Original Article

Prevalence, progression, and outcomes of diabetic retinopathy during pregnancy in Indian scenario

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Purpose: The objective of this study is to evaluate pattern of diabetic retinopathy (DR) during pregnancy in females with pregestational diabetes mellitus (DM). **Methods:** This is an ambispective observational cohort study conducted at an Indian tertiary care centre. A total of 50 pregnant females with pregestational DM were included while those with gestational DM were excluded from the study. Ocular examination (inclusive of fundus photography) was conducted and systemic parameters (inclusive of Glycated hemoglobin) were assessed during each of the 3 trimesters and 3 months postpartum. The prevalence and progression of DR during pregnancy in the study cohort were the main outcome measures. **Results:** Three of the 50 patients had type 1 DM while 47 had type II DM. All the patients with type I DM were insulin dependent while 19 patients with type II DM were insulin dependent. Overall prevalence of DR was 8% (4/50); 2 cases had nonproliferative DR (NPDR), and 2 had proliferative DR (PDR). During the study period, worsening was seen in both the patients with PDR and one required vitrectomy. Mean visual acuity in patients with PDR decreased from 0.77 logMAR units at presentation to 1.23 logMAR at final follow-up. There was no change in the mean visual acuity of patients with NPDR. None of the patients with NPDR converted to PDR. There was no new onset DR in the patients without DR at presentation. Assessment of risk factors for DR revealed significantly higher duration of DM (14 ± 6.32 years vs. 3.43 ± 1.43 years, $P = 0.0008$). The median age was also higher in the DR patients (31 years vs. 29 years, $P = 0.32$). **Conclusion:** No new onset cases were seen during the course of pregnancy and no conversion from NPDR to PDR was seen; however, a worsening of the two PDR cases was observed. No cases of DR were seen in noninsulin-dependent DM. None of the four participants with DR showed a spontaneous resolution of DR postpartum. Patients with PDR and long-standing DM require careful observation during pregnancy. A registry of diabetic mothers should be set up for development of guidelines for managing such cases.

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Diabetic retinopathy (DR) is the most common microvascular complication of diabetes mellitus (DM), and pregnancy is well known to accentuate it.[1-3] Numerous studies have been done in developed nations and progression of DR during pregnancy has been documented very well.[4-7] In some cases, DR can accelerate quickly to advanced stages requiring surgery. For these reasons, screening protocols have been developed for sequential observation of pregnant females with DM, though these are not universal and are surrounded by controversies.[1-7] The presence of retinopathy has also been analyzed for its association with poor outcomes of pregnancy.[7-10] However, majority of these studies have been done in developed countries where primordial and primary prevention is much better as compared to a developing nation. The current study has been done in the perspective of a developing nation. We have aimed to evaluate the prevalence of DR in mothers with pregestational DM, the incidence of new-onset DR during gestation, and the clinical course and associated risk factors for DR in such cases.

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Methods

This is an ambispective observational cohort study conducted at a tertiary eye care center of Northern India between June 2015 and January 2017. The study was approved by the Institute Ethics committee (IECPG-72/27.11.2015), and written informed consent was obtained from all the patients.

A total of 50 pregnant diabetic females were evaluated during and after pregnancy for the presence and progression of DR. These patients were recruited from the departments of obstetrics and gynecology, endocrinology, and ophthalmology. All the cases had preexisting DM before the current pregnancy, while those with gestational DM were excluded from the study.

History with regard to age of onset of diabetes and control of diabetes was recorded. Body mass index, blood pressure (systolic and diastolic), hemoglobin, glycated hemoglobin (HbA1c), renal

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function tests (blood urea and creatinine), proteinuria, fasting and postprandial blood glucose values values were noted for all the females at presentation, during each of the 3 trimesters and 3 months postpartum [Table 1]. Following childbirth, fetal data were obtained for birth weight, Apgar score at birth, and presence of any fetal defects. Ocular examination was carried out at presentation, during each of the 3 trimesters and 3 months postpartum. Visual acuity was noted, and dilated fundus examination and clinical fundus photography (VISUCAM 500 ZEISS, Germany) were done. DR and its progression were graded according to the early treatment of DR study classification. If the patient had proliferative DR (PDR), standard pan-retinal laser photocoagulation was undertaken promptly.

