The relationship between leptin and steroid hormones during different trimesters in gestational diabetes mellitus and obese pregnant women

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Abstract:
Leptin is one of the adipokines hormones, it is important for energy expenditure, it is affected by complications during pregnancy such as gestational diabetes mellitus (GDM) and obesity. Women who develop GDM and obesity have elevated metabolic changes. Recently, a series of studies has suggested that the leptin role change with these complications. However, it is unclear if this change effected by steroidal hormones during different trimesters. Thus, we study the relationship between leptin and steroid hormones in GDM and obese pregnant women during different trimesters. The study included (90) pregnant women, aged (25 - 35) years it is classified into two groups: The first group [control]: healthy pregnant women. Second group: a pregnant woman with GDM. Third group: obese pregnant women. The study has from November 2018 to February 2019. Parameters diagnosed by ELISA, and Cobase-411. Our results revealed all parameters increased during trimesters within different groups, no significant increase in leptin levels between the second and third groups, steroid hormones increased in the 3rd group in comparison with the other groups. Conclusions: Results of the current study showed clearly the following conclusion in GDM and obese pregnant women leptin hormone in our study elevated during different trimesters in different groups, this elevation associated with high levels of steroid hormones.

Keywords: GDM, obesity, leptin, steroid hormones

Introduction:
The gestation is a critical and unique period in a women's life \(^[1]\). And unique metabolic condition because of the changes in maternal metabolism needed to provide for fetal growth and increased maternal energy requirements \(^[2]\). In this period much dynamic change for a mother need a lot of care and rapid changes in the hormones like progesterone and estradiol (E2) \(^[3]\). Progesterone is a steroidal hormone \(^[4]\). A major function to promote secretory changes in the endometrium. Of uterine, preparing the uterus for implantation, and increased secretion by the mucosal lining of the fallopian tubes, it is produced by the corpus luteum after ovulation \(^[5]\). Estradiol (E2) another steroidal hormone that is crucial role during pregnancy, in addition to its function as a gonadal hormone, is involved in the regulation of metabolism through the modulation of body weight, food intake, glucose/insulin balance, body fat distribution, lipogenesis and lipolysis, and energy consumption \(^[6]\). The gestation is a physiological process that can involve the development of maternal pathologies, metabolic disorders (maternal obesity, and such as gestational diabetes mellitus (GDM) \(^[7]\).

Adipokines
White adipose tissue is now recognized to be a multifunctional organ, storage lipid is the main function, and however, it has a major endocrine function secreting several hormones \(^[8]\). Adipokines are cytokines (i.e. leptin, adiponectin, omentin, resistin...) produced mainly by adipose tissue, besides many other tissues such as (placenta, ovaries, peripheral - blood mononuclear cells, liver, muscle, kidney, heart, and bone marrow) \(^[9]\). Leptin discovered in (1994), 167 amino acid product of the human leptin gene (ob. Gene), it is primarily secreted by the white adipose tissue but it’s also produced by placenta, mammary gland, stomach \(^[10,11]\). It is an adipocyte-derived hormone, plays a key role in the control of energy balance \(^[12]\). It plays a functional role during pregnancy, it’s important in

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implantation, induces human chorionic gonadotropin production in trophoblast cells, and regulates placental growth\[^{13}\]. And their levels increased during pregnancy trimesters, lowest in the first trimester then increased in the first butin the second trimester may be fluctuated (increased - decreased or unchangeable)\[^{14,15}\]. Messinis and his colleagues (2001) mentioned that progesterone and estradiol hormones stimulated leptin production\[^{16}\], thus, Al-Atawiet al. (2004) concluded that a positive correlation between leptin high levels and many hormones such as progesterone and estradiol\[^{17}\].

