Gestational diabetes and long-term risk for dyslipidemia: a population-based historical cohort study

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ABSTRACT

Objectives To assess the course of lipid levels over time in postpartum women according to gestational diabetes status, taking into account potential confounders, such as comorbid conditions and body weight.

Methods The data for the present analysis were collected from a 2.3 million member integrated care provider in Israel. Included were all female members aged 15–50 years who performed a 50 g glucose challenge test (GCT) between March 1995 and May 2009. We collected all follow-up lipid consecration tests performed from date of delivery following the GCT (index date) until April 2017. Data analysis was performed for each lipid component individually (triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)) and the effects of the several risk factors (history of gestational diabetes mellitus (GDM), age at delivery, obesity status and smoking status) were investigated using general linear model taking into account potential confounders.

Results A total of 160 527 women (6.1 million person-years of actual follow-up) were eligible for the analysis, including 10 234 women with GDM (6.4% of the entire cohort). During the study follow-up period, a total of 2.1 million lipid tests were performed. When adjusting for follow-up time, age at index date, body mass index status, and smoking status, GDM was associated with a 1.8-fold risk (95% CI 1.73 to 1.88) for dyslipidemia defined by TG, 1.45-fold risk (95% CI 1.38 to 1.52) for dyslipidemia defined by LDL-C, and 1.44-fold risk (95% CI 1.39 to 1.50) for dyslipidemia defined by HDL-C.

Discussion The results of this retrospective cohort analysis indicate that gestational diabetes confers added risk for developing hyperlipidemia post partum, particularly dyslipidemia defined by TG, as compared with women with normal glucose tolerance.

Significance of this study

What is already known about this subject?
► While it has been suggested that women with gestational diabetes mellitus (GDM) history may have higher prevalence of dyslipidemia, data from large and long-term studies are lacking.

What are the new findings?
► Women with history of gestational diabetes have a significantly greater risk for dyslipidemia defined by triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

How might these results change the focus of research or clinical practice?
► The study results underline the need for an increased awareness among patients and caregivers and focusing on healthy lifestyle modification to mitigate the risk of dyslipidemia among women with GDM history.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance first diagnosed in the second or third trimester of the pregnancy.[1] The prevalence of this gestational complication is between 1% and 28% of pregnancies[2] and rising over time.[3] GDM is associated with short and long-term outcomes for both mother and child.[4]

Women with GDM history are at an increased risk for developing major cardiovascular risk factors, such as type 2 diabetes,[5–8] metabolic syndrome,[9] hypertension[10] and subclinical[11] and clinical[12] atherosclerosis. The increased risk for complications has been documented despite normalizations of glucose levels shortly after delivery.[13] However, less attention has been given to the association between GDM and long-term risk of dyslipidemia, a metabolic disorder characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C), low levels of high-density lipoprotein cholesterol (HDL-C), and elevated levels of triglycerides (TG).

While it has been suggested[14] that women with GDM history are characterized by higher prevalence of dyslipidemia compared with their normoglycemic peers, analysis of parous women from the 2007 to 2014 cycles of the National Health and Nutrition Examination Survey indicated that history of GDM is not significantly related with increasing levels of LDL-C.[15] Thus, the aims of the current historical cohort study were to assess the course of lipid levels over time in postpartum women

according to gestational diabetes status, taking into account potential confounders, such as comorbid conditions and body weight.

METHODS

The data for the present analysis were collected from the central mainframes of Maccabi Healthcare Services (MHS), a 2.3 million member integrated care provider in Israel.

Study population

Included were all female MHS members who performed a 50 g glucose challenge test (GCT) between March 1995 and May 2009 (to allow at least 9 years of potential retrospective follow-up) and were aged 15–50 years at day of testing with at least one lipid test post partum. We excluded all women who had pre-existing diabetes mellitus, dyslipidemia, or infertility treatments. Date of delivery following the GCT was defined as index date. If a woman had several pregnancies during the study observation period, the most recent one was selected.

