Review Article

Pregnancy and diabetic retinopathy

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ABSTRACT

Background: An increase in the worldwide prevalence of diabetes, especially among younger populations, has led to a higher prevalence of pre-existing diabetes among pregnant women. The precise mechanisms underlying the development or progression of diabetic retinopathy (DR) during pregnancy are not entirely understood. This narrative review incorporates all available data to offer fresh insights into the pathogenesis and mechanisms of the pregnancy-induced development and/or progression of DR. Moreover, the author aims to offer clinical recommendations for DR both before conception and during pregnancy to appropriately counsel these susceptible patients.

Methods: A literature search was performed using various combinations of the following keywords: diabetes, pregnancy, diabetic retinopathy, ocular, eye, retina, microangiopathy, mechanism, pathophysiology, hyperglycemia, hypoxia, neovascularization, growth factors, immune system, blood flow, and recommendations. The search was conducted using PubMed/MEDLINE, ISI Web of Science, Scopus, and Google Scholar, and only English articles published from January 1, 2020, to December 31, 2023, involving human participants, were considered. The International Diabetes Federation Diabetes Atlas website was searched for clinical recommendations.

Results: Pregnancy-induced hyperglycemia, blood flow changes, growth factors, and the immune system play important roles in the development and progression of DR. Hyperglycemia leads to significant stress on the capillary endothelium through increased glucose flux via the polyol and hexosamine pathways, activation of protein kinase C, and increased formation of advanced glycation end-products. These pathways act in several ways that may lead to increased oxidative stress, inflammation, and vascular blockage. Thus, eye examinations are crucial before, during, and up to 12 months after pregnancy. Individuals with severe non-proliferative and proliferative DR should gradually decrease their blood glucose levels to near-normal levels over a period of 6 months before conception. Statins and medications inhibiting the renin–angiotensin system should be discontinued before pregnancy or at the initial antenatal visit if they are still being used. Retinal examinations should be performed shortly after conception and during the first trimester using tropicamide eye drops and digital imaging. Subsequent examinations should be scheduled based on DR severity at the initial examination.

Conclusions: While the precise mechanism underlying the progression of DR during pregnancy remains uncertain, the available literature suggests that pregnancy-induced hyperglycemia, blood flow changes, growth factors, and the immune system play important roles in its development and progression. Pregnant women with diabetic eye manifestations benefit from the expertise of multidisciplinary teams comprising ophthalmologists, diabetologists, and gynecologists to improve both maternal and perinatal outcomes. Moreover, postpartum follow-up requires special attention.

KEYWORDS

gestational diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, diabetic retinopathies, hyperglycemias, hexosamine, protein kinase c delta, advanced glycation endproducts, blood flow, immune systems, care, preconception, conception

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INRODUCTION

Diabetes mellitus (DM) is one of the most prevalent metabolic disorders [1]. With its increasing global incidence, DM can be characterized as a pandemic [1]. In 2021, the International Diabetes Federation (IDF) estimated that approximately 537 million individuals aged 20–79 years will have DM [2].

Long-term DM can lead to numerous complications [3]. Diabetic retinopathy (DR) is an ocular manifestation of advanced DM [4]. This complication is widespread and associated with inadequately managed DM, affecting approximately 93 million individuals worldwide [1, 5]. It results from hyperglycemia-induced injury to the retinal blood vessels and is a primary cause of visual impairment in the working-age population [6].

DM affects women of childbearing age [7] and occurs in 1–2% of pregnant women [8]. Evidence suggests that pregnancy may increase the risk of development and progression of DR [9]. Pregnancy induces a wide spectrum of physiological and pathological alterations in the eye [10]. It can affect blood vessel autoregulation, as observed in microangiopathy [11]. Although all components of the eye can be affected, the retinal tissue, along with its vasculature, is particularly vulnerable [12]. In pregnant women with DM, DR may develop in approximately 10% of cases and may worsen if already present [12]. DR affects 1 in 7 pregnant women with type 2 DM and 50% of pregnant women with type 1 DM [13].

