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Gestational diabetes mellitus is a significant risk factor for long-term ophthalmic morbidity

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Abstract
Purpose To investigate whether patients with a history of gestational diabetes mellitus (GDM) have an increased risk for long-term ophthalmic morbidity.
Methods *Design* a population-based study compared the incidence of long-term maternal ophthalmic morbidity in a cohort of women with and without a history of GDM. *Setting* Soroka University Medical Center. Participants: All singleton pregnancies of women who delivered between 1988 and 2013. *Main outcome measure(s)* Diagnosis of ophthalmic morbidity. *Analyses* A Kaplan–Meier survival curve was used to estimate cumulative incidence of ophthalmic morbidity. Cox proportional hazards models were used to estimate the adjusted hazard ratios (HR) for ophthalmic morbidity.
Results During the study period, 104,751 deliveries met the inclusion criteria; 9.4% ($n=9888$) of which occurred in patients with a diagnosis of GDM during at least one of their pregnancies. Patients with GDM had a significantly higher incidence of ophthalmic morbidity such as glaucoma, diabetic retinopathy, and retinal detachment compared with controls (0.1 vs. 0.02%, $p<0.001$; 0.2 vs. 0.04%, $p<0.001$; 0.2 vs. 0.1%, $p<0.001$, respectively). Patients with concurrent GDM and preeclampsia had a significantly higher incidence of total ophthalmic complications compared to patients with GDM only (1 vs. 0.6%, respectively, $p<0.001$). Using Kaplan–Meier survival curve, patients with a previous diagnosis of GDM had significantly higher cumulative incidence of ophthalmic morbidity ($p<0.001$, log-rank test). In the Cox proportional hazards model, a history of GDM remained independently associated with ophthalmic morbidity (adjusted HR 2.0; 95% CI 1.5–2.8; $p<0.001$).
Conclusions GDM is an independent risk factor for long-term maternal ophthalmic morbidity.

Keywords Gestational diabetes mellitus · Ophthalmic morbidity · Cohort study · Maternal complications

Abbreviations

AAPP	American academy of ophthalmology practice
CI	Confidence Interval
DM	Type 2 diabetes mellitus
GDM	Gestational diabetes mellitus
HR	Hazard ratio
ICD-9	International Classification of Diseases, 9th revision
NICE	National institute for health and care excellence

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Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that is first recognized during pregnancy [1]. Its prevalence varies between 1 and 14% in different pregnant populations and ethnic groups [2, 3], with a significant gradual increase in rates due to obesity epidemic [4]. Almost all women who develop GDM during pregnancy are normoglycemic after birth [5]. However, these women maintain a higher risk for recurrent GDM [6], impaired glucose tolerance, and type 2 diabetes mellitus (DM) [7]. In fact, in the first 5 years following delivery, these women have a fivefold increased risk of developing type 2 DM compared to women with normoglycemic pregnancies.

As in DM, GDM is associated with impaired insulin secretion and insulin resistance [8, 9]. The two disorders share the same risk factors, which have a similar genetic susceptibility and corresponding prevalence within a given population. Therefore, they are assumed to be etiologically indistinct, with GDM preceding DM [10].

Diabetes is the leading cause of blindness in adults. The disease affects both visual function and structure [11]. Diabetic eye disease refers to conditions that are attributable, either directly or indirectly, to hyperglycemia. Diabetic-related ophthalmic morbidity includes: cataract, glaucoma, ocular surface disease, non-arteritic ischemic optic neuropathy, cranial mono-neuropathy, extraocular muscle palsy, and most importantly, diabetic retinopathy [11, 12]. Diabetic retinopathy is a well-known risk factor for visual impairment in diabetic patients [13], resulting in 12,000–24,000 new cases of blindness in the United States every year [14]. Studies suggest that the most consistent risk factors for the development and severity of retinopathy are duration of diabetes, younger age at diagnosis, high glycosylated hemoglobin levels, and high systolic blood pressure [15–17]. The association between diabetes and cataract was reported by several studies [18–20]. Risk factors for this ocular disease include impaired fasting glucose, increased duration of diabetes, and severity of hyperglycemia [20, 21]. Primary open angle glaucoma can be a result of impaired blood flow to the anterior optic nerve due to diabetes-mediated damage to the vasculature [22, 23]. In addition, patients with uncontrolled diabetes often suffer from neovascularization of the iris, an early event leading to neovascular glaucoma [24].