GDM definition

In MHS, all pregnant women are routinely screened for GDM with a 50 g GCT between 24 and 28 weeks of gestation. Women with a serum glucose concentration >140 mg/dL (7.8 mmol/L) 1 hour after GCT are referred to a diagnostic 100 g oral glucose tolerance test (OGTT). GDM was defined according to Carpenter and Coustan,[16] based on the presence of two or more of the following values in the OGTT: fasting serum glucose ≥95 mg/dL (5.3 mmol/L), 1 hour serum glucose ≥180 mg/dL (10.0 mmol/L), 2 hours serum glucose ≥155 mg/dL (8.6 mmol/L) or 3 hours serum glucose ≥140 mg/dL (7.8 mmol/L), all other women were defined as non-GDM. Further subcategorization was made according to obesity status and smoking status. Prepregnancy obesity status prior to conception was defined according to documented body mass index (BMI) taken at least 1 year prior to date of delivery and was categorized into normal weight (BMI <25 kg/m^2), overweight (BMI 25–29 kg/m^2), and obesity (BMI ≥30 kg/m^2). Smoking status was categorized into non-smoker, past or current.

Dyslipidemia

We collected all follow-up lipid consecration tests performed from index date until April 2017. Data analysis was performed for each lipid component individually (TG, LDL-C, and HDL-C) and the effects of the several risk factors (history of GDM, age at delivery, obesity status and smoking status) were investigated. Dyslipidemia was defined according to the Adult Treatment Panel III,[17] which was the relevant guidelines for the time of the study period: TG >200 mg/dL (2.26 mmol/L), LDL-C >160 mg/dL (4.14 mmol/L) and HDL-C <40 mg/dL (1.30 mmol/L). For LDL-C follow-up, initiation of statin therapy was defined as censor. All study patients had at least one measurement of TG, 99.5% and 77.4% had at least one HDL and LDL measure, respectively.

Other study variables

Socioeconomic level was categorized into quartiles according to the poverty index of the member's enumeration area as defined by the 1995 national census based on several parameters including household income, educational qualifications, crowding, material conditions, and car ownership.

Statistical analysis

Baseline characteristics were compared between women with history of GDM to those without, by χ^2 for categorical variables and by t-test for continuous variables.

We used general linear model to assess the influence of several risk factors such as: time since delivery, history of GDM, women's age at delivery, obesity status and smoking status on the risk of an increase in lipid levels. Significant level was set at p=0.05.

We used Cox proportional hazards regression model to estimate the adjusted HR of history of GDM to the development of dyslipidemia (for each component separately). The proportional hazard assumption was checked graphically and found to reasonably fulfill.

RESULTS

A total of 160 527 women (6.1 million person-years of actual follow-up) were eligible for the analysis, including 10 234 women with GDM (6.4% of the entire cohort). Baseline characteristics of GDM status are presented in table 1. Patients with GDM were more likely to be older (31.45 years vs 33.24 years), overweight or obese (11% vs 17.3% and 7.6% vs 20.6%, respectively) and to have a single delivery during the study period (50.7% vs 88.3%).

During the study follow-up period, a total of 2.1 million lipid tests were performed. When adjusting for follow-up time, age at index date, BMI status, smoking status and baseline lipid levels using general linear models, we found participants with history of GDM to have 5 mL/dL increase in TG levels, 0.7 mg/dL decrease in HDL-C level and 0.65 mg/dL increase in non-HDL-C levels, compared with those without history of GDM. Trends in lipid levels over follow-up time are given in figures 1–3. Stratified figures by age and BMI are shown in online supplementary appendix.

