Journal of Diabetes & Metabolic Disorders (2023) 22:639–648
https://doi.org/10.1007/s40200-023-01188-3

RESEARCH ARTICLE

Association between serum interleukin-6, leptin and insulin in gestational diabetes mellitus – a cross- sectional study

Neha Srivastava[1] · **Kalpana Singh**[1] · **Nisha Singh**[2] · **Abbas Ali Mahdi**[1]

Received: 19 August 2022 / Accepted: 14 January 2023 / Published online: 13 February 2023

Abstract

Purpose Gestational diabetes mellitus (GDM) is a state of leptin resistance which develops a vicious cycle of hyperinsulinemia and hyperleptinemia leading to aggravation of an inflammatory situation. This study was done to find out the association between IL-6, leptin and insulin in gestational diabetes among North Indian women.

Method This cross-sectional study included 100 GDM, 100 non-GDM and 50 non-pregnant women. *DIPSI* (Diabetes in Pregnancy Study Group India) criteria was used for screening GDM among pregnant women. GDM and non-GDM pregnant women were further categorized into three groups according to the trimester of pregnancy. Serum IL-6, leptin and insulin were measured in all the enrolled women.

Results Serum IL-6 levels were significantly higher among GDM women as compared to non-GDM and non-pregnant women. Although the mean serum leptin and insulin levels were higher in GDM, but the difference was not statistically significant. When GDM and non-GDM women were categorized into three trimester, serum leptin levels were found to be significantly higher in 3rd trimester ($p < 0.002$) and IL-6 in 1st trimester ($p < 0.017$) among GDM women. No correlation was found between serum IL-6, leptin and insulin in GDM.

Conclusion Absence of any significant association between leptin and IL-6 signifies that leptin may not be associated with inflammation in gestational diabetes. However, IL-6 may serve as an early marker for screening glucose intolerance during pregnancy.

Keywords Gestational diabetes mellitus · *DIPSI* criteria (Diabetes in Pregnancy Study Group India) · Hyperinsulinemia · Hyperleptinemia · Proinflammatory cytokine

Introduction

Leptin, an adipokine is produced and secreted by white adipose tissue as well as by other tissues, including, skeletal muscle, bone marrow, placenta, ovaries, mammary epithelium, stomach, liver and lymphoid tissues [1, 2]. It is well established that leptin modulates whole-body energy homeostasis [3, 4] but overwhelming evidence shows the existence of relationship between leptin and reproductive functions like oocyte maturation, regulation of embryo development as well as implantation and placentation [5, 6]. Leptin deficiency/ resistance has been found to be associated with various diseases including type 2 diabetes mellitus and pregnancy induced diabetes mellitus. It is estimated that in India at any given point of time, over 4 million women are affected with diabetes during pregnancy, commonly known as pregnancy induced diabetes or gestational diabetes mellitus [7]. The prevalence of GDM varies from 4 to 18% in Indian population due to difference in age and/or socioeconomic status of the women or incomplete implementation of screening programs [8]. Timely detection and treatment of gestational diabetes may prevent various complications like spontaneous abortion, still birth, congenital anomalies, macrosomia, etc. [9]. The pathogenesis of GDM is still controversial but the basic theory of GDM involve insulin insensitivity and raised level of anti-insulin hormones like human placental lactogen, prolactin, glucocorticoid, and

✉ Kalpana Singh
kalpanasinghdr@gmail.com

[1] Department of Biochemistry, King George's Medical University, 226003 Lucknow, Uttar Pradesh, India

[2] Department of Obstetrics & Gynaecology, King George's Medical University, 226003 Lucknow, Uttar Pradesh, India

progesterone which are secreted by placenta during pregnancy [10].

Maternal leptin level increases and remain elevated during the pregnancy but highest concentration is achieved in the second trimester between 24 and 28 weeks of pregnancy [11]. Recently, leptin emerged as a first trimester biomarker to predict diabetes during pregnancy [12]. Evidence from previous studies suggest that expression of leptin and its receptor increases in placental tissue of women with GDM [13] along with the increase in soluble form of leptin receptor (LEPRe). Despite high level of serum leptin in GDM, leptin resistance may occur due to the formation of leptin and LEPRe complex which decreases the availability of free leptin thereby preventing the binding of leptin to the bound form of leptin receptor [14]. The exact mechanism by which leptin regulate glucose homeostasis is still under experiment. However, few studies proposed that in leptin sensitive individuals, leptin secreted from adipose tissue inhibit the secretion of insulin from the pancreatic β- cells while individuals who are leptin resistant, secretion of insulin increases due to diminished leptin signalling resulting in hyperinsulinemia. In pregnancy, both insulin sensitivity and responsivity decreases but in most of the pregnant women it get adjusted with the increase in insulin secretion. While in some pregnant women secretion of insulin does not increase or insulin is not able to act on target tissues, leading to insulin resistance and hyperglycaemia [15, 16].

It is well known that pregnancy is a state of low-grade inflammation which gets exaggerated in GDM. The production of proinflammatory cytokines including interleukin-6 (IL-6) is known to be elevated in GDM women as compared to healthy pregnant women [17, 18]. IL-6 is also secreted by the placenta during pregnancy, the concentration of which may further increases in response to hyperleptinemia in GDM [19]. Role of IL-6 in the pathophysiology of glucose intolerance has been studied in type 2 diabetes mellitus and recommended that cytokine may serve as a potential biomarker for screening glucose intolerance in early stage [20]. Gestational diabetes which is similar to type 2 diabetes may be characterized by elevated level of IL-6 leading to insulin resistance. In addition, leptin increases the production of inflammatory cytokines like IL-6 by activating monocytes via jak2/stat3 and p-38 MAPK/ERK1/2 signalling pathways [21]. Gestational diabetes is a state of leptin resistance characterized by a vicious cycle of hyperinsulinemia and hyperleptinemia aggravating an inflammatory situation. Despite the availability of sufficient literature, the exact molecular mechanism which causes insulin resistance in GDM remains unclear. The aim of our study was to estimate the level of serum leptin, insulin and IL-6 among GDM, non-GDM and healthy non- pregnant women and to find out the correlation among study groups.

