ABSTRACT

Background: Obesity becomes one of the most universal medical problems that affects women at reproductive period. It has a complicated drawback on mother and child health.

Aims: To evaluate the placental histological changes of obese mothers in comparison to pregnant women with normal body mass index.

Methods: This work is a prospective case-control study in which the placentae were obtained from 40 singleton pregnant women who delivered at Al-Khansaa Maternity Teaching Hospital, Mosul, Northern of Iraq, starting from December 2019 to February 2020. The women were classified into two groups: Group 1 which includes 20 women with BMI ranged between 18-24.9 kg/m², Group 2 which includes 20 women with BMI ≥ 30. Two placental biopsies were obtained from maternal side and fetal side of each case and prepared for histological examination via light microscope.

Results: The histological examination of placental sections obtained from obese mothers showed several placental changes compared to those of control group. The most frequent feature among these sections is the presence of syncytial knotting in 13(65%) out of 20 placentae. In addition, features of hypovascular villi, villous fibrinoid necrosis are noticed in 10 (50%) of these specimens, while thickening of trophoblastic basement membrane was noticed in 9 (45%) of these sections. On the other hand, the histological examination of placental sections obtained from obese mothers revealed presence of perivillous fibrin deposition which appeared in 10 (50%) of these sections. Features of stromal fibrosis were noticed in (40%) of sections. Other placental changes seen in placental sections obtained from obese mothers include presence of nucleated red blood cells (NRBC) in fetal capillaries, chorangiosis, villous edema, paucity of vasculosyncytial membrane (VSM), inflammation, apoptosis and decidual fibrinoid necrosis.

Conclusion: this work revealed a marked increase in the frequencies of different placental changes in obese mothers in comparison with controls. Further studies are recommended to clarify the exact mechanisms that stand behind these histological changes.

Keywords: Placenta, obesity, histological changes.
Obesity is among rapid raising medical issues that affect women at reproductive periods. A marked increase in obesity has been shown during last few decades. Modification in life style, advances in economic state and technologies have resulted in an abundance of nonexpensive high calory diet with a decrease in physical activities. Food consuming by the people is higher with a decrease in their movements.

Maternal obesity is defined as body mass index (BMI) >30 kilogram/square meter (kg/m²) that is reported in the first antenatal visit. Universally the epidemiology of obesity has been increased, and the prevalence of overweight and obese women of reproductive age also increases in comparison with those of normal weight.

In the United States the prevalence of obesity in adult women was 35.8 % in 2009-2010. In 2006 according to the Iraqi Ministry of Health report the prevalence of obese adult women was 38.2%. Moreover the obese adult women percentage increased from 23-25 in Baghdad from 1997 to 2007.

Obesity can spread to the offspring through bad behavioral effect. It is the most common health problem in adult women and pregnant. It has a complicated drawback on mother and child.

Infertility, spontaneous abortion, congenital anomalies and placental insufficiency were occurred in obese women in early gestation. Obese women are mostly suffered from the gestational metabolic syndrome including inflammation, hypertension, pre-eclampsia, and nutrient metabolism disturbance.

Also Obesity is the strongest causative factor of gestational diabetes mellitus (GDM).
SUBJECTS, MATERIALS, And METHODES
This work is a prospective case-control study that examined placentae which were obtained from 40 singleton pregnant women who delivered at Al-Khansaa Maternity Teaching Hospital in Mosul city in north of Iraq. This study was started from December 2019 to February 2020. Ethical approval was obtained from Committee of Ethics at Nineva Health Directorate, Mosul /Iraq. Depending on a history was obtained from women, The gestational age was calculated depending on last menstrual period or the early ultrasonographic examination report. Pregnant women with non-gestational diabetes mellitus, essential hypertension, abortion placenta, multiple pregnancy, smoking and Rh negative blood group were excluded.

According to their BMI, the women were classified into two groups as follows:
1- Group 1. (Control): Includes 20 women with BMI ranged between 18-24.9 kg/m².
2- Group 2. (Obese) Includes 20 women with BMI ≥ 30 kg/m².

BMI of each mother was calculated via dividing the weight in kilogram (Kg) by height in square meter (M²). The weight was obtained according to methods described by Davis et al. and Al-Kubaissy et al. by subtracting 12.5 kg from the current weight. Two biopsies of placental tissue were obtained from maternal side (decidua) and fetal side (chorionic plate) and were prepared for histological examination after staining with (H&E) using light microscope.

According to criteria of Amsterdam Placental Workshop Group, Placental lesions are classified into three categories: placental stromal-vascular lesions which include (malperfusion, infarction, villous maturation disorder, villous edema), inflammatory lesions which include (villitis and deciduitis) and other placental lesions which include (increase nucleated red blood cells and perivillous fibrin deposition).

The statistical analysis of data was done using excel program and SPSS version. To compare the frequencies of different placental lesions between two groups chi square (χ²) was used, were P value <0.05 was considered as significant.

RESULTS
This study has examined placentae from 40 women who were categorized into two groups. The maternal clinical characteristics of all cases are shown in Table 1.

