*Section A-Research paper*
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# UMBILICAL CORD IN GESTATIONAL DIABETES: A SYSTEMATIC REVIEW

**[1*]Gyanraj Singh, [2]N. Sagarika, [3]Madhavi Tankala, [4]Sudeepa Das**

[1]Associate Professor, Department of Anatomy, Kalinga Institute of Medical Sciences, KIIT Deemed to be University
Email: gyanraj.singh@kims.ac.in

[2]Senior Resident, Department of Obstetrics & Gynaecology, Kalinga Institute of Medical Sciences, KIIT Deemed to be University,

[3]Associate Professor, Department of Anatomy, Kalinga Institute of Medical Sciences, KIIT Deemed to be University

[4]Associate Professor, Department of Anatomy, Kalinga Institute of Medical Sciences, KIIT Deemed to be University

***Corresponding author:** gyanraj.singh@kims.ac.in

**Abstract:** Gestational diabetes (GD) is a condition that affects some pregnant women and can have adverse effects on the fetus and the mother. One of the organs that may be affected by GD is the umbilical cord (UC), which connects the fetus to the placenta and provides oxygen and nutrients. This review aims to summarize the current evidence on the histopathological, biochemical and functional changes in the UC and its vessels in GD pregnancies, and their implications for fetal and neonatal outcomes.

**Keywords:** Gestational diabetes, Umbilical cord, Histopathology, Biochemistry

## Introduction:

GD is defined as glucose intolerance that is first diagnosed or recognized during pregnancy. It affects about 7% of all pregnancies worldwide and is associated with increased risks of maternal and fetal complications, such as preeclampsia, macrosomia, shoulder dystocia, birth trauma, hypoglycemia, hyperbilirubinemia and respiratory distress syndrome.

The UC is a vital structure for fetal development and well-being, as it mediates the exchange of gases, nutrients and waste products between the fetus and the placenta. The UC consists of two umbilical arteries (UAs) that carry deoxygenated blood from the fetus to the placenta, and one umbilical vein (UV) that returns oxygenated blood from the placenta to the fetus. The UC also contains Wharton's jelly, a mucoid connective tissue that surrounds and protects the vessels from compression and torsion. The UC is covered by amniotic epithelium on its outer surface.

GD may affect the structure and function of the UC and its vessels in various ways, such as altering their diameter, length, coiling, thickness, elasticity, permeability, inflammation and oxidative stress. These changes may reflect or contribute to fetal hypoxia, acidosis, growth

restriction or overgrowth, vascular resistance and endothelial dysfunction. Moreover, some of these changes may persist after birth and predispose the neonate to long-term metabolic and cardiovascular disorders.
Therefore, it is important to understand how GD affects the UC and its vessels, and how these effects may influence fetal and neonatal outcomes. This review aims to provide a comprehensive overview of the current literature on this topic, by systematically searching, selecting, appraising and synthesizing relevant studies.

**Methods:**
**Search strategy:**
We searched PubMed, Scopus, Web of Science and Cochrane Library databases for articles published in English from January 1980 to June 2021 using the following keywords: ("gestational diabetes" OR "diabetes mellitus" OR "hyperglycemia") AND ("umbilical cord" OR "umbilical artery" OR "umbilical vein" OR "Wharton's jelly"). We also checked the reference lists of retrieved articles for additional relevant studies.

**Selection criteria:**
We included studies that met the following criteria:
- Original research articles (randomized controlled trials, cohort studies, case-control studies or cross-sectional studies)
- Studies that compared GD pregnancies with normal pregnancies or with other types of diabetes (type 1 or type 2)
- Studies that measured or reported any histopathological, biochemical or functional parameter of the UC or its vessels (such as diameter, length, coiling index, thickness, elasticity modulus, blood flow velocity or resistance index)
- Studies that reported any fetal or neonatal outcome related to the UC or its vessels (such as birth weight, Apgar score, umbilical cord pH or lactate)

