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Effects of Gestational Metabolic Abnormalities on Placenta

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Abstract. The increasing prevalence of gestational diabetes mellitus (GDM) highlights the critical role of nutritional imbalances and metabolic disorders in its development. These conditions not only contribute to GDM but also lead to adverse pregnancy outcomes such as fetal hypothyroidism and severe morning sickness. As the vital bridge between mother and fetus, the placenta plays a pivotal role in nutrient delivery and gas exchange during metabolism. Abnormal placental morphology and function can predict maternal health risks, making GDM research particularly valuable for understanding placental impacts. This study employed secondary analysis of a clinical cohort, comparing 15 healthy controls with 30 GDM patients (divided into two groups: a daily 36g Extra Virgin Olive Oil (EVOO) supplementation group [n=15] vs. a control group [n=15]). Monitoring indicators from 24-28 weeks of gestation through delivery, we investigated GDM's effects on placental development and EVOO's therapeutic efficacy. Results demonstrated that GDM induces insulin resistance, pro-inflammatory responses, increased placental thickness, collagen/glycogen accumulation, and abnormal endocytosis-related gene expression. Conversely, EVOO intervention effectively mitigated these abnormalities while regulating maternal metabolism and inflammation, optimizing placental morphology and function. This study elucidates GDM's pathogenic mechanisms and validates EVOO's therapeutic potential as a novel nutritional strategy for GDM prevention and management.

Keywords: gestational metabolic abnormalities, placenta, influence

1. Introduction

Gestational Diabetes Mellitus (GDM) refers to abnormal glucose metabolism first observed during pregnancy, with a global prevalence of 1%-10%. It shows higher incidence rates in developed, less-developed, and developing countries [1]. GDM significantly increases maternal risks. It also raises placental risks. Additionally, it leads to neonatal complications. These pose serious threats to maternal and infant health [2]. GDM raises risks for the mother. It causes problems with the placenta. It also harms the newborn's health. These issues are serious threats [3]. Newborns may experience macrosomia. They may have respiratory distress syndrome. They can develop neonatal hypoglycemia. They also face increased long-term risks of metabolic and cardiovascular diseases [4]. Studies have shown that GDM causes morphological changes in the placenta. It also causes histological changes. Furthermore, it causes functional changes. These changes expose the placenta to pro-oxidative environments. They also expose it to pro-inflammatory molecular environments.

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These environments impair multiple regulatory functions. These functions are essential for maternal adaptation. They are also essential for fetal development [5].

This study investigates the effects of gestational metabolic disorders on the placenta. GDM served as a case study. The research used a secondary analysis from a clinical cohort study. It included a control group of 15 participants. It also included 30 GDM patients. The GDM patients were divided into two subgroups. One subgroup was an intervention group. This group received a daily supplementation of 36g of extra-virgin olive oil (EVOO). It had 15 patients. The other subgroup was a control group. This group received no supplementation. It also had 15 patients. The EVOO supplementation started between weeks 24 and 28 of pregnancy. It continued until delivery.

2. Pathophysiological changes of gestational diabetes mellitus

The pathophysiological mechanism of GDM is complex, involving insulin resistance, inflammatory response, oxidative stress and placental dysfunction.

2.1. Insulin resistance

Insulin resistance is a hallmark feature of gestational diabetes mellitus (GDM). While normal pregnancy sees insulin resistance as a physiological adaptation to ensure fetal nutrition, GDM patients exhibit abnormally elevated levels of this resistance. Studies show that GDM patients demonstrate higher triglyceride-to-HDL cholesterol ratios, elevated fatty acid-binding protein 4 (FABP4) levels, and greater body mass index (BMI) during late pregnancy compared to healthy pregnant women—all critical markers of insulin resistance. This condition arises from multiple factors including abnormal adipocyte factor secretion and chronic inflammatory responses.

2.2. Insulin resistance

Chronic low-grade inflammation plays a significant role in the pathophysiology of gestational diabetes mellitus (GDM). In GDM patients, inflammatory conditions are observed in both placental and maternal blood, with elevated activity of pro-inflammatory markers such as matrix metalloproteinase 9 (MMP9). As a proteolytic enzyme involved in embryonic and placental development, MMP9's overactivation is closely associated with inflammatory responses. This process may exacerbate insulin resistance and placental dysfunction by influencing vascular remodeling and extracellular matrix degradation [6].

2.3. Oxidative stress

Oxidative stress constitutes a pivotal component in the pathophysiology of gestational diabetes mellitus (GDM). In GDM, the delicate balance between oxidative and antioxidant processes in both maternal and placental tissues is disrupted, leading to excessive reactive oxygen species production. This triggers damage to lipids, proteins, and DNA. Furthermore, oxidative stress activates inflammatory signaling pathways, exacerbates insulin resistance, and impairs placental vascular endothelial function, thereby compromising the placenta's material exchange capacity and metabolic regulation [7].

