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DIABETIC RETINOPATHY IN PREGNANCY

Narrative Review

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Acknowledgement: The author gratefully acknowledges the contributions of the researchers whose work formed the basis of this review, as well as the platforms PubMed and Google Scholar for providing access to essential literature.

Conflict of Interest: None
Grant Support & Financial Support: None

ABSTRACT

Background: Diabetic retinopathy (DR), a microvascular complication of diabetes, presents a unique clinical challenge during pregnancy. Gestational diabetes (GD) can either trigger new-onset DR or exacerbate pre-existing retinopathy due to the complex physiological changes associated with gestation. These changes—metabolic, vascular, hormonal, and immunological—can rapidly worsen retinal damage, potentially leading to irreversible vision loss if left unmonitored or untreated.

Objective: This narrative review aims to explore the prevalence, pathogenesis, risk factors, and management strategies of diabetic retinopathy in pregnant women, with a focus on clinical challenges and evidence-based recommendations.

Main Discussion Points: The review synthesizes current literature on maternal risk factors including obesity, previous GD, and glycemic control, and discusses how pregnancy itself contributes to DR progression. The effectiveness and timing of screening and treatment modalities such as fluorescein angiography, laser photocoagulation, intravitreal corticosteroids, and surgical options are critically evaluated. Particular attention is paid to safe clinical practices that protect both maternal vision and fetal development. The prevalence of GD and DR in countries like Pakistan is also highlighted, emphasizing regional disparities in healthcare access and screening protocols.

Conclusion: Effective management of DR during pregnancy requires early identification, individualized monitoring, and a multidisciplinary approach. There remains a pressing need for standardized clinical guidelines and robust, longitudinal research to improve outcomes and guide safe treatment in this vulnerable population.

Keywords: Diabetic Retinopathy, Gestational Diabetes, Pregnancy, Retinal Management, Risk Factors, Narrative Review.

INTRODUCTION

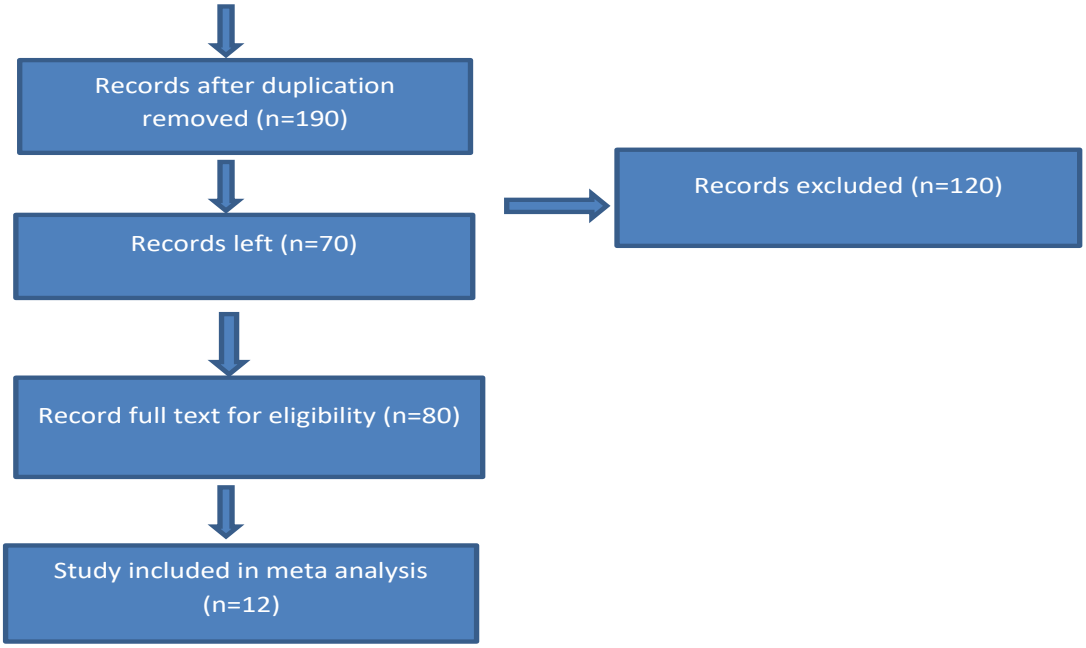
Diabetes mellitus has emerged as a major global health challenge, with its prevalence steadily increasing across both developed and developing nations. Among its various subtypes, gestational diabetes mellitus (GDM) presents a unique set of challenges due to its temporary yet impactful manifestation during pregnancy (1). It not only poses immediate risks to maternal and fetal health but also significantly increases the likelihood of future type 2 diabetes mellitus (T2DM) for both mother and child. Of particular concern is its association with diabetic retinopathy (DR), a microvascular complication of diabetes that can threaten vision (2). As the global burden of diabetes continues to rise, the incidence of GDM and its ophthalmologic implications are expected to become more prominent, especially in low- and middle-income countries where healthcare systems are often ill-equipped to manage complex, comorbid conditions during pregnancy (3). The prevalence of diabetes is particularly alarming in densely populated countries such as India, China, and Pakistan, where urbanization, dietary transitions, and genetic predispositions have contributed to a diabetes epidemic. India alone is home to over 77 million individuals with diabetes, while China has over 116 million, both figures expected to escalate further in coming decades (4). These countries have initiated public health strategies to mitigate the impact of diabetes and its complications. In contrast, Pakistan, with a population surpassing 240 million, is predicted to experience a surge in diabetes prevalence, with limited national programs in place to specifically address diabetes-related visual impairments like DR (5,6). Despite the high-risk environment, DR in the context of GDM has not received the clinical attention it warrants in public health policies, leaving many pregnant women vulnerable to preventable vision loss (7).

