Pregnancy in women is associated with several metabolic and immunological changes. These alterations occur naturally in response to increased serum estrogen and progesterone levels and changes in insulin sensitivity (1, 2). During pregnancy, significant changes occur in lipid metabolism that are crucial for fetal development, as well as delivery readiness, and lactation preparation (3). For example, triglyceride (TG) and total cholesterol (TC) levels elevate as pregnancy advances (4).

The placenta takes up maternal TC and TG via receptor-mediated and receptor-independent processes, metabolizes, and transports them to the fetus. Cholesterol is necessary for cell proliferation, formation of the cell membrane, and normal fetal growth and development (5-7). The anabolic phase occurs in the first two trimesters of human gestation, which is characterized by increased lipid synthesis and fat accumulation, preparing the mother’s body to increase the needed energy by the fetus in late pregnancy. Lipid synthesis eventually leads to a 2- to 3-fold increase in plasma TG in the second and third trimesters of pregnancy, accompanied by lower increases in TC, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) (6).

The rise in lipid production from 10 to 30 weeks of pregnancy is promoted by both increased maternal food intake during early pregnancy and heightened insulin sensitivity (8). During the third trimester, lipid metabolism changes to a pure catabolic phase, which is associated with the breakdown of fat deposits.

On the one hand, the catabolic phase provides adequate substrates for the developing fetus, and on the other hand, it can lead to complications for the mother and newborn. The increase in maternal serum lipids at late gestation is related to increased odds of cesarean section (OR = 2.622, CI: 1.170-5.876, P = 0.019) and preeclampsia (OR = 4.452, CI: 1.719-11.530, P = 0.002). Newborns in the hyperlipidemia group had lower 1-minute Apgar scores than those in the non-hyperlipidemia group (P < 0.001). Moreover, the risk of fetal macrosomia was 5.833 times higher in the hyperlipidemia group than in the non-hyperlipidemia group (OR = 5.833, CI: 1.576-21.586, P = 0.008).

The Association of Hyperlipidemia at Late Pregnancy With Maternal and Neonatal Outcomes in Women With Gestational Diabetes

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Abstract

**Background:** There is evidence that hyperlipidemia during early pregnancy is linked to adverse consequences for expecting mothers and newborns. This study assessed how hyperlipidemia in the third trimester affected outcomes in pregnant women with gestational diabetes mellitus (GDM).

**Materials and Methods:** This study was conducted on 116 pregnant women with GDM. Maternal serum lipids were measured in the first and third trimesters of gestation. The participants were split into two groups: pregnant women with GDM and hyperlipidemia as the hyperlipidemia group (n = 58) and pregnant women with only GDM as the non-hyperlipidemia group (n = 58). The association between dyslipidemia and maternal and neonatal outcomes was evaluated.

**Results:** Significant differences were observed between the two groups regarding maternal serum lipids at late gestation, body mass index (BMI), mean neonatal weight, preeclampsia, fetal macrosomia, and cesarean section. Maternal dyslipidemia was significantly related to increased odds of cesarean section (OR = 2.622, CI: 1.170-5.876, P = 0.019) and preeclampsia (OR = 4.452, CI: 1.719-11.530, P = 0.002). Newborns in the hyperlipidemia group had lower 1-minute Apgar scores than those in the non-hyperlipidemia group (P < 0.001). Moreover, the risk of fetal macrosomia was 5.833 times higher in the hyperlipidemia group than in the non-hyperlipidemia group (OR = 5.833, CI: 1.576-21.586, P = 0.008).

**Conclusion:** Hyperlipidemia at late gestation is related to complications and unfavorable maternal and neonatal outcomes. The evaluation of lipid profiles before and during pregnancy is needed to diagnose and manage maternal and neonatal complications, especially in high-risk populations like women with GDM.