Moreover, hyperleptinaemia in early pregnancy appears to be predictive of an increased risk to develop GDM later in pregnancy independent of maternal adiposity\[^{18}\]. However, Mosavat and his colleagues (2017) considered the lower leptin levels as a risk factor for GDM developing\[^{19}\]. Furthermore, a strong linear correlation between increased maternal plasma leptin and increased risk of GDM\[^{20}\]. In the other hand a close relationship between leptin and the obesity via their regulation of energy metabolism and their action as a central satiety-signaling hormone, thus, obesity is associated with increased serum leptin levels, proportional to the BMI and percentage of body fat in humans\[^{21}\].

Materials and methods
The current study has been done at al - Sadr educational hospital, child and birth governmental hospital, golden medical clinic, altayf laboratory, from November 2018 to February 2019 in Misan province. The study included (90) pregnant women, aged (25 - 35) years it is classified into three groups first one healthy pregnant woman, the second group with GDM, and third group obese pregnant women. WHO recommended high levels of sugar, or glucose, in the blood first detected at any time during pregnancy should be classified as either GDM according to WHO criteria\[^{22}\]. Fasting plasma glucose was examined in vitro after 8 hours of fasting, at 9 am. Also, obese pregnant women are classified according to the WHO criteria\[^{23}\]. Leptin hormone diagnosed by mybiosourse(USA) ELISA human kit, E2 and progesterone hormones by Co bas e-411.

Statistical analysis: Statistical analysis was performed by IBM SPSS statistics, version 23. It was performed by ANOVA, followed by LSD at (p≤0.05) significant level.

Results
The levels of leptin hormone in different trimesters within each group
First group
Results revealed that the leptin level in the second trimester (6.150±0.492 mg/ml) increased significantly (p<0.05) in comparison with the first trimester (1.860±0.295 mg/ml). The leptin level in the third trimester (6.890±0.622 mg/ml) increased significantly (p<0.05) in comparison with the first and second trimesters. (Table 1, Figure 1).

Second group
The leptin level in the second trimester (1.640±0.320 mg/ml) have no significant difference (p<0.05) in comparison with the first trimester (1.360±0.435 mg/ml). The leptin level in the third trimester (2.180±0.628 mg/ml) increased significantly (p<0.05) in comparison with the first and second trimesters. (Table 1, Figure 1).

Third group
The leptin level in the second trimester (1.610±0.280 mg/ml) increased significantly (p<0.05) in comparison with the first trimester (1.220±0.187 mg/ml). The leptin level in the third trimester (2.300±0.323 mg/ml) increased significantly (p<0.05) in comparison with the first and second trimesters. (Table 1, Figure 1).

The levels of leptin hormone in similar trimesters within different groups
First trimester
Results revealed that the leptin level in the first trimester in the second group (1.360±0.435 mg/ml) decreased significantly (p<0.05) in comparison with the first trimester in the first group (1.860±0.295 mg/ml). The leptin level in the first trimester in the third group (1.220±0.187 mg/ml) decreased significantly (p<0.05) in comparison with the first trimester in the first group, but have no signs with the first trimester in the second group. (Table 1, Figure 1).

Second trimester: Results revealed that the leptin level in the second trimester in the second group (1.640±0.320 mg/ml) decreased significantly (p<0.05) in comparison with the second trimester in the first group (6.150±0.492 mg/ml). The leptin level in the second trimester in the third group (1.610±0.280 mg/ml) decreased significantly...
(p<0.05) in comparison with the second trimester in the first group, but have no significant difference with the second trimester in the second group. (Table 1, Figure 1).

**Third trimester**

Results revealed that the leptin level in the third trimester in the second group (2.180±0.628 mg/ml) decreased significantly (p<0.05) in comparison within the third trimester in the first group (6.890±0.622 mg/ml). The leptin level in the third trimester in the third group [2.300±0.323 mg/ml] decreased significantly (p<0.05) in comparison with the third trimester in the first group, but have no significant difference with the third trimester in the second group. (Table 1, Figure 1).