A total of 99.3% of the study population were tested for blood lipids and the cumulative risk of LDL-C, HDL-C, and TG dyslipidemia during the follow-up period (mean 11 years) was 11.9%, 24.3%, and 13.3%, respectively. In a multivariable survival analysis adjusting for age, BMI, and smoking status, GDM was associated with a 1.8-fold risk (95% CI 1.73 to 1.88) for dyslipidemia defined by TG, 1.45-fold risk (95% CI 1.38 to 1.52) for dyslipidemia defined by LDL-C, and 1.44-fold risk (95% CI 1.39 to 1.50) for dyslipidemia defined by HDL-C. HRs adjusted for baseline lipid levels are also presented in table 2.

Table 1 Baseline and end of follow-up characteristics of study participants, by GDM status

	Gestational diabetes				Total	
	No (n=150 293)		Yes (n=10 234)		(n=160 527)	
Age						
Years, mean (±SD)	31.45	(±5.02)	33.24	(±5.42)	31.07	(±5.08)
Socioeconomic status						
Lowest quartile	27 395	18.2	1974	19.3	29 369	18.3
Second	57 181	38	3608	35.5	60 789	37.9
Third	26 003	17.3	1890	18.5	27 893	17.4
Highest	34 795	23.2	2415	23.6	37 210	23.2
NA	4919	3.3	347	3.4	5266	3.3
Smoking						
Current	16 118	10.7	1094	10.7	17 212	10.7
Past	3027	2	231	2.3	3258	2
Never	125 204	83.3	8559	83.6	133 763	83.3
Unknown	5944	4	350	3.4	6294	3.9
Parity						
1	76 126	50.7	9034	88.3	85 160	53.1
2	47 461	31.6	1019	10	48 480	30.2
3	18 719	12.5	160	1.6	18 879	11.8
4+	7987	5.3	21	0.2	8008	5
Body weight						
Normal or underweight	33 404	22.2	1576	15.4	34 980	21.8
Overweight	16 556	11	1766	17.3	18 322	11.4
Obese	11 694	7.6	2111	20.6	13 805	8.6
NA	88 639	59	4781	46.7	93 420	58.2
Lipids levels						
TG, mean log (mg/dL) (±SD)	1.95	(±0.21)	2.06	(±0.23)	1.95	(±0.21)
LDL-C, mean mg/dL (±SD)	107.05	(±26.66)	111.13	(±31.26)	107.48	(±28.87)
HDL-C mean mg/dL (±SD)	54.33	(±12.46)	52.02	(±12.59)	54.18	(±12.48)
End of follow-up						
Mean TG tests (±SD)	1.18	(±0.53)	1.27	(±0.63)	1.19	(±0.54)
Mean LDL-C tests (±SD)	1.16	(±0.48)	1.24	(±0.6)	1.17	(±0.49)
Mean HDL-C tests (±SD)	1.17	(±0.49)	1.25	(±0.6)	1.17	(±0.5)
Mean follow-up years (±SD)		4.75	11	4.64	10.85	(±4.75)
Incident DM		0.7	1012	9.9	1994	1.2

DM, diabetes mellitus; GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; TG, triglyceride.

In addition to GDM, age and smoking, baseline BMI was also strongly related to dyslipidemia. Weaker associations were observed with dyslipidemia defined by HDL. Overweight, but not obesity, was also significantly (p<0.01) associated with dyslipidemia defined by LDL-C with an HR.

DISCUSSION

The results of this retrospective cohort analysis indicate that gestational diabetes confers added risk for developing hyperlipidemia post partum, particularly dyslipidemia defined by TG, as compared with women with normal glucose tolerance. We also found that HDL-C is significantly lower in women who develop GDM, and that the gap develops within months post partum. Similarly, the elevated postpartum LDL-C levels in GDM women remain relatively stable, while increasing with age among normal glucose tolerance women.