The main outcome measures were prevalence and progression of DR. Risk factors for DR, and maternal and fetal outcomes were also analyzed. Statistical analysis was performed after compilation of data using software Stata 14.0 (StataCorp LLC, USA). Arithmetic mean, standard deviation (SD), and frequency distribution were calculated for all the descriptive parameters. Categorical variables were summarized as frequency (%). Quantitative variables were summarized as mean ± SD or median. Cases with DR were compared with those without retinopathy. For nonparametric data, Wilcoxon rank-sum test (Mann–Whitney test) was applied for analysis. Chi-square test/Fischer exact test was used to analyze two categorical variables. A two-tailed $P < 0.001$ was considered statistically significant.

Results

In this study, 23 patients were enrolled prospectively while retrospective data were obtained in some form from 27 patients. Nineteen (38%) were primigravid. Median age at conception was 29 years. Mean duration of diabetes was 4.28 years. Three cases (6%) had Type I DM, and 47 (94%) had Type II DM. All patients with type 1 diabetes had some form of DR. In patients with Type 2 DM, only 1 patient (2.13%) was noted to have DR during the study period. Twenty-six diabetic mothers were insulin dependent, and four of these developed DR. The overall prevalence of DR during the study was determined to be 8% ($n = 4$).

Progression of diabetic retinopathy and visual outcomes

Four patients were detected to have DR at presentation, of which two had nonproliferative DR (NPDR) and two had PDR. The disease was always bilateral. Both patients with PDR worsened during pregnancy and 1 of these developed severe fibrovascular proliferation with vitreous hemorrhage and underwent surgery [Fig. 1]. Mean visual acuity in eyes with NPDR was 0.0 logMAR units at presentation and final follow-up. Mean visual acuity in eyes with PDR was 0.77 ± 0.83 logMAR units at presentation and 1.45 ± 1.28 logMAR units at final follow-up (1 patient underwent surgery in left eye). Three months after the pregnancy, DR did not spontaneously regress in any patient.

Risk factors for diabetic retinopathy

Baseline parameters of mothers with and without DR are depicted in Table 2. The median age at conception was 31 years and 29 years in the group with DR and without respectively ($P = 0.3231$). The mean duration of diabetes was 14 ± 6.32 years in patients with DR whereas in patients without DR, the mean duration of diabetes was 3.43 ± 1.43 years. P value was statistically significant ($P = 0.0008$), and thus there was a strong association between the duration of DM and the presence

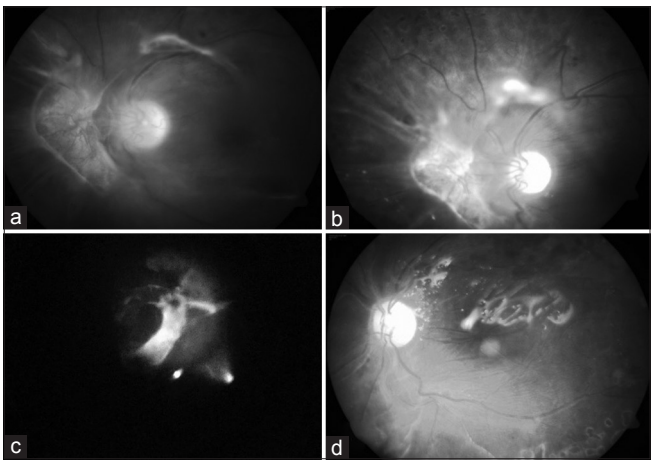

Figure 1: (a) Fundus photograph of the left eye of Case 3 [details in Table 2] showing aggressive nasal fibrovascular frond with tractional retinal detachment. (b) Postlaser photocoagulation fundus picture of the eye in Figure 1a shows regression of the front. (c) Intraoperative photograph of the left eye of Case 4 [details in Table 2] after core vitrectomy showing tense fibrotic bands with underlying subhyaloid hemorrhage. (d) Postoperative photograph of the same eye as in Figure 1c showing attached retina, laser spots, and silicone oil *in situ*

