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Prevalence of diabetic retinopathy in women with pregestational diabetes during pregnancy and the postpartum

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Abstract

Background: Diabetic retinopathy (DR) may be affected by pregnancy. The majority of prevalence data regarding DR in pregnancy predate the advent of contemporary guidelines for diabetes management during pregnancy. This study reports DR prevalence and associated risk factors in women with pregestational diabetes during pregnancy and the postpartum in Australia.

Methods: A total of 172 pregnant women with type 1 (T1DM) or type 2 diabetes diagnosed pre-pregnancy were prospectively recruited from two obstetrics hospitals in Melbourne (November 2017–March 2020). Eye examinations were scheduled in each trimester, at 3-, 6-, and 12-months postpartum. DR severity was graded from two-field fundus photographs by an independent grader

utilising the Airlie House Classification. Sight-threatening DR (STDR) was defined as the presence of diabetic macular oedema or proliferative DR.

Results: Overall, 146 (84.9%) women had at least one eye examination during pregnancy. The mean age was 33.8 years (range 19–51), median diabetes duration was 7.0 years (IQR 3.0–17.0), 71 women (48.6%) had T1DM. DR and STDR prevalence during pregnancy per 100 eyes was 24.3 (95% CI 19.7–29.6) and 9.0 (95% CI 6.1–12.9); while prevalence in the postpartum was 22.2 (95% CI 16.5–29.3) and 10.0 (95% CI 5.4–17.9), respectively. T1DM, longer diabetes duration, higher HbA1c in early pregnancy, and pre-existing nephropathy were significant risk factors.

Conclusions: The prevalence of DR in pregnant women was similar to the non-pregnant diabetic population in Australia. One in nine participants had STDR during pregnancy and the postpartum, highlighting the need to optimise DR management guidelines in pregnancy given the significant risk of vision loss.

KEYWORDS

Australia, diabetic retinopathy, pregestational diabetes, pregnancy, risk factors

1 | INTRODUCTION

The prevalence of diabetes mellitus (DM) is likely to reach epidemic proportions in Australia and worldwide, which will result in a concurrent increase in the incidence of diabetic retinopathy (DR). DR is a leading cause of blindness among people of reproductive age and is thought to be worsened by pregnancy, an effect which continues up to 1 year postpartum.[1,2] The International Diabetes Federation estimates that pregnant women with pregestational diabetes account for 7.9% of global pregnancies with live births.[3] Although the rate is lower in Australia (1.1%),[4] it is projected to increase significantly with an increasing number of pregnant women with type 2 DM (T2DM).[5–7] Therefore, sequelae from the impact of pregnancy on DR will become a more significant public health problem, especially when clinical decisions in managing DR in pregnancy (particularly diabetic macular oedema) can be a challenge due to the limited treatment options in pregnancy.

Prior studies that have reported on DR prevalence have indicated increased rates of progression in pregnant women with pregestational diabetes. However, many are outdated (>20 years), have suboptimal methodologies and limited numbers of subjects. The reported DR prevalence in pregnancy thus ranges from 8%[8] to 63%[9] (double the prevalence in the non-pregnant population). The reported progression rates also vary significantly, and very few studies explicitly report the prevalence in the postpartum period. In Australia, only one study has been published in this field.[10] Horvat and colleagues studied pregnant women with 'latent' (now known as gestational) and 'clinical' (pregestational) diabetes from the Royal Women's Hospital, Melbourne and performed full routine ocular examinations during pregnancy and after delivery in 1967–1978. No DR was found in women with latent diabetes; however, among 172 clinical diabetic pregnant women, 47 (27.3%) had DR at baseline, 25 (14.5%) of whom demonstrated worsening during pregnancy.

In addition to the wide range of reported DR prevalence rates and the lack of contemporary data, most available publications have only studied women with type 1 DM (T1DM), with very few studies reporting the DR prevalence in pregnant women with T2DM. As T2DM is becoming more common in pregnant women in Australia,[11] the current evidence on DR prevalence is not reflective of, and may have limited applicability to, Australia's present-day population. More contemporary evidence is needed to update national DR guidelines for this unique and growing population. Herein, we report the prevalence of DR and sight-threatening DR (STDR) and its associated risk factors in women with pregestational diabetes during pregnancy and the postpartum in metropolitan Melbourne.

2 | METHODS

This study was a prospective cohort study. Among 221 pregnant women with T1DM or T2DM diagnosed

before pregnancy who attended a Diabetes Clinic at the Royal Women's Hospital or the Mercy Hospital for Women, 197 (89%) were recruited between November 2017 and March 2020. Participants were followed-up from their first trimester of pregnancy through to 12-months postpartum. Eye examinations were performed at one of two study-site clinics [the Melbourne Eyecare clinic (ME) and the Austin Repatriation Hospital (ARH)] to accommodate the different geographic areas of recruitment. Ten participants were excluded due to either miscarriage ($n = 8$) or because they moved residence and were no longer contactable ($n = 2$).

