Lymphocytes Prediction of Homeostasis Model Assessment of Beta-cells Function (HOMA-B) and C-peptide Level during Pregnancy: New Insight into Beta-cells Proliferation and Insulin Sensitivity

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Abstract:

This work aims to detect the associations of C-peptide and the homeostasis model assessment of beta-cells function (HOMA2-B%) with inflammatory biomarkers in pregnant-women in comparison with non-pregnant women. Sera of 28 normal pregnant women at late pregnancy versus 27 matched age non-pregnant women (control), were used to estimate C-peptide, triiodothyronine (T3), and thyroxin (T4) by Enzyme-linked-immunosorbent assay (ELISA), fasting blood sugar (FBS) by automatic analyzer Biolis 24i, hematology-tests by hematology analyzer and the calculation of HOMA2-B% and homeostasis model assessment of insulin sensitivity (HOMA2-S%) by using C-peptide values instead of insulin. The comparisons, correlations, regression analysis tests were performed by the software of statistical package for the social sciences (SPSS). In pregnant women group, HOMA2-B%, T3, T4, white blood cell (WBC), MID cells, granulocytes (GRAN) increased significantly (p-values<0.05), while C-peptide level raised about 11% compared to control. Lymphocytes, red blood cells (RBC), platelets (PLT) and hemoglobin (HGB) decreased significantly (p-values<0.05). Lymphocytes predicted both HOMA2-B% and C-peptide level during pregnancy ($R^2 =0.516$, $p <0.0004$; $R^2=0.31$, $p <0.009$ respectively). Prediction of HOMA2-B% and C-peptide levels by lymphocytes account clarifies that the adaptation in beta-cells might be a part of the defense system mechanism of the body against oxidative stress, and this highlights new insight on the proliferation of beta-cells during pregnancy and insulin sensitivity.

Keywords: HOMA-B, Inflammation, Insulin resistance, Leukocytes, Pregnant women.

Introduction:

Normal pregnancy exhibits expansion in mass and an increase in the functional activity of pancreatic beta-cells as a part of the occurring adaptation in this critical period. These modifications will ensure an adequate supply of insulin for maintaining blood glucose levels and regulating lipid metabolism. The proliferation of beta-cell and the rise in insulin secretion, especially in late pregnancy, have been manifested by several investigations [1], [2]. The homeostasis model assessment of β-cell function (HOMA-β) and the homeostasis model assessment of insulin sensitivity (HOMA-S) are used predominately to estimate beta-cell function depending on insulin level. Recently, studies revealed that the use of C-peptide instead of insulin in both models is more accurate [3], [4].

C-peptide is a peptide composes of 31 amino acids, and it is released equally to the amount of insulin after cleaving the produced proinsulin from beta-cell. The C-peptide test is more preferred over insulin to assess pancreatic beta-cells function in several ways; C-peptide is a more stable circulating molecule than insulin. A half-life of C-peptide is about 30 minutes in comparison with 5 minutes for insulin [5], [6]. C-peptide is not cleared variably by the liver like insulin because it has a constant clearance rate in peripheral circulating. Also, the measurement of C-peptide level gives an idea of the actual blood insulin level for insulin-dependent diabetics patients. All these properties have given C-peptide priority to be fit to estimate the function of beta-cell and insulin resistance during pregnancy [3].

Studies have revealed that C-peptide is a biologically active peptide independent of insulin and is a peptide with roles during inflammations. C-peptide has an anti-inflammatory effect on the level of microvascular, vascular endothelium, and vascular smooth muscle cells [7, 8, 9]. Also, a low level of C-peptide was strongly associated with severe preeclampsia that is characteristic of endothelial dysfunction and low blood protein [10]. Another study found that the low level of C-peptide is weakly associated with type one diabetes T1D patients [11]. The role of C-peptide as an anti-inflammatory peptide might highlight its probable associations with the inflammations' biomarkers during pregnancy. Similar influences of pancreatic beta-cells expansion and activation, particularly during late pregnancy, are expected.

Pregnancy is a condition of low-grade inflammation and oxidative stress [12]. Low-grade inflammations associate with a decrease in insulin sensitivity, and the leukocyte species have significant roles during inflammations and disorder of the immune system [13]. The complete blood account (CBC) inflammation biomarkers alter during pregnancy; in a recent study, the change in CBC was related to the risk assessment of spontaneous abortion [14]. The physiologic stress induces an elevation in white blood cells WBC account, specifically in the account of granulocytes and MID cells with a reduction in lymphocyte account [15, 16]. Also, red blood cells, hemoglobin, and platelets have a noticeable decrease during pregnancy due to hemodilution and increased platelets' activation with accelerating clearance [16, 17]. More recently, it has been found that lymphocytes can predict insulin resistance in gestational diabetes women patients [18]. On the other hand, studies revealed a protective function of thyroid hormones in inflammations conditions [19]. In nondiabetic individuals, an association between decreased thyroid hormone levels and insulin resistance has been noticed [20].