The pathogenesis of DR during pregnancy is not fully understood [14]. Therefore, this review incorporates all available data to clarify the mechanisms of pregnancy-induced alterations in the development and/or progression of DR. Moreover, the author aims to offer clinical recommendations for DR, both before conception and during pregnancy, to appropriately counsel this susceptible patient group.

METHODS

In this narrative review, a literature search was performed using the keywords diabetes, pregnancy, diabetic retinopathy, ocular, eye, retina, microangiopathy, mechanism, pathophysiology, hyperglycemia, hypoxia, neovascularization, growth factors, immune system, blood flow, and recommendations. Only studies reported in English involving human participants from January 01, 2020, to December 30, 2023, were considered. The articles encompassed original studies, case series, case-control studies, letters to the editor, and narrative or systematic reviews. Academic search engines, such as PubMed/MEDLINE, ISI Web of Science, Scopus, and Google Scholar, were used. In addition, numerous relevant studies were added by screening the reference lists of the included articles. The abstracts were reviewed to exclude irrelevant and duplicate investigations. Moreover, the IDF Diabetes Atlas website [15] was explored to develop pre- and post-conception clinical recommendations for women with pre-existing DM.

RESULTS

DR has traditionally been described as a microvascular disorder affecting the retina [16] (Figure 1A, B). Nevertheless, emerging evidence indicates that retinal neurodegeneration is the primary manifestation of DR and potentially contributes to the onset of microvascular abnormalities [16]. DR can be classified as non-proliferative DR (NPDR) or proliferative DR (PDR) [5].

Microaneurysms and intraretinal hemorrhages are the earliest visible signs of DR [5]. Microvascular impairment results in retinal capillary nonperfusion, cotton wool spots, venous abnormalities, hemorrhages, and intraretinal microvascular abnormalities. At this stage, heightened vasopermeability may lead to retinal thickening or edema and the appearance of exudates, potentially deteriorating central visual acuity [5]. The proliferative stage leads to the formation of new vessels, often associated with major retinal ischemia, which in advanced stages can culminate in retinal detachment and severe vision impairment [5].

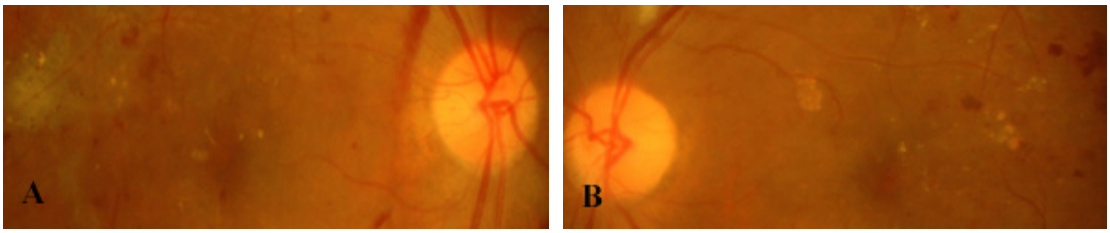

Figure 1. Color fundus photograph of the right (A) and left (B) eyes with moderate to severe non-proliferative diabetic retinopathy.