Ethics Committee approval was initially obtained from the University of Melbourne's Medicine and Dentistry Human Ethics Sub-Committee (Ethics ID: 1749108), followed by additional approvals from the Human Research Ethics Committees (HRECs) of the local hospitals involved in this study. Research procedures were performed according to the principles of the Declaration of Helsinki and each participant provided written informed consent.

2.1 | Eye examination procedure

Diabetic eye screening examinations were scheduled during the first, second and third trimesters, then at 0–13 weeks, 14–26 weeks, and 27–52 weeks postpartum. Comprehensive eye examinations, including assessment of best-corrected visual acuity, intraocular pressure, abnormalities in the external eye, anterior segment and posterior segment, were performed by trained examiners using a standardised protocol. In each visit, 2-field (optic disc-centred and macula-centred), 45°, colour fundus photographs and an optical coherence tomography (OCT) scan centred on the macula were obtained from each eye after pupil dilatation using 1% tropicamide eye drops. Although the eye clinics used different cameras [DRI OCT Triton, Swept Source OCT (Topcon Corp.) at the ME; VISUCAMPRO NM fundus camera (Carl Zeiss) and OCT Spectralis (Heidelberg Engineering Inc.) at the ARH], the images are considered comparable.[12] For participants who preferred to have eye examinations at their local clinics due to the government-mandated COVID-19 restrictions, similar eye data were collected from these clinics.

2.2 | DR and diabetic macular oedema grading

DR was graded from the fundus photographs by an independent grader (MBS) masked to the participants' details. DR severity was assigned for each eye-visit according to the modified Airlie House Classification,[13] and categorised as follows: no DR [early treatment diabetic retinopathy study (ETDRS) levels 10 and 15], mild non-proliferative DR (NPDR; levels 20–35), moderate NPDR (levels 43–47), severe NPDR (level 53) or proliferative DR (PDR; levels 61–85). If no fundus photography was taken during the eye examination (primarily at the local clinics) or the photography was ungradable, DR severity was assigned using clinical grading from the optometrist or ophthalmologist who saw the participant as part of their routine clinical care. The agreement between five-level severity DR grading and binary DR grading (presence vs. absence of DR or STDR) by clinicians (extracted from examination reports) and the independent grader (from fundus photographs) was estimated as 97.7% and 84.5%, respectively.

The presence of diabetic macular oedema (DMO) was determined from the quantitative data and morphology assessment of the OCT scan by two ophthalmologists (RCAS at ME; XF at ARH). The presence of DMO was defined as having a central sub-field thickness (CSFT) value two standard deviations beyond the normal mean or the presence of intra-retinal fluid (IRF) or sub-retinal fluid (SRF) within the OCT scan, regardless of the CSFT.[14] CSFT is defined as the distance between the inner limiting membrane (ILM) and the boundary of the outer layer and the retinal pigment epithelium (OS/RPE) within a 1-mm diameter of an ETDRS grid.[12] DMO diagnoses for visits at local clinics were made based upon the shared OCT results and the clinical diagnosis.

2.3 | Demographic and clinical data collection

At the baseline visit, the participant's demographic and clinical data regarding general health, history of diabetes and pregnancy were collected through a structured questionnaire. Blood pressure, height and weight measurements were performed at the first antenatal visit using a standardised method. Blood pressure (BP) was also recorded at each eye-exam visit. A diagnosis of hypertensive disorders in pregnancy, which is defined as the presence of any one of chronic hypertension, gestational hypertension, preeclampsia or eclampsia, was made according to criteria in the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) guidelines.[15] Body mass index (BMI) in early pregnancy was calculated using the formula (BMI = weight [kg]/height [m^2]) and categorised as underweight (BMI <18.5 kg/m^2), normal (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2) or obese (BMI >30 kg/m^2).[16] Pathology results, including glycated haemoglobin A1c (HbA1c) and albumin/

creatinine ratio (ACR) or protein/creatinine ratio (PCR), were retrieved from tests done as part of routine clinical care pre-pregnancy (if any), in each trimester, and up until 12-months postpartum. All data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the University of Melbourne.[17,18]

2.4 | Calculating the prevalence

Three outcomes of interest were assessed: (1) prevalence of DR, which included any cases with ETDRS levels 20 to 85; (2) prevalence of DMO and (3) prevalence of STDR, defined as the presence of PDR or DMO. Each prevalence was calculated at eight time periods: (1) Trimester 1 (from around conception to 13 weeks of gestation); (2) Trimester 2 (from 14 weeks to 27 weeks of gestation); (3) Trimester 3 (from 28 weeks of gestation to delivery); (4) 3-months postpartum (from delivery to 13 weeks postpartum); (5) 6-months postpartum (from 14 to 26 weeks postpartum); (6) 12-months postpartum (from 27 to 52 weeks postpartum); (7) Pregnancy (from around conception to delivery); and (8) Postpartum (from delivery to 52 weeks postpartum).

