Diabetic Retinopathy in Pregnant Women with Pre-gestational Diabetes: An Ambispective Study in the Eastern Part of India on Prevalence, Progression, Risk Factors, and Outcomes

Original Article

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ABSTRACT

Background: Pregnancy significantly exacerbates diabetic retinopathy (DR) progression in women with diabetes mellitus (DM). Despite extensive research showing this deterioration, data on DR risk and progression in women with pre-gestational DM in eastern India remains sparse. This study focuses on addressing this data gap, aiming to inform clinical practices and healthcare policies.

Aim of The Study: To evaluate the prevalence and progression of DR in pregnant women with pre-gestational diabetes and analyze associated risk factors and pregnancy outcomes.

Method: This ambispective study included pregnant women with diabetes. The retrospective component collected personal and medical histories, while the prospective component systematically collected data during each trimester and postpartum. DR progression was graded using the ETDRS classification.

Of 44 patients, 6 (13.6%) were diagnosed with DR, with 5 cases of non-proliferative DR and 1 case of proliferative DR. The DR progression rate was 66.66%. Patients with DR had a significantly longer mean diabetes duration (10.5 years) compared to those without DR (4.84 years). Diastolic blood pressure was significantly associated with DR in the second and third trimesters. Among patients without DR, 63.1% had full-term deliveries, while 66.66% of those with DR had preterm deliveries.

Conclusion: This research highlights the need for data on DR prevalence and progression in pregnant women with pre-gestational diabetes in eastern India. The study emphasizes the importance of diabetes duration and diastolic blood pressure in DR progression during pregnancy. Good glycemic control, timely interventions, comprehensive monitoring, and multidisciplinary care are crucial for improving maternal and neonatal outcomes.

Key Words: Diabetes mellitus, diabetic retinopathy in pregnant women, non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, pre-gestational diabetes.

Received: 25 July 2024, **Accepted:** 11 December 2024.

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ISSN: 2735-3540, vol. 75, No. 4, December 2024.

INTRODUCTION

Pregnancy is a pivotal time, and for women with diabetes, it poses additional challenges, particularly regarding diabetic retinopathy (DR). The connection between pregnancy and the worsening of DR is well-documented, with women who have Type 1 Diabetes Mellitus (T1DM) being especially vulnerable to these ocular changes. The International Diabetes Federation highlights that diabetes affects about 17% of pregnancies globally, with gestational diabetes (GDM) making up 2.7% of these cases.[1] Despite this, there's a notable lack of information on the risk and progression of DR in women with pre-gestational diabetes, especially in the eastern states of India.

Our study aims to address this gap by examining the prevalence of DR among pregnant women with pre-gestational diabetes at our hospital. We analyzed the

DOI: 10.21608/ASMJ.2024.307118.1288

progression of the disease, identified risk factors for retinopathy, and assessed its impact on both maternal and fetal outcomes. This research seeks to fill the gap in knowledge regarding DR in pre-gestational diabetes in our area and contribute to better management strategies for this vulnerable population.

METHODOLOGY

This ambispective observational study took place in the Department of Ophthalmology at M.K.C.G. Medical College and Hospital in Berhampur. It involved pregnant women having history of diabetes who either visited the Eye OPD or were referred from other departments for diabetes-related eye evaluations. The study period extended from October 2018 to September 2020.

Pregnant women attending the Eye OPD or referred from other departments for ocular evaluation, who had a known history of diabetes mellitus (either Type 1 or Type 2) and met the American Diabetes Association's (ADA) 2011 diagnostic criteria—fasting blood glucose (FBS) ≥ 126 mg/dl, random glucose levels (RBS) ≥ 200 mg/dl, and HbA1c ≥ 6.5% at the time of diagnosis—were included in the study. Exclusion criteria included (1) patients with gestational diabetes mellitus and (2) patients meeting the inclusion criterion but unwilling to participate.

Before starting the study, we obtained approval from the Institutional Ethics Committee and informed consent from each participant. We collected personal information and detailed medical histories, including the age of onset of diabetes, current medications, diabetes control measures, past glycemic control documentation, and previous obstetric histories, as part of the retrospective component of the study.