**Keywords:** Cesarean section, Hyperlipidemias, Fetal macrosomia, Apgar score, Gestational diabetes
other hand, it increases insulin resistance in the mother (1,5,7,9,10). Elevated lipid levels during late pregnancy, along with increasing insulin resistance and gestational diabetes mellitus (GDM), can lead to preeclampsia, which has an adverse outcome for both mother and fetus. Some studies have suggested a clinical link between maternal hyperlipidemia and preterm birth (11,12), pregnancy-induced hypertension (13), and birth weight (14,15), especially in pregnancies with GDM (16). Others reported no association between hyperlipidemia and preterm birth (17). However, the effect of maternal hyperlipidemia on fetal growth and pregnancy complications is still uncertain. Against this background, the present study aimed to explore the impact of hyperlipidemia in late pregnancy on maternal and neonatal outcomes in women with GDM.

Materials and Methods

Study Type and Population

This study was carried out in the obstetrics and gynecology ward of Shariati Hospital affiliated to Hormozgan University of Medical Sciences between April 2021 and June 2022.

The inclusion criteria were: age between 20 to 40 years, live-born singleton pregnancy, naturally conceived, and lipid measurement in the first (6th week) and third trimesters (28th week) of gestation. The exclusion criteria included twin or multiple pregnancies, diabetes mellitus, family history of hyperlipidemia, a high-fat diet, received assisted reproductive technology, hypertensive disorders, liver and kidney diseases, abortions ≥ 3, polycystic ovary syndrome, smoking, and alcohol abuse.

The eligible participants were allocated into two groups: pregnant women with GDM and hyperlipidemia as the hyperlipidemia group (n = 58) and pregnant women with only GDM as the non-hyperlipidemia group (n = 58). GDM was diagnosed based on a 3-hour 100-g oral glucose tolerance test (OGTT) between 24 and 28 weeks of pregnancy. The threshold values used for the OGTT were fasting glucose ≥ 95, 1-hour glucose 180, 2-hour glucose 155, and 3-hour glucose 140 mg/dL. Women with two or more abnormal values were defined as GDM (18).

Blood samples were taken after 12 hours of fasting to assess lipid profiles, including cholesterol, TG, HDL-C, and LDL-C. Serum lipid levels in the first trimester (6th week) and third trimester (28th week) were measured. Dyslipidemia is considered as the presence of one of the following criteria: serum cholesterol level ≥200 mg/dL, TG level ≥150 mg/dL, HDL-C level ≤45 mg/dL, and LDL-C level ≥130 mg/dL (19). Serum cholesterol, TG, and glucose levels were assessed using the audit biochemistry kit (Farazmed, Iran), while HDL-C and LDL-C were specifically measured with the Biomed biochemistry kit (Farazmed, Iran). All biomedical assessments were performed using an automatic biochemical analyzer (Biotecnica, BT1500).

Kidney function tests including the measurements of BUN-Cr, albumin, and protein were performed by automatic biochemical analyzer (Biotecnica, BT1500) using audit, Pars, and Biomed biochemistry kits, respectively (data not shown).

Preeclampsia is characterized by high blood pressure (systolic ≥ 140 mm Hg and/or diastolic ≥ 90 mm Hg) and high protein levels in urine (≥ 300 mg/24 hours or positive results in random urine protein tests) in women who were normotensive before 20 weeks of gestation.

After forming the groups and performing physical examinations, clinical and laboratory data of all women were recorded. Full medical history was taken through clinical records.

Maternal and neonatal outcomes including mode of delivery, preeclampsia, preterm labor, placental abruption, complicated delivery and its type, macrosomia, stillbirth, birth weight, 1- and 5-minute Apgar scores, and thick meconium were evaluated.

Sample Size

The sample size was calculated using G power 3.1 statistical software assuming lipid disorder ratio indices \( P_1 = 0.908, P_2 = 0.684 \). A sample size of 58 patients was required in each group at a significance level of 0.05 and a power of 80.

Statistical Analysis

All data were analyzed using Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, Illinois, USA). The relationship between hyperlipidemia and maternal and neonatal outcomes was assessed before and after the adjustment for the effects of confounding factors. The continuous variables were compared between groups by student's \( t \) test and Mann–Whitney \( U \) test. The normal distribution of continuous data was tested using the Shapiro–Wilk test. The chi-square or Fisher's exact test was applied to compare the categorical variables between groups, and the results were reported as numbers and percentages. To compare the relationship of hyperlipidemia and maternal and neonatal outcomes with non-hyperlipidemia group, the logistic regression test and the odds ratio were used. The significance level was set at \( P \) value < 0.05.