Data from eye-visits within each time period was used to calculate the prevalence in each period of interest (as detailed above). In situations where a participant had more than one eye-visit within the time of interest (e.g., within a particular trimester), the worst (i.e., most severe eye disease) eye-visit contributed to the prevalence calculation. This approach was also applied when calculating the prevalence during pregnancy and the postpartum, using the most severe grading per eye at any eye examination from each period.

2.5 | Statistical analysis

Statistical analyses were carried out using Stata IC 15.1 for Windows (College Station, TX, USA). The normality of the distribution of each continuous variable was tested with the Skewness and kurtosis test for normality, the Shapiro–Wilk test and the Shapiro-Francia test to reach a consensus before presenting the summary statistics as means and 95% confidence intervals (95% CI), or medians and interquartile ranges (IQR), as appropriate. Demographic characteristics were compared between dichotomous analytical groups of interest, such as diabetes type or women who did and did not have STDR during pregnancy, using the unpaired *t* test, Wilcoxon rank-sum test or Fisher's exact test. Differences were considered to be statistically significant at a two-sided *p*-value of <0.05. Prevalence rates were calculated and presented as the number of cases per 100 eyes, with 95% CIs for these rates calculated using the Agresti-Coull, Wilson or Hanley and Lippman-Hand methods, as appropriate.

3 | RESULTS

3.1 | Study participants' demographics

Overall, 146 out of 172 participants had at least one eye examination during pregnancy and were eligible for the final analysis. Participant characteristics are shown in Table 1. Mean maternal age was 33.8 years (95% CI 33.0–34.6), median diabetes duration was 7.0 years (IQR 3.0–17.0), and median HbA1c at the first measurement during pregnancy was 6.4% (IQR 5.8–7.4). A history of hypertension, diabetic nephropathy, thyroid disease and dyslipidaemia before pregnancy was found in 17, 3, 37 and 27 participants, respectively. Two participants (four eyes) had treated PDR predating their pregnancy.

This cohort comprised 71 (49%) participants with T1DM and 75 (51%) participants with T2DM. Most participants with T1DM were of Caucasian ethnicity (82%), whereas participants with T2DM were mostly Asian and Indian (60%). Participants with T1DM were slightly but significantly younger ($p < 0.001$), had a much longer duration of diabetes ($p < 0.001$), had a higher HbA1c at the first measurement during pregnancy ($p = 0.017$) and had a lower early pregnancy BMI ($p = 0.009$) compared with participants with T2DM. The timing of the first HbA1c measurement during pregnancy was earlier in pregnancy for participants with T1DM than the T2DM group [median 8 weeks (IQR 6–13) vs. 11 weeks (7–19); $p = 0.002$].

Across all eye-visits, fundus photography was not taken or ungradable in 135 eye-visits (out of 758 eye-visits), most of which were eye examinations performed at local eye clinics, and the DR grading for these visits was therefore assigned based on the clinical diagnosis. Three ungradable photographs were from a participant who had a congenital cataract in her left eye and attended three eye-exams during the study period. Eye-visits without fundus photographs had more severe DR grades and a higher proportion of DMO than eye-visits with gradable photographs (*p*-values <0.001; Table 2).

3.2 | Prevalence of DR and STDR during pregnancy and its risk factors

During pregnancy, 64, 103 and 83 participants had at least one eye-visit at the first, second and third trimester, respectively. The overall prevalence rates of DR, DMO

TABLE 1 Demographic characteristics of participants with at least one eye examination during pregnancy, by type of diabetes

	Overall ($n = 146$)	T1DM ($n = 71$)	T2DM ($n = 75$)	p-value[a]
Age at enrolment (years), mean (95% CI)	33.8 (33.0–34.6)	32.3 (31.1–33.5)	35.3 (34.3–36.3)	<0.001
Gestational age at the first exam (weeks), median (IQR)	14.5 (11.0–22.0)	14 (10.0–21.0)	16 (11.0–24.0)	0.192
Duration of diabetes at enrolment (years), median (IQR)	7.0 (3.0–17.0)	17.0 (8.0–23.0)	4.0 (1.8–6.0)	<0.001
HbA1c in early pregnancy[b] (%), median (IQR)	6.4 (5.8–7.4)	6.8 (6.1–7.5)	6.1 (5.7–7.3)	0.017
Ethnicity, *n* (%)				<0.001
ATSI	1 (0.7)	0	1 (1.3)	
South Pacific Islanders	4 (2.7)	0	4 (5.3)	
Caucasian	68 (46.6)	58 (81.7)	10 (13.3)	
Asian	51 (34.9)	6 (8.5)	45 (60.0)	
Other	22 (15.1)	7 (9.8)	15 (20.0)	
Education, *n* (%)				0.146
Primary school	3 (2.1)	0	3 (4.0)	
Secondary school	20 (13.8)	10 (14.3)	10 (13.3)	
Trade certificate	17 (11.7)	11 (15.7)	6 (8.0)	
Diploma	18 (12.4)	5 (7.1)	13 (17.3)	
University degree	87 (60.0)	44 (62.9)	43 (57.3)	
BMI in early pregnancy[c] (kg/m^2), *n* (%)				0.009
< 25	41 (33.9)	26 (44.1)	15 (24.2)	
25–29 (overweight)	26 (21.5)	15 (25.4)	11 (17.7)	
≥ 30 (obese)	54 (44.6)	18 (30.5)	36 (58.1)	
History of medical condition (present)				
Chronic hypertension, *n* (%)	17 (11.6)	5 (7.0)	12 (16.0)	0.122
Diabetic nephropathy, *n* (%)	3 (2.1)	3 (4.2)	0	0.112
Other conditions,[d] *n* (%)	58 (39.7)	25 (35.2)	33 (44.0)	0.312

