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Fatty Liver Index and Serum Copeptin as Early Predictors of Gestational Diabetes Mellitus in Non-diabetic Pregnant Women

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Abstract

Objectives: *To evaluate value of determination of fatty liver disease (FLD) and estimation of serum co-peptin (CP) at the 6th gestational week (GW) as early predictors for development of gestational diabetes mellitus (GDM) later on during pregnancy in non-diabetic pregnant women.*

Methods: *The study included 385 pregnant women at the 6th GW for clinical evaluation, determination of body mass index (BMI) and waist circumference and gave blood samples for estimation of serum triglyceride (TG), γ-glutamyl transferase (GGT) insulin and CP and underwent the 75-oral glucose tolerance test (75-OGTT). Fatty liver index and homeostasis model assessment of IR (HOMA-IR) were calculated. At the 24th GW, 75-OGTT and serum insulin were re-evaluated and women developed GDM were collected as GDM group and women who were free of GDM till the 24th GW as control group.*

Results: *At 24th GW, all studied women had higher blood glucose, serum insulin, TG and GGT with increased HOMA-IR and FLI scores in comparison to 6th GW measures. The increase was non-significant in 338 women (controls) and was significant in 47 women (GDM group) who showed significantly higher measures compared to controls for a frequency of GDM of 12.2%. At 6th GW serum CP levels were significantly higher in GDM than in control women. Statistical analyses defined high FLI and serum CP at the 6th GW as significant predictors for subsequent development of GDM.*

Conclusion: *Development of GDM is closely associated with pregnancy-induced IR and is more frequent in women who had FLD. Increased serum CP levels may be concomitant event or underlying cause for GDM. Calculation of FLI at the 6th GW could discriminate women at risk for GDM later during pregnancy especially if associated with high serum CP levels.*

Keywords: *Fatty liver index, Co-peptin, Insulin resistance, Gestational diabetes mellitus*

1. INTRODUCTION

The body responses to metabolic demands of pregnancy still a challenging concern for physicians [1] and became a stressful target with the global increasing prevalence of obesity [2]. During pregnancy glucose metabolism is governed by equilibrium between lactogenic hormones stimulating insulin production and counter-regulatory hormones inducing insulin resistance (IR) [3].

Multiple peptides play a major role in pathogenesis of metabolic disorders [4] and substances of hormonal character secreted by adipose tissue (Adipokines) are of great importance for carbohydrate metabolism [5]. Multiple studies documented disturbed adipokines levels early in pregnancy among women who later develop GDM than women completed their pregnancy free of GDM [6].

Copeptin (CP), a 39-aminoacid glycopeptide, is the COOH-terminal portion of the precursor pre-pro-vasopressin [7]. Activation of the Arginine vasopressin (AVP) system stimulates CP secretion into the circulation from the posterior pituitary gland in equimolar amounts with AVP [8]. Therefore, CP directly reflects AVP concentration and can be used as a surrogate biomarker of AVP secretion [9].

Fatty liver disease (FLD) is one of the most frequent liver diseases and includes non-alcoholic and alcoholic FLD, each of which is increasing in prevalence [10]. Obesity and its

complications, especially type 2 diabetes mellitus (DM) and hyper-triglyceridemia, are the main responsible factors for the development of the epidemic of FLD [11]. Body mass index (BMI) is a surrogate index of body adiposity and a strong risk factor for FLD [12]. Waist circumference was hypothesized to be a predictor of FLD independently from BMI [13].

Imaging procedures and liver biopsy are the most common methods used for FLD diagnosis, but no single procedure was reliable enough [14] and liver biopsy, despite being the gold standard, it is invasive and expensive tool and has some health risks [15]. A number of indices that consist of simple measures were introduced to diagnose FLD [16]. Fatty liver index (FLI) is one of these indices developed as a convenient tool based on BMI, waist circumference (WC), triglyceride (TG), and gamma glutamyl transferase (GGT) levels [17, 18].

The current study tried to evaluate the validity of determination of FLD and estimation of serum CP at the 6th gestational week (GW) as early predictors for development of gestational DM (GDM) later on during pregnancy in non-diabetic pregnant women.