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2.4. Abnormal placental function

Placental dysfunction is a key manifestation of GDM's pathophysiology. In GDM, the placenta undergoes morphological and metabolic changes, including increased thickness and accumulation of collagen and glycogen deposits. The excessive collagen deposition may lead to placental fibrosis, impairing blood perfusion and substance exchange. Glycogen buildup could be linked to abnormal glucose uptake and storage in the placenta under maternal hyperglycemic conditions. Abnormal expression of endocytosis-related molecules in GDM-placenta—such as decreased megalin levels, downregulated LRP2/LRP1/LDLR/CLTC gene expression, and significantly elevated miR-199—impairs the placenta's ability to absorb and transport lipoproteins, ultimately affecting fetal nutrient supply [8].

3. The impact of gestational diabetes

3.1. Effects on the mother

Gestational Diabetes Mellitus (GDM) affects multiple systems in the mother, potentially increasing short-term risks of various complications and long-term susceptibility to metabolic disorders.

According to the data in Table 1, from a metabolic perspective, women with gestational diabetes mellitus (GDM) exhibit significant insulin resistance. Studies show that during the third trimester of pregnancy, GDM patients have a significantly higher triglyceride/high-density lipoprotein (TG/HDL) cholesterol ratio compared to normal pregnant women ($p<0.05$), and elevated levels of adip 4 (FABP4) ($p<0.05$)—all crucial markers of insulin resistance. Additionally, GDM patients demonstrate a higher body mass index (BMI) in the third trimester than control groups ($p<0.05$). However, those who supplemented with 36g of extra virgin olive oil daily showed these indicators return to near-normal levels (TG/HDL ratio: $p<0.01$ vs. GDM group; FABP4 and BMI: $p<0.05$ vsGDM group). These metabolic abnormalities not only affect pregnancy outcomes but also increase maternal long-term risks of type 2 diabetes. Research indicates that women with a history of GDM face a several times greater likelihood of developing type 2 diabetes later in life compared to normal pregnancies. Furthermore, GDM patients exhibit a pronounced inflammatory state, such as increased matrix metalloproteinase 9 (MMP9) activity in the third trimester ($p<0.05$) compared to controls. The EVOO diet significantly reduces MMP9 activity ($p<0.05$ vsGDM group), which may adversely impact maternal cardiovascular health and elevate long-term cardiovascular disease risks.

Table 1. Effects of GDM on maternal metabolism and inflammatory indicators and effects of EVOO intervention

Metric	Control group	GDM group	GDM+EVOO group	Statistical differences (vs. control group)	Statistical differences (vs GDM group)
TG/HDL cholesterol ratio (late pregnancy)	-	go up	Close to normal	p<0.05	p<0.01
FABP4 levels (late gestation)	-	go up	Close to normal	p<0.05	p<0.05
BMI (late gestation)	-	go up	Close to normal	p<0.05	p<0.05
MMP9 activity (late gestation)	-	go up	reduce	p<0.05	p<0.05

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3.2. Effects on the fetus

3.2.1. Abnormal fetal growth

The hyperglycemic environment in gestational diabetes (GDM) patients can cross the placenta into the fetal body, stimulating insulin-producing β-cells and increasing insulin secretion. This leads to excessive insulin production that promotes fetal tissue growth, resulting in macrosomia. Macrosomia not only complicates delivery and increases cesarean section rates but may also cause complications such as shoulder dystocia and clavicle fractures during labor. Although this study excluded obese patients with well-controlled metabolism and showed no significant differences in placental or fetal weight, clinical evidence consistently indicates GDM as a major risk factor for macrosomia. Conversely, severe placental dysfunction—such as fibrosis causing inadequate blood perfusion or abnormal endocytosis affecting nutrient transport—may lead to fetal growth restriction due to insufficient oxygen and nutrient supply.

3.2.2. Perinatal complications

Neonatal hypoglycemia is a common perinatal complication of gestational diabetes mellitus (GDM). When the fetus remains in a hyperglycemic environment during pregnancy, insulin secretion continues to increase. When deprived of maternal hyperglycemia, persistently elevated insulin levels may lead to hypoglycemia, which can severely impact neurological development. GDM newborns are also prone to respiratory distress syndrome. High insulin levels may inhibit the synthesis and release of pulmonary surfactant [9].