Abbreviations: ATSI, Aboriginal and Torres Strait Islander People; BMI, body mass index; DM, diabetes mellitus; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

[a]*p*-value relates to the difference between two groups examined using *t* test, Wilcoxon rank-sum test or Fisher's exact test as appropriate to the distribution of each variable.

[b]Total number for HbA1c data: 62 women with T1DM and 63 women with T2DM.

[c]Total number for BMI data: 59 women with T1DM and 62 women with T2DM.

[d]Includes thyroid diseases, heart disease and dyslipidaemia.

TABLE 2 Comparison of characteristics between eye-visits with no photographs/ungradable photographs and with gradable photographs

	Fundus photographs unavailable or ungradable ($n = 135$ eye-visits)	Fundus photographs gradable ($n = 623$ eye-visits)	p-value[a]
DR severity, *n* (%)			<0.001
None	52 (38.5)	504 (80.9)	
Mild NPDR	34 (25.2)	70 (11.2)	
Moderate NPDR	11 (8.1)	26 (4.2)	
Severe NPDR	8 (5.9)	0	
PDR	30 (22.2)	23 (3.7)	
DMO[b] (present), *n* (%)	38 (28.6)	28 (4.5)	<0.001

Abbreviations: DMO, diabetic macular oedema; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

[a]*p*-value relates to the difference between the two groups examined using *t* test, Wilcoxon rank-sum test or Fisher's exact test as appropriate to the distribution of each variable.

[b]Total number for DMO data: 133 eye-visits without gradable photographs and 623 eye-visits with gradable photographs.

and STDR at the worst eye-visit per eye at any examination during pregnancy were 24.3% (95% CI 19.7–29.6), 8.6% (95% CI 5.9–12.5) and 9.0% (95% CI 6.1–12.9), respectively (Figure 1 and Table 3). Corresponding prevalence rates per woman were 26.0% (95% CI 19.6–33.7), 10.3% (95% CI 6.3–16.5) and 11.0% (95% CI 6.8–17.3), respectively. Two eyes from one participant were excluded from the analysis regarding DMO and STDR prevalence because their DMO status could not be confirmed as they had no OCT scans nor any mention of the presence or absence of DMO clinically. Among the 26 eyes (from 16 participants) with a worst eye-visit grade of STDR during pregnancy, 2 eyes had DMO only, 1 eye had PDR only and the remaining 23 eyes had DMO and some level of DR (10 with mild NPDR; 3 with moderate DR; 2 with severe NPDR and 8 with PDR). STDR prevalence was higher in the second trimester compared with the other trimesters and impaired vision was documented in two women with active PDR during their third trimester (VA changed from 6/6 to 1/300 and from 6/6 to 6/24).

Characteristics of participants with at least one eye-visit with DR compared with participants without DR

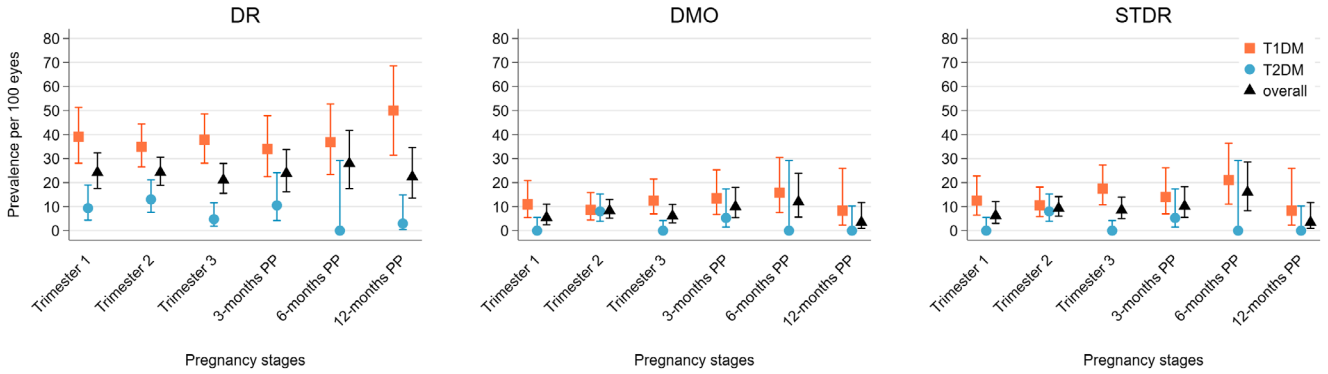

FIGURE 1 Prevalence of DR, DMO and STDR during pregnancy and postpartum. Filled shapes indicate the crude prevalence rate; error bars indicate 95% CIs for the crude rate. DMO, diabetic macular oedema; DR, diabetic retinopathy; PP, postpartum; STDR, sight-threatening diabetic retinopathy; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