Materials and methods

Study participants and ethical approval

This cross-sectional study was conducted from April 2017 to March 2019 in the Department of Biochemistry and Department of Obstetrics and Gynaecology, King George's Medical University, Lucknow, Uttar Pradesh India. Ethical clearance for this study was obtained from Institutional Ethical Committee (*Ref code:83rd ECM IIA/P5 dated 04/02/2017*). Informed and written consent was obtained from all the enrolled study subjects. The flowchart of enrollment of pregnant women and their sample collection is shown in Fig. 1. In this study *DIPSI* criteria was adopted for screening GDM [22].

Study procedure

Blood sample was collected under aseptic precaution for estimation of all the biochemical parameters. 2-hour plasma glucose was estimated by glucose oxidase-hydrogen peroxide method on fully autoanalyzer (ELITech Selectra). Serum was separated for the analysis of insulin, IL-6 and leptin by centrifuge at 1,000–2,000 x g for 10 min and stored at -80˚C until batch analysis. All the samples were thawed at room temperature before analysis. Serum leptin and insulin were measured by commercially available ELISA kit according to guidelines of manufacturer (DRG International, Inc. U.S.A) [23, 24] and IL-6 was measured by DIACLONE ELISA kit manufactured in France [25].

Statistical analysis

All statistical analysis was performed by using MS-excel and Graph pad prism 5 (version 5.01). Continuous variables were expressed as mean ± standard deviation. For comparison of mean between three groups, one-way ANOVA analysis with post-hoc by Tukey's adjustment for group differences was used. Unpaired student t-test was used for the comparison of mean between two groups. To find out the correlation, Pearson correlation was applied. p-value < 0.05 was considered significant.

Results

The baseline characteristics of GDM, non-GDM healthy pregnant women and healthy non-pregnant women

The mean age of women was similar in all the three groups. Diastolic and systolic pressure (mmHg) was significantly

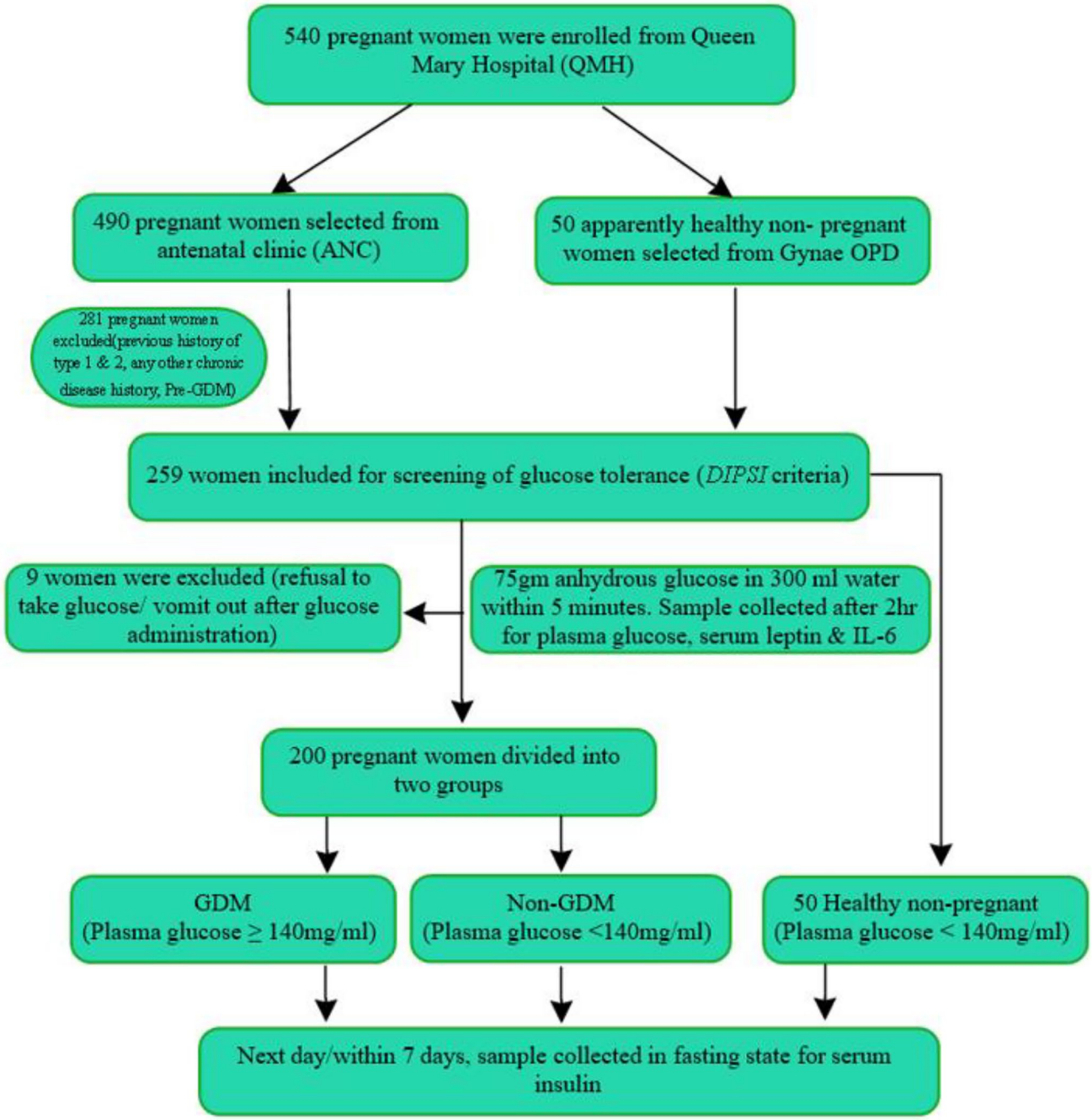

Fig. 1 Flowchart representing the selection of GDM, non-GDM and healthy non-pregnant women