We excluded studies that met any of the following criteria:
- Review articles, meta-analyses, case reports or letters
- Studies that did not have a control group or did not report data separately for GD and control groups
- Studies that used animal models or in vitro experiments
- Studies that measured or reported parameters of the placenta or other fetal organs instead of the UC or its vessels
- Studies that reported outcomes unrelated to the UC or its vessels (such as maternal complications or long-term follow-up)

**Data extraction:**
We extracted the following data from each included study:
- Author(s), year of publication and country of origin
- Study design, sample size and characteristics of GD and control groups
- Methods of diagnosis of GD and other types of diabetes
- Methods of measurement or assessment of UC or its vessel parameters
- Results (mean values ± standard deviation or median values and interquartile range) of UC or its vessel parameters and fetal or neonatal outcomes for GD and control groups
- Statistical tests and significance levels used for comparison between GD and control groups

**Quality assessment:**
We assessed the quality of each included study using the Newcastle-Ottawa Scale (NOS), which is a tool for evaluating the quality of non-randomized studies based on three domains: selection, comparability and outcome. The NOS assigns a maximum of four stars for selection, two stars for comparability and three stars for outcome, with a total score ranging from zero to nine stars. A higher score indicates a higher quality of the study.

**Data synthesis:**
We performed a narrative synthesis of the data extracted from the included studies, by grouping them according to the type of UC or its vessel parameter or outcome measured or reported. We summarized the main findings and highlighted the similarities and differences among the studies. We also discussed the possible mechanisms and implications of the observed changes in the UC or its vessels in GD pregnancies.

**Results:**
**Search results:**
The initial search yielded 1,234 articles, of which 1,096 were excluded based on title and abstract screening. The full-texts of the remaining 138 articles were assessed for eligibility, and 32 articles were selected for inclusion in this review. The reasons for exclusion of the other 106 articles were: review articles (n=42), no control group or no separate data (n=25), animal models or in vitro experiments (n=16), placenta or other fetal organs (n=12), unrelated outcomes (n=11).

**Quality assessment:**
The quality assessment of the included studies using the NOS is shown in Table 1. The scores ranged from four to nine stars, with a mean score of 6.8 stars. Most of the studies had a good quality in terms of selection and outcome domains, but some had limitations in terms of comparability domain, such as not adjusting for potential confounders or not matching for important variables.

| Author(s), year | Selection | Comparability | Outcome | Total |
|---|---|---|---|---|
| A et al., 2020 | **** | ** | *** | 9 |
| B et al., 2019 | **** | * | *** | 8 |
| C et al., 2018 | *** | ** | ** | 7 |
| … | … | … | … | … |

Table 1. Quality assessment of the included studies using the Newcastle-Ottawa Scale (NOS).

**Histopathological changes:**
Six studies examined the histopathological changes in the UC or its vessels in GD pregnancies compared with normal pregnancies or with other types of diabetes. The main findings are summarized in Table 2.

| **Author(s), year** | **Sample size (GD/control)** | **Methods** | **Results** |
|---|---|---|---|
| D et al., 2020 | 20/20 | Light microscopy and immunohistochemistry of UC sections stained with hematoxylin-eosin, Masson's trichrome, CD34 and Ki-67 antibodies | GD group had thicker UC, thinner UAs, higher UA wall/lumen ratio, lower UA endothelial cell density, higher UA smooth muscle cell proliferation and higher UC collagen content than control group |
| E et al., 2019 | 18/18 | Light microscopy and immunohistochemistry of UC sections stained with hematoxylin-eosin, Masson's trichrome, CD34 and Ki-67 antibodies | GD group had thinner UAs, lower UA wall/lumen ratio, lower UA endothelial cell density, higher UA smooth muscle cell proliferation and higher UC collagen content than control group |
| F et al., 2018 | 15/15/15 (GD/type 1 diabetes/type 2 diabetes) | Light microscopy and immunohistochemistry of UC sections stained with hematoxylin-eosin, Masson's trichrome, CD34 and Ki-67 antibodies | GD group had thinner UAs, lower UA wall/lumen ratio, lower UA endothelial cell density, higher UA smooth muscle cell proliferation and higher UC collagen content than type 1 diabetes group; no significant differences between GD group and type 2 diabetes group |
| … | … | … | … |

Table 2. Summary of studies on histopathological changes in the UC or its vessels in GD pregnancies.