TABLE 3 Prevalence of DR, DMO and STDR during pregnancy

		Overall			T1DM			T2DM		
Outcome	**Pregnancy stages**	***N* case, eye**	***N* at risk, eye**	**Prevalence per 100 eyes (CI[a])**	***N* case, eye**	***N* at risk, eye**	**Prevalence per 100 eyes (CI[a])**	***N* case, eye**	***N* at risk, eye**	**Prevalence per 100 eyes (CI[a])**
DR	Pregnancy[b]	71	292	24.3 (19.7–29.6)	56	142	39.4 (31.8–47.7)	15	150	10.0 (6.1–15.9)
	Trimester 1	31	128	24.2 (17.6–32.4)	25	64	39.1 (28.1–51.3)	6	64	9.4 (4.4–19)
	Trimester 2	50	206	24.3 (18.9–30.6)	37	106	34.9 (26.5–44.4)	13	100	13.0 (7.6–21.1)
	Trimester 3	35	166	21.1 (15.5–27.9)	31	82	37.8 (28.1–48.6)	4	84	4.8 (1.9–11.6)
DMO	Pregnancy[b]	25	290	8.6 (5.9–12.5)	17	140	12.1 (7.6–18.7)	8	150	5.3 (2.6–10.3)
	Trimester 1	7	128	5.5 (2.5–11.1)	7	64	10.9 (5.4–20.9)	0	64	0.0 (0.0–5.5)
	Trimester 2	17	204	8.3 (5.2–13.0)	9	104	8.7 (4.4–15.8)	8	100	8.0 (3.9–15.2)
	Trimester 3	10	164	6.1 (3.2–11.0)	10	80	12.5 (6.9–21.5)	0	84	0.0 (0.0–4.2)
STDR	Pregnancy[b]	26	290	9.0 (6.1–12.9)	18	140	12.9 (8.2–19.5)	8	150	5.3 (2.6–10.3)
	Trimester 1	8	128	6.3 (3.0–12.0)	8	64	12.5 (6.5–22.8)	0	64	0.0 (0.0–5.5)
	Trimester 2	19	204	9.3 (6.0–14.2)	11	104	10.6 (5.9–18.1)	8	100	8.0 (3.9–15.2)
	Trimester 3	14	164	8.5 (5.1–13.9)	14	80	17.5 (10.7–27.3)	0	84	0.0 (0.0–4.2)

Abbreviations: DMO, diabetic macular oedema; DR, diabetic retinopathy; STDR, sight-threatening diabetic retinopathy; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

[a]95% CI was estimated using the Agresti-Coull, the Wilson, or the Hanley and Lippman-Hand methods, as appropriate depending on the number of cases and at-risk eyes.

[b]From conception to delivery.

TABLE 4 Characteristics of women who did and did not have DR or STDR in at least one eye-visit during pregnancy

	DR[a]			Sight-threatening DR (STDR)[a]		
	DR absent ($n = 108$ women)	**DR present ($n = 38$ women)**	***p*-value[b]**	**STDR absent ($n = 129$ women)**	**STDR present ($n = 16$ women)**	***p*-value[b]**
Age at enrolment (years), mean (95% CI)	34.0 (33.1–35.0)	33.3 (31.7–34.9)	0.431	33.8 (33.0–34.6)	34.3 (30.9–37.6)	0.784
Type of diabetes, *n* (%)			<0.001			0.112
T1DM	41 (38.0)	30 (78.9)		59 (45.7)	11 (68.8)	
T2DM	67 (62.0)	8 (21.1)		70 (54.3)	5 (31.3)	
Duration of diabetes at enrolment (years), median (IQR)	5.7 (2.0–9.5)	20.0 (11.0–24.0)	<0.001	6.0 (2.8–14.5)	20.5 (10.5–27.5)	0.002
HbA1c in early pregnancy[c] (%), median (IQR)	6.3 (5.8–7.3)	7.0 (6.2–8.0)	0.026	6.4 (5.8–7.4)	7.0 (6.0–7.2)	0.551
Systolic BP[d] (mmHg), mean (95% CI)	112.6 (110.1–115.0)	112.6 (107.5–117.7)	0.987	110.0 (101.0–120.0)	112.5 (110.0–130.0)	0.657
Diastolic BP[d] (mmHg), mean (95% CI)	67.1 (65.0–69.3)	66.6 (63.4–69.9)	0.804	70.0 (60.0–70.0)	67.5 (60.0–75.0)	0.752
Ethnicity, *n* (%)			<0.001			0.253
ATSI	1 (0.9)	0		1 (0.8)	0	
South Pacific Islanders	4 (3.7)	0		4 (3.1)	0	
Caucasian	38 (35.2)	30 (78.9)		57 (44.2)	11 (68.8)	
Asian	46 (42.6)	5 (13.2)		48 (37.2)	2 (12.5)	
Other	19 (17.5)	3 (7.9)		19 (14.8)	3 (18.8)	
History of medical condition (present)						
Chronic hypertension, *n* (%)	12 (11.1)	5 (13.2)	0.771	14 (10.9)	2 (12.5)	0.691
Diabetic nephropathy, *n* (%)	0	3 (7.9)	0.017	2 (1.6)	1 (6.3)	0.298
Obesity,[e] *n* (%)	40 (44.9)	14 (43.8)	1.000	48 (44.9)	6 (46.2)	1.000
Other conditions,[f] *n* (%)	42 (38.9)	16 (42.1)	0.847	53 (41.1)	5 (31.3)	0.591
Hypertensive disorder in pregnancy[g] (present), *n* (%)	17 (16.5)	7 (18.4)	0.803	21 (16.9)	3 (18.8)	0.738