Table 1: Risk factors for diabetic retinopathy

	1st trimester			2nd trimester			3rd trimester		
	No DR	DR present	*P*	No DR	DR present	*P*	No DR	DR present	P
Mean BMI (kg/m^2)	26.34	27.525	0.5294	27.97	28.3	0.8745	29.74	31.5	0.5357
Mean hemoglobin (g/dl)	11.18	10.85	0.5036	10.95	10.87	0.8837	11.09	11.73	0.2932
Systolic BP (mmHg)	126.17	124.5	0.7049	127.91	128	0.9863	128.97	134	0.2272
Mean diastolic BP (mmHg)	81.28	82.5	0.76	79.77	82	0.6139	79.38	91.33	0.0017
Mean HbA1c (%)	6.50	6.77	0.6499	6.5	6.75	0.6360	6.3	6.2	0.7400
Mean FBS (mg/dl)	102.58	142.5	0.5721	103	138.25	0.0171	102.153	143.33	0.0427
Mean PPBS (mg/dl)	171.65	211	0.1858	171.29	203.25	0.0313	172.38	218.67	0.1175
Mean blood urea (mg/dl)	20	23.25	0.1557	20.77	25	0.0535	20.76	23.66	0.2025
Mean blood creatinine (mg/dl)	0.54	0.52	0.7984	0.54	0.55	0.9565	0.54	0.43	0.2289
Proteinuria	0	0		0	0		0	0	

DR: Diabetic retinopathy, BMI: Body mass index, BP: Blood pressure, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, HbA1c: Glycated hemoglobin

Table 2: Summary of cases with diabetic retinopathy

Age (years)	Pattern and duration of DM	Control before pregnancy	Previous pregnancies	Current pregnancy	Status of DR during and after pregnancy	Outcome of pregnancy
28	Type 1, 16 years, insulin dependence	Good control (HbA1c 6.2)	No previous conception	Good systemic control	Moderate NPDR with hemorrhages, from 1st trimester, stable postpartum. BCVA maintained at 6/6 in both eyes throughout pregnancy and postpartum	No adverse outcomes
30	Type II, 8 years	Good control (HbA1c 5.9)	No previous conception	Good systemic control	Moderate NPDR, first examined in the second trimester, dot blot hemorrhages. Hemorrhages decreased, but postpartum NPDR persisted. BCVA maintained at 6/6 in both eyes throughout pregnancy and postpartum	Emergency LSCS at term due to fetal distress. Fetal defect of the left axial polydactyly present
38	Type I, 22 years, insulin dependence	Poor control (HbA1c 7.9)	No previous conception	Poor systemic control of blood sugar and blood pressure during pregnancy (HbA1c 10.8), pregnancy-induced hypertension)	Complained of sudden diminution if vision during the first trimester. Diagnosed to have PDR in both eyes with tractional retinal detachment in left eye, underwent laser photocoagulation in the second trimester, stable in the third trimester, postpartum developed vitreous hemorrhage, and tractional retinal detachment in the right eye. Presenting BCVA in 1st trimester: RE-6/12, LE-6/24 2nd trimester: RE-6/12, LE-counting fingers at 1/2 m 3rd trimester: RE-6/24, LE-6/24 Postpartum RE-counting fingers, LE-6/18	Preterm birth at 35 weeks. No adverse fetal outcome
28	Type I, 10 years, insulin dependence	Poor control (HbA1c 10.1)	One spontaneous abortion	Poor control of blood sugars during pregnancy	Diagnosed to have PDR with fibrous frond in both eyes at optic disc in the first trimester, underwent laser photocoagulation in the right eye, vitrectomy with silicone oil injection done during 14th week of pregnancy in the left eye. Presenting BCVA in 1st trimester: RE-6/9 LE-counting fingers at 1/2 m Postpartum: RE-6/12, LE-hand motions close to face (oil-filled eye)	Spontaneous abortion at 15 weeks (excluded from analysis accordingly)

DR: Diabetic retinopathy, DM: Diabetes mellitus, NPDR: Nonproliferative DR, PDR: Proliferative DR, LSCS: x cesarean section, BCVA: Best-corrected visual acuity, RE: Right eye, LE: Left eye, HbA1c: Glycated hemoglobin

of DR. There was no significant association of the presence of DR with the gravida, number of live births, and previous history of abortions. Systemic parameters were compared between these patients separately for all the trimesters. The diastolic blood pressure was found to have a significant association with presence of DR in the third trimester ($P = 0.0017$) while the rest

of the parameters did not have significant association [Table 1]. Nearly 44% of the cases also had concurrent pregnancy-induced hypertension (n = 22/50). There was no association (P = 0.1052) between HbA1c before conception and presence of DR. However, the mean value of HbA1c was higher in the group with DR.

Maternal and fetal outcomes

Eight patients had either an abortion or a pregnancy loss. In mothers without retinopathy, full-term delivery, preterm delivery, intrauterine death, and abortions were noted in 77.9%, 4.4%, 6.7%, and 11.1%, respectively. In patients with DR (n = 4), 2 had full-term delivery, 1 had preterm delivery, and 1 had abortion. Outcomes in patients with DR have been summarized in Table 2.