2. Materials and Methods

2.1. Setting

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2.2. Design

Prospective Observational Study

2.3. Methodology

The study was started since Aug 2015 till December 2018; the study protocol was approved by the Local Ethical Committee and only couples signed a written fully informed consent were included in the study. All pregnant women who attended the Antenatal Outpatient Clinics (OPC), Menufia University hospital; for assurance of diagnosis of being pregnant were eligible for study inclusion.

At the 6thGW, women's demographic and clinical data were collected. Then, waist circumference was determined twice and the median of both measurements was obtained. Body weight and height were determined for calculation of BMI in kg/m^2 as weight (kg)/ height (m^2) and patients were classified according to BMI using the World Health Organization ranges [19].

Baseline clinical and obstetric data were collected and verified to assure inclusion and exclusion criteria.

Exclusion criteria included pre-pregnancy DM, history of previous GDM, essential hypertension, previous exposure to hepatotoxins, positive serum testing for hepatitis B or C, hepatic masses, gall bladder or biliary tree diseases. Women lost during the course of pregnancy were excluded.

At the 6thGW, all women were asked to attend the OPC next day fasting for 18 hours to give blood samples to determine baseline fasting blood glucose (FBG), triglycerides and serum levels of CP, insulin, γ-glutamyl transferase, and to undergo the 75-OGTT. The 75-OGTT entails obtaining three blood samples; a fasting sample and two samples 1-hr and 2-hrs after taking an oral snack containing 75 gm glucose for estimation of postprandial blood glucose (PPBG). All women underwent abdominal ultrasonongraphy to determine the presence of fatty liver. At the 24thGW, women were asked to attend after overnight fasting to the OPC to give blood sample for re-estimation of serum insulin and undergo the 75-OGTT. The study plan was to include pregnant women who developed GDM at the 24th week visit as GDM group and women who were free of GDM till the 24th GW as control group.

2.4. Investigations

2.4.1. Sampling

Venous blood samples (5 ml) were collected from the antecubital vein under complete aseptic conditions and were divided into two parts:

1. The first part was put in a tube containing sodium fluoride (2 mg sodium fluoride/ ml blood) to prevent glycolysis and plasma was separated by centrifugation to be used for estimation of blood glucose levels, at hospital lab.
2. The second part was collected in plain tube, allowed to clot, centrifuged at 1500×g for 15 min and the serum was divided into two parts; one was used for immediate estimation of serum GGT and TG (at hospital lab) and the second part was collected in clean dry Eppendorf tube to be stored at –70°C until assayed.

2.4.2. Laboratory Investigations

Serum levels of insulin and CP were measured using enzyme linked immunosorbent assay (ELISA) kits according to the manufacturer's

instructions and were read using a 96 well microplate ELISA reader (Dynatech MR 7000).

1. Human insulin was measured with the enzyme linked immunoassay (ELISA) kit (catalogue no. ab200011, Abcam Inc., Cambridge, UK) by quantitative sandwich enzyme immunoassay technique [20].
2. Human CP was measured with the enzyme linked immunoassay (ELISA) kit (catalogue no. MBS703328, MyBioSource, Inc., California, San Diego, USA) by quantitative sandwich enzyme immunoassay technique [21].

2.4.3. Clinical Parameters

1. Insulin resistance (IR) was evaluated using the homeostasis model assessment of IR (HOMA-IR) on the basis of insulin and glucose levels and according to the formula fasting serum insulin (µU/ml) x [fasting plasma glucose (mg/ml)/18])/22.5; HOMA-IR score of >2 is considered abnormal [22].
2. GDM was defined according to the American Diabetes Association [23] as the first recognition of any degree of glucose intolerance during pregnancy and determined according to the results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [24] and International association of diabetes and pregnancy study groups recommendations [25] as follows: FBG ≥92 mg/dl, 1-h BG ≥180 mg/dl and 2-h BG ≥153 mg/dl.
3. Fatty liver index (FLI) calculated by using 4 variables: BMI (kg/m^2), waist circumference (cm), TG (mg/ml), and GGT (U/L) and ranges from 0 to 100. A FLI value < 30 rules out FL, so needs no intervention, while FLI value ≥60 indicates FL that needs therapy and in between is the grey zone that can be adjusted by lifestyle change and dieting regimen (17).