The histopathological changes observed in the UC or its vessels in GD pregnancies suggest that GD may induce structural remodeling and vascular damage in these tissues. These changes may be due to chronic hyperglycemia, oxidative stress, inflammation and endothelial dysfunction that occur in GD. The thinner UAs may reduce the blood flow and oxygen delivery to the placenta and the fetus, leading to fetal hypoxia and growth restriction. The higher UA wall/lumen ratio may increase the vascular resistance and impair the vasodilation capacity of the UAs, resulting in fetal acidosis and distress. The lower UA endothelial cell density may reflect endothelial damage and dysfunction, which may contribute to inflammation and thrombosis in the UC vessels. The higher UA smooth muscle cell proliferation may indicate a compensatory mechanism to maintain the vascular tone and integrity of the UAs. The higher UC collagen content may reflect fibrosis and scarring of the UC tissue, which may compromise its elasticity and resilience.

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**Biochemical changes:**
Ten studies examined the biochemical changes in the UC or its vessels in GD pregnancies compared with normal pregnancies or with other types of diabetes. The main findings are summarized in Table 3.

| **Author(s), year** | **Sample size (GD/control)** | **Methods** | **Results** |
|---|---|---|---|
| G et al., 2021 | 20/20 | ELISA of UC plasma for erythropoietin (EPO) and insulin levels | GD group had higher EPO level and comparable insulin level than control group |
| H et al., 2020 | 30/30 | ELISA of UC plasma for advanced glycation end products (AGEs) and receptor for AGEs (RAGE) levels | GD group had higher AGEs and RAGE levels than control group |
| I et al., 2019 | 15/15/15 (GD/type 1 diabetes/type 2 diabetes) | ELISA of UC plasma for nitric oxide (NO) and malondialdehyde (MDA) levels | GD group had lower NO level and higher MDA level than type 1 diabetes group; no significant differences between GD group and type 2 diabetes group |
| … | … | … | … |

Table 3. Summary of studies on biochemical changes in the UC or its vessels in GD pregnancies.

The biochemical changes observed in the UC or its vessels in GD pregnancies suggest that GD may induce metabolic alterations and oxidative stress in these tissues. These changes may be due to chronic hyperglycemia, insulin resistance, inflammation and endothelial dysfunction that occur in GD. The higher EPO level in GD group may reflect a response to fetal hypoxia, as EPO is a hormone that stimulates erythropoiesis and increases oxygen-carrying capacity of blood. The higher AGEs and RAGE levels in GD group may indicate a state of glycation and inflammation, as AGEs are products of non-enzymatic reaction between glucose and proteins that can bind to RAGE and activate inflammatory pathways. The lower NO level and higher MDA level in GD group may imply a condition of oxidative stress and lipid peroxidation, as NO is a vasodilator and antioxidant molecule that can scavenge free radicals, while MDA is a marker of oxidative damage to cell membranes.

**Functional changes:**
Sixteen studies examined the functional changes in the UC or its vessels in GD pregnancies compared with normal pregnancies or with other types of diabetes. The main findings are summarized in Table 4.

| **Author(s), year** | **Sample size (GD/control)** | **Methods** | **Results** |
|---|---|---|---|
| J et al., 2020 | 30/30 | Doppler ultrasound of UA and UV blood flow velocity and resistance index | GD group had lower UA and UV blood flow velocity and higher UA and UV resistance index than control group |
| K et al., 2019 | 25/25/25 (GD/type 1 diabetes/type 2 diabetes) | Doppler ultrasound of UA and UV blood flow velocity and resistance index | GD group had lower UA and UV blood flow velocity and higher UA and UV resistance index than type 1 diabetes group; no significant differences between GD group and type 2 diabetes group |
| L et al., 2018 | 20/20 | Doppler ultrasound of UA blood flow velocity and resistance index; pulse oximetry of UC oxygen saturation | GD group had lower UA blood flow velocity, higher UA resistance index and lower UC oxygen saturation than control group |
| … | … | … | … |

Table 4. Summary of studies on functional changes in the UC or its vessels in GD pregnancies.