According to the latest pieces of evidence, C-peptide might have significant associations with blood inflammations' biomarkers. A similar effect could be expected on the level of homeostasis of beta-cell function. The associations of C-peptide and HOMA-B with inflammatory blood markers such as WBC account, LYM account, MID cells, platelet, and anti-inflammatory thyroid hormones during normal pregnancy have not been elucidated. This study aimed to find the possible associations between C-peptide and HOMA-B with the inflammatory markers in pregnant women and their control to aid in understanding the association of

physiological changes of beta-cells and inflammations during pregnancy.

Materials and Methods:
Patients and Control

This study was executed as a cross-sectional study in the maternal hospital in Zakho city. All women involved in this study were chosen apparently normal with fasting blood sugar less than five mmol/L, where women with a history of diabetes, hypertension, dyslipidemia, and thyroid hormones' dysfunction were excluded according to the study criteria. The selected women were divided into two groups; the pregnant women group included twenty-eight pregnant women in the late pregnancy (median of gestational week=34.3± interquartile range 11.6). Neither pregnancy complications nor multiple pregnancy were proved for them. The control group consisted of twenty-seven non-pregnant married women of reproductive age. They were selected among women who had regular visits to the hospital for checkups and employed women in the same hospital. The ethics committee of the maternal hospital had approved this study before sample collecting. The procedures fulfilled the requirements of the Declaration of Helsinki and written informed consents were provided by the participants.

Methods

Five mL of whole blood was drawn from each woman, and one ml was added into the EDTA tube with shaking for performing blood account tests. The remaining blood was added into a serum separator tube and left to clot for 15 min in a water bath at 37 °C. The separated serum at 3000 rpm was carefully drawn and stored in a labeled Eppendorf tube at -70 °C for other biochemical tests after portioning it into aliquots.

Measurements: The height and weight of each woman were recorded, and the body mass index was calculated as weight in kilograms divided by the square of height in meter. C-peptide concentration was estimated using an enzyme-linked immunosorbent assay (ELISA) kit (EIA-1293, DRG International, Inc., USA). Fasting blood sugar was estimated by the automatic analyzer Biolis 24i Premium which uses CORMAY kits. Total triiodothyronine (T3) and total thyroxin (T4) were assessed by competitive ELISA (bioactive diagnostic, Germany, catalog No. BDT301-BA, BDT402-BA). The function of the beta-cell and insulin sensitivity were assessed by the homeostasis model assessment of beta-cell function HOMA2-B% and homeostasis model assessment of insulin sensitivity HOMA2-S%, using the values of C-

peptide instead of insulin. The calculator of these models, which was edited by the oxford center of diabetes, endocrinology, and metabolism, was downloaded from the following link: https://www.dtu.ox.ac.uk/homacalculator.

White blood cells (WBC), lymphocytes (LYM), MID-cells, granulocytes (GRAN), red blood cells (RBC), hemoglobin (HGB) and platelets (PLT) were estimated by the hematology analyzer.

Statistical Analysis:

Normal distributing data were expressed as means (±standard deviation, SD) while skewed distributing data were expressed as median (interquartile range, IQR). For the comparison between two groups independent-samples T-test and Mann-witney tests were used. Spearman and Pearson correlations were used for detecting the possible correlations between the variables.

Multiple linear regression analysis was performed to predict dependent variables. The SPSS software (version 25.0 for Windows) was used, and the p-value ≤ 0.05 was known as statistically significance.

Results:

The Characteristics and Anthropometric Measurements of Both Pregnant and Control Groups

As shown in Tab.1, the median of C-peptide level raised about 11% in pregnant women group comparing with control group. In addition, HOMA2-B%, WBC, GRAN, MID, T3 and T4 increased significantly in pregnant group comparing with control. however, LYM, HGB, RBC and PLT decreased significantly in pregnant women group.