Although most of the women that experience GDM return to normal glycemic control, their HbA1c was found to be higher than that of normoglycemic women [25]. In some women with GDM, insulin resistance persists postpartum [26]. Hence, while not formally diagnosed as DM patients, these women are exposed to a higher mean glucose level, a key player in the development of ophthalmic morbidity [27].

In recent years, pregnancy is being viewed as a window of opportunity. It serves as an optimal opportunity for the early detection of different susceptibilities for future maternal morbidities [28–30] and thus an opportunity for early intervention. To the best of our knowledge, the impact of GDM on future ocular health has not been previously addressed. Thus, the objective of the present population-based study was to investigate whether GDM is a significant risk factor for future significant maternal ophthalmic morbidities.

Methods

Research design

A population-based cohort study was conducted, which was analyzed in a prospective manner. The primary exposure was at least one pregnancy with a diagnosis of GDM, as defined by universal screening (i.e. a GCT of over 200 mg/dL or an abnormal OGTT test) [1]. The main outcome measure was subsequent maternal ophthalmic morbidity, such as glaucoma, diabetic retinopathy, macular degeneration, and retinal detachment (Online Resource 1).

Deliveries occurred between the years 1988–2013, with a mean follow-up duration of 12 years. A comparison was performed between patients who experienced at least one episode of GDM and those who did not. For patients who experienced at least one GDM-affected pregnancy, the first was chosen as the index pregnancy. For patients who did not experience GDM, the index pregnancy was randomly selected. Data were collected from two databases. The first was the computerized perinatal database consisting of information recorded directly after delivery by an obstetrician. Skilled medical secretaries examine the information routinely before entering it into the database. Coding is done after assessing the medical prenatal care records as well as the routine hospital documents. These procedures assure maximal completeness and accuracy of the database.

The second database was the computerized hospitalization database of the Soroka University Medical Center (Demog-ICD9 database-see Online Resource 1), which includes demographic and medical diagnoses during hospitalization, with medical diagnoses drawn directly from the medical records. All diagnoses are classified according to the International Classification of Diseases, 9th revision (ICD-9). Ophthalmic morbidity was defined as a diagnosis of any ophthalmic complication from Online Resource 1. This event was defined as censored. If it did not occur or occurred outside of the area, censored was defined as the end of follow-up period.

The Institutional Review Board approved the study.

Study population

The study population was composed of all singleton pregnancies of women who delivered between January 1988 and December 2013. The study was conducted at the Soroka University Medical Center, the sole hospital in the Negev, the southern region of Israel, which occupies 60% of the land of Israel, serving the entire population in this region, about 14.5% of the population in Israel [31]. Thus, the study is based on non-selective population data. We excluded multiple pregnancies, pregnancies with pre-gestational DM, pregnancies with known ophthalmic disease before or during the index pregnancy, and pregnancies with missing data on key variables due to lack of prenatal care (ICD-9 code-v237).

Statistical analysis

Continuous variables were compered between the study groups using Student t test and Mann–Whitney *U* test. Categorical data were shown in counts and percentages and the differences were assessed by Chi-square test for general association, Fisher's exact test was used when appropriate. Kaplan–Meier survival curve was used to estimate cumulative incidence of ocular morbidity. The differences between the morbidity curves were assessed using the log-rank test. Cox proportional hazards model was used to estimate the adjusted hazard ratios (HR's) for future ophthalmic morbidity while controlling for maternal age, parity, obesity, and preeclampsia. $p<0.05$ was considered statistically significant.

Results

A total of 104,751 women met the inclusion criteria for the study, out of which 9888 (9.4%) women had at least one previous pregnancy with GDM. Maternal characteristics are presented in Table 1. Several differences were observed between women with and without GDM. Specifically, the prevalence of obesity and preeclampsia was higher in women with a history of GDM, compared to the comparison group.

Primary outcome- ophthalmic morbidity

There were significantly more ophthalmic morbidities among the GDM group compared to the normoglycemic group (0.6 vs. 0.2% respectively, OR = 3.13, 95% CI 2.36–4.15; $p<0.001$), as presented in Table 2. Specifically, the incidence for glaucoma, diabetic retinopathy, and retinal detachment was significantly higher among the study group ($p<0.001$ for all).

Further examination, using the Chi-square test for trends, revealed that the risk for ophthalmic morbidity in GDM patients significantly increased if the patient was also affected by preeclampsia (Table 3). The prevalence of ophthalmic morbidity for patients with past GDM and preeclampsia was 1.0 vs. 0.6% for patients with past GDM only.