The physiological changes that accompany pregnancy—including metabolic alterations, vascular remodeling, immune modulation, and hormonal fluctuations—can accelerate the progression of pre-existing DR or precipitate its onset in women with GDM (8). These changes create a complex pathophysiological landscape where the retina becomes increasingly susceptible to damage. Studies have shown that DR tends to worsen during pregnancy, particularly in women with type 1 diabetes, and although regression postpartum has been observed, irreversible damage can occur if left unmanaged (9,10). The phenomenon of DR deterioration during pregnancy is multifactorial, with hyperglycemia, hypertension, and rapid normalization of blood glucose levels after conception all implicated in exacerbating retinal pathology. The risk is amplified in women who already have some degree of DR at conception, with progression to proliferative diabetic retinopathy (PDR) being a possibility. Notably, pregnancy itself is considered an independent risk factor for DR progression. The pathogenesis of DR during pregnancy involves increased vascular permeability and neovascularization driven by the upregulation of vascular endothelial growth factor (VEGF), a process further complicated by systemic changes unique to pregnancy (11). This interplay poses significant therapeutic dilemmas. While laser photocoagulation remains the cornerstone for treating sight-threatening DR, its application during pregnancy is challenging due to concerns about fetal safety and maternal stress. Similarly, anti-VEGF therapies and intravitreal corticosteroids are used with caution, given the limited data on their safety profiles during gestation. The timing, modality, and intensity of interventions must be carefully considered to balance maternal vision preservation with fetal well-being (12).

Despite the growing awareness, clinical guidelines remain ambiguous regarding the optimal management of DR in pregnancy, leading to variability in clinical practice. Although current research underscores the importance of preconception screening and glycemic control, data on longitudinal outcomes and standardized treatment pathways are lacking (13). The management of DR in the pregnant population is further hampered by delayed diagnosis due to insufficient screening infrastructure, especially in resource-limited settings. Additionally, many women, particularly in rural or underprivileged communities, do not undergo routine ophthalmologic evaluations during pregnancy, often leading to late-stage detection when therapeutic options are limited. Recent studies have illuminated the epidemiology of DR in pregnant women, revealing higher rates of progression in those with poor glycemic control, longer diabetes duration, or concurrent hypertension. Yet, the literature reveals significant gaps. There is limited understanding of the exact pathophysiological mechanisms driving DR progression in GDM versus pregestational diabetes, and inconsistent use of screening protocols hampers cross-study comparisons (14,15). Furthermore, psychosocial barriers such as stigma, lack of awareness, and limited access to specialty care often impede timely diagnosis and management, particularly in developing regions.

