shows that leptin levels are significantly elevated in GDM and type 2 DM than in controls. Ponderal index, again is higher in cases than in controls. One way ANOVA has been done to find the significance. Birth weight and Placental weight have also been significantly elevated in cases than in controls. Studies have proved the differences in the leptin concentration between sexes.[37–39] In our study, Table 6 shows significant difference within male and female populations across all 3 groups. But no significant difference between males and females in each individual group.

Various mechanisms have been postulated to explain this difference. The most accepted explanation is the differential adiposity between the genders.[40–42] The gender dimorphism in leptin production which is observed in the very early life may also indicate the genetic difference in leptin production. Although we have observed gender difference in leptin levels in our study ,between males and females in each group, this difference is not very significant as shown in

Table 3: Comparison of Leptin, c peptide levels and Gestational age in all the three populations

Group			Gestational Age	Leptin	C Peptide
		Pearson Correlation	1	.625**	.548*
	Gestational Age	Sig. (2-tailed)	.	.003	.012
		N	20	20	20
		Pearson Correlation	.625**	1	.957**
GDM	Leptin	Sig. (2-tailed)	.003	.	.000
		N	20	20	20
		Pearson Correlation	.548*	.957**	1
	C Peptide	Sig. (2-tailed)	.012	.000	.
		N	20	20	20
		Pearson Correlation	1	.727*	.610*
	Gestational Age	Sig. (2-tailed)	.	.011	.046
		N	11	11	11
		Pearson Correlation	.727*	1	.948**
Type 2 DM	Leptin	Sig. (2-tailed)	.011	.	.000
		N	11	11	11
		Pearson Correlation	.610*	.948**	1
	C Peptide	Sig. (2-tailed)	.046	.000	.
		N	11	11	11
		Pearson Correlation	1	.247	.085
	Gestational Age	Sig. (2-tailed)	.	.376	.764
		N	15	15	15
		Pearson Correlation	.247	1	.956**
Control	Leptin	Sig. (2-tailed)	.376	.	.000
		N	15	15	15
		Pearson Correlation	.085	.956**	1
	C Peptide	Sig. (2-tailed)	.764	.000	.
		N	15	15	15

**. Correlation is Significant at the 0.01 level (2-tailed)*. Correlation is Significant at the 0.05 level (2-tailed)

Table 4: Correlation between Leptin and anthropometric measures of babies

	GDM Leptin		Tyoe 2 DM Leptin		Control Leptin	
	Pearson Correlation	Sig. (2-tailed)	Pearson Correlation	Sig. (2-tailed)	Pearson Correlation	Sig. (2-tailed)
Birth Weight	0.98	0.001	0.98	0.001	0.98	0.001
Placental Weight	0.92	0.001	0.82	0.001	0.90	0.001
Length	0.84	0.001	0.86	0.001	0.93	0.001
Ponderal Index	0.94	0.001	0.97	0.001	0.96	0.001
C Peptide	0.95	0.001	0.94	0.001	0.95	0.001
Gestational Age	0.42	0.01	0.47	0.01	0.83	0.001
Head Circumference	0.94	0.001	0.91	0.001	0.78	0.001

Table 5: Gender difference in Leptin levels in GDM, Type 2 DM and controls

Group		Sex	N	Mean	Std. Deviation	Student independent t-test
GDM	Leptin	Male	20	32.3890	20.26697	t=2.32 P=0.03
		Female	20	48.2255	22.72249	
TYPE 2 DM	Leptin	Male	9	36.7400	20.63124	t=0.93 P=0.36
		Female	11	46.8900	26.67511	
Control	Leptin	Male	15	18.7673	11.63725	t=1.88 P=0.07
		Female	15	28.9640	17.47705	

Table 6: Comparison of Leptin levels in Male and Female babies across all 3 groups

Group		Gender			
		Male		Female	
		Mean	Std Deviation	Mean	Std Deviation
GDM	Leptin	32.39	20.27	48.23	22.72
Type 2 DM	Leptin	36.74	20.63	46.89	26.68
Control	Leptin	18.77	11.64	28.96	17.48
	Oneway ANOVA	F=7.43 P=0.001 Control Vs GDM, Type 2 GDM Vs Control, Type 2 Vs Control		F=7.48 P=0.001 Control Vs GDM, Type 2 GDM Vs Control, Type 2 Vs Control	

Table 7: Comparison of Parity of mothers in all 3 groups

		Group						Chi-square test
		GDM		Type 2 DM		Control		
		n	%	n	%	N	%	
Parity	.00	14	35.0%	11	55.0%	14	46.7%	c2=3.49 P=0.48
	1.00	15	37.5%	7	35.0%	9	30.0%	
	2.00	11	27.5%	2	10.0%	7	23.3%	
Table Total		40	100.0%	20	100.0%	30	100.0%	

Table 5. However, when we compare leptin levels between male babies in all 3 groups, there is a significant difference and we observe a similar significant difference when female babies between the 3 groups are compared as seen in Table 6.

Higher leptin in the offspring of diabetic mother has been largely attributed to the increase in the adiposity of the offspring of diabetic mother. Insulin might regulate the production of leptin. Placental production of leptin might be responsible for hyperinsulinemia in the offspring of DM. The cause for differences in leptin concentration between the genders is also controversial.

Despite leptin resistance, human recombinant leptin administration lessened maternal weight gain and improved glucose tolerance in mouse. One of the main reasons for the effectiveness of peripherally administered human leptin in mouse may be the relatively higher and sustained half-life of the leptin immune adhesion compared with native leptin.[41] High levels of leptin have been shown to reduce fat content in rats by blocking intracellular FFA esterification and by enhancing intra cellular oxidation of lipids. Leptin administration had only marginal effects on appetite, but significantly reduced insulin resistance in pregnant mice, in part through an improvement in skeletal muscle insulin signal transduction at the level of IRS-1. Leptin also down-regulated the endogenous leptin expression levels in mice, which may have contributed to the reduced sensitivity. Previous studies have found that the leptin receptor mediates autocrine regulation of leptin mRNA expression in a tissue-specific manner. Leptin administration reduces leptin synthesis in adipose tissue, whereas in skeletal muscle it induces the protein independently of differences in fat mass or insulin levels. Placental leptin protein was also found to be reduced with leptin administration.

5. Conclusion

Serum leptin levels are significantly elevated in cord blood of newborns born to GDM and type 2 DM mothers, and they correlate well with the neonatal anthropometric measurements. However in our study we did not find a significant difference in the leptin levels between male and female babies born to GDM and type 2 DM mothers.

Leptin's ability to influence fetal growth could have important implications for susceptibility to adult disease and will be an important area for future research.

6. Source of Funding

None.

7. Conflict of Interest

None.

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