Figure 1 presents the Kaplan–Meier survival curve for the cumulative incidence of ophthalmic complications in unexposed patients (no GDM), patients affected by GDM, and those affected by both GDM with preeclampsia. As shown, patients with a history of GDM and preeclampsia

Table 1 Characteristics of patients with and without a history of GDM

Characteristics	GDM ($n=9888$)	No GDM ($n=94{,}863$)	p value
Maternal characteristics			
Maternal age at birth (years ± SD)	31.8 ± 5.90	28.1 ± 5.92	<0.001
Maternal age at hospitalization (years ± SD)	46.11 ± 11.08	40.78 ± 11.00	0.001
Gravidity, mean (median)	4.48 (4)	3.14 (2)	<0.001
Parity at index birth, mean (median)	3.75 (3)	2.66 (2)	<0.001
Obesity % (*n*)	1.1% (106)	0.9% (824)	0.04
Preeclampsia % (*n*)	7.4% (728)	4.5% (4292)	<0.001

Table 2 Ophthalmic complications for patients with and without the history of GDM

	GDM (%)	No GDM (%)	Odds ratio	95% confidence interval	p value
Glaucoma	0.1	0.02	5.03	2.42–10.44	<0.001
Diabetic retinopathy	0.2	0.04	4.19	2.37–7.40	<0.001
Macular degeneration	0.02	0.01	2.74	0.57–13.20	0.21
Retinal detachment	0.2	0.1	2.98	1.85–4.81	<0.001
Other ophthalmic complications	0.2	0.1	1.90	1.09–3.30	0.03
Total ophthalmic complications	0.6	0.2	3.13	2.36–4.15	<0.001

Table 3 Ophthalmic complications for patients with and without a history of GDM or GDM and preeclampsia

	No GDM ($n=94,773$)	GDM ($n=9157$)	GDM + preeclampsia ($n=727$)	p value[a]
Total ophthalmic complications	0.2% (168)	0.6% (55)	1.0% (7)	<0.001

[a]Chi-square test for trends

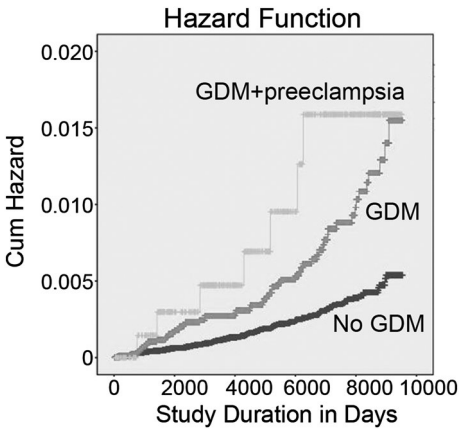

Fig. 1 Kaplan–Meier curve for ophthalmic morbidities of patients with and without a history of GDM or GDM and preeclampsia. Survival analysis (presenting the hazard function) ($p<0.001$, log-rank test)

Table 4 Cox multivariable regression model for the risk of long-term maternal ophthalmic morbidity

	Adjusted HR	95% CI	p value
GDM	2.08	1.54–2.80	<0.001
Maternal age at index pregnancy	1.06	1.03–1.09	<0.001
Parity	1.05	0.99–1.10	0.097
Obesity	2.21	0.91–5.36	0.08
Preeclampsia	1.57	0.99–2.48	0.055

GDM gestational diabetes mellitus, *HR* hazard ratio, *CI* confidence interval

had a significantly higher cumulative incidence of ophthalmic morbidity as compared to patients with a history of GDM alone, and the lowest risk was observed in unexposed patients.

Table 4 presents Cox multivariable regression model used to evaluate an independent relationship between GDM and long-term ophthalmic complications while controlling for recognized clinical confounders related to GDM including: obesity, preeclampsia, and maternal age. In the multivariable model, GDM remained independently associated with an increased risk for long-term maternal ophthalmic morbidity, with an adjusted hazard ratio of 2.0 (95% CI 1.5–2.8; $p<0.001$).

Discussion

The major finding of this population-based cohort analysis is that GDM is a significant risk factor for long-term maternal ophthalmic morbidity. Specifically, we found GDM to be associated with an increased risk of developing glaucoma, diabetic retinopathy and retinal detachment. In addition, the study marks women with a co-morbidity of GDM and preeclampsia as a group with a substantial additive increased risk for future ophthalmic morbidity.