The objective of this review is to explore the epidemiological landscape, underlying mechanisms, and clinical challenges associated with diabetic retinopathy in pregnancy, with a particular focus on gestational diabetes. It aims to synthesize recent evidence on risk factors, disease progression, and treatment options, while critically evaluating existing gaps in research and clinical practice. By doing so, this review endeavors to guide future efforts in optimizing maternal and fetal outcomes through improved screening, earlier detection,

and tailored management strategies. This review will encompass findings from clinical trials, observational studies, and public health reports published in the past five years, emphasizing literature that highlights regional disparities, treatment outcomes, and evolving management paradigms. The inclusion criteria will focus on studies involving pregnant women with either gestational or pre-existing diabetes, where DR progression or treatment was a documented outcome. Through a comprehensive synthesis of current data, this review will provide insight into the nuanced challenges faced in managing DR during pregnancy and propose evidence-based recommendations to mitigate these risks. The significance of this review lies in its potential to contribute to a more unified and proactive approach in addressing DR among pregnant women. With diabetes rates soaring and maternal health increasingly threatened by vision-impairing complications, a nuanced understanding of the interplay between pregnancy and diabetic retinopathy is crucial. Timely identification and intervention can prevent long-term disability and improve quality of life for both mother and child. Moreover, this review seeks to raise awareness among clinicians, researchers, and policymakers about the urgent need for integrated care models and targeted public health interventions. By bridging current knowledge gaps, it paves the way for more effective and equitable healthcare delivery in the context of maternal diabetes care.



Thematic Discussion

The interplay between diabetic retinopathy (DR) and pregnancy has become a subject of critical clinical importance as the incidence of diabetes, particularly gestational diabetes mellitus (GDM), continues to rise globally. Synthesizing recent evidence reveals distinct yet interrelated themes that define the progression, risk factors, underlying mechanisms, and management of DR during pregnancy. This thematic discussion offers a comprehensive synthesis of emerging literature, highlighting the complex physiological and clinical landscape of DR in the context of maternal diabetes.

Epidemiological Trends and Risk Factors

The literature consistently identifies pregnancy as a pivotal modifier in the natural history of DR, particularly in women with pre-existing diabetes. Several maternal risk factors have been associated with the development of GDM, which may subsequently influence the trajectory of DR. These include elevated body mass index (BMI), advanced maternal age, polycystic ovarian syndrome (PCOS), prior

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history of GDM, macrosomic deliveries, stillbirths, smoking habits, and a family history of diabetes (8). Epidemiological findings estimate the prevalence of DR in women with GDM to range between 15% and 28%, with rates markedly higher in women with type 1 diabetes (up to 70%) compared to type 2 diabetes (14%–25%) during the first trimester (9–12). These disparities highlight the need for stratified risk assessment early in pregnancy. In Pakistan, DR prevalence in diabetic populations varies significantly, with some studies reporting rates as high as 41%, reflecting variations in healthcare access, awareness, and screening practices (10).

Pathophysiology and Progression Mechanisms

The progression of DR during pregnancy is multifactorial, involving a confluence of angiogenic, hemodynamic, and inflammatory processes. Placental hormones, particularly placental growth hormone (PGH), stimulate the insulin-like growth factor (IGF) axis, which is implicated in retinal neovascularization. Elevated levels of angiogenic mediators such as VEGF and IGF-1 have been observed in patients with proliferative DR (PDR) (13). However, angiopoietin levels appear to remain stable or even decrease during pregnancy, suggesting that a shift in the angiogenic-angiostatic balance, rather than absolute levels, may drive disease progression (13). Disruption in this balance, particularly with increased angiopoietin-2, promotes neovascularization in early pregnancy. Hemodynamically, pregnancy induces a hyperdynamic circulatory state, characterized by increased cardiac output and reduced vascular resistance. In the context of diabetes, these changes are poorly tolerated due to impaired autoregulation of retinal blood flow. Several studies have demonstrated increased retinal capillary perfusion during pregnancy, with enhanced macular and perivascular blood flow observed across trimesters (14,15). However, this is not universally beneficial, as elevated shear stress on retinal vessels may exacerbate endothelial injury and capillary leakage, compounding ischemic damage. Retinal hypoperfusion and ischemia, particularly in patients with long-standing diabetes, drive the release of pro-angiogenic factors and facilitate DR progression. Inflammation also plays a key role in DR pathogenesis during pregnancy. The placenta induces a pro-inflammatory state, characterized by increased levels of C-reactive protein (CRP), endothelin-1, and decreased anti-inflammatory markers such as glycodelin. These mediators contribute to endothelial dysfunction and compromise the integrity of the retinal vasculature (13,14). Interestingly, studies report that interleukin-6 (IL-6) levels remain consistent across diabetic and non-diabetic pregnant women, suggesting that not all inflammatory pathways are equally modulated during gestation (13).