higher among GDM women and healthy non-pregnant women as compared to non-GDM pregnant women ($p < 0.0001$). Pulse rate (/min) was significantly higher ($p < 0.04$) among non-GDM pregnant women as compared to non-pregnant women. Body mass index (BMI) was higher among GDM women as compared to non-pregnant women which was statistically significantly ($p < 0.002$). In addition, haemoglobin levels were significantly lower among GDM and non-GDM pregnant women as compared to healthy non-pregnant women ($p < 0.0001$). Family history of diabetes mellitus was 13.6%, 12% and 9.5% in GDM, non-GDM pregnant women and healthy non-pregnant women respectively. 7.4% GDM women and 6% of non-GDM women had family history of hypertension while it was 14.2% in non-pregnant women (Table 1).

Table 1 Baseline and clinical characteristics of GDM, Non-GDM pregnant women and healthy non-pregnant women

Baseline Characteristics	GDM women (n = 100) Mean ± SD	Non-GDM pregnant women (n = 100) Mean ± SD	Healthy non-pregnant women (n = 50) Mean ± SD
Age (yrs.)	26.63 ± 9.6	25.84 ± 4.02	28.04 ± 4.7
Clinical characteristics			
Diastolic blood pressure(mmHg)	111.36 ± 9.63***	107.57 ± 9.84	122.15 ± 7.63***
Systolic blood pressure (mmHg)	72.1 ± 7.67***	68.05 ± 8.02	81.71 ± 3.93***
Pulse rate (per min)	83.82 ± 10.6	85.14 ± 7.77*	78.95 ± 4.67
BMI (kg/mt^2)	25.27 ± 4.49**	23.97 ± 3.85	22.89 ± 3.16**
Family history of diabetes mellitus (%)	13.6	12	9.5
Family history of hypertension (%)	7.4	6	14.2
Biochemical parameters			
Hemoglobin (gm/dl)	10.64 ± 1.01	10.78 ± 0.87	11.52 ± 0.74¶
2 h post prandial (mg/dl)	149.49 ± 13.6	106.76 ± 14.9	103.5 ± 16.6
HOMA-IR	2.82 ± 1.19	2.58 ± 1.52	2.83 ± 1.34

***p < 0.0005 GDM vs. non-GDM and healthy non-pregnant women

* p < 0.05 non-GDM vs. healthy non-pregnant women

**p < 0.005 GDM vs. healthy non-pregnant

¶p < 0.005 GDM vs. healthy non-pregnant

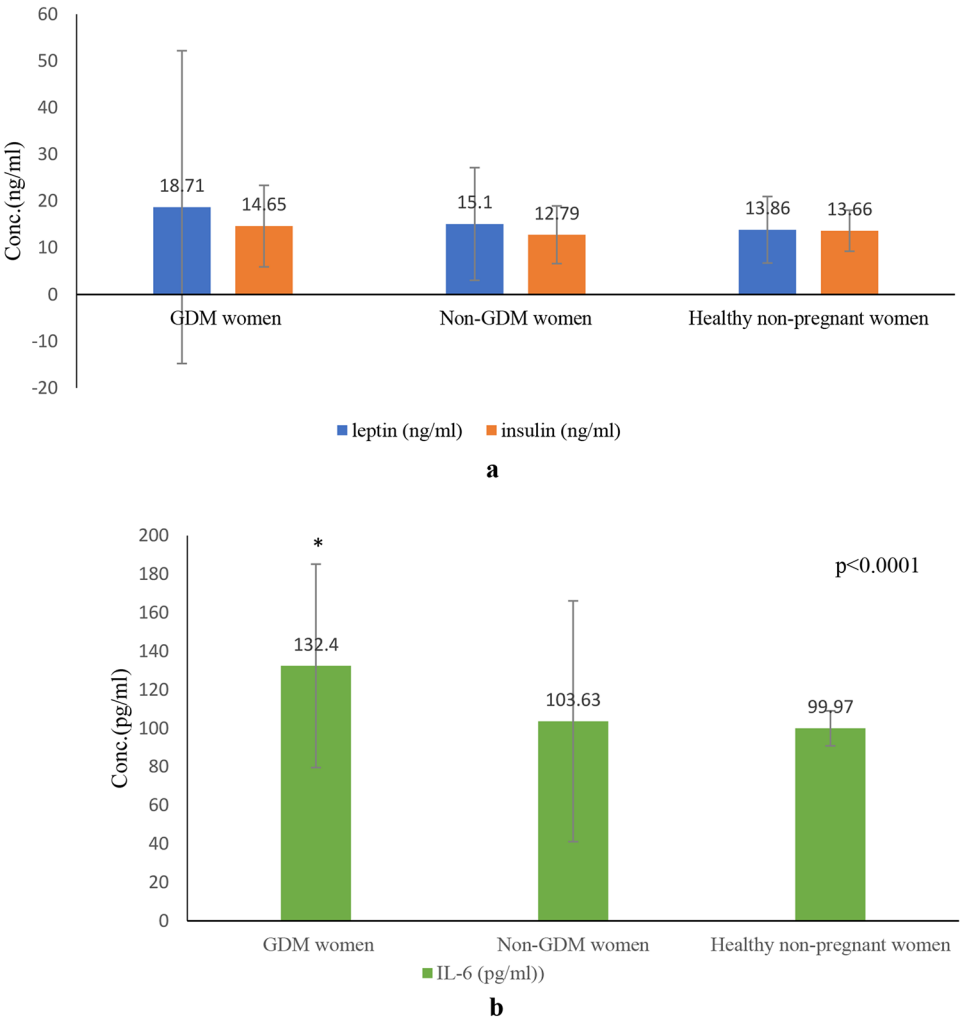

Fig. 2 **a** Mean serum leptin and insulin level in GDM, non-GDM pregnant and healthy non-pregnant women **b** Mean serum IL-6 level in GDM, non-GDM pregnant and healthy non-pregnant women

Mean serum leptin, insulin and IL-6 level in GDM, non-GDM pregnant women and healthy non-pregnant women

Mean level of serum leptin, insulin and IL-6 were higher among GDM as compared to non-GDM pregnant and non-pregnant women (Fig. 2a and b) however, statistically significant difference was observed only in IL-6 levels.