Results

Descriptive Findings

Demographic characteristics and laboratory data of the study participants are shown in Table 1. The mean age of women participating in this study was 29.07 ± 5.32 years. No significant difference was found between the two groups regarding the age of women (28.81 ± 5.64 vs. 29.33 ± 5.00, \( P = 0.123 \)). The mean body mass index (BMI) was significantly higher in the hyperlipidemia group.
than in the non-hyperlipidemia group (30.49 ± 5.72 vs. 28.27 ± 4.02, P = 0.03). Based on the results, hyperlipidemia was positively correlated with BMI, as each unit increase in BMI increased the chance of hyperlipidemia by 12.2% (OR = 1.122, CI = 1.029-1.224, P = 0.009). The two groups had no statistically significant difference in mean amniotic fluid index (AFI) (P = 0.273).

### Maternal Lipid Profiles
Women in hyperlipidemia group had higher levels of TG (165.71 ± 15.75 vs 153.03 ± 13.00, P = 0.001), cholesterol (202.36 ± 8.96 vs 173.03 ± 13.12, P = 0.001), and LDL-C (106.72 ± 11.69 vs 72.69 ± 12.89, P = 0.001) and lower levels of HDL-C (41.45 ± 8.37 vs 55.09 ± 9.86, P = 0.001) than women in the non-hyperlipidemia group (Table 1).

### Maternal and Neonatal Outcomes
There were no statistically significant differences between the two groups regarding preterm birth, difficult delivery, and placental abruption (P = 1, P = 0.438, respectively). Preeclampsia was more frequent in the hyperlipidemia group (37.9%) than in the non-hyperlipidemia group (12.1%) (P = 0.001) (Table 2). Compared to the non-hyperlipidemia group, women in the hyperlipidemia group had a higher rate of cesarean section (56.9% vs 77.6%, P = 0.018). Overall, hyperlipidemia was associated with a significantly increased risk of cesarean section delivery, with an OR of 2.622 (95% CI = 1.170-5.876, P = 0.019), and maternal preeclampsia (OR = 4.452, CI:1.719-11.530, P = 0.002).

Regarding the neonatal outcomes, the mean birth weight was 3159.83 ± 528.17 g in the non-hyperlipidemia group and it was 3513.45 ± 598.7 g in infants born to women with hyperlipidemia (P = 0.002). The rate of fetal macrosomia was significantly higher in the hyperlipidemia group than in the non-hyperlipidemia group (24.1 % vs 5.2, P = 0.004). The risk of fetal macrosomia was 5.833-fold higher in the hyperlipidemia group compared to the non-hyperlipidemia group (OR = 5.833, CI = 1.576-21.586, P = 0.008). In addition, 1-minute Apgar score was 8.62 ± 0.62 in the non-hyperlipidemia group and it was 7.95 ± 0.89 in infants born to women with hyperlipidemia (P < 0.001). Other maternal and neonatal outcomes were also comparable. Moreover, there was no stillbirth in either group.

### Discussion
This study found a significant association between maternal dyslipidemia and a higher risk of preeclampsia, fetal macrosomia, cesarean section, and a lower Apgar score in newborns. Despite extensive research into the impact of maternal dyslipidemia on maternal and neonatal outcomes, numerous unresolved issues and controversies persist in this field. This is especially true in high-risk populations.

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**Table 1. Demographic Characteristics and Lipid Levels**

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Non-hyperlipidemia Group</th>
<th>Hyperlipidemia Group</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>28.81 ± 5.64</td>
<td>29.33 ± 5.00</td>
<td>NS</td>
</tr>
<tr>
<td>Gestational age at delivery (wk)</td>
<td>38.57 ± 1.94</td>
<td>39.17 ± 1.52</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>28.27 ± 4.02</td>
<td>30.49 ± 4.72</td>
<td>0.009</td>
</tr>
<tr>
<td>AFI</td>
<td>19.02 ± 3.71</td>
<td>18.21 ± 4.25</td>
<td>NS</td>
</tr>
<tr>
<td>TG</td>
<td>153.03 ± 13.00</td>
<td>165.71 ± 15.75</td>
<td>0.001</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>173.03 ± 13.12</td>
<td>202.36 ± 8.96</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>55.09 ± 9.86</td>
<td>41.45 ± 8.37</td>
<td>0.01</td>
</tr>
<tr>
<td>LDL</td>
<td>72.69 ± 12.89</td>
<td>106.72 ± 11.69</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; AFI, amniotic fluid index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, not significant.