Table 1. Characteristics and anthropometrics measurements of pregnant women and control groups

Parameters	Late pregnancy group; No.=28	Control group; No.=27	p-value
Age	25.8±4.7	27.8±5.6	0.147
Gestational weeks	34.3(11.6)	-----------	---------
BMI (kg/m^2)	28.8±3.9	25.6±3.3	0.002 *
C-peptide (nmol/l)	1.22 (0.76)	1.1(0.74)	0.095
FBS (mmol/L)	4.24±0.54	4.3±0.49	0.481
HOMA2-B%	273.5 (212)	203 (119.2)	0.045 *
HOMA2-S%	41.7(21)	41.6 (36.6)	0.130
WBC*10^9/L	9.4±1.9	6.9±1.1	$8*10^{-7}$ *
MID *10^9/L	0.81±0.35	0.4 (0.1)	$2*10^{-6}$ *
LYM*10^9/L	1.9±0.46	2.2±0.6	0.01*
GRAN*10^9/L	6.65±1.58	4.1±0.8	$3*10^{-9}$ *
RBC*10^{12}/L	4.06±0.4	4.6±0.3	$6*10^{-7}$ *
HGB (g/dL)	11.5±1.1	13.1±1.3	$2*10^{-6}$ *
PLT*10^{10}/L	18.0 (6.3)	28.2 (12.0)	0.001 *
T3 (nmol/L)	3.2(1.07)	2.23(0.9)	0.0002 *
T4 (nmol/L)	104.9±14.9	90.0±16.1	0.001*

BMI: body mass index; FBS; fasting blood sugar; HOMA2-B%: homeostasis Model Assessment of beta-cell function; HOMA2-S%: homeostasis model assessment of insulin sensitivity; WBC: white blood cells account; LYM: lymphocytes account; MID: MID-cells account; GRAN: granulocytes account; RBC: red blood cells account; HGB: hemoglobulin; PLT: platelet account; T3: triiodothyronine; T4; thyroxin. *: P-value ≤ 0.05 is considered statistically significant.

Bivariate Analysis of HOMA-B% with the Studied Parameters in Pregnant Women and Control Groups.

In pregnant group, HOMA2-B% negatively correlated with the FBS and positively correlated with LYM and T4. In control group, HOMA2-B% negatively correlated with the FBS and T3, and positively correlated with the BMI, WBC, MID, LYM, and GRAN as shown in Tab. 2. In addition, Fig 1A shows the Pearson correlation between log-HOMA2-B% and LYM in pregnant women group.

Table 2. Bivariate analysis of HOMA2-B% with the studied parameters in pregnant and non-pregnant groups.

Parameters	Bivariate analysis in pregnant women		Bivariate analysis in non-pregnant women	
	r	p-value	r	p-value
BMI	-0.194	0.323	0.437*	0.023
FBS	-0.596*	0.001	-0.479*	0.012
WBC*10^9	0.311	0.108	0.710*	0.00003
MID	0.097	0.625	0.399*	0.039
LYM	0.577*	0.001	0.515*	0.006
GRAN	0.146	0.458	0.512*	0.006
RBC*10^{12}	-0.051	0.796	0.142	0.479
HGB	-0.047	0.813	-0.125	0.534
PLT*10^{10}	0.313	0.105	-0.238	0.232
T3	-0.089	0.652	-0.470*	0.013
T4	0.401*	0.034	0.148	0.460

BMI: body mass index; FBS; fasting blood sugar; WBC: white blood cells account; LYM: lymphocytes account; MID: MID-cells account; GRAN: granulocytes account; RBC: red blood cells account; HGB: hemoglobulin; PLT: platelet account; T3: triiodothyronine; T4; thyroxin. *: P-value ≤ 0.05 is considered statistically significant.
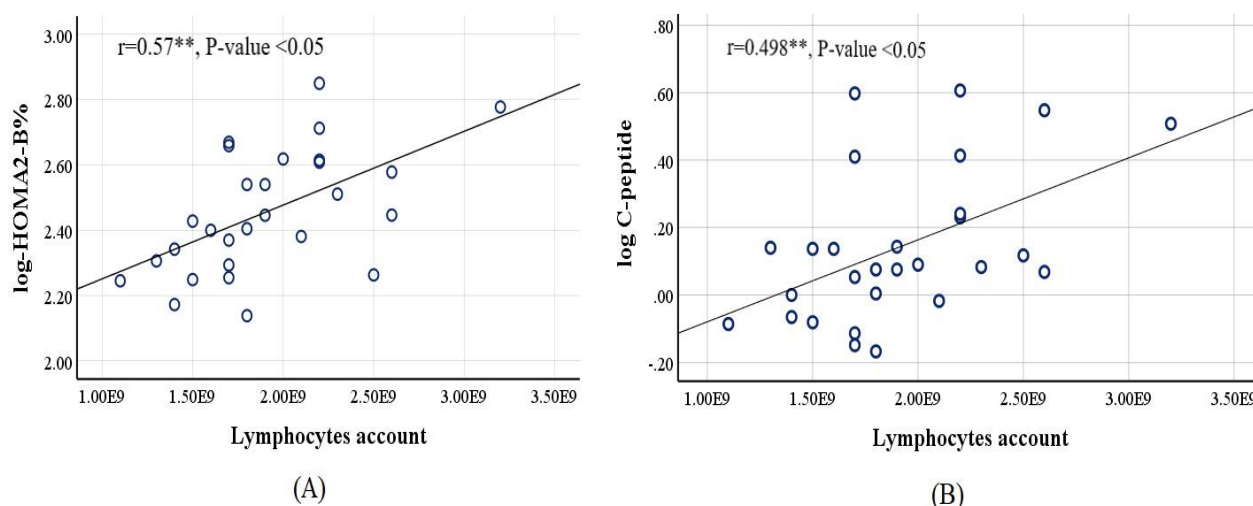