In the prospective part of the methodology, we conducted a general examination for each patient, followed by a local examination that included torch light examination, slit lamp examination, visual acuity assessment with a Snellen's chart, and dilated fundus examination using indirect ophthalmoscopy. We took fundus photographs at the initial assessment, throughout all three trimesters, and three months post-delivery. We classified DR and its progression as per the Early Treatment Diabetic Retinopathy Study (ETDRS) classification. We defined progression as at least one stage of deterioration of DR and/or development of diabetic macular edema in at least one eye between two examinations.

Measurements of body mass index (BMI), blood pressure (BP - systolic and diastolic), hemoglobin levels, glycated hemoglobin (HbA1c), renal function tests (blood urea and creatinine), proteinuria, and fasting and postprandial blood sugar values were recorded at the initial presentation, throughout all three trimesters, and three months post-delivery. We also recorded data on gestational age and mode of delivery. After childbirth, we collected fetal data including birth weight, APGAR score at birth, and fetal malformations.

We compiled the collected data and performed statistical analysis applying Stata 14.0 (Stata Corp LLC, USA). Descriptive statistics, including arithmetic mean, standard deviation (SD), and frequency distribution, were determined for each parameter. Categorical variables were aggregated as frequencies and percentages, while quantitative variables were aggregated as mean ± SD or median. We compared cases with DR to those not having DR using the Mann–Whitney test for nonparametric data and the chi-square test for categorical variables. A two-tailed *P-value* of < 0.001 was measured statistically significant.

RESULTS

In our study, we included 44 patients with a median age of 28 years at conception and an average diabetes duration of 5.61 years. Among them, 25 were experiencing their first pregnancy. The study group consisted of 3 patients (6.81%) with Type 1 Diabetes Mellitus (T1DM) and 41 patients (93.18%) with Type 2 Diabetes Mellitus (T2DM). At the initial evaluation, 6 patients were diagnosed with diabetic retinopathy (DR), resulting in a DR prevalence of 13.6%.

All three patients with T1DM showed varying stages of DR at the start. Among the T2DM patients, 3 (6.81%) had DR. Of the 6 patients diagnosed with DR, 5 had Non-Proliferative Diabetic Retinopathy (NPDR) and 1 had Proliferative Diabetic Retinopathy (PDR), all presenting bilateral disease. Out of the 18 patients dependent on insulin, 4 developed DR.

Risk Factor Analysis: We compared systemic parameters across the three trimesters for all patients (see Table 1). The median age at conception for those with DR was 30.5 years, versus 28 years for those without DR. While the median age was greater in the DR patients, the difference was not statistically significant, indicating that the age of conception does not significantly impact DR development.

Table 1: Risk factor analysis of patients across the three trimesters. BMI- Body mass index, Hb- Haemoglobin, BP- blood pressure, FBS- fasting blood sugar, PPBS- post-prandial blood sugar, DR- diabetic retinopathy.

	1st Trimester			2nd Trimester			3rd Trimester		
	No DR (n=6)	DR (n=38)	*p-value*	No DR (n=6)	DR (n=38)	*p-value*	No DR (n=6)	DR (n=38)	*p-value*
Mean BMI (kg/m2)	26.40	27.62	0.5209	27.40	28.50	0.825	29.68	30.55	0.62
Mean Hb (g/dl)	11.20	10.12	0.5024	10.80	10.02	0.8932	10.92	10.98	0.3416
Mean Systolic BP (mm Hg)	118.14	116.50	0.8124	130.12	131.41	0.9872	130.24	135.86	0.3164
Mean Diastolic BP (mm Hg)	78.14	79.81	0.8462	80.0	94.2	0.0014	80.12	92.84	0.0052
Mean HbA1C (%)	6.48	8.82	0.0024	6.12	7.98	0.0033	6.21	7.40	0.0051
Mean FBS (mg/dl)	106	148	0.5816	110	145.26	0.0261	05.21	146.14	0.0558
Mean PPBS (mg/dl)	175.10	216.14	0.1896	172.94	204.60	0.0381	178.26	224.50	0.1186
Mean Sr. Urea (mg/dl)	22	25	0.1621	21.50	26.44	0.0578	22.41	24.98	0.2068
Mean Sr. Creatinine (mg/dl)	0.62	0.59	0.8291	0.56	0.57	0.9861	0.60	0.49	0.3016
Proteinuria (mg/dl)	1	0	0.5081	1	1	0.8931	1	1	0.8931