The light microscopical examination of sections obtained from the fetal surface of placental disc of control group(Group1) using H&E preparation showed that each chorionic villous with normal histology as vascular stroma lined or covered with multinucleated syncytiotrophoblastic layer with indistinct cell boundaries and dark stained nuclei with occasional inconspicuous cytotrophoblastic cells (Figure 1). While the microscopical examination of sections from the maternal surface of this group showed normal appearance of maternal decidual cells (Figure 2).

On the other hand, the present study revealed that the histopathological examination of placental sections obtained from obese mothers (Group 2) showed several placental changes compared to those of control group. Table 2.

The most frequent feature among these sections is the presence of syncytial knotting in 13(65%) out of 20 placentae. (Figure 3). In addition, features of hypovascular villi are noticed in 10 (50%) of these sections (Figures 3&4). hypovascular villi are small villi and they have decrease numbers and small diameter capillaries or in some sections there is absent of capillaries (avascular villi).

Moreover, villous fibrinoid necrosis occurs in 10 (50%) of placentical sections of obese mothers (Figure 6), while thickening of trophoblastic basement membrane occurs in 9 (45%) of these sections. (Figure 5).

On the other hand, the histopathological examination of placental sections obtained from obese mothers (group 2) revealed presence of perivillous fibrin deposition which was appeared in 10 (50%) of these sections (Figure 6). Features of stromal fibrosis were noticed in 8 (40%) of sections. (Figures 6&7).

The present study revealed that the histopathological examination of placental sections obtained from obese mothers (group 2) showed presence of nucleated red blood cells (NRBC) in fetal capillaries and this finding was identified in 7 (35%) of these sections. (Figures 7&8), while features of chorangiosis was found in 4 (20%) of these sections. (Figure 9). histologically appear as ten or more capillaries in ten or more terminal villi in ten or more areas in placenta use microscopic examination with 10x objective.

Features of villous edema was shown in 4(20%) out of 20 placenta of group 2. (Figure 10). On the other hand, paucity of vasculosyncytial membrane VSM was found in 35% of sections of obese mothers. (Figure 11).

This study observed features of villitis in 4(20%) out of 20 placental sections that belong to obese mothers. (Figure 12), while deciduitis was noticed in 7(35%) of these sections. (Figure 12).

The classification of various placental histological changes in both groups according to criteria of Amsterdam Placental Workshop Group was shown in Table 3.
The Effect of Maternal Obesity

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Figure 1. A photomicrograph of a placental section obtained from control group with normal architecture of villi. The vascular stroma lined with multinucleated syncytiotrophoblastic layer with indistinct cell boundaries and dark stained nuclei (black arrow) with occasional cytotrophoblastic cells (red arrow). (H&E×250).

Figure 2. A photomicrograph of a placental section obtained from women of control group with normal architecture of decidua. (H&E×400).

Figure 3. A photomicrograph of a placental section obtained from women of group 2 with excessive syncytial knotting in hypo-vascular villi with decreased VSM. (H&E×100).

Figure 4. A photomicrograph of a placental section obtained from women in group 2 with excessive syncytial knotting (arrow) in hypo-vascular villi with decreased VSM. (H&E×400).

Figure 5. A photomicrograph of a placental section obtained from women of group 2 showing villous with thickening of basement membrane (arrow). (H&E×400).

Figure 6. A photomicrograph of a placental section obtained from women of group 2. Fibrotic avascular villi are embedded in a sea of fibrin (perivillous fibrin deposition) (arrows). (H&E×100).

Figure 7. A photomicrograph of a placental section obtained from obese mother in group 2. Fibrotic hypovascular villi with NRBC are seen (arrow). (H&E×400).

Figure 8. A photomicrograph of a placental section obtained from women of group 2 with presence of NRBCs (arrows). (H&E×400).
Table 1. Maternal characteristics in control and obese groups

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>Group 1. (Control) N=20 (%)</th>
<th>Group 2. (Obese) N=20 (%)</th>
<th>P-Value P&lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age less than 35 years</td>
<td>18 (90 %) *</td>
<td>12(60 %)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Age more than 35 years</td>
<td>2 (10 %)</td>
<td>8 (40 %)*</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Primigravidas</td>
<td>8 (40 %)*</td>
<td>0(0 %)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Multigravidas</td>
<td>12(60 %)</td>
<td>20(100 %)*</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Normal vaginal delivery</td>
<td>14(70 %)*</td>
<td>8(40 %)</td>
<td>0.00002</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>6(30 %)</td>
<td>12(60 %)*</td>
<td>0.00002</td>
</tr>
<tr>
<td>Previous abortion</td>
<td>4(20 %)</td>
<td>10(50 %)*</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

Figure 9. A photomicrograph of a placental section obtained from obese mother. Features of chorangiosis are seen (arrows). (H&E×400).

Figure 10. A photomicrograph of a placental section obtained from obese mother with villous oedema. (H&E×250).

Figure 11. A photomicrograph of a placental section obtained from obese mother with features of fibrinoid necrosis (red arrow) and syncytial knotting (black arrow) in hypo vascular villi with decreased VSM (blue arrow). (H&E×400).