Clinical Management and Diagnostic Strategies

The management of DR during pregnancy is shaped by the dual need to preserve maternal vision while ensuring fetal safety. Diagnostic tools such as fluorescein angiography (FA) remain controversial due to concerns about teratogenicity. Nevertheless, recent studies suggest that when performed before 15 weeks of gestation, FA poses minimal risk, although its use is often limited to cases where diagnostic clarity is essential (16,17). Laser photocoagulation remains the primary treatment for PDR and diabetic macular edema (DME) during pregnancy. Evidence supports the effectiveness of early intervention; one study reported stabilization of neovascularization in 64% of women treated prepartum, while another found that 57% of women treated in early pregnancy exhibited disease progression (18). These findings underscore the importance of preconception screening and treatment optimization, particularly in high-risk women. Intravitreal therapies, including anti-VEGF agents and corticosteroids, are generally avoided during pregnancy due to insufficient safety data. However, limited observational studies suggest that intravitreal steroids may be cautiously used in refractory DME, particularly when laser treatment is ineffective (19,20). The systemic absorption of these agents is minimal, but concerns persist regarding potential fetal exposure and adverse outcomes. Surgical interventions such as vitrectomy are reserved for severe cases where vision is at immediate risk. Local anesthetics such as lidocaine and prilocaine are considered safe during pregnancy (FDA categories A and B), while agents like bupivacaine and mepivacaine (category C) should be avoided due to associations with fetal bradycardia (21,22). Sub-Tenon's anesthesia is often preferred to avoid systemic complications and minimize fetal exposure.

Gaps, Controversies, and Future Directions

Despite advances in understanding the pathophysiology and management of DR during pregnancy, several gaps remain. One major limitation is the lack of pregnancy-specific guidelines for DR management. Most recommendations are extrapolated from non-pregnant populations, failing to account for the unique physiological and pharmacokinetic changes during gestation. Moreover, evidence regarding the safety and efficacy of anti-VEGF therapy and corticosteroids in pregnant women is scarce and primarily limited to case reports or small series. Another area of controversy is the optimal timing and frequency of retinal screening during pregnancy. While preconception screening is widely endorsed, there is variability in follow-up intervals, particularly in resource-limited settings. Furthermore, discrepancies exist in the definition and grading of DR across studies, complicating efforts to establish standardized management pathways. This review also highlights the need for longitudinal studies examining postpartum outcomes in women with

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DR. Although some regression of DR is observed after delivery, long-term visual outcomes and the potential for recurrence in subsequent pregnancies remain poorly understood. Investigations into the molecular mechanisms linking GDM with DR progression may also yield therapeutic targets, potentially allowing for safer and more effective interventions during pregnancy.

Table 1: Maternal and Fetal Complications Associated with Gestational Diabetes

Maternal problems	Fetal complication
C-section	Macrosomia
Eclampsia	Hypoglycemia
Type 2 DM in future	Respiratory issues
Cardiovascular disease	Stillbirth

Table 2: Prevalence and Patterns of Diabetic Retinopathy in Diverse Patient Populations

Title	Author /Year	Type of Study	Sample size	Frequency DR
Prevalence of microvascular complications among diabetic patients	Rahman and Zia (2004)		573	102(55%)
Incidence of retinal complications in a cohort of newly diagnosed diabetic patients	Martín et al. (2014)	Cohort study	6498	1650(28%)
Patterns of retinopathy among diabetic patients at tertiary care hospital	Ghouri et al. (2010)	Descriptive comparative	100	24(24%)
Prevalence of Diabetic Retinopathy among Type 2 Diabetes Patients in Pakistan	Sohail (2014)	Descriptive	500	207(41%)