Our findings corroborate the results of a previous study[18] indicating that while patients with GDM history
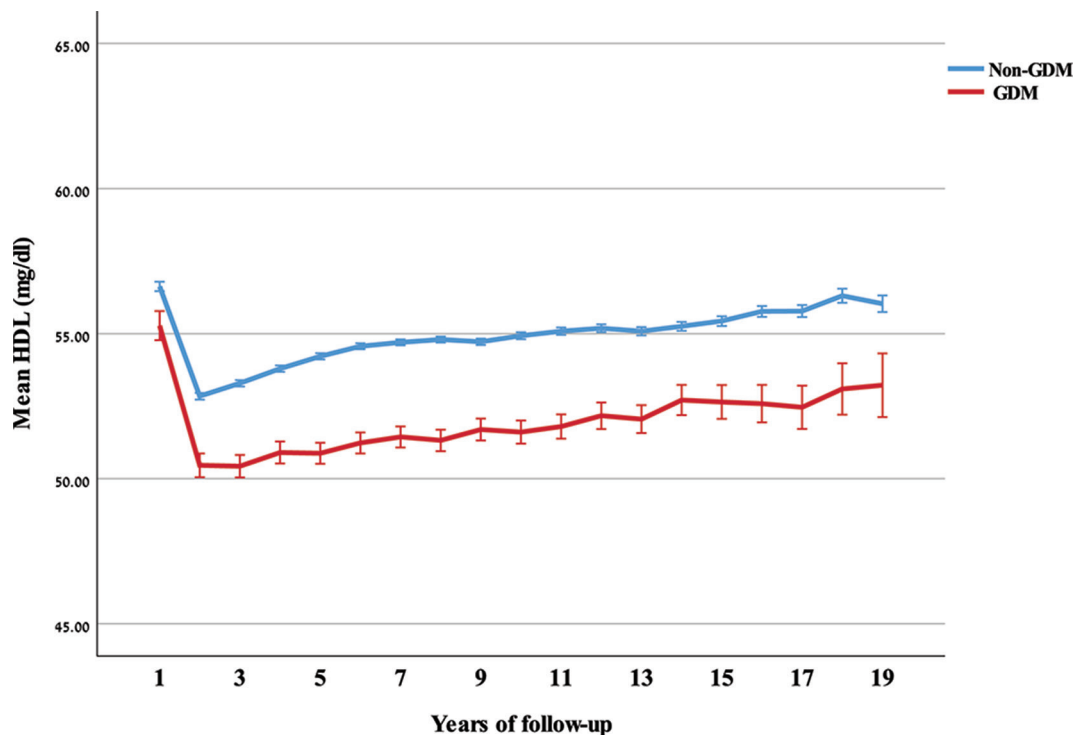
Figure 1 Mean and 95% CI of high-density lipoprotein cholesterol (HDL-C) over years of follow-up, by gestational diabetes mellitus (GDM) status.

show similar lipid profile during screening, but by 3 months post partum, there were significant differences in total cholesterol, LDL, TGs, and total cholesterol-to-HDL ratio. Long-term trends in lipid profile in women with previous GDM were rarely investigated. In a