Figure 1. Bivariate Pearson correlation analysis in pregnant women group. (A) Between log HOMA2-B% and Lymphocytes account. (B) Between log C-peptide and Lymphocytes account.

Multivariate Regression Analysis of HOMA2-B% with the Correlated Parameters in Pregnant Women.

The multiple regression analysis was performed to predict log-HOMA2-B% values based on their FBS, LYM and T4 levels. A significant regression equation was found to be ($R^2 = 0.516$, $F_{(3,24)} = 8.539$, $p < 0.0004$, and showed that 52% of the change in log-HOMA2-B% could be attributed to the changes in LYM a count and FBS level, $p = 0.009$, 0.012 respectively whereas T4 was excluded from the equation, $p = 0.126$. Participants' predicted log-HOMA2-B% is equal to $2.409 + 1.7 \times 10^{-10}$ (LYM) $- 0.138$ (FBS).

Bivariate Analysis of C-peptide with the Studied Parameters in Pregnant Women and Control Groups

In pregnant women group, C-peptide correlated with LYM and T4. In control group, C-peptide correlated with the BMI as shown in Tab. 3. In addition, the Pearson correlation between log C-peptide and lymphocytes account in pregnant women group is shown in Fig 1B.

Table 3. Bivariate analysis of C-peptide with parameters studied in pregnant and non-pregnant groups.

parameters	Bivariate analysis in pregnant women		Bivariate analysis in non-pregnant women	
	r	p-value	r	p-value
BMI	0.01	0.96	0.459*	0.016
FBS	-0.135	0.492	0.009	0.966
WBC*10^9	0.278	0.152	0.365	0.061
MID	-0.021	0.915	0.182	0.364
LYM	0.448*	0.017	0.281	0.155
GRAN	0.192	0.328	0.304	0.123
RBC*10^{12}	0.053	0.788	0.171	0.395
HGB	0.115	0.56	0.067	0.738
PLT*10^{10}	0.076	0.702	-0.288	0.145
T3	-0.112	0.570	-0.136	0.498
T4	0.413*	0.029	0.129	0.522

BMI: body mass index; FBS; fasting blood sugar; WBC: white blood cells account; LYM: lymphocytes account; MID: MID-cells account; GRAN: granulocytes account; RBC: red blood cells account; HGB: hemoglobulin; PLT: platelet account; T3: triiodothyronine; T4; thyroxin. *: P-value ≤ 0.05 is considered statistically significant.

Multivariate Regression Analysis of C-peptide with the Correlated Parameters in Pregnant Women.

The enter multiple regression analysis was performed after logarithmic transforming of C-peptide data to predict log C-peptide based on their LYM and T4 levels. A significant regression equation was found to be ($F_{(2,25)}$ = 5.67, p <0.009, with an R^2 of 0.312. participants' predicted log C-peptide is equal to $-0.689 + 2.2 \times 10^{-10}$ (LYM). LYM was significant predictor of Log C-peptide, P =0.013 whereas T4 was excluded from the equation, p=0.138.

