Maternal Serum Insulin and Gestational Diabetes

Prof. Ahmed Amin Fetouh[1] Dr. Fayza Ahmed Abd Al-Hakam[2], Dr. Rayyh Abdel-Azim Mohammed Saleh[3] and Eman Sha'ban Mohammed[4]

[1]Professor of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[2]Lecturer of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[3]Lecturer of Clinical Pathology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
Spescialist of Obstetrics and Gynecology Railway Hospital, Cairo, Egypt
drfaizafouad@icloud.com

Abstract: Background: Resistance to insulin hormone is considered as normal changes in the metabolic processes throughout pregnancy, which keep enough levels of glucose for the metabolic requirements of the hastily developing fetus. The placenta carrying an important function during gestational period for regualting metabolic processess by secreting human placenta lactogen (HPL), cortisol and other hormones. The action of HPL and some secretions from placenta as diabetogenic materials are normally controlled by augmented the pancreas to release the insulin in the blood. Nevertheless, in about 5% of all gestational cases the mentioned mode of action are failed, leading to induction of diabetes during pregnancy. Therefore, the target from this work was to investigate the levels of maternal serum insulin along gestational period in normal and in diabetic mellitus women. **Patients and methods**: This study is a prospective case-controlled study that was conducted in Al-Zahra´a University Hospital in the period from October 2011 to June 2013 in order to examine the changes in maternal serum insulin during pregnancy from 26 – 28 weeks to 36 – 38 weeks. **Results**: A highly statistically significant difference between the two groups as regard Fasting insulin, the homeostasis model assessment–insulin resistance (HOMA-IR). Discusion; The current study showed that there was a highly significant variation ($p < 0.001$) within the two groups as regard Fasting insulin at 26-28 weeks gestation and a statistically significant difference (p - value = 0.002) at 36-38 weeks gestation. Summary and conclusions; the present work indicated that there was a highly significant variation between the two groups as regard (HOMA-IR) at 26-28 weeks GA (p - value = 0.003) and at 36-38 weeks GA (p - value = 0.001). we recommened the measurment of (HOMA-IR) as an early inducator of gestational diabetes.
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1. Introduction

Insulin is a polypeptide hormone and secreted from the pancrease, formed from amino acides (polypeptides) after removal of C peptide during the hydrolysis processes of two chains of 21 and 30 amino acids, attached by two disulfide bridges. Insulin is secreted from the pacrease from the islets of Langerhans ß cells and carry hypoglycemic effect. It is one of belongs to the group of peptides called IGF (insulin like growth factors) or somatomedins (1).

During normal pregnancy there is hyperplasia of the pancreatic beta cells resulting in increased insulin secretion and an intial increase in insulin senstivity followed by progressive insulin resistanc. When pancreatic function is not well sufiencent to over come the insulin resisitance, gestational diabetes will be devolpes. Women diagnosed as GDM have well-known insulin resistance inspite of compensatory insulin release and are exposed to development of diabetes type II (2).

So the gestation period particularly the mid-trimester stage is known with progressive insulin resistance. Sensitivity to insulin has been establish to be suppressed during gestation in women having gestational diabetes (3). Whereas lower in the sensitivity to insulin has been known in expressions by the homeostasis model assessment (HOMA) (4).

Decreased in the biological response of a nutrient to a determined level of insulin at the target tissue (liver, muscle, or adipose tissue) is due to decreased sensitivity of insulin or elevated in insulin resistance (Kirwan et al., 2002). Throughout the gestation period, there is non-insulin mediated glucose clearance from the dam to the fetus via facilitated diffusion of glucose from placental. For that reason, all measures of insulin sensitivity in gestation are over estimates of maternal insulin sensitivity, particularly in late gestation (5).

Aim of the Work

The purpose of this work to measure the changes in the insulin concentration in the serum along gestational period in normal and diabetic women.

2. Patients and Methods

This study was a prospective case-controlled study that was conducted in Al-Zahra´a University Hospital in the period from October 2011 to June 2013 in order to examine the changes in maternal serum insulin during pregnancy both in normal women as well as in 45 women from 26 – 28 weeks and 36 -38 weeks with gestational diabetes mellitus.