cross-sectional study[19] among women after an average of 30 years from delivery, responders with GDM history were more likely to demonstrate an atherogenic lipid profile, treated for dyslipidemia (ie, statins), and to be diagnosed with lipidemia at a younger age. Their overall OR for
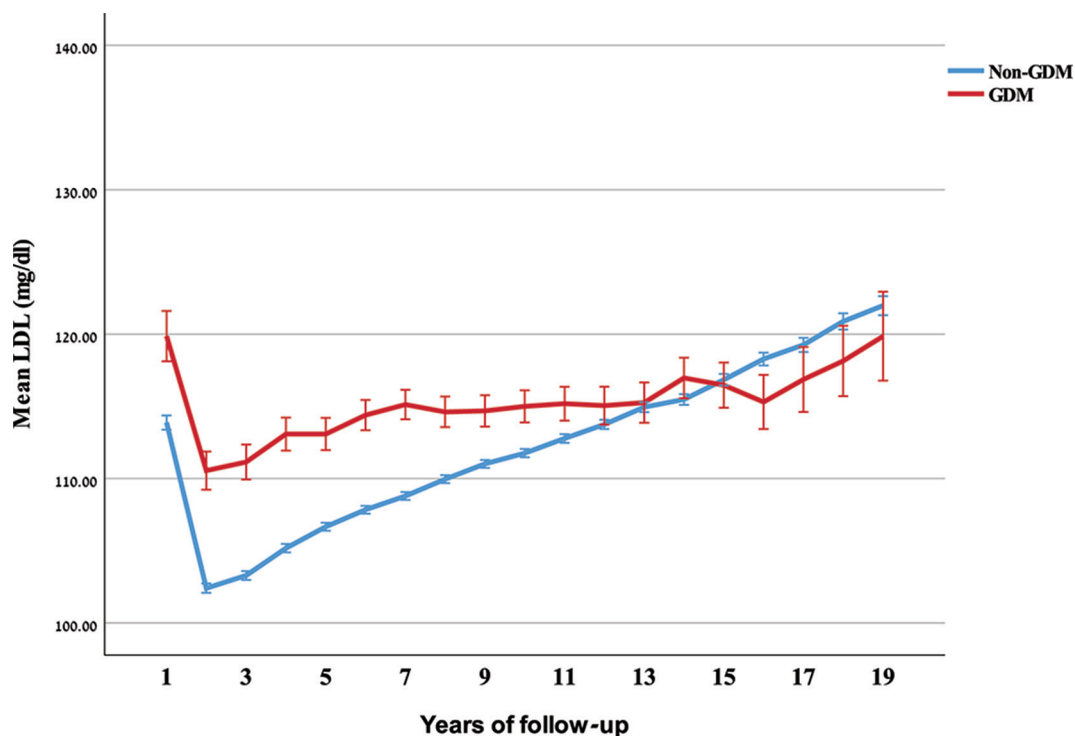

Figure 2 Mean and 95% CI of low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) over years of follow-up, by gestational diabetes mellitus (GDM) status.
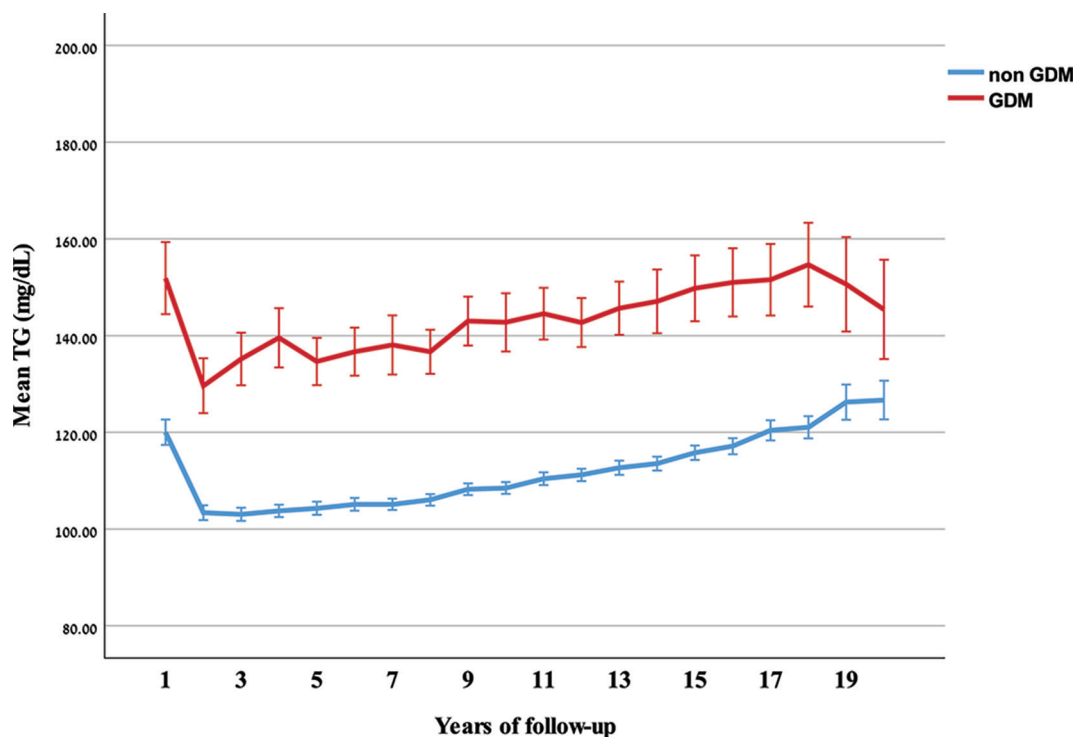
Figure 3 Mean and 95% CI of triglyceride (TG) over years of follow-up, by gestational diabetes mellitus (GDM) status.