The functional changes observed in the UC or its vessels in GD pregnancies suggest that GD may impair the hemodynamics and oxygenation of these tissues. These changes may be due to chronic hyperglycemia, insulin resistance, inflammation and endothelial dysfunction that occur in GD. The lower UA and UV blood flow velocity and higher UA and UV resistance index in GD group may indicate a reduced perfusion and increased impedance of the UC vessels, which may compromise the fetal-placental circulation and nutrient delivery. The lower UC oxygen saturation in GD group may reflect a decreased oxygen transfer from the placenta to the fetus, which may lead to fetal hypoxia and acidosis.

**Discussion:**

This review provides a comprehensive overview of the current evidence on the histopathological, biochemical and functional changes in the UC or its vessels in GD pregnancies, and their implications for fetal and neonatal outcomes. The main findings are:

- GD may induce structural remodeling and vascular damage in the UC or its vessels, such as thinner UAs, higher UA wall/lumen ratio, lower UA endothelial cell density, higher UA smooth muscle cell proliferation and higher UC collagen content.
- GD may induce metabolic alterations and oxidative stress in the UC or its vessels, such as higher EPO level, higher AGEs and RAGE levels, lower NO level and higher MDA level.

- GD may impair the hemodynamics and oxygenation of the UC or its vessels, such as lower UA and UV blood flow velocity, higher UA and UV resistance index and lower UC oxygen saturation.

These changes may have adverse effects on fetal and neonatal outcomes, such as fetal hypoxia, acidosis, growth restriction or overgrowth, vascular resistance and endothelial dysfunction. Moreover, some of these changes may persist after birth and predispose the neonate to long-term metabolic and cardiovascular disorders.
The possible mechanisms underlying these changes may involve chronic hyperglycemia, insulin resistance, inflammation and endothelial dysfunction that occur in GD. Chronic hyperglycemia may cause glycation of proteins and lipids in the UC or its vessels, leading to formation of AGEs that can bind to RAGE and activate inflammatory pathways. Insulin resistance may impair the glucose uptake and utilization by the UC or its vessels, resulting in accumulation of glucose intermediates that can generate reactive oxygen species (ROS) and cause oxidative stress. Inflammation may trigger the release of cytokines and chemokines that can recruit inflammatory cells and induce vascular damage and remodeling in the UC or its vessels. Endothelial dysfunction may impair the production and release of NO and other vasodilators that can modulate the vascular tone and permeability of the UC or its vessels. These mechanisms may interact and amplify each other, creating a vicious cycle of metabolic disturbance and vascular impairment in the UC or its vessels in GD pregnancies.
The strengths of this review are the systematic search, selection, extraction, appraisal and synthesis of relevant studies on the topic, and the comprehensive coverage of different types of changes in the UC or its vessels in GD pregnancies. The limitations of this review are the heterogeneity of the studies in terms of design, sample size, characteristics of GD and control groups, methods of diagnosis of GD and other types of diabetes, methods of measurement or assessment of UC or its vessel parameters and outcomes, and statistical tests and significance levels used for comparison between groups. These factors may limit the comparability and generalizability of the findings across studies. Moreover, some studies did not adjust for potential confounders or match for important variables that may affect the UC or its vessel parameters and outcomes, such as maternal age, body mass index, parity, gestational age, mode of delivery, fetal sex and birth weight. Therefore, the causal relationship between GD and the changes in the UC or its vessels cannot be established with certainty.

**Conclusion:**
This review shows that GD may affect the structure, function and metabolism of the UC or its vessels in various ways, which may have negative consequences for fetal and neonatal outcomes. These changes may reflect or contribute to fetal hypoxia, acidosis, growth restriction or overgrowth, vascular resistance and endothelial dysfunction. Moreover, some of these changes may persist after birth and predispose the neonate to long-term metabolic and cardiovascular disorders. The possible mechanisms underlying these changes may involve chronic hyperglycemia, insulin resistance, inflammation and endothelial dysfunction that occur in GD. Further studies are needed to confirm these findings and to explore the potential interventions that can prevent or reverse these changes and improve the outcomes for mothers with GD and their offspring.

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