Abbreviations: ATSI, Aboriginal & Torres Strait Islander People; BP, blood pressure; DM, diabetes mellitus; DR, diabetic retinopathy; STDR, sight-threatening diabetic retinopathy; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

[a]*p*-value relates to the difference between the two groups examined using *t* test, Wilcoxon rank-sum test or Fisher's exact test as appropriate to the distribution of each variable.

[b]Women were categorised based on the most severe grading seen in their worst eye at any time during pregnancy.

[c]Total number of data: 97 women in the DR absent group, 28 women in the DR present group; 114 women in the STDR absent group and 10 women in the STDR present group.

[d]Measured at the first eye-exam in pregnancy. Total number of data: 94 women in the DR absent group, 25 women in the DR present group; 108 women in the STDR absent group and 10 women in the STDR present group.

[e]Total number of data: 89 women in the DR absent group, 32 women in the DR present group; 107 women in the STDR absent group and 13 women in the STDR present group.

[f]Includes thyroid diseases, heart disease, and dyslipidaemia.

[g]Total number of data: 103 women in the DR absent group, 38 women in the DR present group; 124 women in the STDR absent group and 16 women in the STDR present group.

TABLE 5 Prevalence of DR, DMO and STDR in the postpartum

Outcome	Postpartum stages	Overall			T1DM			T2DM		
		N case, eye	*N* at risk, eye	Prevalence per 100 eyes (CI[a])	*N* case, eye	*N* at risk, eye	Prevalence per 100 eyes (CI[a])	*N* case, eye	*N* at risk, eye	Prevalence per 100 eyes (CI[a])
DR	Postpartum[b]	36	164	22.0 (16.3–28.9)	31	92	33.7 (24.9–43.8)	5	72	6.9 (3.0–15.2)
	3-months PP	21	90	23.3 (15.8–33.0)	17	52	32.7 (21.5–46.2)	4	38	10.5 (4.2–24.1)
	6-months PP	14	50	28.0 (17.5–41.7)	14	38	36.8 (23.4–52.7)	0	12	0.0 (0.0–29.2)
	12-months PP	13	58	22.4 (13.6–34.7)	12	24	50.0 (31.4–68.6)	1	34	2.9 (0.5–14.9)
DMO	Postpartum[b]	12	164	7.3 (4.1–12.5)	10	92	10.9 (6.0–18.9)	2	72	2.8 (0.8–9.6)
	3-months PP	9	90	10.0 (5.4–17.9)	7	52	13.5 (6.7–25.3)	2	38	5.3 (1.5–17.3)
	6-months PP	6	50	12.0 (5.6–23.8)	6	38	15.8 (7.4–30.4)	0	12	0.0 (0.0–29.2)
	12-months PP	2	58	3.4 (1.0–11.7)	2	24	8.3 (2.3–25.8)	0	34	0.0 (0.0–10.3)
STDR	Postpartum[b]	14	164	8.5 (5.0–13.9)	12	92	13.0 (7.6–21.4)	2	72	2.8 (0.8–9.6)
	3-months PP	9	90	10.0 (5.4–17.9)	7	52	13.5 (6.7–25.3)	2	38	5.3 (1.5–17.3)
	6-months PP	8	50	16.0 (8.3–28.5)	8	38	21.1 (11.1–36.3)	0	12	0.0 (0.0–29.2)
	12-months PP	2	58	3.4 (1.0–11.7)	2	24	8.3 (2.3–25.8)	0	34	0.0 (0.0–10.3)

Abbreviations: DMO, diabetic macular oedema; DR, diabetic retinopathy; PP, postpartum; STDR, sight-threatening diabetic retinopathy; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

[a]95% CI was estimated using the Agresti-Coull, the Wilson, or the Hanley & Lippman-Hand methods, as appropriate depending on the number of cases and at-risk eyes.