**Table (1):** The levels of parameters in different groups and trimesters in pregnant women:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Leptin (mg/ml)</th>
<th>Estradiol (ng/L)</th>
<th>Progesterone (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trimesters</strong></td>
<td><strong>Group (1)</strong></td>
<td><strong>Group (2)</strong></td>
<td><strong>Group (3)</strong></td>
</tr>
<tr>
<td>1st</td>
<td>a 1.860±0.295</td>
<td>A</td>
<td>0.393±0.050</td>
</tr>
<tr>
<td>2nd</td>
<td>a 6.150±0.492</td>
<td>B</td>
<td>3.417±0.308</td>
</tr>
<tr>
<td>3rd</td>
<td>a 6.890±0.622</td>
<td>C</td>
<td>4.563±0.371</td>
</tr>
<tr>
<td>1st</td>
<td>a 1.360±0.435</td>
<td>A</td>
<td>0.176±0.026</td>
</tr>
<tr>
<td>2nd</td>
<td>a 1.640±0.320</td>
<td>A</td>
<td>3.941±0.287</td>
</tr>
<tr>
<td>3rd</td>
<td>a 2.180±0.628</td>
<td>B</td>
<td>5.458±0.378</td>
</tr>
<tr>
<td>1st</td>
<td>a 1.220±0.187</td>
<td>A</td>
<td>0.589±0.049</td>
</tr>
<tr>
<td>2nd</td>
<td>a 1.610±0.280</td>
<td>B</td>
<td>4.779±0.378</td>
</tr>
<tr>
<td>3rd</td>
<td>a 2.300±0.323</td>
<td>C</td>
<td>5.624±0.424</td>
</tr>
</tbody>
</table>

The values represent mean ± SD.

Similar capital letters represent no significant difference between trimesters.

Different capital letters represent a significant difference (p<0.05) between trimesters.

Similar small letters represent no significant difference between groups.

Different small letters represent a significant difference (p<0.05) between groups.

**Figure (1):** The levels of serum leptin hormone (mg/ml) during different groups and trimesters in pregnant women.
The levels of estradiol hormone (E2) in different trimesters within each group

First group
Results revealed that the E2 level in the second trimester (3.417±0.308 ng/L) increased significantly (p<0.05) in comparison with the first trimester (0.393±0.050 ng/L). E2 level in the third trimester (4.563±0.371 ng/L) increased significantly (p<0.05) in comparison with the first and second trimesters. (Table 1, Figure 2).

Second group
The E2 level in the second trimester (3.941±0.287 ng/L) increased significantly (p<0.05) in comparison with the first trimester (0.176±0.026 ng/L). The E2 level in the third trimester (5.458±0.402 ng/L) increased significantly (p<0.05) in comparison with the first and second trimesters. (Table 1, Figure 2).

Third group
The E2 level in the second trimester (4.779±0.378 ng/L) increased significantly (p<0.05) in comparison with the first trimester (0.589±0.049 ng/L). The E2 level in the third trimester (5.624±0.424 ng/L) increased significantly (p<0.05) in comparison with the first and second trimesters. (Table 1, Figure 2).

The levels of estradiol hormone in similar trimesters within different groups

First trimester
Results revealed that the E2 in the first trimester in the second group (0.176±0.026 ng/L) decreased significantly (p<0.05) in comparison with the first trimester in the first group (0.393±0.05 ng/L). The E2 level in the first trimester in the third group (0.589±0.049 ng/L) increased significantly (p<0.05) in comparison with the first trimester in the second group and the first trimester in the first group. (Table 3, Figure 3).

Second trimester:
The E2 level in the second trimester in the second group (3.941±0.287 ng/L) increased significantly (p<0.05) in comparison with the second trimester in the first group (3.417±0.308 ng/L). The E2 level in the second trimester in the third group (4.779±0.378 ng/L) increased significantly (p<0.05) in comparison with the second trimester in the first group, and the second trimester in the second group (3.941±0.287 ng/L). (Table 1, Figure 2).

Third trimester:
The E2 level in the third trimester in the second group (5.458±0.402 ng/L) increased significantly (p<0.05) in comparison with the third trimester in the first group (4.563±0.371 ng/L). The E2 level in the third trimester in the third group (5.624±0.424 ng/L) increased significantly (p<0.05) in comparison with the third trimester in the first group, but have no significant difference with the third trimester in the second group. (Table 1, Figure 2).