The average duration of diabetes in patients with DR was 10.5 years, whereas it was 4.84 years in those without DR. This difference was statistically significant, with a *P-value* of 0.0015, showing a striking correlation between the duration of diabetes and DR development. No significant associations were found between DR occurrence and gravida, prior live births, or abortions.

When examining systemic parameters by trimester, diastolic blood pressure (BP) was significantly correlated with DR in the second and third trimesters, with *P-values* of 0.0014 and 0.0052, respectively suggesting a more robust link in the second trimester. Additionally, 17 patients (38.6%) had pregnancy-induced hypertension (PIH).

No link was found among preconception HbA1c levels and DR presence, although mean HbA1c values were significantly greater in the DR group across all trimesters. Other factors, such as body mass index (BMI), hemoglobin levels, systolic BP, FBS, postprandial blood sugar (PPBS), serum urea, creatinine levels, and proteinuria, showed no significant relationship with DR.

Progression of DR During Pregnancy During the study period, 3 patients with NPDR and 1 patient with PDR experienced a worsening of their condition, resulting in a DR progression rate of 66.66%. No new cases of DR were reported. Among the 4 patients whose DR worsened, 3 were on insulin therapy. Two patients progressed to severe NPDR and PDR and were advised to undergo urgent photocoagulation based on AAO guidelines[2]. Following this treatment, no further progression or regression of DR was observed during and after pregnancy. These patients were monitored for up to three months postpartum, with no spontaneous DR regression noted (see Table 2).

Table 2: Summary of cases with diabetic retinopathy. DM- diabetes mellitus, BP- blood pressure, NPDR- Non-proliferative diabetic retinopathy, LSCS - Lower segment caesarean section, PROM- Premature rupture of membranes, NICU- Neonatal intensive care unit, OHA- Oral hypoglycaemic agents, PIH- Pregnancy induced hypertension, OU- oculus uterque (both eyes), OS- oculus sinister (left eye).

AGE	TYPE OF DM	DURATION OF DM	Glycemic control status before pregnancy	Previous Pregnancy	Control status during current pregnancy	Status of DR during and after pregnancy	Pregnancy Outcome
36 years	Type 2	10 years on insulin	Poor HbA1C – 9.6%	Normal full-term delivery	Poor control of sugar and BP HbA1c – 10.5% PIH	Moderate NPDR on first examination, Progressed to severe NPDR in 3rd trimester, Adv for urgent laser photocoagulation. On post-partum examination severe NPDR, VA – 6/9,6/9(p)	Preterm delivery at 33weeks, Emergency LSCS for fetal distress
30 years	Type 1	12 years on insulin	Good HbA1C - 5.8%	No previous conception	Good glycemic control	Mild NPDR on first examination, No progression during pregnancy, Stable post-partum	Preterm delivery at 30 weeks due to PROM, NICU care needed
31 years	Type 2	10 years on OHA	Good HbA1c – 6.2%	One spontaneous abortion	Good glycemic control	Moderate NPDR with 6/6 VA throughout pregnancy and post-partum	Full term delivery, No fetal malformation
26 years	Type 1	9 years on insulin	Good HbA1c – 5.9%	No previous conception	Good glycemic control, PIH	Mild NPDR with VA 6/6 in 1st and 2nd trimester, Progress to moderate NPDR with macular oedema (OU) in 3rd trimester with VA – 6/12, Post-partum – Moderate NPDR (OU) with VA – 6/9	Full term delivery, No fetal malformation
33 years	Type 2	8 years on OHA	Good HbA1c – 5.0%	No previous conception	Good glycemic control	Mild NPDR in 1st trimester, progress to moderate NPDR in 2nd trimester, BCVA 6/9 throughout, No regression post-partum	Preterm delivery at 32weeks, Emergency LSCS for fetal distress, No malformation
35 years	Type 1	19 years on insulin	Poor control HbA1c – 7.2%	Normal full-term delivery	Poor glycemic control Hba1c – 8.6%, PIH	On first examination PDR (OS) and Severe NPDR (OD) VA – 6/9,6/12, Same picture in 2nd trim, In 3rd trimester VH (OS) and Severe NPDR (OD) with VA – 6/12, CF 2m. Adv for urgent PRP	Preterm delivery at 29 weeks due to PROM, No fetal malformations, NICU care was needed