[b]From delivery to 52-weeks postpartum.

during pregnancy, as well as between participants with at least one eye-visit with STDR and without, are presented in Table 4. HbA1c data were not available for 21 participants (6 of whom had STDR) and early pregnancy BMI data were incomplete in 25 participants (3 of whom had STDR and three had DR). Women with DR or STDR at any time during pregnancy, compared with those without, had significantly longer durations of diabetes (*p*-values ≤0.002). Furthermore, a significantly higher HbA1c at early pregnancy ($p = 0.026$), as well as higher proportions of women with T1DM ($p < 0.001$), with pre-existing diabetic nephropathy ($p = 0.017$), and of Caucasian ethnicity ($p < 0.001$) were evident in the DR group compared with the no-DR group.

3.3 | Prevalence of DR and STDR during the first year postpartum

Overall, 82 out of 146 (56%) participants had at least one eye examination after delivery. More specifically, 45, 25 and 29 participants had an eye-visit around 3-, 6- and 12-months postpartum, respectively. During the first year postpartum, the overall prevalence rates of DR, DMO, and STDR (Figure 1 and Table 5**)** were 22.0 (95% CI 16.3–28.9), 7.3 (95% CI 4.1–12.5) and 10.0 (95% CI 5.4–17.9) per 100 eyes, which corresponds with prevalence rates of 23.2 (95% CI 15.4–33.4), 11.0 (95% CI 5.5–19.6) and 11.0 (95% CI 5.9–19.6) per 100 women, respectively. There were 14 eyes (9 participants) with STDR during the postpartum: 1 eye had DMO only, 2 eyes had PDR only and 11 eyes had DMO and some level of DR (4 with mild NPDR; 2 with moderate NPDR; and 5 with PDR). All prevalence rates were higher at 6-months postpartum compared with rates in the other postpartum periods.

4 | DISCUSSION

This prospective cohort study is the first since 1980 to study the prevalence of DR in an Australian pregnant population with pregestational diabetes, and the first to report on the postpartum DR prevalence in both T1DM and T2DM women. We found that the prevalence of DR and STDR per eye during pregnancy were 24.3% and 9.0%, respectively, while the prevalence per woman were 26.0% and 11.0%. Interestingly, although the DR prevalence per woman in the first year postpartum was slightly lower than the rate during pregnancy (23.2% vs. 26.0%), the STDR prevalence was similar (11.0% for both), showing that the presence of STDR persisted even after delivery.

A wide range of studies have reported the prevalence of DR in early pregnancy, although very few have observed T2DM patients. Globally, it has been estimated that 25%–72% of pregnant women with T1DM[2,19] and 14%–33% of those with T2DM[20,21] have DR in early

pregnancy. In our study, the prevalence of DR per woman in the first trimester was 40.6% in T1DM and 9.4% in T2DM. Our apparently low rates of DR in the first trimester may result from ascertainment bias, from methodological differences, or from changes in disease management. Our participants' rate of eye examination attendance in the first trimester was low (32 women from each diabetes type; the lowest attendance of the three trimesters) and our cohort had well-controlled diabetes (with HbA1c IQR 5.8%–7.4%); thus, our prevalence may be underestimated. Most of the prior studies focused on assessing progression rate rather than prevalence; thus, a proportion of women with fewer than two eye exams during pregnancy (the required number to make a comparison for change) were excluded. Consequently, women with no DR who were more likely to have only one examination were likely underrepresented in these estimations. Another possible explanation is related to the 1989 Saint Vincent Declaration which established a new standard of multi-disciplinary care for diabetic pregnant women.[22] The lower DR rates in the current study may reflect the outcomes of improved diabetes care in contemporary practice. Similar trends of improvement in the rates of other adverse pregnancy outcomes, such as hypertensive disorder during pregnancy, have been reported which supports our hypothesis.[23] Interestingly, our DR prevalence in early pregnancy approximates that reported in the previous Australian study by Horvat et al.[10]

Our prevalence findings are similar to those in the non-pregnant diabetic population. The National Eye Health Survey (NEHS) in Australia reported that 28.5% of their non-Indigenous participants with diabetes had DR and 4.5% had STDR.[24] Although the NEHS-reported prevalence of STDR was slightly lower than that seen in our pregnant population, this difference is likely due to differences in the definition of STDR. In our study, STDR was defined as the presence of PDR or DMO whereas in the NEHS study, it was defined as the presence of severe NPDR, PDR or clinically significant macular oedema (CSMO).[13] Since our definition included all types of DMO (due to the small numbers of eyes affected by DMO), it is most likely that our higher STDR prevalence is due to the inclusion of women with less severe DMO who would not have been counted as STDR in the NEHS. Additionally, since we used OCT to diagnose DMO, we may have detected more cases of DMO compared with the NEHS which only used fundus photography. A meta-analysis by Yau et al. that used a similar STDR definition estimated a comparable STDR prevalence to ours (10.2%).[25] Considering the much broader range of ages covered by these two studies, a similar DR rate in the pregnant population, which is in a much younger age group, would conceivably cause an even greater societal burden in terms of vision loss and lost work productivity.