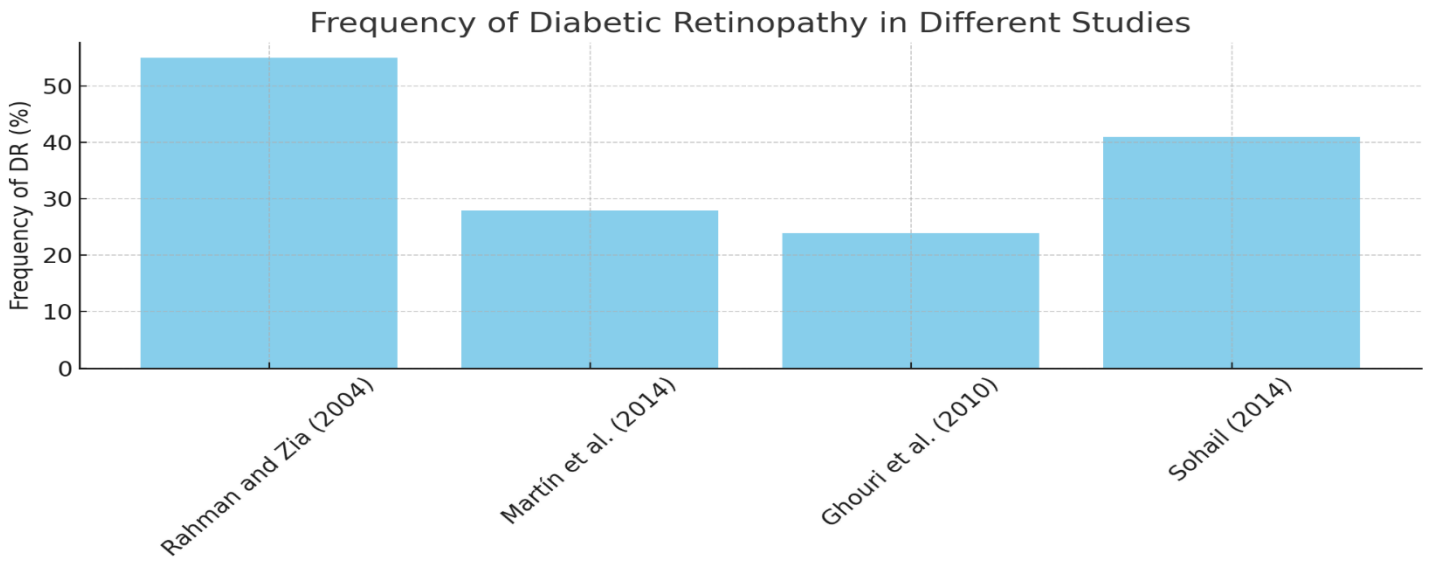

Figure 1 Frequency of Diabetic Retinopathy in Different Studies

Critical Analysis and Limitations

The literature on diabetic retinopathy (DR) during pregnancy, while growing in volume, remains subject to several critical limitations that constrain its interpretability, reliability, and broader clinical applicability. A common limitation observed across many of the reviewed studies is the relatively small sample size, often due to the ethical and logistical challenges of enrolling pregnant women in clinical research. Small cohorts restrict statistical power and reduce the ability to detect meaningful associations between gestational diabetes (GDM), DR progression, and treatment outcomes. For example, the majority of studies assessing laser therapy or retinal blood

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flow dynamics during pregnancy relied on observational or descriptive designs with sample sizes often under 100 participants, thereby limiting the robustness of the conclusions (23). Moreover, a notable paucity of randomized controlled trials (RCTs) in this domain severely impairs the strength of evidence. Ethical concerns about administering certain interventions to pregnant women often lead to the exclusion of RCTs, resulting in a reliance on retrospective analyses and case series. These study designs, while valuable for hypothesis generation, lack the methodological rigor to establish causality or inform clinical guidelines. Furthermore, short follow-up durations commonly reported in existing studies fail to capture the long-term progression or regression of DR postpartum. Most studies are confined to the antenatal period, with limited data on maternal visual outcomes beyond delivery, leaving clinicians without a comprehensive understanding of the temporal evolution of DR in this population (24).