Maternal and Fetal Outcomes: Outcomes were generally better for patients without DR (see Table 3). Specifically, 24 patients (63.1%) had full-term deliveries, 9 patients (23.68%) had preterm deliveries, 3 patients (7.89%) experienced pregnancy loss or abortion, and 2 patients (5.26%) had intrauterine deaths. Among patients with DR, 2 (33.33%) had full-term deliveries, while 4 (66.66%) had preterm deliveries. There were no cases of abortion or intrauterine death among the DR patients.

Table 3: Maternal and fetal outcome. DR- diabetic retinopathy.

	DR	No DR
Pregnancy loss/ Abortion	00	02
Full term delivery	02	24
Preterm delivery	04	10
Intra – uterine death	00	02

DISCUSSION

Studies reveal a wide range in the prevalence of diabetic retinopathy (DR) during pregnancy among women with pre-gestational diabetes, typically reported between 10% and 27%, although higher rates have been noted in some research.[3]

In Denmark, ***Rasmussen et al.*** discovered that 14% of women with Type 2 Diabetes Mellitus (T2DM) had DR during early pregnancy.[4] Similarly, J. ***Cassar et al.*** observed a 17.14% prevalence of DR among 70 diabetic patients.[5] ***Rehmaan et al.'s*** study in Saudi Arabia reported that 20.37% of 55 pregnant women with Type 1 Diabetes Mellitus (T1DM) had DR.[6] In France, ***Stalnikiewicz et al.*** documented a 27.3% prevalence of DR in 77 diabetic pregnant women.[7] Another study by ***Dibble et al.*** found a 34.5% prevalence of DR among 55 women.[8]

In a more focused study, J.B. ***Moloney et al.*** examined 53 pregnant women with T1DM and discovered that 62% had retinopathy at their initial checkup, with an additional 15% developing it as the pregnancy progressed, bringing the total prevalence to 77.4%.[9] Similarly, M. ***0*** found a DR prevalence of almost 63% among pregnant women with T1DM.[10]

It is essential to highlight that most of these studies were executed in high-income, developed countries. However, ***T. Makwana et al***. executed research in India and found a DR prevalence of 8%, marking it as the sole study from a low- to middle-income country.[3] Our study's findings align with those of ***Rasmussen et al.*** and ***Makwana et al.,*** showing a DR prevalence of 13.6%. Higher prevalence rates in some studies could be due to focusing solely on patients with Type 1 Diabetes Mellitus (T1DM). In contrast, our study included both T1DM and T2DM patients, with T1DM patients being fewer but having a higher likelihood of developing DR. This broader inclusion criterion might explain the variations in prevalence rates observed across different studies.

Additionally, our research suggests that the age of conception does not significantly impact the development of DR. According to our understanding, no studies contradict this finding. The mean duration of diabetes in patients with DR was 10.5 years, compared to 4.84 years in those without DR, a statistically significant difference with a *P-value* of 0.0015. This indicates a more robust connection between the duration of diabetes and the development of DR.

Our study emphasizes the significant role that the duration of diabetes plays in the development of diabetic retinopathy (DR) during pregnancy, corroborating findings from previous research. For instance, ***Jernald et al***. identified a statistically significant link among the duration of diabetes and the prevalence of DR.[11] Similarly, ***Kahn et al.*** and ***M. Horvat et al.*** reported robust correlations between the duration of diabetes and DR in pregnant women.[12,13] ***Ayed et al.*** also noted that the risk of developing and progressing DR during pregnancy is primarily influenced by how long a woman has had diabetes.[14] However, ***Egan et al.*** found no significant impact of diabetes duration on DR progression in their logistic regression model[15].