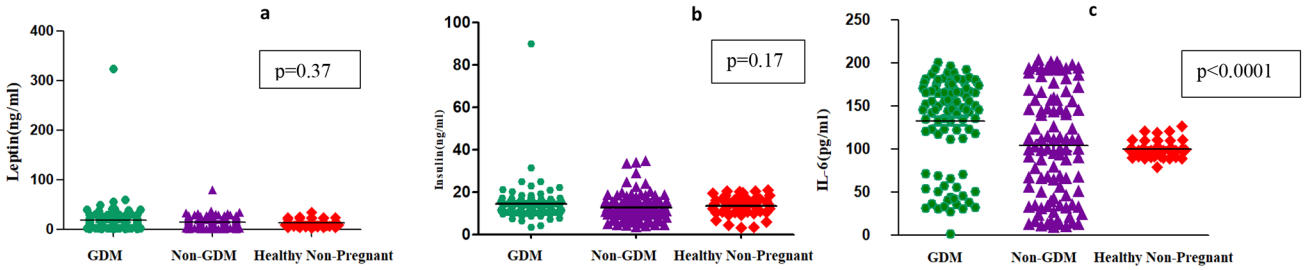

Fig. 3 **(a)** Serum leptin **(b)** insulin and **(c)** IL-6 levels among GDM, non-GDM pregnant women and healthy non-pregnant women

Comparison of serum leptin, insulin and IL-6 level among GDM, non-GDM pregnant and healthy non-pregnant women

Mean serum leptin level was higher among GDM women as compared to non-GDM pregnant women and healthy non-pregnant women though the difference not statistically significant as shown in Fig. 3a. Serum insulin level was almost similar among GDM, non-GDM pregnant and healthy non-pregnant women as shown in Fig. 3b. However, serum IL-6 level was significantly higher in GDM women as compared to non-GDM and healthy non-pregnant women ($p < 0.0001$) (Fig. 3c). Post hoc analysis was done to confirm the finding of IL-6 in the study groups as shown in supplementary Table 1.

Trimester-wise comparison of mean serum leptin, insulin and IL-6 level of GDM and non-GDM women

GDM and non-GDM pregnant women were further classified into 3 trimesters (1st trimester: ≤12weeks; 2nd trimester: 13–26 weeks; 3rd trimester: ≥27 weeks) depending upon weeks of pregnancy. Mean level of serum leptin, insulin and IL-6 are shown in Fig. 4a and b.

Comparison of serum leptin, insulin and IL-6 level in 1st, 2nd and 3rd trimester between GDM and non-GDM women

Serum leptin

In 1st trimester serum leptin levels were lower in GDM women as compared to non-GDM women which was statistically significant ($p < 0.027$) as shown in Fig. 5a. While in 2nd and 3rd trimester serum leptin levels were higher among GDM women as compared to non-GDM pregnant women however, statistically significant difference was found only in 3rd trimester ($p < 0.002$) as shown in Fig. 5b.

Serum insulin

Serum insulin levels were almost similar in all the three trimester when compared between GDM and non-GDM women ($p > 0.374$).

Serum IL-6

Serum IL-6 levels were significantly higher in 1st trimester of GDM women ($p < 0.017$) as compared to non-GDM pregnant women (Fig. 6).

Correlation between serum leptin, insulin and IL-6 in the study groups (GDM, non-GDM pregnant women and healthy non-pregnant women)

No significant correlation was found between serum leptin, insulin and IL-6 in GDM women. Negative correlation was observed between serum insulin and IL-6 in 2nd trimester of non-GDM women ($p < 0.033$, $r = -0.312$) (Fig. 7a). While in healthy non-pregnant women positive association was observed between serum insulin and IL-6 (p value 0.016, $r = 0.339$) (Fig. 7b). Leptin was not found to be associated with insulin and IL-6 in non-GDM as well as healthy non-pregnant women.

Discussion

In the present study, serum leptin levels were higher in GDM women compared to non-GDM and healthy non-pregnant women although the difference was not statistically significant. Furthermore, leptin levels were higher in 2nd and 3rd trimesters as compared to the 1st trimester in GDM women, but the difference was not statistically significant. However, in non-GDM women, serum leptin levels were almost similar in all three trimesters. Regarding leptin levels between GDM and non-GDM women, statistically significant differences were observed in the 1st and 3rd trimesters. In the 1st trimester, serum leptin levels were lower while in the 3rd trimester, the levels were significantly higher in GDM