Another critical limitation lies in methodological bias, particularly selection and performance bias. Many studies include only patients with pre-existing diabetes, often excluding those diagnosed with GDM during pregnancy, which narrows the scope of findings and limits the applicability to the broader diabetic population. This selective inclusion potentially underrepresents the true burden of DR in gestational cohorts. Additionally, several observational studies lack proper blinding and rely on subjective assessments of DR progression, increasing the likelihood of performance and detection bias. The absence of standardized protocols for assessing retinopathy severity, such as consistent use of Early Treatment Diabetic Retinopathy Study (ETDRS) grading or optical coherence tomography (OCT), further exacerbates variability in outcome reporting (12,16). Publication bias also appears to skew the current evidence base. Studies reporting significant or positive associations between pregnancy and DR progression are more likely to be published, while those with negative or inconclusive findings remain underreported. This trend limits a balanced understanding of the condition and may overstate the risks associated with pregnancy in diabetic populations. As a result, the evidence may not fully reflect the spectrum of clinical experiences, particularly among women who experience stable or regressed retinopathy during gestation.

Inconsistencies in outcome measurements represent another obstacle to cross-study comparisons. While some studies evaluate DR progression using fundoscopic examination alone, others incorporate fluorescein angiography, OCT, or Doppler imaging to assess retinal blood flow. The use of heterogeneous diagnostic tools and varying definitions of "progression" or "worsening" of DR complicates synthesis of findings and limits the potential for meta-analysis. Similarly, differences in how treatment success is measured—ranging from visual acuity preservation to anatomical improvements—further impair the ability to compare outcomes across therapeutic modalities such as laser photocoagulation, intravitreal steroids, or anti-VEGF agents (14,17). Perhaps one of the most significant challenges in interpreting current literature is the limited generalizability of findings. The majority of studies originate from high-income or urban settings with better access to ophthalmic and prenatal care. This raises concerns about the external validity of the results, particularly when considering low-resource environments such as rural regions of South Asia or sub-Saharan Africa, where DR screening and management during pregnancy may be vastly different. Cultural, genetic, and healthcare infrastructure differences likely influence the course and management of DR in pregnant women, but these variables are rarely addressed in existing literature (9,11). Collectively, these limitations underscore the need for more rigorous, well-powered, and methodologically sound research to inform clinical decision-making. Future studies should prioritize inclusive sampling of women with both pregestational and gestational diabetes, incorporate standardized diagnostic criteria, and adopt longer follow-up durations to capture postpartum changes in DR. Equally important is the need to generate data from diverse geographic and socioeconomic contexts to enhance the generalizability of findings and support the development of context-sensitive clinical guidelines.

Implications and Future Directions

The findings from this review highlight several critical implications for clinical practice, especially in the context of managing diabetic retinopathy (DR) in pregnancy. As the prevalence of gestational diabetes mellitus (GDM) rises globally, there is a growing need for a more standardized, proactive approach to ophthalmic care in pregnant women with pre-existing or gestational diabetes. The literature underscores the importance of early and repeated retinal evaluations, adjusted based on the severity of DR. For women with no or minimal DR, bi-trimester assessments may suffice, while those with moderate or severe proliferative diabetic retinopathy (PDR) require more frequent monitoring, sometimes monthly, to prevent complications. Tailoring the frequency of retinal evaluations to disease severity not only optimizes visual outcomes but also reduces the burden on healthcare systems by avoiding unnecessary interventions in low-risk individuals (13,22). From a clinical standpoint, integrating ophthalmic assessments into prenatal care workflows is paramount. The recommendation for a comprehensive dilated eye examination at the initial prenatal visit—particularly for those with known diabetes—has the potential to shift the paradigm from reactive to preventive ophthalmologic care. Early screening facilitates timely interventions, such as laser photocoagulation in cases of PDR, which has demonstrated efficacy in preventing vision-threatening complications during gestation (17). Furthermore, the recommendation to avoid triamcinolone and similar teratogenic agents reinforces the necessity of safer, evidence-backed pharmacologic strategies tailored for use during pregnancy. Importantly, DR should not be

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considered a contraindication for vaginal delivery, a clarification that can help guide obstetric decisions and reduce the frequency of unnecessary cesarean deliveries based on misinformed ocular risk perceptions (25).