3. RESULTS

Through duration of the study, 412 pregnant women were eligible for evaluation; 27 were excluded for not fulfilling inclusion criteria and 385 women were enrolled in the study. At the 24th GW, 47 women developed GDM (GDM group) for a frequency of 12.2%. Patients enrolment data concerning age, gravidity and parity and at enrolment blood pressure measures showed non-significant (p>0.05) difference between women developed GDM and women continued their pregnancy free of DM (Control group).

Table1. *Patients' data determined at time of enrolment*

Data		Control group (n=338)	GDM group (n=47)	P value
Age (years)		28.3±3.5	29.1±4.6	0.362
Gravidity		2.3±1.1	1.9±0.8	0.093
Parity		1.2±0.8	1±0.6	0.286
Blood pressure	Systolic	114.6±9.7	116.5±7.9	0.582
	Diastolic	74.9±5.9	78±6.1	0.783
Fasting blood glucose (mg/dl)		84.7±11.4	87.1±14.9	0.541

Data are presented as mean±SD; p indicates significance of difference between both groups; p>0.05: indicates non-significant difference

Mean FBG, 2-hr PPBG and serum insulin estimated at the 6th GW were non-significantly higher in GDM versus control women. All women had increased blood glucose and serum insulin levels at the 24th GW; however, the difference, in comparison to levels estimated at the 6th GW, was non-significant (p>0.05) in control, but was significant in GDM women with significantly higher estimates compared to control women (Table 2).

Table2. *Laboratory data of women of studied groups*

Variable	Time	Control group (n=338)	GDM group (n=47)	P value
FBG (mg/dl)	At 6th WG	92.7±13.6	94.9±16.5	0.122
	At 24th WG	93.5±6.8	107.9±9.9*	<0.001
2-hr PPBG (mg/dl)	At 6th WG	115.8±11.7	119.1±7.5	0.342
	At 24th WG	118.5±13.1	193.7±19*	<0.001
Serum insulin	At 6th WG	7.4±3.6	8.3±5.2	0.069
	At 24th WG	8.2±4.7	12.5±4.3*	<0.001

*Data are presented as mean±SD; p indicates significance of difference between both groups; *: indicates significant difference versus at 6th GW estimates; p>0.05: indicates non-significant difference*

According to BMI calculated at the 6th GW (time of enrolment), 89 women were obese, 221 women were overweight and only 75 women had average weight with significantly higher

(p<0.001) frequency of obese women among GDM group. Moreover, mean BMI was significantly higher in GDM versus control groups. HOMA-IR score calculated at the 6th GW defined 92 insulin resistant women with HOMA-IR score of ≥2, while 293 women had HOMA-IR score of <2. According to calculated FLI 69 women had fatty liver with FLI score >60, only 89 control women were rules out concerning FL with FLI <30, while 237 women were in the grey-zone with significantly higher frequency of women had FL among GDM than control women. Mean HOMA-IR score and FLI were significantly higher in GDM women than control women (Table 3). Mean at enrollment serum CP levels were significantly higher in GDM women than in controls (Fig. 2).

Table3. *Clinical scores of studied women determined at time of enrolment*

Data			Control group (n=338)	GDM group (n=47)	P value
BMI (Kg/m^2)	Frequency	<25	73 (21.6%)	2 (4.3%)	<0.001
		25-30	202 (59.8%)	19 (40.4%)	
		>30	63 (18.6%)	26 (55.3%)	
	Mean		28±2.9	30.3±2.4	<0.001
HOMA-IR	Frequency	<2	268 (79.3%)	25 (53.2%)	<0.001
		≥2	70 (20.7%)	22 (46.8%)	
	Mean		1.73±0.51	2±0.54	<0.001
FLI	Frequency	>60	169.6±3.4	169.9±3.1	<0.001
		30-60	28.3±3	29.6±2.7	
		<30	2±0.8	1.7±0.7	
	Mean		43.3±14.1	71.4±13.1	<0.001

Data are presented as mean±SD, numbers & percentages; BMI: Body mass index; HOMA-IR: Homeostasis model assessment of insulin resistance; FLI: Fatty liver index; p indicates significance between both groups; p<0.05: indicates significant difference