3.2.3. Congenital malformations and long-term effects

Gestational Diabetes Mellitus (GDM) significantly elevates the risk of congenital malformations in fetuses, particularly cardiac and neurological abnormalities, which may stem from maternal hyperglycemia's teratogenic effects during early embryonic development. Long-term studies indicate that GDM induces metabolic programming in fetuses, increasing susceptibility to obesity, type 2 diabetes, cardiovascular diseases, and other metabolic disorders. These developmental impacts stem directly from placental dysfunction: within the GDM-placenta milieu, oxidative stress, inflammatory cascades, and deranged endocytosis generate an adverse intrauterine environment that disturbs fetal gene expression and metabolic wiring.

3.3. Effects of gestational diabetes on placenta

3.3.1. Effects on placental growth and development

Gestational Diabetes Mellitus (GDM) causes morphological changes in the placenta. According to data from Table 2, the thickness of GDM placental tissue significantly increased from 2.04±0.09 cm in the control group to 2.4±0.07 cm in the GDM group ($p<0.05$). This thickening could be reversed by an EVOO diet, with the EVOO group showing a thickness of 1.9±0.12 cm ($p<0.01$ vsGDM group). However, no significant differences were observed in placental diameter or circumference across groups. The placental thickening may be associated with increased collagen deposition: GDM placental villi contained higher collagen levels compared to the control group ($p<0.01$), and collagen deposition in chorionic villous vessels was also significantly elevated ($p<0.05$). The EVOO diet effectively reduced excessive collagen deposition ($p<0.01$ and $p<0.05$ vsGDM group). As a major

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component of the extracellular matrix, excessive collagen deposition can lead to placental fibrosis, impairing normal placental structure and blood perfusion, thereby compromising its function.

Table 2. Effects of GDM on placental morphology and collagen deposition and effects of EVOO intervention

Metric	Control group	GDM group	GDM+EVOO group	Statistical differences (vs. control group)	Statistical differences (vs GDM group)
Fetal plate thickness (cm)	2.04±0.09	2.4±0.07	1.9±0.12	$p<0.05$	$p<0.01$
Fetal diameter (cm)	19.4±0.5	18.6±0.3	20.2±0.7	no significant differences	no significant differences
Cervical circumference (cm)	60.6±1.0	57.8±1.3	62.3±2.1	no significant differences	no significant differences
Villi collagen content of placenta	-	go up	reduce	$p<0.01$	$p<0.01$
Vascular collagen content in chorion of placenta	-	go up	reduce	$p<0.05$	$p<0.05$

3.3.2. Metabolic abnormalities affect the exchange of substances and energy in the placenta

The metabolic abnormalities of GDM disrupt the placenta's material and energy exchange functions. According to Table 3, in terms of glucose metabolism, the placental glycogen content in GDM was significantly increased ($p<0.001$), which may be an adaptive response of the placenta to the maternal hyperglycemic environment. However, excessive glycogen accumulation can impair the placenta's energy metabolism and function. The EVOO diet significantly reduced glycogen deposition ($p<0.001$ vsGDM group). In lipid metabolism, although GDM placental lipid levels (e.g., triglycerides, cholesterol, phospholipids) and fatty acid composition showed no significant difference from the control group, maternal hypertriglyceridemia may affect the placenta's lipid uptake and transport. More importantly, GDM placental endocytosis pathways exhibited marked abnormalities: Megalin (a key protein involved in lipoprotein endocytosis) levels decreased ($p<0.05$), mRNA expression of endocytosis-related genes including LRP2 (encoding Megalin), LRP1, LDLR, and CLTC was significantly downregulated ($p<0.05$), while the negative regulator miR-199 expression increased by 30-fold ($p<0.01$). The EVOO diet reversed these changes, restoring Megalin levels and related gene expression to normal values ($p<0.05$ vsGDM group) while reducing miR-199 overexpression ($p<0.01$ vsGDM group).

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Table 3. Effects of GDM on placental metabolism and endocytosis related molecules and effects of EVOO intervention

Metric	Control group	GDM group	GDM+EVOO group	Statistical differences (vs. control group)	Statistical differences (vs GDM group)
Glucose content of placenta	-	Significantly increased	reduce	p<0.001	p<0.001
Placental lipid levels (triglycerides, etc.)	-	no significant differences	no significant differences	no significant differences	no significant differences
Placenta megalyne level	-	reduce	epistrophy	p<0.05	p<0.05
LRP2 mRNA expression	-	down regulation	epistrophy	p<0.05	p<0.05
LRP1 mRNA expression	-	down regulation	-	p<0.05	no significant differences
LDLR mRNA expression	-	down regulation	epistrophy	p<0.05	p<0.05
CLTC mRNA expression	-	down regulation	epistrophy	p<0.05	p<0.05
MIR-199 expression	-	That's a 30-fold increase	reduce	p<0.01	p<0.01