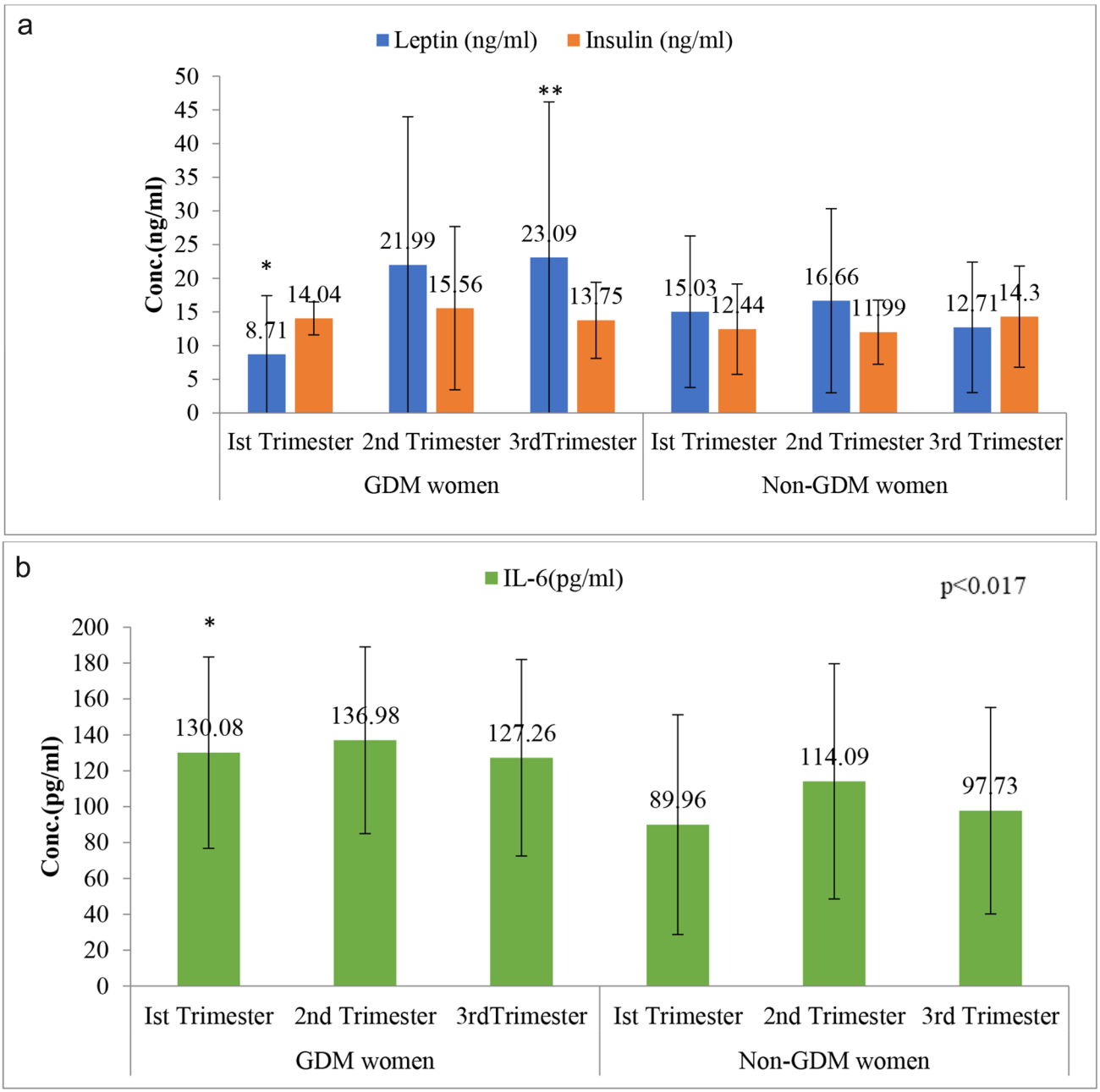

Fig. 4 **a** Serum leptin and insulin level in 1st, 2nd and 3rd trimester in GDM and non-GDM pregnant women *1st trimester serum leptin GDM versus non-GDM ($p < 0.027$) **3rd trimester serum leptin GDM versus non-GDM ($p < 0.002$) **b** Mean serum IL-6 level in 1st, 2nd and 3rd trimester between GDM and non-GDM pregnant women

women. In our study, 27 GDM and 23 non-GDM pregnant women constituted the 1st trimester and significantly higher leptin levels were observed in the non-GDM group. This difference can be explained by the fact that three non-GDM women had serum leptin levels of 37.88, 34.28, and 31.28 ng/ml in the 1st trimester, which possibly affected the mean leptin levels. In the literature, the highest maternal leptin concentration has been reported around 24–28 weeks of gestation and in our study, pregnant women with ≥ 27 weeks of gestation comprised the 3rd trimester which might have resulted in significantly higher serum leptin levels. Serum insulin levels were higher in GDM women compared to non-GDM and healthy pregnant women but the difference was not statistically significant. Furthermore, in all three trimesters serum insulin levels were similar in both GDM and non-GDM women. We found significantly higher levels of serum IL-6 in GDM women. Post hoc analysis showed that IL-6 levels were significantly higher in GDM women

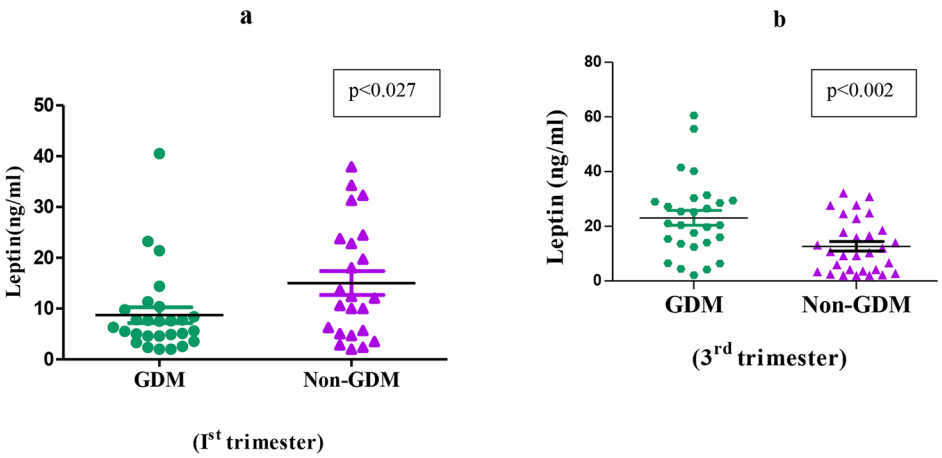

Fig. 5 Serum leptin level in 1st trimester (a) and 3rd trimester (b) of GDM and non-GDM pregnant women