These 45 women were divided into two groups:

Group (A) study group:

Comprises of 25 women with gestational diabetes mellitus.

Group (B) control group:

Comprises of 20 healthy pregnant women with normal GTT.

All women included in the study were subjected to the following:

History taking, complete physical and abdominal examination, abdominal ultrasound.

3-h oral glucose tolerance test (GTT):

The 3 hour OGTT is done after an overnight fast for at least 8 hours but not more than 14 hours after at least three days of unrestricted diet with more than 150gm of carbohydrates and client was at rest during the study (Carol., 2007).

Abnormal 3-hour 100 gram OGTT values according to the criteria established by Carpenter and Coustan (1982).

- Fasting > 95 mg/dl One hour > 180 mg/dl
- Two hour > 155 mg/dl Three hour > 140 mg/dl

At least two out of four values must be equalled or exceeded to diagnose gestational diabetes.

1) **Blood Sampling:** Blood samples were obtained by peripheral venipuncture with minimal stasis after aseptic conditions. 10 ml of blood were withdrawn from each case and control. The blood samples were taken in plain tubes, put in water bath at 37 °C for 30 minutes and centrifugation were done for 10 minutes at 4000 rpm, the resultant serum was collected, divided serum Glucose was measured at time then the rest of sample stored at -20°C for subsequent analysis of Resistin and Insulin.
2) **Follow up:** Patients were followed up at Out Patient Clinic for antenatal care and immediately after diagnosis of GDM, these women were placed on an1800 kcal/day low lipid (30%) and 20% protein diet, with special care to avoid simple carbohydrates.
3) **Glucose measurement:** Fasting blood glucose was measured using a glucose peroxidase kits on Hitachi (Cobas C311) autoanalyzer using Rouche reagent kits (Neese, 1982).
4) **Insulin measurement:** Using of ELISA Kit Cat. No.: 10801, supplied by Chemux Bioscience, Inc, USA (Turkington et al., 1982).
5) **HOMA-IR calculation:** The HOMA-IR was calculated according to the formula: HOMA-IR = fasting insulin (mU/mL) X-fasting glucose (mmol/L)/22.5(Matthews et al., 1985).

Statistical methodology:

Data were analyzed using Statistical Program for Social Science (SPSS) version 18.0.

3.Results

This study included 45 pregnant women, admitted to Al-Zahra´a University Hospital, pregnant at 26-28wks gestational age are divided into two groups;

Group A: 25 pregnant women in singleton pregnancy suffering from gestational diabetes mellitus.

Group B: 20 pregnant women in singleton pregnancy with normal GTT.

Table (1): Demographic data of all included women:

Parameters	Group A N=25	Group B N=20	t	p-value	sig
Age (years)	32.08±2.84	29.33±4.23	1.337	0.148	NS
Ht.	1.68±0.04	1.60±0.05	0.146	0.862	NS
Deliveries	1.88±1.12	1.51±1.09	1.031	0.309	NS
abortions	1.05±0.63	1.10±0.83	0.638	0.207	NS
GA (26-28wks)	27.18±0.80	27.16±0.71	0.096	0.924	NS
GA (36-38wks)	36.67±0.69	36.27±0.97	1.124	0.114	NS

This table shows that there was no significant difference variation was recorded among the two groups regarding height, age, gravidity and Gestational age (GA) at 26 – 28 wks and 36 - 38 wks gestation.

Table (2): Descriptive statistics of Fasting insulin, HOMA-IR, EFW and BMI in all included women at 26-28wk gestation:

	Group A (n=25)	Group B (n=20)	t	P-value	Sig.
Fasting insulin (µU/ml)	26.30±10.99	16.81±4.88	4.064	<0.001	HS
HOMA-IR	7.22±3.85	2.98±1.17	3.141	0.003	HS
EFW	1163.15±117.71	1112.78±117.42	1.171	0.199	NS
BMI	36.02±2.33	23.50±4.42	1.365	<0.001	HS

This table shows: A highly statistically significant difference between the two groups as regard Fasting insulin, HOMA-IR and BMI.