Discussion:

The present study showed a significant increase in HOMA2-B in pregnant women with an increase in the C-peptide level of about 11% compared with control, consistent with other findings [1, 2]. In addition, there were significant increases in WBC, MID, GRAN, PLT accounts and a significant decrease in LYM in pregnant women compared to control, which might be an indicator for low-grad inflammation and adaptive immune system [21]. Pregnancy is a condition of physiological variations and adaptation that ensures the maximum possible protection for mother and fetus. That can be achieved by improving inflammatory response, glucose uptake, insulin sensitivity, and oxidative stress [22]. The hyperplasia in islet beta cells could be one of the vital defense mechanisms for adaptation during pregnancy. The prediction of elevated HOMA2-B% values and C-peptide levels by one or more inflammatory signs during pregnancy might reflect C-peptide-related function as a clinical indicator to clarify the change in the beta-cells during pregnancy. To the best of the author's knowledge, this is the first work that found the direct association between LYM and both HOMA2-B% and C-peptide in non-diabetic pregnant women.

Many studies have expressed the physiological roles of C-peptide in different circumstances. In diabetic mice induced by streptozotocin, C-peptide showed anti-inflammatory properties by inhibiting the production of reactive oxygen species (ROS) in endothelial cells [23]. Another study revealed the effect of C-peptide to inhibit endothelial dysfunction, which is induced by high glucose levels and thereby reduces the lesion of atherosclerosis [24]. The ability of C-peptide to stimulate nitric oxide production in endothelial cells and improve blood flow in the vessels was also detected [25]. In addition, a high concentration of C-peptide in vitro study was found to be a stimulator of lymphocytes chemotaxes [26]. During pregnancy, the adaptive immune system implies an increase in the WBC species except lymphocytes, which decreases significantly compared with control. The decline in the immune system might be offset by increased other types of leukocytes and increased production of C-peptide as a part of the defense against ROS.

The present study showed that lymphocytes account in pregnant women predict both C-peptide and HOMA2-B in pregnant women group. A similar result showed that the B lymphocytes served as predictors of insulin resistance in pregnant women with GDM [18]. An association between insulin resistance and oxidative stress and increasing lymphocytes' production during pregnancy was declared [27]. The proliferation of beta-cells in pregnancy might be activated for two reasons; firstly, hyperglycemia, a common condition in late pregnancy, induces insulin generation. In a longitudinal study of non-diabetic and non-obese pregnant women, the 1-hour postprandial blood glucose values were correlated

with fetal abdominal circumference. There was an increase of about 8.87% in daily mean glucose values between 28 to 38 weeks of pregnancy [28]. Secondly, the rise in the metabolic rate of glucose and lipid stimulates an increase in ROS generation. It thus triggers an increase in oxidative stress and inflammation biomarkers such as lymphocytes [29]. The regression analysis showed an increase in HOMA2-B% about $I.7*10^{-10}$ for each LYM cell per liter. That might be due to the urgent need to increase C-peptide production as anti-inflammatory factors able to reduce ROS production and therefore reduce oxidative stress. At the same time, the decrease in HOMA2-B%, about 0.138 for each mmol of glucose, indicates that the blood glycemia is sustained by reducing insulin production to match the growing fetus's need for glucose. In this context, glucotoxicity induced by abnormally high glucose levels negatively affects beta-cell function through the rise in the levels of free radicals. The previous two factors might be considered as potential regulators of beta-cell function during pregnancy. Therefore, the proliferation of beta-cells during pregnancy serves to provide insulin and C-peptide even if the increased glucose level is demanded during the third trimester. Thus, C-peptide metabolizes at a constant rate while increased insulin secretion initiates a decrease in insulin sensitivity.

In the control group, HOMA2-B% negatively correlated with the FBS and positively correlated with BMI, WBC, LYM, MID, and GRAN, C-peptide level positively correlated with the BMI. A study found that the ratio of beta-cell over pancreas area is about 50% higher in obese nondiabetic subjects than lean controls [30], which could be another indicator for the anti-inflammation property of C-peptide. Similarly, a study found a direct correlation between WBC and FBS and triglyceride levels in patients with type 2 diabetes [31]. The associations of HOMA2-B% with the BMI and leukocyte types suggest that the initiation of insulin resistance in obese patients might be due to the demand for C-peptide, not insulin, as new insight on insulin resistance.

Other factors that may also affect the proliferation of pancreatic beta-cells and improve insulin sensitivity are thyroid hormones. It was found that a low level of T4 at early pregnancy impacts the development of GDM [32]. The current study showed significantly elevated levels of both T3 and T4 in the pregnant group. It is also detected that T4 had positive correlations with both HOMA2-B% and C-peptide levels in the pregnant women group, which might manifest the anti-inflammatory effect of thyroid hormones against oxidative stress during pregnancy. On the other hand, T3 correlates negatively with the HOMA2-B% in the control group. Several investigations outside pregnancy found that hypothyroidism associates with high glucose concentration and vice versa [20]. Moreover, an animal study found that thyroid hormones regulate the cytokine production of lymphocytes and regulate lymphocytes' activity [33].