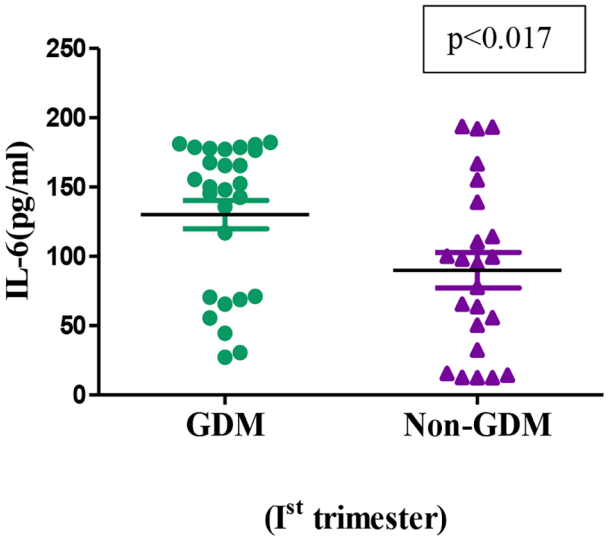

Fig. 6 Serum IL-6 level in 1st trimester of GDM and non-GDM pregnant women

than in non-GDM women as well as healthy non-pregnant women. Although IL-6 levels were higher in all three trimesters of GDM women, significantly higher levels were observed only in the 1st trimester of GDM women compared to non-GDM women.

Furthermore, IL-6 showed a negative correlation with insulin during the 2nd trimester of non-GDM women while a positive correlation was observed between IL-6 and insulin in healthy non-pregnant women. No correlation was observed between serum IL-6 and leptin levels in all three study groups.

Our findings are consistent with those of Mokhatri et al. [26] who also observed no significant differences in the levels of serum leptin between GDM and non-GDM women. In their case-control study, serum leptin levels were higher in the non-GDM group. Similarly, Saucedo et al. [27] found no significant difference in the plasma leptin concentration between GDM and non-GDM women. Simmons et al. [28] observed no difference in the maternal leptin levels among Polynesians, South Asians, and GDM women, although mean leptin levels were higher among GDM women. Goel et al. [29] reported higher serum leptin levels in GDM women during 28–32 weeks of pregnancy, which is consistent

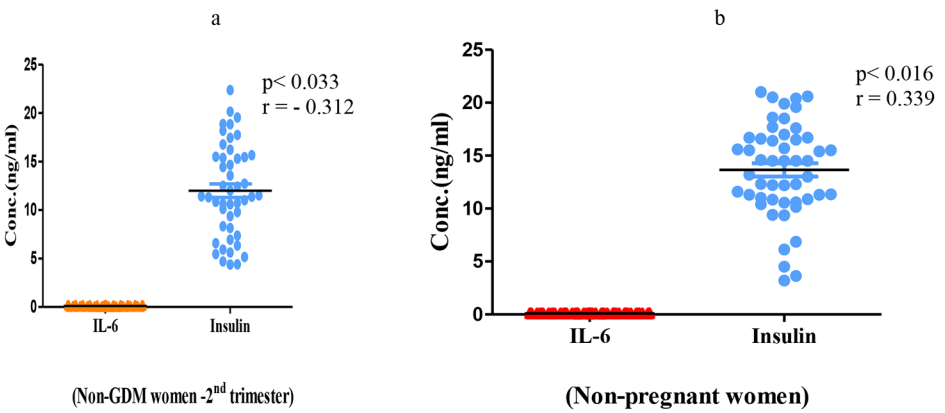

Fig. 7 **a** Correlation of IL-6 with insulin in 2nd trimester of non-GDM pregnant women **b** Correlation of IL-6 with insulin in non-pregnant women

with our observation in the 3rd trimester GDM women. Similarly, Gao et al. [10] found significantly higher levels of serum leptin during 14–20 weeks and 24–32 weeks of pregnancy among GDM women. Kautzky-Willer et al. [30] also observed significantly higher leptin levels at 28 weeks of gestation among GDM women compared to non-GDM as well as patients with type 1 diabetes mellitus. In contrast to our findings, Saini et al. [23] observed significantly higher serum leptin levels in 30 GDM women compared to 60 non-GDM women. Noureldeen et al. [31] reported lower serum leptin levels in the 3rd trimester among GDM women compared to non-GDM women, which is in contrast with our observations. Consistent with our study, Shalayel et al. [32] found no significant difference in serum insulin levels during 3rd trimester among GDM, non-GDM, and IGT (Impaired Glucose Tolerance) women. Contrary to our results, Fakhrul-Alam et al. [33] in a recent study measured serum insulin levels during 24–40 weeks of gestation and found higher insulin levels in GDM women compared to non-GDM. Wang et al. [34] measured serum insulin levels in 55 GDM and 87 non-GDM women during late pregnancy and found significantly higher levels in GDM women. Similarly, Sarma et al. [35] and Wang et al. [36] found significantly higher serum insulin levels during 24–28 weeks of gestation and Kautzky-Willer et al. [30] found significantly higher insulin levels at 28 weeks of gestation among GDM women. Yang Y et al. [37] observed significantly higher IL-6 levels during the 1st trimester of GDM women compared to non-GDM women, which is similar to our observation. Similarly, Hassiakos et al. [38] found significantly raised IL-6 levels in GDM women during 11–14 weeks of pregnancy. Sarma et al. [35] reported significantly higher IL-6 levels in 52 East Indian women with GDM at 24–28 weeks of pregnancy compared to 48 non-GDM women. Contrary to our findings, Abell et al. [39], and Lain et al. [40] found no difference in IL-6 levels between GDM and non-GDM women during 12–15 weeks and 9.3 weeks of gestation, respectively. Similarly, Braga et al. [41] observed no significant difference at 24–28 weeks of gestation. Simjak et al. [42] included 12 GDM, 12 non-GDM, and 10 healthy non-pregnant women, and reported lower IL-6 levels in non-pregnant women and higher levels in GDM women during 28–32 weeks and 36–38 weeks of gestation, though the difference was not statistically significant.