Table (3): Descriptive statistics of Fasting insulin, HOMA-IR, EFW and BMI in all included women at 36-38wks gestation

	Group A (n=25)	Group B (n=20)	t	P-value	Sig.
Fasting insulin (µU/ml)	**31.59±11.81**	**21.05±8.20**	**3.269**	**0.002**	**S**
HOMA-IR	**9.93±4.31**	**4.01±1.79**	**3.756**	**0.001**	**HS**
EFW	**3272.65±462.18**	**3078.89±270.86**	**1.596**	**0.118**	**NS**
BMI	**38.77±1.87**	**30.90±3.69**	**9.322**	**<0.001**	**HS**

This table shows:

1- A statistically significant difference between the two groups as regard Fasting insulin.
2- No statistically significant difference as regard EFW.
3- A highly statistically significant difference as regard HOMA-IR and BMI

Between 36-38wks gestation.

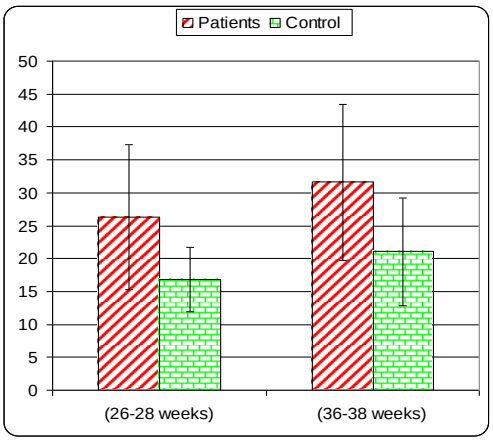

Figure 1: Comparison between patients and control as regard insulin (uiu/ml).

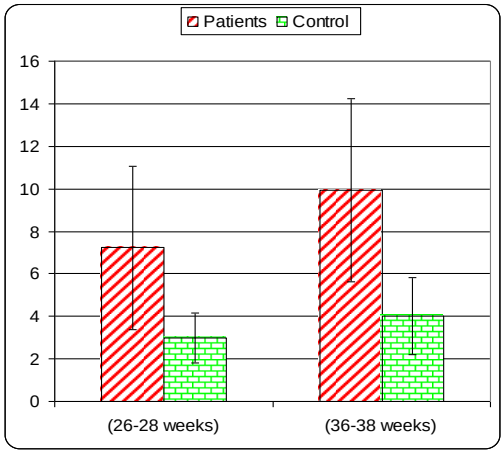

Figure 2: Comparison between patients and control as regard HOMA-IR.

Table (4): shows:

To define the best cut off in the present work receiver operating characteristics (ROC) curve was used, value of HOMA-IR at 26-28 wks gestation which was ≥3.78, with 73.1% sensitivity, 94.4% specificity, 95% positive predictive value, 70.8 % negative predictive value with 84% diagnostic accuracy and p-value <0.001which is highly significant.

Table (4): ROC curve between study group (group A) and control group (group B) as regard HOMA-IR at 26-28wks gestation:

Cut off	Sens.	Spec.	PPV	NPV	Accuracy	p-value
3.78	**73.1%**	**94.4%**	**95%**	**70.8%**	**84%**	**<0.001 HS**

4. Discusion

It is well documented that gestation is characterized by progressive resistance to insulin that starts at the mid-trimester of gestation. Some authors reported that insulin sensitivity has been establish to be diminished during gestation in gestational diabetes women, whereas, depress in insulin sensitivity has also been termed as `the homeostasis model assessment` (HOMA) (4).

Some researchers have paying attention on many recent possible mediators of insulin resistance, such as free fatty acids, adiponectin, resistin and leptin (6). Women with gestational diabetes mellitus established to have drop in insulin sensitivity in relationship to weight matched controls during all the gestational period (7).

The current work found that no significant variation was recorded among the two groups with respect to age, heightand gravidity.

In agreement with our results Nikolaos et al. (8) found that no statistically significant difference between pregnant women with gestational diabetes mellitus and healthy pregnant women as regard age, height and gravidity.

On contrary to our results **Bo et al.** (9) found that the Prevalence of gestational diabetes mellitus elevated

with progress in age, from 1.5 per1000 deliveries for women aged ≤ 20 to 4.2 for women aged ≥ 30. And on contrary to our results **Jang et al.** (10) examined 3581 successive Korean women and established a 2.2% incidence of gestational diabetes mellitus. The suffered women were older with many parities (Parity ≥ 2 in 9.8% of gestational diabetes mellitus, 4.7% of impaired glucose tolerance (IGT) groups and 2.6% of controls) and higher frequencies of known diabetes in the family. Also Kralisch et al., (2009) (11) found that Patients with gestational diabetes mellitus were significantly older as compared with control subjects.