The link between GDM and future type 2 DM is well established [7]. Up to 50% of women who experienced GDM will develop type 2 DM during a 10 year follow-up [32]. At the time of diagnosis of type 2 DM, up to 20% are already affected by retinopathy [32] and most will develop some degree of retinopathy over subsequent decades [32]. Therefore, the American Academy of Ophthalmology Practice (AAPP) and National Institute for Health and Care Excellence (NICE) guidelines recommend annual eye examination as a screening test of retinopathy for all patients affected by DM [33]. Several studies have demonstrated that women who develop GDM do not require an eye examination during pregnancy and do not appear to be at increased risk of developing diabetic retinopathy during pregnancy [34]. However, the impact of GDM as a risk factor for future ocular morbidity has not been previously addressed. Our data link between GDM and future ophthalmic morbidities. This link is consistent with the common concept that GDM and DM are two of the same entity, with GDM preceding type 2 DM later in life [10]. Although we cannot roll-out the possibility that DM, diagnosed years after GDM, have led to diabetic retinopathy, it is possible that at the time of diagnosis, some of the women are already affected by retinopathy, as previously reported [32]. Thus, marking GDM as a significant risk factor for future maternal ophthalmic morbidity may offer the early detection and intervention strategies via specific screening programs.

Preeclampsia is often associated with a new onset of ophthalmic morbidity [35]. Although preeclampsia is a pregnancy-specific disorder and most ophthalmic morbidities resolve post-partum [35–37], women with a history of preeclampsia are at an increased risk for future ophthalmic complications [38]. GDM was found to be associated with increased rates of preeclampsia [39, 40]. This finding may express a predisposition of GDM

patients towards endothelial dysfunction [41]. Given the rising incidence of GDM, the portion of patients that experience both GDM and preeclampsia is growing [39]. We, therefore, evaluated the risk of women with a history of both, GDM and preeclampsia, to develop future ophthalmic morbidity. Our finding of a fivefold risk (Table 3) compared to women with past normoglycemic pregnancy highlights the need for special consultation to this group of women.

Routine screening of DM patients with annual ophthalmologic examination saves sight at a relatively low cost [42]. One of the main motivations for screening is the established efficacy of laser photocoagulation surgery in preventing visual loss of patients with diabetic retinopathy [43]. The need to include GDM patients in any screening program was not addressed until now, because data regarding their risk of developing ophthalmic complications was not available. Our results emphasize the future risks associated with GDM and require further investigation. Further accumulation of data supporting our findings may lead to a policy change in standard of care, which may prove to save sight for a growing group of women.

The strength of our population-based study lies within the fact that our hospital is the only hospital serving the entire population of southern Israel, providing both obstetrical services and ophthalmic medical services including outpatient clinics. Data were obtained from computerized files, which eliminate the risk of recall bias. The database allowed us to present a large cohort of women with a long follow-up period, revealing the long-term risks of GDM in the context of ophthalmic morbidity. However, the study has some limitations that should be acknowledged. Medical care provided in an outpatient setting outside of the hospital was not logged in our system and, therefore, not included. It is possible that the actual prevalence of ophthalmic morbidity in our population is higher than that reflected in our results. Yet, it is reasonable to assume that the trend for outpatient medical services does not differ between patients with and without a history of GDM, and therefore, it should not alter our results.

In conclusion, GDM is a significant risk factor for long-term ophthalmic morbidity. These data are important not only to obstetricians but also to primary care physicians providing counseling to patients on future morbidity. Moreover, it may also prove significant for ophthalmologists who encounter patients many years after pregnancy. This study may initiate a discussion regarding the importance and possible benefits of adding specific ophthalmic screening programs to patients that experienced GDM or GDM and preeclampsia. These programs will help to identify and treat patients with the early signs of ophthalmic illness using the benefits of primary prevention.

Author contributions OB: protocol/project development, data management, manuscript writing (original draft preparation), and editing. RS: data collection and management, Other: methodology and manuscript editing. RK: protocol/project development, data management, and manuscript editing. ISS: data management, manuscript writing, and editing. AW: data management and manuscript writing/editing. ES: protocol/project development and manuscript editing. ET: manuscript editing; Other: ophthalmic consultation. ES: project development and manuscript editing; other: methodology.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest. The authors are responsible for study design, the collection, analysis and interpretation of data, the writing of the report, and the decision to submit the article for publication.

Ethical approval The Institutional Review Board approved the study. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. For this type of study, formal consent is not required.

Animal rights This article does not contain any studies with animals performed by any of the authors.

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