Values are presented as mean ± SD.

<sup>a</sup> Mann–Whitney U test.

---

**Table 2. Comparison of Maternal and Neonatal Outcomes in the Two Groups**

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Non-hyperlipidemia Group</th>
<th>Hyperlipidemia Group</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-section</td>
<td>33 (56.9%)</td>
<td>45 (77.6%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Vaginal</td>
<td>25 (43.1%)</td>
<td>13 (22.4%)</td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (12.10%)</td>
<td>22 (37.9%)</td>
<td>0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>No</td>
<td>51 (87.90%)</td>
<td>36 (62.1%)</td>
<td></td>
</tr>
<tr>
<td>Placental abruption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (3.40%)</td>
<td>5 (8.6%)</td>
<td>0.438</td>
</tr>
<tr>
<td>No</td>
<td>56 (96.60%)</td>
<td>53 (91.40%)</td>
<td></td>
</tr>
<tr>
<td>Preterm birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (1.70%)</td>
<td>2 (3.40%)</td>
<td>1.000&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>No</td>
<td>57 (98.30%)</td>
<td>56 (96.60%)</td>
<td></td>
</tr>
<tr>
<td>Type of difficult delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episiotomy</td>
<td>5 (35.70%)</td>
<td>11 (61.10%)</td>
<td></td>
</tr>
<tr>
<td>Grade 1 rupture</td>
<td>5 (35.70%)</td>
<td>1 (5.60%)</td>
<td>0.121</td>
</tr>
<tr>
<td>Grade 2 rupture</td>
<td>4 (28.60%)</td>
<td>3 (16.70%)</td>
<td></td>
</tr>
<tr>
<td>Grade 3 rupture</td>
<td>0 (0.00%)</td>
<td>1 (5.60%)</td>
<td></td>
</tr>
<tr>
<td>Grade 4 rupture</td>
<td>0 (0.00%)</td>
<td>2 (11.1%)</td>
<td></td>
</tr>
<tr>
<td>Macrosomia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (5.20%)</td>
<td>14 (24.10%)</td>
<td>0.004&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>No</td>
<td>55 (94.80%)</td>
<td>44 (75.09%)</td>
<td></td>
</tr>
<tr>
<td>Thick meconium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (8.6%)</td>
<td>4 (6.90%)</td>
<td>1.000&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>No</td>
<td>53 (91.40%)</td>
<td>54 (93.10%)</td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td>3159.83 ± 528.17</td>
<td>3513.45 ± 598.7</td>
<td>0.002&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>1-Minute Apgar score</td>
<td>8.62 ± 0.62</td>
<td>7.95 ± 0.89</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5-Minute Apgar score</td>
<td>9.81 ± 0.51</td>
<td>9.69 ± 0.54</td>
<td>0.117&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviation: GDM, gestational diabetes mellitus.

Values are presented as mean ± SD or N (%).

<sup>a</sup> Chi-square test; <sup>b</sup> Fisher’s exact test; <sup>c</sup> Mann–Whitney U test.
such as mothers with GDM. Our data showed that the lipid profiles of women with GDM differed significantly, and the levels of three lipid markers (TC, LDL-C, and TG) were higher in some diabetic mothers in late pregnancy. A previous study by Layton et al demonstrated that women diagnosed with GDM exhibit specific lipid profiles depending on their GDM subtype (20). However, a potential limitation of this study is that we needed to determine the subtype of GDM. Further, our analysis indicated a significant association between BMI and the risk of hyperlipidemia. Probably, maternal obesity results in the disturbance of the typical feedback loops in metabolic pathways that maintain homeostasis during pregnancy (21). Compared to studies that evaluated the correlation between BMI and hyperlipidemia (22,23), our finding was similar to that shown by O’Malley et al who suggested that the epidemiological link between GDM and dyslipidemia is mediated through maternal obesity, and those women with a higher BMI are at a greater risk of developing hyperlipidemia. Interestingly, women with obesity or GDM alone have reduced chances of developing dyslipidemia (24).