Similar to our findings, Sarma et al. [35] found no correlation between IL-6 and insulin levels in GDM women. In contrast to our findings, Kautzky-Willer et al. [30] found a positive correlation between fasting leptin and fasting insulin levels in GDM women.

This study was conducted on the North Indian population and compared the levels of leptin, insulin, and IL-6 trimester-wise in GDM and non-GDM women. Several studies on GDM women measured the levels of leptin, insulin, and IL-6 independently, although very few focused on their relationship. Our study tried to explore whether any association exists between inflammation, hyperleptinemia, and hyperinsulinemia in gestational diabetes. There are a few limitations of our study. First, the population screened for gestational diabetes was restricted to women from the city and adjoining areas only. Hence, the outcomes of this study cannot be generalized. Also, women in all three trimesters of GDM and the non-GDM groups were different. To study the changes in adipokines and inflammatory markers, longitudinal studies are required so that the same group of women enrolled in the 1st trimester is followed up during 2nd and 3rd trimesters as well as after the delivery.

Conclusion

Serum leptin and IL-6 levels are altered during pregnancy, a condition that further worsen in patients with gestational diabetes mellitus. The absence of any significant correlation between leptin and IL-6 levels signifies that leptin is not associated with inflammation during pregnancy. Altogether, our study suggests that IL-6 may be used as a biomarker, especially during the first trimester, for screening gestational diabetes mellitus. Further study with a larger sample size may pave the way for the discovery of an early diagnostic marker for gestational diabetes mellitus.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40200-023-01188-3.

Acknowledgements The authors express their gratitude to Council of Science and Technology, U.P., India (UPCST) for providing financial support during the study.

Declarations

Ethics approval and consent to participate This study was approved by our Institutional (King George's Medical University, Lucknow, Uttar Pradesh, India) Ethical Committee. Informed and written consent was obtained from all the enrolled participants.

Consent to publish Not applicable.

Competing interests The authors declare that they have no competing interest.

References

1. Margetic S, Gazzola C, Pegg GG, Hill RA. Leptin: a review of its peripheral actions and interactions. Int J Obes Relat Metab Disord. 2002;26:1407–33.