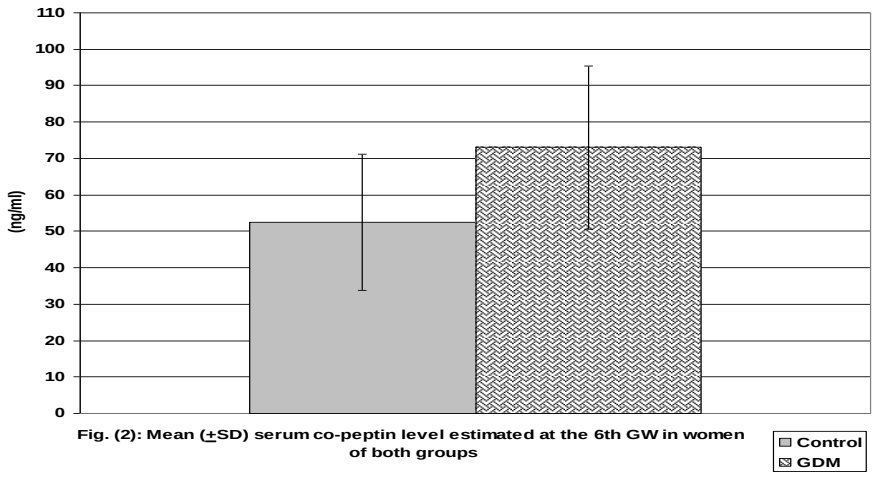

Fig. (2): Mean (±SD) serum co-peptin level estimated at the 6th GW in women of both groups

Development of GDM at the 24th GW positively correlated with FLI, serum CP, BMI and HOMA-IR score determined at the 6th GW, in decreasing order of significance and ROC curve analysis considered these four variables as positive early predictors for later development of GDM, in the same decreasing order of significance (Fig. 3). Regression analysis defined at 6th GW high FLI and serum CP as early predictors for development of GDM at the 24th GW (Table 4).

Table4. *Statistical analyses for variables determined at the 6th GW as early predictors for later development of GDM*

	Correlation		ROC curve analysis		Regression analysis	
Variable	r	p	AUC (95% CI)	p	β	p
BMI	0.233	<0.001	0.745 (0.677-0.813)	<0.001	0.011	0.030
HOMA-IR	0.175	0.001	0.656 (0.569-0.743)	0.001	0.130	0.002
FLI	0.548	<0.001	0.903 (0.855-0.950)	<0.001	0.557	<0.001
Serum CP	0.345	<0.001	0.775 (0.710-0.840)	<0.001	0.222	<0.001

BMI: Body mass index; HOMA-IR: Homeostasis model assessment of insulin resistance; FLI: Fatty liver index; CP: Co-peptin; p indicates significance of calculated value; p<0.05: indicates significant difference

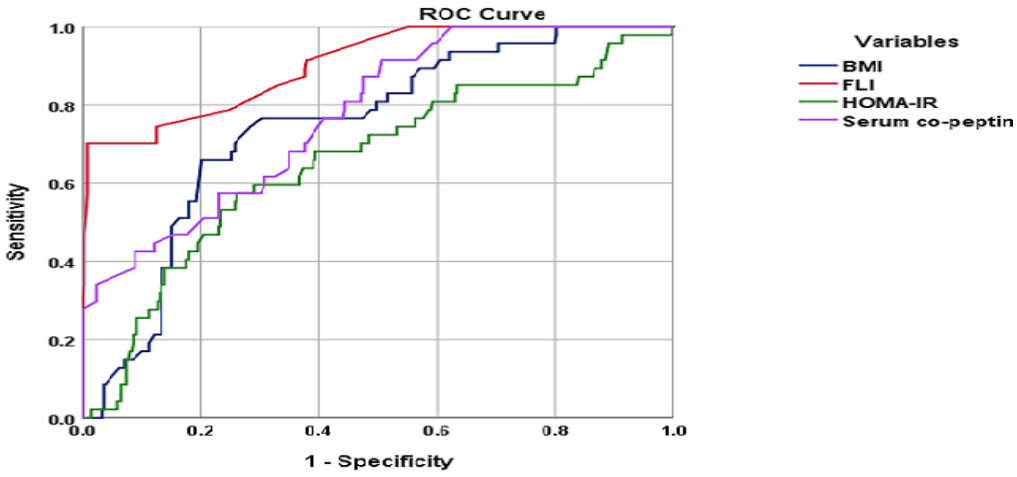

Figure3. *ROC curve analysis of variables determined at the 6th GW as early predictors for later development of GDM*

Kaplan-Meier regression analysis of calculated FLI defined value of 77.75 (95% CI: 75.8-79.7) and mean serum at 90.96 mg/ml (95% CI: 85.59-96.32) as cutoff points beyond which the hazard for development of GDM increases sharply (Fig. 4 & 5).