Maternal hyperlipidemia has been recognized as a factor that raises the likelihood of pregnancy complications. The odds of cesarean section increased in women with hyperlipidemia compared to women with only GDM. These results are in line with the results of the study carried out by Li et al (3). They found that the incidence of cesarean section was lower in women with normal lipid profiles. There exists another hypothesis on the associations between maternal hyperlipidemia and preeclampsia. It has been illustrated in some publications that dyslipidemia was positively associated with an increased risk of preeclampsia (19). Jin et al discovered that in the Chinese population, elevated maternal TG levels in late pregnancy were linked independently to higher risks of GDM, preeclampsia, and macrosomia. Conversely, there was a decreased risk of having smaller-than-average babies (small for gestational age) (17). Consequently, our findings showed that women with maternal dyslipidemia are approximately 4.5 times more likely to develop preeclampsia.

Another striking finding was that maternal hyperlipidemia was significantly associated with an increased risk for fetal macrosomia. Since all mothers in the present study had GDM, and stringent glycemic control occasionally proved ineffective in averting macrosomia (25), hyperlipidemia may play a more or at least as critical role as hyperglycemia in fetal macrosomia. However, this interpretation still deserves further exploration. There are relevant reports suggesting that hyperlipidemia is associated with macrosomia (26). Kitajima et al illustrated that hypertriglyceridermia at 24-28 weeks of gestation is positively associated with birth weight at term, independent of maternal plasma glucose levels and obesity (25). However, others did not find any associations (27,28). The inconsistency may be due to differences in race/ethnicity, sample size, and maternal prediabetes status.

Another study by Herrera and Ortega-Senovilla showed that changes in lipid metabolism increase the risk of macrosomia among women diagnosed with GDM (10). Enhanced insulin resistance (29) and heightened fetal exposure to fatty acids (26) could partially elucidate the heightened risk of fetal overgrowth among women with hyperlipidemia. Moreover, maternal cholesterol can traverse the placenta and potentially influence fetal cholesterol production, consequently impacting the weight of the fetus (29).

As for the conditions of the newborn, the current study also showed that maternal dyslipidemia results in a lower 1-minute Apgar score. To the best of our knowledge, this finding has rarely been reported in previous studies (19, 30), and further research on this issue is needed.

**Conclusion**

Our findings suggest that dyslipidemia in late pregnancy could potentially contribute to the etiology of maternal preeclampsia, fetal macrosomia, cesarean delivery, and lower 1-minute Apgar score in newborns of diabetic mothers. The results of this research support the practice of lipid screening for women of reproductive age. Further investigations are required to ascertain whether the detection and proper management of dyslipidemia during pregnancy can lead to a reduced likelihood of complications for both mothers and neonates.

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**Authors’ Contribution**

**Conceptualization:** Maryam Azizi Kutenaei.

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**Funding acquisition:** Maryam Azizi Kutenaei.

**Investigation:** Firoozeh Shakeri.

**Methodology:** Maryam Azizi Kutenaei.

**Resources:** Maryam Azizi Kutenaei.

**Software:** Ensieh Salehi.

**Supervision:** Maryam Azizi Kutenaei.

**Validation:** Ensieh Salehi.

**Visualization:** Maryam Azizi Kutenaei.

**Writing—original draft:** Fatemeh Eini, Ensieh Salehi.

**Writing—review & editing:** Ensieh Salehi.

**Competing Interests**

The authors declare that they have no competing interests.

**Ethical Approval**

The study was approved by the Ethics Committee of Hormozgan University of Medical Sciences, Bandar Abbas, Iran (IR.HUMS.REC.1401.007), and confidentiality of the data was ensured.
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