2. Mantzoros CS, Magkos F, Brinkoetter M, Sienkiewicz E, Dardeno TA, Kim SY, et al. Leptin in human physiology and pathophysiology. Am J Physiol Endocrinol Metab. 2011;301:567–84.
3. Ceddia RB, Koistinen HA, Zierath JR, Sweeney G. Analysis of paradoxical observations on the association between leptin and insulin resistance. FASEB J. 2002;16:1163–76.
4. Al-Dahhri N, Bartlett WA, Jones AF, Kumar S. Role of leptin in glucose metabolism in type 2 diabetes. Diabet Obes Metab. 2002;4:147–55.
5. Cervero A, Horcajadas JA, Dominguez F, Pellicer A, Simon C. Leptin system in embryo development and implantation: a protein in search of a function. Reprod Biomed Online. 2005;10(2):217–23.
6. Dos SE, Serazin V, Morvan C, Torre A, Wainer R, de Mazancourt P, et al. Adiponectin and leptin systems in human endometrium during window of implantation. Fertil Steril. 2012;97(3):771–78.
7. Mithal A, Bansal B, Kalra S. Gestational diabetes in India: Science and society. Indian J Endocrinol Metab. 2015;19(6):701–4.
8. Swaminathan G, Swaminathan A, Corsi DJ. Prevalence of gestational diabetes in India by Individual Socioeconomic, demographic, and clinical factors. JAMA Netw Open. 2020;3(11):e2025074.
9. Suhonem L, Hiilesma V, Teramo K. Glycemic control during early pregnancy and fetal malformations in women with type 1 diabetes mellitus. Diabetologia. 2000;43:79–82.
10. Gao XL, Yang HX, Zhao Y. Variations of tumor necrosis factor-alpha, leptin and adiponectin in mid-trimester of gestational diabetes mellitus. Chin Med J (Engl). 2008;121:701–5.
11. Henson MC, Castracane VD. Leptin in pregnancy. Biol Reprod. 2000;63:1219–28.
12. Thagaard IN, Krebs L, Holm JC, Lange T, Larsen T, Christiansen M. Adiponectin and leptin as first trimester markers for gestational diabetes mellitus: a cohort study. Clin Chem Lab Med. Oct 2017;26(11):1805–12.
13. Perez-Perez A, Sanchez-Jimenez F, Maymo J, Duenas L, Varone J, Sanchez-Margalet C. Insulin and leptin signaling in placenta from gestational diabetic subjects. Horm Metab Res. 2015;48:62–9.
14. Perez-Perez A, Maym_o JL, Gambino YP, et al. Activated translation signaling in placenta from pregnant women with gestational diabetes mellitus: possible role of leptin. Horm Metab Res. 2013;45:436–42.
15. Dahlgren J. Pregnancy and insulin resistance. Metab Syndr Relat Disord. 2006;4(2):149–52.
16. Baban RS, Kasar KA, Al-Karawi IN. Fasting glucose to leptin ratio as a new diagnostic marker in patients with diabetes mellitus. Oman Med J. 2010;25(4):269–75.
17. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011;11:85–97.
18. Kuzmicki M, Telejko B, Szamatowicz J, Zonenberg A, Nikolajuk A, Kretowski A, et al. High resistin and interleukin-6 levels are associated with gestational diabetes mellitus. Gynecol Endocrinol. 2009;25(4):258–63.
19. Sun D, Li F, Zhang Y, Xu X. Associations of the prepregnancy BMI and gestational BMI gain with pregnancy outcomes in chinese women with gestational diabetes mellitus. Int J Clin Exp Med. 2014;7:5784–9.
20. Kleiblova P, Dostalova I, Bartlova M, Lacinova Z, Ticha I, Krejci V, et al. Expression of adipokines and estrogen receptors in adipose tissue and placenta of patients with gestational diabetes mellitus. Mol Cell Endocrinol. 2010;314:150–6.
21. Agrawal S, Gollapudi S, Su H, Gupta S. Leptin activates human B cells to secrete TNF-α, IL-6, and IL-10 via JAK2/STAT3 and p38MAPK/ERK1/2 signaling pathway. J Clin Immunol. 2011;31:472–8
22. Anjalakshi C, Balaji V, Balaji MS et al. A single test procedure to diagnose gestational diabetes mellitus. Acta Diabetol. 2009; 46:51–4.
23. Saini V, Kataria M, Yadav A, Jain A. Role of leptin and adiponectin in gestational diabetes mellitus: a study in a north indian tertiary care hospital. Inter J Medi Update. 2015;10:11–4.
24. Imoh LC, Ocheke AN. Correlation between maternal weight and insulin resistance in second half of pregnancy. Niger Med J. 2014;55(6):465–8.
25. Pieczynska J, Płaczkowska S, Pawlik-Sobecka L, Kokot I, Sozanski R, Grajeta H. Association of Dietary Inflammatory Index with serum IL-6, IL-10, and CRP concentration during pregnancy. Nutrients. 2020;12(9):2789.
26. Mokhtari M, Hashemi M, Yaghmaei M, Naderi M, Shikhzadeh A, Ghavami S. Evaluation of the serum leptin in normal pregnancy and gestational diabetes mellitus in Zahedan, southeast Iran. Arch Gynecol Obstet. 2011;284:539–42.
27. Saucedo R, Zarate A, Basurto L, Hernandez M, Puello E, Galvan R, et al. Relationship between circulating adipokines and insulin resistance during pregnancy and postpartum in women with gestational diabetes. Arch Med Res. 2011;42:318–23.
28. Simmons D, Breier BH. Fetal over nutrition in polynesian pregnancies and in gestational diabetes may lead to dysregulation of the adipoinsular axis in offspring. Diabet Care. 2002;25:1539–44.
29. Goel R, Chugh K, Duhan N, Ghalaut VS, Kumar HD, Sehgal PK, et al. Maternal serum leptin concentration in gestational diabetes mellitus. Imp J Interdisp Res. 2016;2(2):2454–1362.
30. Kautzky-Willer A, Pacini G, Tura A, Bieglmayer C, Schneider B, Ludvik B, Prager R, Waldhäusl W. Increased plasma leptin in gestational diabetes. Diabetologia. 2001;44:164–72.
31. Noureldeen AF, Qusti SY, Al-Seeni MN, Bagais MH. Maternal leptin, adiponectin, resistin, visfatin and tumor necrosis factor-alpha in normal and gestational diabetes. Indian J Clin Biochem. 2014;29:462–70.
32. Shalayel MHF, Al-Noaemi MC, Ahmed SA. In: Radenkovic M, editor. Insulin resistance in the third trimester of pregnancy suffering from gestational diabetes mellitus or impaired glucose tolerance. Gestational Diabetes, Croatia: In Tech; 2011 In.
33. Fakhrul-Alam M, Sharmin-Jahan M-H, Rakibul-Hasan Nusrat-SultanaMohona-Zaman. Insulin secretory defect may be the major determinant of GDM in lean mothers. J Clin Transl Endocrinol. 2020;20:100226.
34. Wang X, Yang T, Miao J, Liu H, Wu K, Guo J, et al. Correlation between maternal and fetal insulin resistance in pregnant women with gestational diabetes mellitus. Clin Lab. 2018;64:945–53.
35. Sarma GD, Khemka VK, Sanyal R, Hossaini SSA, Mitra A. Altered interleukin 6 level in gestational diabetes across eastern India. Int J Health Clin Res. 2021;4:182–5.
36. Wang Q, Huang R, Yu B, Cao F, Wang H, Zhang M, et al. Higher fetal insulin resistance in chinese pregnant women with gestational diabetes mellitus and correlation with maternal insulin resistance. PLoS ONE. 2013;8:e59845.
37. Yang Y, Liu L, Liu B, Li Q, Wang Z, Fan S, et al. Functional defects of regulatory T cell through interleukin 10 mediated mechanism in the induction of gestational diabetes mellitus. DNA Cell Bio. 2018;37:278–85.
38. Hassiakos D, Eleftheriades M, Papastefanou I, Lambrinoudaki I, Kappou D, Lavranos D, et al. Increased maternal serum interleukin-6 concentrations at 11 to 14 weeks of gestation in low-risk pregnancies complicated with gestational diabetes mellitus: development of a prediction model. Horm Metab Res. 2016;48:35–41.
39. Abell SK, Shorakae S, Harrison CL, Hiam D, Moreno- Asso A, Stepto NK, et al. The association between dysregulated adipocytokines in early pregnancy and development of gestational diabetes. Diabetes Metab Res Rev. 2017;33:26–9.

40. Lain KY, Daftary AR, Ness RB, Roberts JM. First trimester adipocytokine concentrations and risk of developing gestational diabetes later in pregnancy. Clin Endocrinol (Oxf). 2008;69:407–11.
41. Braga FO, Negrato CA, Matta MFBD, Carneiro JR, Gomes MB. Relationship between inflammatory markers, glycated hemoglobin and placental weight on fetal outcomes in women with gestational diabetes. Arch Endocrinol Metab. 2019;63:22–9.
42. Simjak P, Cinkajzlova A, Anderlova K, Kloučkova J, Kratochvilova H, Lacinova Z, et al. Changes in plasma concentrations and mRNA expression of hepatokines fetuin A, fetuin B and FGF21 in physiological pregnancy and gestational diabetes mellitus. Physiol Res. 2018;67:531–42.