In our study, we observed no significant relationship between the presence of DR and factors like gravida, previous live births, and abortions. This aligns with observations from ***Klein et al.*** and ***Hemachandra et al.,*** who also reported no significant correlation between these obstetric factors and DR[16,17].

We found a significant association between diastolic BP and the presence of DR during the second and third trimesters, with *P-values* of 0.0014 and 0.0052, respectively. The association was notably stronger in the second trimester. This result is consistent with findings by T. ***Makwana et al.,*** who also observe a significant correlation between diastolic BP in the second trimester and DR.[3] Comparable findings were stated by Junko ***Toda et al.***[18] and ***Klein et al.*** However, ***Lauszus et al***. did not stated any significant correlation between blood pressure and DR, indicating some variability in findings across different studies[19].

In our study, 17 patients (38.6%) also experienced pregnancy-induced hypertension (PIH), which is similar to the 44% reported by ***Makwana et al***.[3] Other studies, such as those by ***Rosenn et al***., ***Rehmaan et al***., and ***Stalnikiewicz et al***., have also identified a significant association between PIH and the progression of diabetic retinopathy (DR) during pregnancy.[20,6,7] These findings highlight the essentiality of monitoring BP and PIH in pregnant women with diabetes as potential factors influencing DR progression.

Furthermore, our study found no significant association among preconception HbA1c levels and the presence of DR. Yet, the mean HbA1c values were higher in the DR group and were statistically significant across all three trimesters. This observation aligns with ***Tangjai et al***., who reported a strong relationship between HbA1c levels and DR in the over-all population.[21] Similarly, studies by ***Axer-Siegel et al***. and the Diabetes Control Complications

Trial Research Group demonstrated a robust correlation between poor glycemic levels and the progression of DR in both T1DM and T2DM.[22,23] These findings underscore the essentiality of maintaining good glycemic control, as indicated by HbA1c levels, to effectively manage DR.

Haukkamma et al. observed that diabetic retinopathy progressed in half of the cases during pregnancy, while the other half showed no changes.[24] Several studies have documented differing rates of diabetic retinopathy progression during pregnancy.[24] For example, ***Axer-Siegel et al***.[22] observed a progression rate of 77.5%, whereas ***Sameshima et al***.[25] documented a rate of 16.7%.

In our study, the rate of diabetic retinopathy (DR) progression aligned in line with the observations of ***Haukkamma et al***. and ***Axer-Siegel et al***.[24,22] Notably, three of the four patients who experienced DR progression during pregnancy were on insulin therapy. This observation is in agreement with that of ***Rasmussen et al.,*** who identified a link between DR progression and pre-pregnancy insulin use[4].

In our study, two patients progressed to severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR), necessitating urgent photocoagulation in line with American Academy of Ophthalmology (AAO) guidelines.[2] Following this treatment, no further progression or regression of DR was observed during or after pregnancy. This outcome is supported by studies from ***Cassar et al***. and ***Dibble et al***., which suggest that photocoagulation before pregnancy may help prevent rapidly advancing DR, and that proactive management during pregnancy can avert the worsening of proliferative retinopathy and related vision loss[5,8].

Patients in our study were monitored for up to three months postpartum, with no instances of spontaneous DR regression. These observations are consistent with research by ***Arun et al***., which also reported that pregnancy did not contribute to postpartum deterioration of retinopathy[26]. Additionally, studies by ***Hemchandra et al.*** and ***Arun et al.*** indicated that pregnancy did not elevate the risk of progressing to PDR or necessitate laser treatment at 5 and 10 years postpartum[17,26].

Li-Jie Xiang et al. conducted a meta-analysis involving 3,239 pregnancies to evaluate the impact of microangiopathy on unfavourable pregnancy outcomes in individuals with T1DM, finding a modest link between DR and preterm delivery.[27] Our study supports this observation, as nearly two-thirds of patients with DR experienced preterm births.