Figure 12. A photomicrograph of a placental section obtained from obese mother with features of villitis (red arrow) and deciduitis (black arrow) (H&E×250).
The placenta is considered as the persistent Holy Grail, and a supposed record of intrauterine life that gives promise to clarify the mysteries that stand behind the adverse pregnancy outcome in several conditions including obesity. Practically, placental pathology, is finally emerging as a respectable specialty after many years of confusion related to experts with divergent views, pathologists with varying levels of interest and relevant training, and nomenclature having little relationship to either the underlying biology or clinical presentation.

This study evaluated prospectively and systematically the histological observations of placentae of obese mothers. Several changes were shown in placental sections of obese mothers in comparison with those of controls. A significant increase in the frequency of syncytial knots and thickening of trophoblastic basement membrane was found in placental sections of obese mothers. These observation are in accordance with other works.

That suggested these lesions may occur as a feature of placental adaptive response. The oxygen in intervillous space exchanged through terminal villi to fetal villous capillaries crosses VSM then reach fetal blood circulation, so any increase in the thickening of VSM leads to reduction of placento-fetal blood circulation and accumulation of syncytiotrophoblasts. Moreover, Sanker et al. reported that the increase in thickness of VSM is related to accumulation of large number of high density and big diameter syncytial knots as a reflex of hypoxia.

On the other hand, this work revealed that 10(50%) of placental sections in obese group showed features of villous hypovascularity. These findings are in accordance with those of other workers. It has been reported that there is an increase in the frequency of abnormal modifications of the spiral arteries which lead to an alteration in the placental vascular function. On the other hand, hyperplasia of the tunica muscularis was shown in the main stem vessels of the villous tree that leads to the reduction of the blood flow in cases of obese mother.

Villous fibrinoid necrosis was found markedly in placental sections of obese mothers in the present work. Benirschke and Kaufmann described that this lesion may be resulted from injury of syncytiotrophoblasts. However, a previous study suggested that this lesion may be a sequence of accelerated villous maturation (AVM). The maternal vascular malperfusion and abnormal flow of spiral artery characterized by high velocity and
low volume maternal blood. AVM represented by short hypovascular villi with increase intervillous fibrin and syncytial knots in addition to increased thickness of VSM.

A previous study of Brouwers et al. found an increased AVM in the placenta of obese women. They suggested that it may be present when the rate of fetus growth is quicker than the capacity of placenta.

This study showed a marked increase of the frequency of perivillous fibrin deposition in placental sections of obese mothers. Authors reported that this lesion is due to an increase in vessels' muscularity which lead to maternal blood stasis in intervillous space that causes coagulative reflex.

So fibrin deposition was occurred as a result of increased maternal cytokines in obese women.

The light microscopic examination of placental sections of obese mothers revealed a presence of nucleated red blood cells (NRBCs). These findings are similar to those of others who suggested that fetal hypoxia in obese women lead to stimulation of an erythropoietin which in turn lead to increased NRBCs in fetal circulation of obese mothers and even in that of overweight mothers, as maternal BMI was significantly correlated with their erythropoietin values.

On contrary, this work showed features of chorangiosis significantly in placental sections of obese women accompanied with a paucity of VSM and stromal fibrosis. In fact, villous chorangiosis occurs as a result of placental response to hypoxia.

Moreover, Redline reported that the chorangiosis, paucity of VSM and stromal fibrosis were considered as features of delayed villous maturation (DVM) which occurs in placenta of obese mothers as a result of insulin resistance and hypoxia. Insulin resistance was more frequent in obese mothers which lead to increase proliferation of villi in early gestational period that lead to increased placental stroma and decreased numbers of VSM layers with increased its thickness.

In addition, these lesions cause an inadequate oxygen diffusion and placental insufficiency. In healthy placenta the functional unit was represented by dilated capillaries with perfect contact with VSM. Additionally, a study of Kaufmann et al. showed features of placenta from obese women characterized mostly by branching angiogenesis.

On the other hand, this study found presence of villous edema in 20% of placenta of obese group which may be due to fetal vascular malperfusion and weak blood circulation in the villous tree as shown in previous works.

High incidence of deciduitis and villitis was seen in placental sections of obese women. These observations were similar to those shown in other studies which reported a relation between obesity and inflammation of placenta with an increased pro-inflammatory cytokines in maternal circulation and over-production of mononuclear cells in obese mothers' blood circulation.

A high concentrations of C-reactive protein (CRP) and interleukin-6 (IL-6) have been observed in obese women with increased insulin resistance and high concentrations of leptin.

Previous histological studies on placenta of obese women found the infiltration of pro-inflammatory macrophages.

In fact, pro- and anti-inflammatory cytokines balance in any woman, is essential for normal function of placenta. So the disturbance in this balance may lead to increased inflammation in placenta.

In conclusion, this work revealed a marked increase in the frequencies of different placental changes in obese mothers in comparison with controls. These lesions may reflect the adaptive response to protect the fetus from the harmful effect of metabolic disorder in obese mothers but it can lead to diminished nutrients and oxygen supply to fetus. Further studies are recommended to clarify the exact mechanisms that stand behind these histological changes.

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REFERENCES