These insights carry broader implications for policy development and the formulation of clinical guidelines. Currently, there is a conspicuous lack of standardized protocols specific to DR management during pregnancy. Most recommendations are extrapolated from general diabetes care, failing to address the unique pathophysiological shifts and pharmacologic considerations in pregnancy. This gap calls for the urgent development of evidence-based national and international guidelines that provide stratified care pathways based on DR severity, pregnancy stage, and comorbid conditions. Policymakers and healthcare authorities should also consider integrating DR screening into maternal health programs, particularly in low- and middle-income countries where access to ophthalmic care is limited. Universal retinal screening in pregnant women with diabetes, coupled with education on the risks of DR, could significantly reduce the incidence of preventable vision loss (9,11). Despite recent advances, several unanswered questions remain that merit further investigation. The long-term ocular outcomes of DR progression during pregnancy, particularly postpartum regression patterns, are poorly characterized. Additionally, the exact molecular and inflammatory mechanisms that differentiate DR progression in gestational versus pregestational diabetes remain unclear. More data are also needed on the safety and efficacy of intravitreal therapies during pregnancy, including anti-VEGF agents, which are often avoided despite their established benefits in the non-pregnant diabetic population. Understanding whether alternative delivery methods or drug formulations could minimize fetal exposure may pave the way for safer ophthalmic pharmacotherapy in this vulnerable group (14,26).

Future research should prioritize prospective, multicenter studies with adequate sample sizes and longer follow-up periods to capture both antepartum and postpartum DR trajectories. Ideally, randomized controlled trials (RCTs) should be designed to evaluate treatment modalities such as laser therapy, intravitreal agents, and emerging pharmacological compounds, though ethical considerations must be meticulously addressed. Furthermore, future studies should employ standardized diagnostic criteria, including uniform grading scales for DR severity and consistent use of imaging modalities like optical coherence tomography (OCT) or fluorescein angiography when appropriate. Incorporating diverse patient populations from various ethnic, geographic, and socioeconomic backgrounds will also enhance the generalizability of findings and help identify population-specific risk factors and treatment responses (10,27). In conclusion, this review underscores the need for a multidisciplinary, evidence-based approach to managing DR in pregnancy. It emphasizes the role of early detection, risk stratification, and individualized care planning in preventing adverse maternal and fetal outcomes. With appropriate clinical guidelines and targeted research, the burden of DR in pregnancy can be significantly mitigated, improving both vision and quality of life for affected women.

CONCLUSION

In summary, this review emphasizes the clinical significance of diabetic retinopathy (DR) during pregnancy, particularly its association with gestational and pre-existing diabetes. It highlights that pregnancy, through a cascade of hormonal, metabolic, vascular, and inflammatory shifts, can act as a catalyst for the progression of DR, with risk being markedly higher in individuals with poor glycemic control or pre-existing retinopathy. Current evidence supports early and tailored retinal assessments, especially during the first and third trimesters, alongside cautious therapeutic interventions such as laser photocoagulation and, in select refractory cases, intravitreal corticosteroids. However, the overall strength of evidence remains limited due to small sample sizes, short follow-up periods, and the lack of randomized trials, necessitating cautious interpretation. For clinicians, a multidisciplinary and patient-centered approach—emphasizing education, preconception counseling, risk stratification, and postpartum follow-up—is vital in optimizing maternal and fetal outcomes. Future research must focus on generating robust, longitudinal, and ethically sound data to better understand the safety and efficacy of pharmacological interventions, the long-term impact of DR in postpartum women, and the development of context-sensitive guidelines for diverse healthcare settings.

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Author Contribution

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M Mumtaz Chaudhry	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Rabia Akhtar	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Adila Anwar	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Samra Ahmed	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Qurat ul Ain Malik	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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