Our analysis highlights the substantial influence of DR on pregnancy end results, especially the elevated rate of preterm delivery among patients with DR. This relationship is likely due to a complex interaction of microvascular complications, systemic inflammation, and metabolic dysregulation, which are often present in diabetes and its related complications. These factors can negatively affect placental function and fetal development, leading to higher rates of preterm delivery.

Further, the observed high rate of preterm delivery in our cohort underscores the necessity for enhanced monitoring and management of pregnant women with DR. It suggests that these patients may benefit from multidisciplinary care strategies that include not only ophthalmologists, endocrinologists but also obstetricians specializing in high-risk pregnancies.

Our study offers important understanding into the prevalence and progression of DR among pregnant women with pre-gestational diabetes in the eastern regions of India. Nevertheless, there are various shortcomings that should be taken into account when analysing the results.

To begin with, the limited sample size of 44 participants may not fully represent the broader population, which limits the generalizability of our findings. Larger studies are necessary to validate these results. Moreover, since the study was carried out at our institution only, it may not capture regional differences in healthcare practices and patient demographics.

The ambispective design of the study, incorporating both retrospective and prospective data, introduces potential biases related to the accuracy and completeness of historical records. Moreover, the short follow-up period of three months postpartum may not capture the long-term progression of DR and its effects on maternal and neonatal health. Future studies should consider extended follow-up periods for a more comprehensive understanding of DR progression.

Furthermore, variability in the treatment and management of diabetes among participants was another limitation. Differences in glycemic control measures, including the types and regimens of insulin used, were not standardized, which could have impacted the outcomes. Detailed information on these measures is essential for understanding their influence on DR progression.

Despite these limitations, this study highlights key associations between DR progression and features like diabetes duration, diastolic BP in the second and third trimesters, and pregnancy-induced hypertension (PIH). These findings align with existing literature and emphasize the importance of integrated management strategies, including multidisciplinary care, to enhance end results for pregnant women with pre-gestational diabetes.

CONCLUSION

This observational study provides key insights into diabetic retinopathy (DR) in pregnant women with pre-gestational diabetes in eastern India. We observed a 13.6% prevalence of DR, with notable associations involving diabetes duration, diastolic blood pressure in late pregnancy, and pregnancy-induced hypertension (PIH). While our findings contribute valuable information, the study has certain shortcomings, including a limited sample size, a brief follow-up period, and the exclusion of gestational diabetes cases.

The results underscore the importance of maintaining good glycemic control, as indicated by elevated HbA1c levels in those with DR, and the need for timely interventions like photocoagulation for severe cases. Our findings suggest that DR should be viewed not just as a localized eye condition but as part of a broader systemic issue affecting both maternal and fetal health. Recognizing and managing DR in pregnant women is essential for preserving vision and improving overall pregnancy outcomes, including reducing the risk of preterm delivery.

Future research should aim to overcome these limitations by including larger sample sizes and longer follow-up periods. Additionally, exploring the influence of environmental factors could enhance the comparability of results. Addressing these aspects will help provide more comprehensive and actionable findings, leading to better clinical practices and healthcare policies for this vulnerable group.

In conclusion, our study supports existing evidence on the systemic implications of DR and its impact on pregnancy outcomes, particularly preterm delivery. These findings highlight the need for integrated management approaches and further research to improve care for pregnant women with DR, ultimately enhancing both maternal and neonatal health.

ACKNOWLEDGEMENT

We express our gratitude to all the faculty members, technical staff, and patients for their assistance, teamwork and energetic involvement in the study.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil.

AUTHOR CONTRIBUTIONS

All contributing authors have signed a declaration form confirming their contribution to the research as follows:

Rahul Singh, Shagufa Jamal, Suchitra Dash: Conceptualization, Methodology, Data Collection, Writing - Original Draft.

Charu Sagar: Data Analysis, Writing - Review & Editing.

Kanchan Verma: Supervision, Validation, Resources.

REDUNDANT OR DUPLICATE PUBLICATION

We confirm that this paper has not been published in its current form or substantially similar form elsewhere, including on any website. Additionally, it has not been accepted for publication elsewhere.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper, including financial or other relationships that could bias the results.

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