The current study showed that there was a highly significant variation ($p < 0.001$) within the two studied groups as regard Fasting insulin at 26 - 28 weeks gestation and a statistically significant difference (p - value = 0.002) at 36-38 weeks gestation.

In agreement with our results **Nikolaos et al. (8)** found that fasting insulin in the mid and third trimester was extensively higher in women having gestational diabetes mellitus compared to healthy pregnant women. Also **Buchanan et al. (1990) (**12) found that; Patients with gestational diabetes mellitus have fasting insulin concentration equivalent to or higher than those of non-diabetic pregnant women, with the highest concentration taking place in overweight women with gestational diabetes mellitus. Also **Xiang et al. (1999) (13**) found that women with gestational diabetes have increased fasting insulin concentrations in females suffering from gestational diabetes in comparison with a weight harmonized control group.

Catalano et al. (1999) (14) also found that in late pregnancy, patients with gestational diabetes have raised fasting insulin levels and less inhibition of hepatic glucose release during insulin therapy, thus representative dropped hepatic insulin sensitivity in females with gestational diabetes in comparison with a weight coordinated control group. They found that females on the increasing in gestational diabetes millitus had minor pregravid insulin sensitivity than did the control group. The variations in insulin sensitivity within the groups were maximum before and during early pregnancy and were a smaller amount prominent but remain large by late pregnancy.

Kuan-Hung et al. (2011) (15) who found that the homeostasis model assessment–insulin resistance (HOMA-IR) ≥ 2.8 are connected with silent diabetes mellitus in postmenopausal women with sensitivity of 75.4% and specificity of 73.1% in these women which yielded the highest accuracy among the parameters tested in their study.

Sokup et al. (2013) (16) found that the homeostasis model assessment- insulin resistance (HOMA-IR) level vary from 0.34 to 1.29 in the lowest quartile, while in the 4th quartile these values ranged from 2.89 to 20.39. Such variations in the homeostasis model assessment- insulin resistance (HOMA-IR) revealed to a significant pathophysiological changes in the harshness of insulin resistance at the judgment of gestational diabetes mellitus in the studied samples. They also suggested that the extent of insulin resistance, as estimated by the homeostasis model assessment- insulin resistance (HOMA-IR) index at the identification of gestational diabetes mellitus, could be a probable predictor of gestational diabetes mellitus sternness and of the future advance of type II diabetes, owing to this factor is liked with both β-cell dysfunction and insulin treatment.

Summary and Conclusions

The data obtained from the present work pointed to a highly significant variation was present between the two groups as regard the homeostasis model assessment–insulin resistance (HOMA-IR) at 26-28 weeks GA (p - value = 0.003) and at 36-38 weeks GA (p - value = 0.001).

The findings from the present work indicated that there was highly significant variation between the two groups as regard body mass index at 26-28 weeks GA (p-value = <0.001) and at 36-38 weeks GA (p- value = <0.001) with highly statistically significant elevation in BMI from 26-28 weeks of gestation to 36-38 weeks of gestation in both groups (p- value <0.001).

Results of the current study showed that there was no statistically significant difference between the two groups as regard estimated fetal weight (EFW) at 26-28 weeks gestation (p- value = 0.199) and at 36-38 weeks gestation (p-value = 0.118).

By doing the Receiver Operator Characteristic (ROC) curve, it was the homeostasis model assessment–insulin resistance (HOMA-IR) of 3.78 or more at 26-28 weeks gestational age that predict the presence of gestational diabetes mellitus with diagnostic accuracy of 84% and p-value <0.001 which is highly significant. In addition, the best cut-off point of 5.58 at 36 -38 weeks gestation predict the presence of gestational diabetes mellitus with a sensitivity of 80.77%, and specificity of 83.33% with diagnostic accuracy of 86% and p-value <0.001which is highly significant. So we recommened the measurment of (HOMA-IR) as an early inducator of gestational diabetes.

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