Diabetic macular oedema is the most common cause of vision loss due to DR.[26] It has been postulated that the increased retinal vascular permeability during pregnancy can result in the development of DMO.[27] Surprisingly, a very limited number of studies have assessed DMO in pregnancy. Vestgaard et al. documented that 16% of pregnant women with T1DM had DMO in early pregnancy, and this condition was a significant risk factor for DR progression during pregnancy.[9] A T2DM study reported that 1.2% of their pregnant women developed CSMO and lost vision.[20] The Atlantic Diabetes in Pregnancy study recorded nine cases (4.9%) of DMO in their mixed diabetes type cohort.[28] However, all of these studies diagnosed DMO using fundus photographs. No previous studies have used OCT, currently the most sensitive technique, to diagnose DMO.[29–31] The present study used OCT and we found that among women with OCT data, 10.3% and 11.0% had DMO during pregnancy and in the first year postpartum, respectively. Although visual impairment (VA ranging from 6/24 to 1/300) was only observed in two participants with active PDR and not in those with DMO (even in two patients with centre-involving DMO), these findings highlight the importance of DMO assessment in this population since worsening of DMO, particularly with central macula involvement, has been associated with vision loss and has limited treatment options in pregnancy, thus complicating management.

In this study, there was a tight correlation between diabetes type and three identified DR risk factors, where most of the women with T1DM were Caucasian, had a significantly longer diabetes duration, and a higher HbA1c level. Therefore, in this study the effect of these three factors on DR prevalence could not be separated from the effect of type of diabetes. Few past reports on pregnant cohorts reported on risk factors for DR in pregnancy. Most considered risk factors relating to the progression rather than the prevalence of DR during pregnancy, and it is very likely that these risk factors differ. Makwana et al. reported that among their pregnant cohort (with a mixture of diabetes type), a longer duration of diabetes was associated with the presence of DR during pregnancy,[8] supporting our findings. Additionally, a higher mean HbA1c was also observed in the DR group of Makwana's study. Despite the limited reports in the pregnant population, these DR risk factors align with those reported for the non-pregnant population.[25,32] We also demonstrated that pre-existing diabetic nephropathy was associated with the presence of DR. Similarly, two Danish studies which observed pregnant women with T1DM and T2DM each found that diabetic nephropathy in early pregnancy was correlated with STDR.[9,20] Unfortunately, since these studies focused on progression of STDR, we do not know the relationships between this condition and the presence of DR in their cohorts.

Interestingly, we found that T1DM was associated with the presence of DR but not associated with the presence of STDR. Instead, only a longer duration of diabetes was associated with the presence of STDR which may suggest that the risk of STDR in this population was similar between both types of diabetes. This finding is expected given that diabetes duration is the strongest predictor for DR progression in the non-pregnant population.[24,33]

This study has several strengths. It provides contemporary evidence on the prevalence of DR and STDR and their risk factors in women with pregestational diabetes during pregnancy and the first year of the postpartum. Rather than just reporting the prevalence of DR in early pregnancy as most earlier studies have done, we reported the prevalence of DR in early, during and after pregnancy, presenting a clearer picture of this disease's burden in the pregnant population. More importantly, with just over half of our participants having T2DM, this study cohort is a good representation of the present-day diabetic pregnant population.[34] The study also provides data on the prevalence of DMO during pregnancy, a crucial condition in DR that has been understudied in pregnant women.

However, there are some limitations. Firstly, only 84.9% of our participants had at least one eye examination during pregnancy and our participants were recruited from just two urban tertiary-referral centres. Therefore, there is a possible selection bias, and our findings might not reflect the rate in the entire population. Secondly, due to COVID-19, only a limited number of women attended the 6- and 12-months postpartum examinations. As it is possible that those women who did attend during the lockdown may have had more severe DR or diabetes, our findings might overestimate the true prevalence in the postpartum. This may also explain why eye-visits without fundus photographs had more severe DR and DMO. Most of our patients attended their local eye clinic during the COVID-19 pandemic and, unfortunately, not all of these clinics routinely took fundus photographs when evaluating their patient's DR status. Thirdly, 135 out of 758 (17.8%) available eye-visits had no fundus photography performed. Consequently, the DR status of this portion of women was determined from the clinical DR grading rather than our independent grader. This risk of bias was unfortunately unavoidable. Lastly, due to the limited number of observed cases, we calculated our prevalence as rates per eye rather than rates per woman to achieve better precision. Nonetheless, our rates per eye were quite similar to those per woman.

To conclude, this study demonstrated that approximately one quarter of Australian diabetic pregnant women had DR. Although this rate was similar to rates from the non-pregnant population, nearly 1 in 9 pregnant women had STDR and this rate persisted up to a year postpartum. Women with T1DM, who were more likely to have long-standing diabetes and poorer glycaemic control, and those with pre-existing diabetic nephropathy were more likely to have DR in pregnancy. However, those with a longer duration of diabetes, irrespective of diabetes type, were at risk of STDR; thus, these individuals need closer follow-up during pregnancy. Given our findings, special attention should be given to optimising DR surveillance and management in pregnancy in order to minimise the risk of vision loss from DR in this population.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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