dyslipidemia was 1.76 (95% CI 1.28 to 2.44) consistent with risk estimated calculated in the current analysis.

Decreased HDL and increased TGs are components of the metabolic syndrome, which has been well described in patients with GDM. In a cohort of women (n=481) with previous GDM, the OR for having the metabolic syndrome according to WHO guideline was 3.4 (95% CI 2.5 to 4.8), after adjustment for BMI and age, as compared with a population-based sample of age-matched women.[20] Similar relationships have been reported in other studies.[21] However, the observed association between GDM and elevated level of LDL-C, which is not specifically part of metabolic syndrome, requires more attention.

Previous analyses of LDL dyslipidemia among women with previous GDM have shown mixed results, while few studies[20 22 23] found no difference in postpartum LDL-C levels between GDM and control women without prior GDM, although some[22 23] included less than 20 patients and were statistically underpowered to avoid type 2 error. Subsequent studies[21 24] on larger cohorts and over longer postpartum follow-up have shown that GDM may confer an increase in LDL. In one study after 11 years of follow-up, 38% of women with GDM had LDL of 143 mg/dL or more, compared with 12% of controls. The association between gestational dysglycemia idea and elevated LDL cholesterol may, thus, contribute to the risk of cardiovascular disease (CVD) in women independently to metabolic syndrome. Elevated LDL-C levels are of specific concern among women with previous GDM in light of previous studies suggesting that women with GDM were characterized by a reduced mean LDL particle size and

preponderance of small dense LDL particles[25 26] that has a greater atherogenic potential than that of other LDL subfractions and contributes to endothelial dysfunction and atherosclerosis that may confer further increase in risk of CVD.

Our results may therefore provide evidence to explain the increased risk of cardiovascular in women with GDM history is not totally dependent on the intercurrent development of type 2 diabetes as was reported in a recently published meta-analysis involving more than 5 million women, where women with GDM were found to have a twofold higher risk of major cardiovascular events post partum. Moreover, our finding that dyslipidemia develops soon after delivery may also explain why despite their relative young age, the risk of CVD in women with GDM was evident by as early as the first decade after delivery. Hence, our data support the emerging concept that women with previous GDM demonstrate a chronic and long-standing dyslipidemia that may contribute to the development of CVD and its manifestation. Consequently, the diagnosis of GDM provides a unique opportunity to identify future risk of vascular disease in young women at an early point in the disease's natural history, when risk modification and primary prevention may potentially be feasible.

The study has several strengths. To the best of our knowledge, this is the largest study of postpartum lipid profile both in terms of number of patients with GDM and follow-up years. Data for this cohort study were systematically collected from computerized files, which make this less likely to be a potential source of bias. The bias resulting from high dropout rate is of a greater