Figure (2): The levels of serum estradiol (E2) hormone (ng/L) during different groups and trimesters in pregnant women.
The levels of progesterone hormone in different trimesters within each group

**First group**
Results revealed that the progesterone level in the second trimester (71.100±6.488 nmol/L) increased significantly (p<0.05) in comparison with the first trimester (19.710±3.684 nmol/L). The progesterone level in the third trimester (109.90±8.00. nmol/L) increased significantly (p<0.05) in comparison with the first and second trimesters. (Table 1, Figure 3).

**Second group**
The progesterone level in the second trimester (73.610±7.554 nmol/L) increased significantly (p<0.05) in comparison with the first trimester [53.310±6.949 nmol/L]. The progesterone level in the third trimester (122.600±10.437 nmol/L) increased significantly (p<0.05) in comparison with the first trimester, and the second trimester. (Table 1, Figure 3).

**Third group**
The progesterone level in the second trimester (100.000±8.366 nmol/L) increased significantly (p<0.05) in comparison with the first trimester (47.620±6.423 nmol/L). The progesterone level in the third trimester (182.600±8.356 nmol/L) increased significantly (p<0.05) in comparison with the first trimester, and the second trimester. (Table 1, Figure 3).

The levels of progesterone hormone in similar trimesters within different groups

**First trimester**
Results revealed that the progesterone in the first trimester in the second group (53.310±6.949 nmol/L) increased significantly (p<0.05) in comparison with the first trimester in the first group (19.710±3.684 nmol/L). The progesterone level in the first trimester in the third group (47.620±6.423 nmol/L) increased significantly (p<0.05) in comparison with the first trimester in the first group, but decreased significantly with the first trimester in the second group. (Table 1, Figure 3).

**Second trimester**
The progesterone level in the second trimester in the second group (73.610±7.554 nmol/L) have no significant difference in comparison with the second trimester in the first group (71.100±6.488 nmol/L). The progesterone level in the second trimester in the third group (100.000±8.366 nmol/L) increased significantly (p<0.05) in comparison with the second trimester in the first group, and the second trimester in the second group. (Table 1, Figure 3).

**Third trimester**
The progesterone level in the third trimester in the second group (122.600±10.437 nmol/L) increased significantly (p<0.05) in comparison with the third trimester in the first group (109.900±7.922 nmol/L). The progesterone level in the third trimester in the third group (182.600±8.356 nmol/L) increased significantly (p<0.05) in comparison with the third trimester in the first group, and third trimester in the second group. (Table 1, Figure 3).

![Figure 3](image_url): The levels of serum progesterone hormone (nmol/L) during different groups and trimesters in pregnant women.
The values represent mean ± SD.
Similar capital letters represent no significant difference between trimesters.
Different capital letters represent a significant difference (p<0.05) between trimesters.
Similar small letters represent no significant difference between groups.
Different small letters represent a significant difference (p<0.05) between groups.
Blue color represents the first trimester.
Green color represents the second trimester.
Red color represents the third trimester.
Discussion:
Results of the present investigation showed that leptin hormone levels increased significantly (p ≤ 0.05) during different trimesters in the first group. This increase might be attributable to the additional amount of leptin levels that come from placenta as new source for leptin synthesis , moreover, a greater GWG that increased with the progressive stages of pregnancy was related also with this increase in leptin levels, progesterone and estradiol hormones which increased in late pregnancy interfered with leptin levels secreted .Kasilovskiené and his team (2004) found an elevation in maternal serum leptin levels during pregnancy especially in the 2nd and 3rd trimesters of pregnancy [25]. Many studies showed that placenta cell (trophoblast) may contribute to leptin levels increase during pregnancy [26]. Lacroix and his colleagues (2016) mentioned that higher leptin levels were associated with greater subsequent weight gain [24].