Discussion

In this study, the overall prevalence of DR was 8% (4/50); 2 cases had NPDR while 2 had PDR. Worsening was seen in both the patients with PDR, whereas patients with NPDR remained stable. None of the patients with NPDR converted to PDR. Assessment of risk factors for DR revealed significantly higher duration of DM in patients with worsening of PDR during pregnancy. Higher diastolic blood pressure was found in the last trimester in patients with DR. Spontaneous resolution was not noted in any of the patients.

Worsening of DR during pregnancy is well documented in women with pregestational DM.[11] Most of the previously done studies on progression of DR in such cases have been done in developed nations and show high rates of progression of retinopathy.[12-27] To the best of our knowledge, this is the first study on DR in pregnancy from a low-middle income country.

Unlike in the past, recent studies show lesser progression rates [bottom half of Table 3]. The cohorts analyzed in most of the previous studies has chiefly comprised of either type 1 DM or insulin dependent patients [Table 3].[12-27] In our study, nearly half (22/50) were insulin dependent, and only 3/50 had type 1 DM. We analyzed these factors for their OR of association with DR and found Type 1 cases and insulin-dependent cases to have higher OR though the CI was large. Omori *et al*. conducted a study on 207 deliveries comprising both the types of DM cases in Japan and found

Table 3: Progression of diabetic retinopathy in pregnant patients

Study	Sample size	Study design	Worsening of DR in pregnancy
Current study, 2017*,#	50	New Delhi - 1.5 years, ambispective	4% overall progression, DR progression 50%
Horvat *et al*., 1980[12] (course after delivery in both latent and clinical diabetics)	279	Melbourne - 12 years, prospective	Progression in, normal fundus: ~10%, background DR: ~25%
Moloney and Drury, 1982*[13]	53	Ireland - 2 years, prospective	Hemorrhages found to increase maximally
Dibble *et al*., 1982*[14]	55	Utah, prospective	16% with background retinopathy and 86% with proliferative progressed
Ohrt, 1984[15]*,$ (resultsafterpregnancy)	100	Denmark - 10 years, prospective	Proliferative retinopathy increased from 2 to 6 cases
Phelps *et al*., 1986*[16]	38	Chicago - 5 years, prospective	55% progression
Klein *et al*., 1990[11]	133	Wisconsin - 4 years, prospective	OR of 2.3 for progression
Rosenn *et al*., 1992*[17]	154	Ohio - 14 years, prospective	30% progression
Axer-Siegel *et al*., 1996*[18]	65	Israel - 5 years, prospective	78% progression
Chew *et al*., 1995*[19]	140 (with no PDR)	United States - (DIEP study), prospective	OR for mild NPDR or less=1, moderate NPDR=5.7
Lövestam-Adrian *et al*., 1997*[20]	86	Sweden - 9 years, retrospective	No retinopathy showed~25% progression
DCCT, 2000*[21]	180	North America - 6.5 years, ancillary report	1.6×risk of worsening (after intensive treatment)
Temple *et al*., 2001*[22]	179	United Kingdom - 8 years, prospective	Progression of retinopathy is uncommon
Rahman *et al*., 2007*[23]	54	Saudi Arabia - 4 years, retrospective	Progression in 24%
Arun and Taylor, 2008*[24]	59	United Kingdom - 5 years, prospective	Not associated with postpartum worsening of DR
Vestgaard *et al*., 2010*[25]	102	Copenhagen - 2 years, prospective	Progression in 27%
Rasmussen *et al*., 2010#[26]	80	Denmark - 5 years, prospective	Progression in 14%
Egan *et al*., 2015*,#[27]	185	Ireland - 6 years, prospective	Progression in 26%

*Type 1 DM or insulin-dependent diabetes mellitus only, #Type 2 DM, $97/100 patients were treated with insulin. DR: Diabetic retinopathy, NPDR: Nonproliferative DR, PDR: Proliferative DR, OR: Odds ratio

10% of insulin-dependent cases to have PDR while only 4% of noninsulin dependent cases developed PDR.[28] On the other hand, Egan *et al*. evaluated 185 patients and did not find type or duration of DM to have a significant effect on the development of DR in a logistic regression model.[27] In our study, however, duration of DM was found to have a significant impact on the development of DR [Table 1].