4. Avoid adverse effects of gestational diabetes on placenta through rational nutrition

4.1. A diet using Extra Virgin Olive Oil (EVOO)

EVOO, rich in polyphenols and oleic acid, demonstrates unique advantages in mitigating the adverse effects of gestational diabetes (GDM) on the placenta. Polyphenols, with their potent antioxidant properties, effectively reduce oxidative stress in GDM patients, minimize reactive oxygen species-induced damage to placental cells, and create a healthier internal environment for these cells. Oleic acid, as a monounsaturated fatty acid, activates peroxisome proliferator-activated receptors (PPARs). These receptors act as key regulators in metabolic, anti-inflammatory, and developmental pathways, actively improving insulin resistance and inflammatory responses. This addresses the root causes of GDM-induced metabolic disorders and inflammation, thereby reducing placental irritation. Studies show that daily supplementation of 36g EVOO in GDM patients significantly improves maternal insulin resistance markers. The placenta's thickness returns to normal, excessive collagen and glycogen deposition is inhibited, and placental endocytosis-related molecular expressions normalize. These improvements ensure proper placental structure and function while securing fetal nutrient supply [10].

4.2. Build a balanced diet structure

Establishing a balanced diet is fundamental for gestational diabetes (GDM) patients to prevent adverse effects on the placenta. When selecting carbohydrates, GDM patients should avoid refined grains like polished rice and white flour, instead increasing intake of complex carbohydrates rich in dietary fiber such as whole grains and tubers. Whole grains, including oats, brown rice, and whole wheat bread, contain abundant dietary fiber that slows carbohydrate digestion, prevents rapid post-meal blood sugar spikes, and maintains stable glucose levels for the placenta. For protein intake,

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prioritize high-quality sources like lean meats, fish, eggs, legumes, and soy products. These proteins not only meet maternal and fetal growth needs but also have minimal impact on blood sugar, helping maintain metabolic health and supporting normal placental function. Regarding fat consumption, limit saturated and trans fats while avoiding fried foods and cream cakes. Prioritize unsaturated fatty acid-rich options like olive oil (particularly EVOO mentioned earlier), nuts, and deep-sea fish. Unsaturated fats benefit fetal brain development and vision, regulate maternal lipid levels, reduce cardiovascular risks, and improve placental circulation [11].

4.3. Scientific meal arrangement and food intake control

Scientific meal planning and portion control play a crucial role in improving placental health for gestational diabetes patients. Moving beyond the traditional three-meal-a-day model, adopting a frequent small meals approach divides daily nutrition into 5-6 portions: 3 main meals paired with 2-3 snacks. This schedule prevents excessive calorie intake at once, avoids sudden spikes in blood sugar levels, maintains stable glucose balance, and reduces adverse impacts on placental metabolism. For example, breakfast at 7:30 AM with protein-rich foods like whole wheat bread, low-fat milk, and boiled eggs; a midday snack of nuts or low-sugar fruits at 10:00 AM; lunch at 11:30 AM, ensuring balanced combinations of staple foods, proteins, and vegetables; another snack of unsweetened yogurt at 3:00 PM; dinner at 3:00 PM, maintaining nutritional balance; and a light snack like whole wheat crackers at 8:00 PM if needed. Strict portion control is essential—staple foods should be limited to 50-75 gramsper meal to prevent blood sugar spikes [12].

5. Conclusion

This study investigated the effects of gestational metabolic abnormalities on the placenta. It also examined the intervention role of an extra virgin olive oil (EVOO) diet. This study confirms the multifaceted adverse effects of gestational diabetes mellitus (GDM) on the placenta. It also elucidates the positive role of an extra-virgin olive oil (EVOO) diet. EVOO helps improve these GDM-related abnormalities. The findings provide new nutritional intervention strategies for the clinical management of GDM. EVOO contains polyphenols and oleic acid. These components may exert beneficial effects through multiple mechanisms. The mechanisms include antioxidant activity and anti-inflammatory properties. They also involve regulation of the peroxisome pathway (PPARs). Additionally, they modulate microRNA expression. These insights offer a foundation for deeper understanding. Researchers can better understand the relationship between nutritional factors and metabolic abnormalities during pregnancy.

This study has certain limitations: First, the relatively small sample size (n=15 per group) may affect the generalizability of the results, requiring future validation through larger cohort studies. Second, the absence of a normal pregnancy control group receiving EVOO supplementation prevents clear assessment of EVOO's impact on normal placenta.

Future research should focus on three key areas. First, studies should expand the sample size through multicenter clinical trials. This expansion will further validate the long-term effects of an EVOO diet on gestational diabetes (GDM). It will also clarify its impact on maternal-fetal outcomes. Second, researchers need to conduct in-depth exploration of EVOO's molecular mechanisms. They should pay particular attention to its specific impacts on signaling pathways. Understanding its role in gene expression regulation is also essential. These efforts will provide evidence for developing more personalized nutritional intervention strategies.

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