Conclusion:

Adaptation in normal pregnancy occurs with a significant increase in beta-cells function, represented by the high HOMA2-B% values and a noticeable increase in C-peptide level. The significant increase in the accounts of leukocyte species except for lymphocytes that decrease significantly during pregnancy indicates a low-grade inflammation due to the rise in glucose and lipid metabolism, which causes increase ROS and, therefore, oxidative stress. In non-pregnant women, the correlation of HOMA2-B% and C-peptide with the BMI, and the correlation of HOMA2-B% with the leukocyte species indicate the protection role of C-peptide against ROS. Moreover, the prediction of HOMA2-B% and C-peptide levels during pregnancy by lymphocytes account as a biomarker of inflammations, clarifying that the adaptation of beta-cells might be a part of the defense system mechanism of the body against oxidative stress. Furthermore, it highlights new insight into the proliferation of beta-cells during pregnancy and insulin sensitivity.

Author's declaration:

- Conflicts of Interest: None.
- I hereby confirm that all the Figures and Tables in the manuscript are mine. Besides, the Figures and images, which are not mine, have been given the permission for re-publication attached with the manuscript.
- Author sign on ethical consideration's approval
- Ethical Clearance: The project was approved by the local ethical committee in University of Zakho.

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تنبؤ الخلايا الليمفاوية بنموذج تقييم توازن وظيفة خلايا بيتا (HOMA-B) ومستوى الببتيد سي أثناء الحمل: نظرة جديدة على تكاثر خلايا بيتا وحساسية الأنسولين

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الخلاصة:

هدفت هذه الدراسة الكشف عن علاقة الببتيد سي ونموذج تقييم توازن وظيفة خلايا بيتا (HOMA2-B%) مع المؤشرات الحيوية الالتهابية في النساء الحوامل بالمقارنة بالنساء غير الحوامل. تم استخدام الأمصال لـ 28 امرأة حامل في أواخر الحمل مقابل 27 امرأة غير حامل (مجموعة التحكم) لتقدير الببتيد سي وهورمونات الغدة الدرقية (T3) و (T4) بواسطة مقايسة الممتز المناعي المرتبط بالإنزيم (ELISA) وتم تقدير سكر الدم الصامي (FBS) بواسطة المحلل التلقائي Biolis 24i، وتعداد خلايا الدم (C.B.C) بواسطة جهاز تحليل أمراض الدم وتم حساب HOMA2-B% ونموذج تقييم توازن حساسية الأنسولين (HOMA2-S%) باستخدام قيم الببتيد سي بدلا من قيم الانسولين. تم إجراء المقارنات والارتباطات واختبارات تحليل الانحدار بواسطة برنامج الحزمة الإحصائية للعلوم الاجتماعية (SPSS). في مجموعة النساء الحوامل، زادت HOMA2-B% وT3 وT4 وخلايا الدم البيضاء (WBC) وخلايا MID والخلايا المحببة (GRAN) بشكل ملحوظ (p-values<0.05)، بينما ارتفع مستوى الببتيد سي حوالي 11٪ مقارنة بمجموعة التحكم. انخفضت الخلايا الليمفاوية وخلايا الدم الحمراء (RBC) والصفائح الدموية (PLT) والهيموغلوبين (HGB) بشكل ملحوظ (p-values<0.05). الخلايا الليمفاوية تنبأت بمستوى كلاً من HOMA2-B% والببتيد سي أثناء الحمل (0.0004> p ، R2 = 0.516 ؛ R2 = 0.31 ،p= 0.009 على التوالي). يوضح التنبؤ بمستويات HOMA2-B% والببتيد سي بواسطة تعداد الخلايا الليمفاوية أن التكيف في خلايا بيتا قد يكون جزءاً من آلية النظام الدفاعي للجسم ضد الإجهاد التأكسدي، وهذا يسلط الضوء على نظرة جديدة حول تكاثر خلايا بيتا أثناء الحمل وحساسية الأنسولين.

الكلمات المفتاحية: نموذج تقييم توازن وظيفة خلايا بيتا، الالتهابات، مقاومة الانسولين، خلايا الدم البيضاء، النساء الحوامل.