The prevalence of retinopathy reported in diabetic pregnancies is 10%–27%,[29] while in our study, it was found to be 8%. DR is influenced by multiple factors including the pregnancy itself, glycemic control before and during pregnancy, and the presence of previous retinopathy. Maternal complications such as pregnancy-induced hypertension, diabetic nephropathy, and preeclampsia are also associated with progression of retinopathy.[20,28,30] A major challenge to improving outcomes is to ensure optimal glycemic control at the time of conception and to maintain this throughout the pregnancy.[31,32] Systemic factors were well controlled in most of our patients, and it can be seen in Table 2 that patients with poor control and PDR fared the worst in our cohort. Hence, patients with advanced forms of preexisting DR and those with poor systemic control should be evaluated more frequently by the ophthalmologist during pregnancy. In this regard, recommendations for retinopathy screening and management in pregnancy vary significantly. The American Diabetes Association advises an eye examination in the first trimester with close follow-up throughout pregnancy.[10] The National Institute for Health and Clinical Excellence in the United Kingdom recommends retinal assessment following the first antenatal clinic appointment and again at 28 weeks if the first assessment is normal. If any DR is present, an additional retinal assessment should be performed at 16–20 weeks.[31] Perhaps, regional data as provided by this study should be taken into account and local screening guidelines should be developed.

Before the advent of laser photocoagulation, proliferative retinopathy was a contraindication to pregnancy because of the substantial risk of severe visual loss, so that women with diabetes who became pregnant were advised to consider termination.[33] With the use of laser photocoagulation and the establishment and recognition of high-risk characteristics,[34] the likelihood of visual loss has been reduced. Appropriate treatment of preexisting PDR with photocoagulation before pregnancy may protect against rapidly progressive PDR during pregnancy. A study of patients with proliferative retinopathy detected in early pregnancy and subsequently treated by laser showed that 58% experienced significant progression and visual loss. On the other hand, only 26% of patients in whom retinopathy was diagnosed and treated before the onset of pregnancy showed the progression of retinopathy during an ensuing gestation.[35] In the study by Rahman *et al*., in three out of the four patients who received laser treatment for PDR before pregnancy, the retinopathy remained stable throughout pregnancy.[23] The fourth patient with the progression of retinopathy required further laser treatment and responded well, maintaining good vision. The number of patients with PDR that were treated before pregnancy in the study was too small to draw any valid conclusions regarding the benefits of treatment. In the study by Temple *et al*., only four women (2.2% pregnancies) required laser therapy for the development of proliferative retinopathy.[22] However, in our study, 50% of the patients with DR had established PDR and worsened despite laser.

In our study, as stated prior, duration of diabetes was found to be significantly associated with DR. The median age at conception was also higher in the group with DR, though this result was not statistically significant. We believe that there is an urgent need to promote early pregnancy planning among women with DM for optimal visual outcomes. Specialized prepregnancy clinics and multidisciplinary antenatal clinics should aim to address this rather than only aiming for good systemic control. Similar suggestions have also been made previously.[18]

Limitations

As the number of patients with DR was too small in our study, it is possible that the results regarding risk factors could have been underestimated. Further, all the patients in the prospective group could not be seen before pregnancy for assessment of baseline retinopathy. In addition, the numbers of patients with retinopathy were less to analyze associated risk of abortion and poor fetal outcomes. However, as per our findings, perhaps young women with long-standing DM require timely counseling and complete ocular examination before conception. In the presence of severe DR, there may be a need to defer pregnancy until retinopathy is adequately controlled (with prompt treatment). Advocacy and counseling regarding the benefits of completing the family early in young women with diabetes is a concern that needs to be addressed with appropriately designed larger sized evaluations. It has been previously also seen that natural course of DM impacts the visual outcomes and that longer duration of DM and older age at the examination is associated with severity of retinopathy in younger-onset diabetic patients.[36] Extrapolating these findings to our subset of patients may simply reflect that pregnancy is a risk factor for worsening of the disease and worsening is most likely to occur in patients with long-standing DM.

Conclusion

To summarize, pregnant females with PDR and those with long duration of preexisting DM should be carefully monitored during pregnancy. PDR should be treated as early possible. Guidelines need to be developed for managing the pregnancy in women with untreated and advanced PDR. Our findings raise the issue of poor visual outcomes in older pregnant females with long-standing DM, and we recommend the development of a separate national registry and referral system for all young women with diabetes.

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Conflicts of interest

There are no conflicts of interest.

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