Table 2 Mutually adjusted HRs (aHR) for outcome lipids

	aHR (95% CI)	aHR* (95% CI)
Outcome: TG		
GDM		
Yes versus no	1.80 (1.73 to 1.88)	1.59 (1.53 to 1.66)
Age		
Per year	1.02 (1.01 to 1.02)	1.01 (1.01 to 1.02)
BMI		
Normal	1 (0 to 0)	1 (0 to 0)
Overweight	2.3 (2.2 to 2.41)	2.22 (2.12 to 2.33)
Obese	3.32 (3.17 to 3.47)	2.75 (2.63 to 2.88)
Smoking		
Never	1	1
Past	1.08 (0.99 to 1.19)	1.12 (1.02 to 1.23)
Current	1.19 (1.14 to 1.24)	1.11 (1.06 to 1.15)
Outcome: LDL		
GDM		
Yes versus no	1.45 (1.38 to 1.52)	1.35 (1.29 to 1.42)
Age		
Per year	1.06 (1.06 to 1.06)	1.04 (1.03 to 1.04)
BMI		
Normal	1	1
Overweight	1.29 (1.23 to 1.36)	1.13 (1.08 to 1.19)
Obese	1.28 (1.21 to 1.35)	1.02 (0.97 to 1.08)
Smoking		
Never	1	1
Past	1.19 (1.08 to 1.32)	1.2 (1.09 to 1.32)
Current	1.22 (1.17 to 1.27)	0.97 (0.93 to 1.01)
Outcome: HDL-C		
GDM		
Yes versus no	1.44 (1.39 to 1.5)	1.34 (1.29 to 1.39)
Age		
Per year	0.99 (0.98 to 0.99)	0.99 (0.99 to 1)
BMI		
Normal	1	1
Overweight	1.74 (1.67 to 1.81)	1.43 (1.38 to 1.49)
Obese	2.63 (2.53 to 2.73)	1.81 (1.74 to 1.88)
Smoking		
Never	1	1
Past	1.14 (1.05 to 1.23)	1.14 (1.05 to 1.23)
Current	1.37 (1.33 to 1.42)	1.05 (1.02 to 1.08)

*Adjusted also for baseline level of outcome lipid.
BMI, body mass index; GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; TG, triglyceride.

importance in long follow-up studies after delivery, such as the present analysis. Therefore, the very low proportion of patients untested for lipids during the follow-up period is an important study advantage. An additional strength of the present database study is the very low turnover rate of the study population (approximately 10% discontinued membership during the entire study period), affording minimal loss to follow-up. Moreover, performance of lipid tests in MHS is free and readily available to all members country-wide. Furthermore, nearly 85% of our cohort were tested for fasting blood glucose during the follow-up period, reducing the potential surveillance bias resulting from closer diabetes screening of GDM women.

The external validity of the study population to the general Israeli population should be assessed. We used the computerized data of MHS—a national health organization that provides care to 25% of the national population. It has a country-wide distribution and the membership is free and open to every citizen. Moreover, the baseline characteristics of prepregnancy baseline characteristics in our study are very similar (Cohen's d<0.1) to the results of a recently published study of Jewish pregnant women in the largest health maintenance organization in Israel,[27] including age (31.07 years±5.08 years vs 30.9 years±6.04 years), HDL (54.2 mg/dL±12.5 mg/dL vs 54.4 mg/dL±13.3 mg/dL), and TG (104±62.5 vs 101±57.9). This underscores the generalizability of our study sample.

Our study has some important limitations that should be discussed. In the present analysis we were unable to characterize fully the metabolic characteristics of the cohort before and after the index pregnancy. This includes missing information on diet, and particularly, dietary carbohydrate consumption that may have affected lipid levels. Although data on weight measurements in the index pregnancy were available for the majority of research cohorts, increased intake of rapidly absorbable carbohydrates that is positively associated with GDM[28] may have explained some of the associations observed in our study. According to a recently published meta-analysis,[29] exercise has no significant effect on the overall risk of GDM. Therefore, it is unlikely that our analysis was confounded by lack of information on physical activity.[30]

Notwithstanding these limitations, our results demonstrate that women with previous GDM present significant increase in the risk of dyslipidemia indicating that increased awareness among caregivers, as well as postnatal interventions, should begin early after delivery focusing on healthy lifestyle modification to ameliorate the excess future risk of dyslipidemia and its complications.

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