On the other hand, Al-Atawiet et al. (2004) found that the increase in leptin levels during different trimesters occurred due to the elevation of some steroidal hormones (progesterone and estradiol) which increased in late pregnancy [17]. In the second group, the leptin levels increased significantly (except first and second trimester). This increase (in addition to causes listed above) occurred due to the high levels of insulin and IR in GDM. The progressive increase of IR observed in pregnancy contributes to the pathophysiology of GDM [29]. Hussein and Al-Samarrai (2012) showed that the increase of leptin level occurred due to the IR and hyperinsulinemia in GDM pregnant women [27]. The leptin levels increased in the third group during different trimesters, and this increase (in addition to the causes in the first and second groups), associated with a high BMI and adipose tissue during gestation, and while this group characterized by a high BMI and a high adipose tissue. Al-Atawi and his colleagues (2004) showed that the increase of BMI and accumulation of adipose tissue during pregnancy lead to an increase in leptin levels [17]. Fattah et al. (2010) showed that the linkage between leptin and fat mass and BMI [28].

Noureldeen and his colleagues (2013) suggested that the differences in the expression of leptin receptors signals between normal and diabetic women might be a considerable reason for the significant differences in maternal leptin between GDM and control subjects [29]. The relative increase of insulin hormone and insulin resistance in the second and third groups might be explained the non-significant difference in leptin levels between these two groups. That’s supported by the metabolic similarities within the endocrine milieu of obesity and GDM [30]. Our results revealed the estradiol and progesterone hormones levels increased significantly (p ≤ 0.05) in all trimesters within all groups, this dramatic increase between trimesters important for the maintenance of pregnancy has long, this increased depending on gestation trimester, in the first group, the placenta plays an important role in fetal growth because it is considered as an endocrine organ as it produces many hormones for gestation such as progesterone, estradiol, and others.

Xiuyuet et al. (2017) showed the placenta plays a crucial role in fetal growth and is also recognized as an endocrine organ as it produces essential hormones for gestation [31]. In addition Pecks et al. (2016) showed the relationship between lipids and steroid hormones are closely linked, cholesterol is the substrate for (placental) steroid hormone synthesis, steroid hormones regulate hepatic lipid production [32]. Furthermore, Dicianni et al. (2003) showed the changes in β-cell function occur in parallel with the development of the fetoplacental unit and the local production of hormones, such as estrogens, progesterone. These hormones have been shown to induce insulin resistance [33]. The third group increased significantly (p ≤ 0.05) in comparison with first and second groups, because the steroid hormone primarily produced by the adipose tissue, interestingly, obesity is often accompanied by a state of the relatively high level of estrogen considering the positive role exerted by estrogens on adipose mass and distribution.

Colleluori et al. (2018) showed obesity is often accompanied by a state of relative hyperestrogenemia due to of the higharomatase expression/activity in the adipocytes of obesesubjects, considering the positive role exerted by estrogens on adipose mass and distribution, E2 elevated with obese levels in obese individuals may appear inconsistent, this scenario raises the possibility that adipocytes in obese individuals, who have high E2 levels, are not as sensitive to the lipolytic effects of estrogens. This in turn may suggest a different mechanism for the increased body fat at both ends of the estrogen [34]. The second group increase significantly (p ≤ 0.05) in comparison with first group (except in first trimester), that’s because a surprising role for estradiol in regulating energy metabolism. Dicianni et al. (2003) showed the important role of estradiol in regulating energy, metabolism, glucose homeostasis, and induce insulin resistance [33].
In addition, Sattaret al. (2017) showed a high increase in estrogen and progesterone seen in pregnancy, especially in GDM in comparison with a healthy pregnancy. The relative increase of insulin hormone and lipid profile in the third trimester in the second and the third groups might be explained the non-significant difference in estradiol hormone levels between these two groups that needs further investigation.

**Conclusions**

In summary, our results suggest that the leptin levels increase during the different trimesters in GDM and obese pregnant women, these increase related to high levels of steroid hormones such as estradiol and progesterone.

**References**