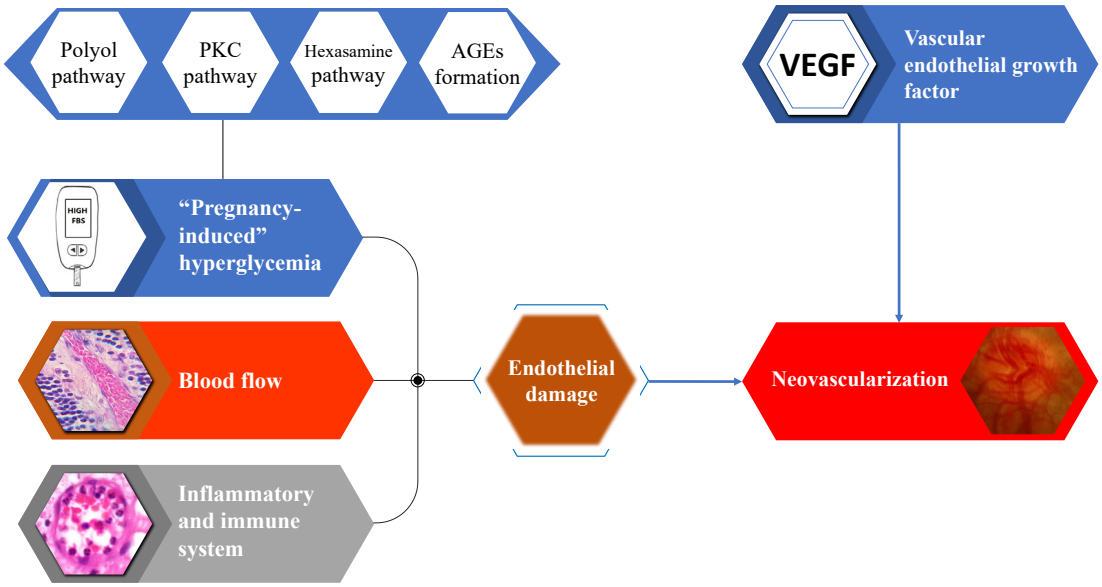

Figure 2. Summary of proposed pathways [12, 14, 17-58] for the pathogenesis of diabetic retinopathy progression in pregnancy. Abbreviations: PKC, protein kinase C; AGE, advanced glycosylated end products.

Although the precise mechanism underlying the progression of DR during pregnancy is not well understood [14], numerous direct and indirect mechanisms have been proposed [12, 14, 17-58]. A summary of these pathways is provided in Figure 2. Based on the data provided in these articles, pregnancy imposes an elevated risk of both the onset and progression of DR. Therefore, the author aims to offer clinical recommendations for DR both before conception and during pregnancy to appropriately counsel these susceptible patients. The author incorporates all available data to offer fresh insights into the pathogenesis and mechanisms of the pregnancy-induced development and/or progression of DR and counseling for DR monitoring in the discussion that follows.

DISCUSSION

Hyperglycemia

During pregnancy, substantial changes occur in maternal metabolism to ensure adequate nutritional reserves during early gestation and to meet the increased maternal and fetal requirements during late gestation and lactation [17]. During normal pregnancy, insulin resistance similar to that detected in type 2 DM is observed. This physiological resistance becomes more evident in the second trimester and persists until term [18, 19].

The major diabetogenic hormones in pregnancy are prolactin, human placental lactogen (hPL), placental growth hormone, cortisol, and progesterone [20-22]. The embryonic syncytiotrophoblasts synthesize hPL, which circulates through the maternal bloodstream [12]. Prolactin is a peptide hormone secreted by lactotrophs in the anterior pituitary gland, a process modulated by estrogen, and has significant structural similarity to hPL [23]. Prolactin and hPL are crucial for maintaining glucose homeostasis during pregnancy, inducing direct effects on beta cells of the maternal endocrine pancreas [12, 23]. All these hormones induce maternal insulin resistance and elevate maternal blood glucose levels. Consequently, a physiological hyperglycemia is associated with pregnancy [20, 22, 24]. Alterations in insulin resistance are crucial for prioritizing the transfer of glucose across the placenta to support fetal growth [19].

Hyperglycemia contributes to the onset of DR [25, 26]. Hyperglycemia leads to significant stress on the capillary endothelium through increased glucose flux via the polyol and hexosamine pathways, activation of protein kinase C (PKC), and increased formation of advanced glycation end products (AGEs) [27]. These pathways act in several ways and may increase oxidative stress, inflammation, and vascular blockage [27].

Increased polyol pathway flux: The polyol pathway involves a two-step metabolic process. Glucose is first reduced to sorbitol, which is then converted into fructose [28]. Activation of this pathway occurs when intracellular glucose levels are elevated [28]. Consequently, intracellular sorbitol levels increase under hyperglycemic circumstances [27]. Sorbitol then accumulates because of its limited ability to diffuse through cell membranes, leading to osmotic injury of vessels [27].