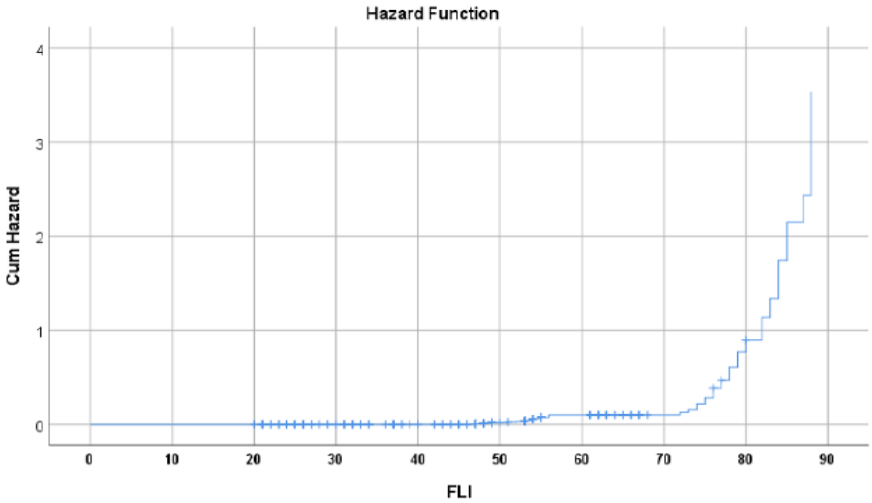

Figure4. *Kaplan-Meier regression analysis for calculated FLI to defined FLI= 77.75 as a cutoff point above which the hazard for getting GDM increases sharply*

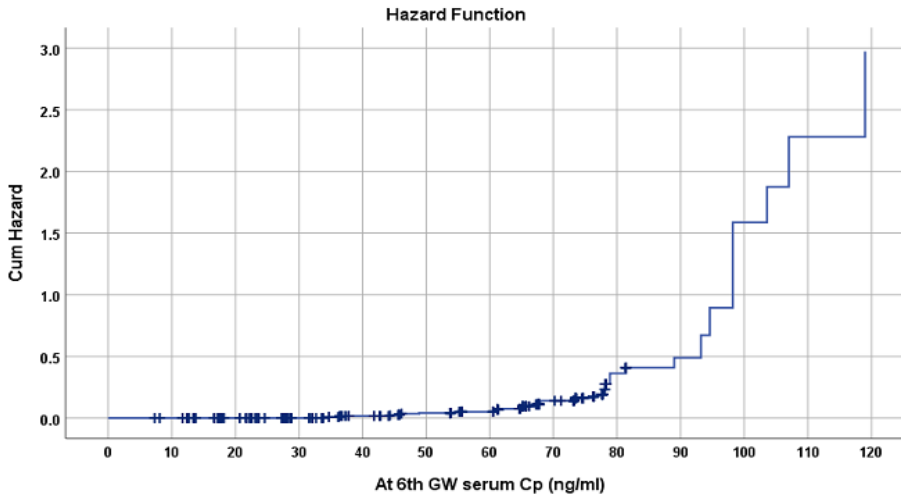

Figure5. *Kaplan-Meier regression analysis for at 6th GW estimated serum CP level defined CP level at FLI= 90.98 mg/ml as a cutoff point above which the hazard for getting GDM increases sharply*

4. DISCUSSION

At the 24th GW, all women showed increased blood glucose measures, serum insulin, TG and GGT with subsequent increased HOMA-IR and FLI scores in comparison to 6thGW measures, but the increase was non-significant in 338 women (controls) and was significant in 47 women (GDM group) who showed significantly higher measures compared to controls for a frequency of GDM of 12.2% among non-diabetic pregnant women. These data are in accordance with Lacaria et al. [26] and Du et al. [27] who reported prevalence rates of GDM of 10.9% and 8.5%, respectively. Through the current study, diagnosis of GDM relied on IADPSG criteria; similarly Sacks et al. [28] reported that among centers that participated in HAPO Study the frequency of GDM had ranged between 9.3 and 25.5% using the IADPSG criteria and Waters et al. [29] out of meta-analysis found 14.3% of studied pregnant women had GDM defined according to IADPSG criteria.