Increased flux through the hexosamine pathway: The hexosamine pathway is a glucose metabolism route that contributes to the synthesis of the amino sugar uridine diphosphate N-acetylglucosamine [29]. This pathway induces various changes in the expressions of genes, such as *Plasminogen Activator Inhibitor-1*, and in the associated protein levels. Collectively, these changes contribute to vascular complications [30-32]. Increased flux through the hexosamine pathway leads to transforming growth factor-beta expression, PKC activation, and extracellular matrix production, all of which are associated with DR development [31, 33].

Activation of PKC: PKC is a group of enzymes with certain isoforms that are particularly associated with DR progression [34, 35]. Activation of this enzyme affects extracellular matrix protein synthesis/expansion, leukocyte adhesion, endothelial cell activation and proliferation, smooth muscle cell contraction, expression of growth factors such as vascular endothelial growth factor (VEGF), endothelial permeability, and retinal blood flow [28]. Therefore, PKC activation likely contributes to certain pathologies observed in DR [27].

Accumulation of AGEs: Prolonged hyperglycemia leads to the accumulation of AGEs [27]. AGEs are implicated in various micro- and macrovascular complications by forming crosslinks between molecules in the basement membrane of the extracellular matrix and AGE receptors [36]. After cellular binding, AGEs increase procoagulant activity, vascular permeability, expression of adhesion molecules, and monocyte influx actions that can lead to vascular damage [27, 37].

In summary, hyperglycemia imposes notable stress on the capillary endothelium by modifying vascular permeability, resulting in edema and hypoxia, and increasing the risk of bleeding and thrombosis [38, 39]. Hypoxia is the primary trigger of both physiological and pathological neovascularization [12]. Throughout physiological angiogenesis, newly formed vessels undergo rapid maturation and become stable [38]. Conversely, pathological vascularization exhibits distinct vessel characteristics, including irregular shape, dilation, tortuosity, and potentially has dead ends [38]. The resulting vascular network is often structurally fragile and predisposed to bleeding [38]. All this occurs in DR, in which the hypoxic stimulus persists beyond the formation of new vessels, which remain immature and delicate [40, 41].

Blood flow

Blood flow velocity directly correlates with DR severity [42]. A hyperdynamic circulatory state is believed to occur during pregnancy and is characterized by a 40% increase in cardiac output [43]. In individuals with diabetes, autoregulatory mechanisms that normally cause compensatory constriction of retinal vessels are disrupted owing to decreased activity of the renin–angiotensin system, leading to vascular dilation and increased blood flow [44, 45]. Retinal capillary blood flow is elevated in pregnant women with DM compared to that in their non-pregnant counterparts [46]. Increased circulatory forces during pregnancy may exacerbate damage, ischemia, and neovascularization in delicate retinal vessels, which are already at risk owing to hyperglycemia [46, 47]. Therefore, the hyperdynamic circulation within retinal capillaries may play a role in advancing DR among pregnant women with DM [46].

Growth factors

Tissue hypoxia is the primary trigger of neovascularization, including that in the retina. Hypoxia-inducible factor-1 is a transcriptional complex that regulates cellular and systemic oxygen levels. Hypoxia-inducible factor-1 stimulates the transcription of various genes, such as *VEGF* [48]. VEGF is a signal protein that activates the formation of blood vessels [49]. Moreover, VEGF-A facilitates the initial glucose-induced injury in retinal endothelial cells [25]. Furthermore, during pregnancy, placental growth hormone assumes the role of growth hormone, modulating the secretion of insulin-like growth factor (IGF) [50-52]. IGF-I exerts a proangiogenic effect on retinal blood vessels [53]. Conversely, IGF binding proteins (IGFBPs) counteract such effects [53]. In non-pregnant women, most circulating IGFBP-1 is extensively phosphorylated, whereas the phosphorylation pattern of IGFBP-1 is disrupted during pregnancy [54].

Inflammation and the immune system

Although the exact cause of DR progression remains unclear, gestational immune activation and chronic inflammation are believed to play significant roles [14]. During pregnancy, the placenta upregulates pro-inflammatory factors and downregulates anti-inflammatory factors. An imbalance in these factors is thought to contribute to the development of PDR [42, 55]. Additionally, the progression of DR has been linked to low levels of the glycoprotein glycodelin, which is secreted by the endometrium and inhibits E-selectin, facilitating leukocyte–endothelium adhesion [56]. Similarly, elevated levels of endothelin-1 have been postulated to cause endothelial damage during pregnancy, resulting in pregnancy-induced hypertension and advancement of DR [57, 58].

During pregnancy, certain components of the immune system that affect DR progression are activated to prevent fetal rejection. These include the generalized activation of leukocytes and elevated plasma levels of certain cytokines [14]. Activated leukocytes with upregulated adhesion molecules demonstrate an increased adherence to blood vessel endothelium [14]. This interaction between leukocytes and the endothelium, which leads to leukostasis, capillary occlusion, ischemia, and vascular leakage, plays a significant role in DR progression [14]. Additionally, elevated levels of certain cytokines are known to induce breakdown of the blood-retinal barrier, while that of others promote angiogenic and fibrovascular proliferation, thereby contributing to the pathogenesis of DR [14].

Clinical recommendations

Based on these mechanisms, pregnancy imposes an elevated risk of both the onset and progression of DR [9]. Upon the diagnosis of DM, suitable management strategies can be applied to prevent adverse outcomes [59]. Proper pregnancy planning, optimal metabolic control, precise diagnosis of pre-existing complications, and implementation of proper medical care during pregnancy are crucial [11]. Additionally, in a systematic review and meta-analysis, Sarvepalli et al. [60] highlighted the importance of closely monitoring pregnant diabetic patients, particularly those at risk of progression to preeclampsia or hypertension, as well as those with elevated glycated hemoglobin levels, longer duration of DM, and higher diastolic pressure [60].

The following are recommendations for the preconception and conception periods. Preconception: 1) Eye examination is crucial before, during, and up to 12 months after pregnancy [2, 61-63]. 2) Individuals with severe NPDR and PDR should gradually reduce their blood glucose levels to nearly normal over a period of six months before conception [57]. 3) Statins and medications blocking the renin–angiotensin system should be discontinued before pregnancy or at the initial antenatal visit if still being used [57].

Conception: 1) The National Institute for Health and Care Excellence (NICE) [62] emphasizes retinal examinations during initial antenatal visits using tropicamide eye drops and digital imaging (unless performed in the previous three months). Additionally, the American Academy of Ophthalmology Preferred Practice Patterns (AAO PPPs) [5] and American Diabetes Association (ADA) [63] suggest that retinal examinations should be performed shortly after conception and during the first trimester. 2) If the initial eye examination findings are normal, a final examination should be considered at 28 weeks. However, if any DR is detected at the first visit, a retinal examination is required at 16–20 weeks [61, 62]. 3) According to the ADA, individuals with minimal or no NPDR should undergo evaluations during the first and last trimesters. Those with mild DR should be assessed every trimester, whereas individuals with moderate to severe NPDR or PDR should undergo monthly evaluations [63]. 4) DR is not a contraindication to vaginal delivery. Nevertheless, in women with untreated PDR, vaginal delivery may lead to retinal and vitreous hemorrhages. Consequently, cesarean delivery must be performed in coordination with both the obstetrician and ophthalmologist [61-63].

This narrative review summarizes the plausible mechanisms for the development and progression of DR during pregnancy and outlines up-to-date practical clinical recommendations. However, it provides no details on DR management during pregnancy and is not based on a systematic review and meta-analysis, possibly introducing bias. A systematic review and meta-analysis focusing on this challenging and potentially blinding health issue could provide more practical guidelines for the daily practice of eye care professionals.

CONCLUSIONS

While the precise mechanisms underlying the progression of DR during pregnancy remain uncertain, the available literature suggests that pregnancy-induced hyperglycemia, blood flow, growth factors, and the immune system play important roles in its development. Understanding the prevalence and risk factors of DR during pregnancy is crucial for effective screening, management, and counseling for future pregnancies. Pregnant women with diabetic eye manifestations benefit from the expertise of multidisciplinary teams comprising ophthalmologists, diabetologists, and gynecologists to enhance both maternal and perinatal outcomes. Moreover, postpartum follow-up should receive special attention.

ETHICAL DECLARATIONS

Ethical approval: This study was a narrative review, and no ethical approval was required.
Conflict of interests: None

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