The obtained results are in line with Layton et al. [30] who found women with GDM are characterized by a predominant insulin sensitivity defect than women with normal glucose tolerance and Wang et al. [31] documented that GDM recurred in more than half of subsequent pregnancies and women who had lower FPG and higher 1-h PPBG during 1st trimester of 1st pregnancy and developed higher 1sttrimester TG levels in subsequent pregnancy were at higher risk for GDM recurrence.

These findings indicated that pregnancy itself imposes glucogenic stresses mostly through inducing insulin resistance (IR) and affection of hepatic function as evidenced by the frequency of IR and FLD among control women despite of the concomitant within normal blood glucose levels. This could be attributed to disturbed regulatory mechanisms of carbohydrate metabolism secondary to pregnancy-induced inflammatory status as previously evidenced by Giacobbe et al. [32] who found markers of chronic inflammation are associated to GDM and IR during pregnancy. Also, Tsiotra et al. [33] suggested that adipose tissue expression of adipokines contribute to increased IR and low-grade inflammation concomitant with GDM.

As another explanation, Silva et al. [34] reported that the central and common mechanism of IR in GDM is defective signalling via Akt/mTOR in response to insulin. On the other hand, Hill [35] attributed peripheral IR during pregnancy to increasing maternal levels of placental variant growth hormone and attributed the progressively increasing insulin levels to the expansion of maternal pancreatic β-cell mass to increase in insulin availability as a counterbalance.

The reported high frequency of women had high FLI goes in hand with multiple recent studies, where Layton et al. [30] found women with GDM had significantly higher TG, lower HDL and higher non-esterified fatty acids in comparison to women with normal glucose tolerance and Lee et al. [36] found women who developed GDM had a higher prevalence, up to 55.6%, of radiological steatosis with higher FLI and hepatic steatosis index than women who did not develop GDM. Also, Correa et al. [37] detected significantly higher 1st trimester concentrations of cholesterol, TG, insulin, LDL with increased HOMA-IR in pregnant women who subsequently developed GDM than those who did not develop GDM.

Furthermore, serum co-peptin (CP) levels estimated at the 6thGW were significantly higher in women of GDM group than in control women. These data support the previously reported association between high plasma CP levels and risk of DM (38, 39) that was higher in women than in men [38] and suggesting a potential role of the AVP system in the pathophysiology of diabetes and its complications [39]. In line with obtained data, Ma et al. [40] found high CP concentrations at the 1stprenatal visit were associated with increased risk of GDM.

However, Ebert et al. [41] found CP level was independently associated with gestational age at blood sampling and GDM remained an independent predictor of circulating CP in multivariate regression analysis, but on contrary to the results of the current study and to that reported by Ma et al. [40]; Ebert et al. [41], found median serum CP levels were significantly lower in women with GDM than controls of cross-matched GA and BMI. However, Ebert et al. [41], failed to explain these results which are contradictory to that well-known about CP which is one of stress hormones [42] that is used as a marker of AVP levels and is linked to low water intake and high diabetes risk [43]. Moreover, Enhörning et al. [43] found water supplementation in habitual

low-drinkers with high CP effectively lowers CP and FBG levels, so reducing diabetes risk

Statistical analyses of the current results defined high FLI and serum CP at the 6thGW as significant predictors for subsequent development of GDM in studied non-diabetic women who had no history of previous GDM. In line with these findings, Ma et al. [40] using the integrated discrimination improvement statistic detected significantly increased discrimination ability for CP levels, estimated on the 1stantenatal visit, between women with and without GDM. Recently, Lee et al. [36] found the risk of developing GDM was positively correlated with the severity of steatosis and the relationship between FLD and GDM remained significant after adjustment for metabolic risk factors and concluded that FLD in early pregnancy is an independent risk factor for GDM.

5. CONCLUSION

Development of GDM is closely associated with pregnancy-induced IR and is more frequent in women had FLD. Disturbed AVP system manifested by increased serum CP levels may be concomitant event or underlying cause for GDM. Calculation of FLI at the 6th GW could discriminate women at risk for GDM later during pregnancy especially if associated with high serum CP levels. However, wider scale studies are mandatory to establish the calculated cutoff points for FLI and CP for identification of women at higher risk of GDM

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