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Prevalence of non-alcoholic fatty liver disease and factors associated with it in Indian women with a history of gestational diabetes mellitus

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ABSTRACT

Aims/Introduction: This study aims to evaluate the prevalence of and factors associated with non-alcoholic fatty liver disease (NAFLD) in Indian women with prior gestational diabetes mellitus (GDM) diagnosed using International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria.

Materials and Methods: This cross-sectional study (2018–2019) enrolled women with and without prior GDM. Study participants underwent detailed assessments, including relevant medical, obstetric and demographic details; 75-g oral glucose tolerance test with glucose and insulin estimation at 0, 30 and 120 min; and other relevant biochemical and anthropometric measurements. NAFLD status was defined by ultrasonography.

Results: We evaluated a total of 309 women (201 and 108 with and without prior GDM, respectively) at a mean age of 31.9 ± 5.0 years and median of 16 months (interquartile range 9–38 months) following the index delivery. The prevalence of NAFLD was significantly higher in women with prior GDM (62.7% vs 50.0%, $P = 0.038$; grade 2 and 3 disease, 13.9% vs 6.5%). On logistic regression analysis (fully adjusted model), the odds of NAFLD were 2.11-fold higher in women with prior GDM (95% confidence interval 1.16–3.85, $P = 0.014$). Overweight/obesity, metabolic syndrome, prediabetes and homeostasis model of assessment of insulin resistance (a measure of insulin resistance) were positively associated with NAFLD, whereas the Matsuda index (a measure of insulin sensitivity) showed a negative association with NAFLD.

Conclusions: The prevalence of NAFLD is high in women with prior GDM. Such women also have a high burden of cardiometabolic risk factors. Future studies should evaluate the intermediate and long-term hepatic and cardiovascular risk, and the impact of lifestyle interventions in reducing morbidity in such women.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), a hepatic manifestation of the metabolic syndrome, is a significant risk factor for liver and cardiovascular disease (CVD)[1–3]. The rising global epidemic of obesity and type 2 diabetes mellitus has resulted in a rapid increase in the number of cases with NAFLD. A meta-analysis of 86 studies from 22 countries found the prevalence of NAFLD to be 25.2% globally and 27.4% in Asia[4]. Various population-based studies from India have similarly reported a high prevalence of NAFLD, varying from 17 to 32%[5–7]. In patients with diabetes, the prevalence of NAFLD is even higher, reported at 55.5% in a recent meta-analysis of 80 studies[8].

Women with a history of gestational diabetes mellitus (GDM) are at an increased risk of developing diabetes and

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CVD compared with those without such history[9]. Because GDM and NAFLD are associated with a high burden of CVD and its risk factors, it would be of interest to study the combined impact of these conditions on various cardiometabolic risk factors. Although there is ample evidence on the prevalence of NAFLD in the general population and persons with diabetes, there has been limited information on the prevalence of this condition in women with prior GDM. The reported prevalence of NAFLD in women with prior GDM varies from 14 to 48%[10–13]. In a retrospective cohort study by Lavrentaki *et al.*[14], the unadjusted and adjusted incidence rate ratios for the development of NAFLD in women with previous GDM, compared with those without, were 3.28 and 2.70, respectively. The risk of NAFLD remained elevated, even after censoring women who developed type 2 diabetes mellitus (incidence rate ratio 2.48), suggesting an association of GDM with NAFLD independent of type 2 diabetes mellitus.

The previous studies recruited women diagnosed with GDM based on criteria other than those recommended by the International Association of Diabetes and Pregnancy Study Groups (IADPSG)[15]. Given the current global adoption of the IADPSG criteria, it becomes incumbent to carry out a study estimating NAFLD in women with a previous diagnosis of GDM based on these criteria. In South Asian people, CVD risk occurs at a lower age and body mass index (BMI) than white people[16]. We have previously reported a high prevalence of dysglycemia (41.5% prediabetes, 10.7% diabetes) in women with a history of GDM at a median follow up of 20 months after delivery[17]. The comparable conversion rates in the Hyperglycemia and Adverse Pregnancy Outcome cohort were observed much later, at 11.4 years postpartum[18].

Thus, considering the distinct South Asian phenotype, we aimed: (i) to estimate the prevalence of NAFLD in women with prior GDM diagnosed using the IADPSG criteria; and (ii) to evaluate factors associated with NAFLD in such women.

METHODS

Settings and study design

This was a cross-sectional study carried out from May 2018 to November 2019 at the Departments of Endocrinology and Metabolism, Radiodiagnosis and Gastroenterology, All India Institute of Medical Sciences, New Delhi, India (tertiary care hospital catering predominantly to a low- and middle-income population). The ethics committee of the institution approved the protocol (Ref. No. IECPG-166/19.04.2018, dated 23 April 2018). The work started after the ethics approval, and it conforms to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). All women gave written informed consent for participation.

Objectives

The primary objective was to evaluate and compare the prevalence of NAFLD in women with and without a previous history of GDM diagnosed using the IADPSG criteria[15]. The secondary objectives were to evaluate: (i) factors associated with NAFLD in women with a history of GDM; and (ii) differences in cardiometabolic risk factors, glycemic profile and insulin sensitivity among women with prior GDM with and without NAFLD.

Inclusion and exclusion criteria

Women diagnosed to have GDM according to the IADPSG criteria (presence of any one or more of three abnormal values ≥5.1, 10.0 or 8.5 mmol/L at 0, 1 and 2 h, after a 75-g glucose load delivered in a fasting state, respectively) during their index pregnancy between 2012 and 2019 were included in the study[15]. The study participants included a follow up of our previous cohort (2012–2016)[17], as well as fresh recruitments (2017 onwards). We also included women with normoglycemia during their index pregnancy. All women with normoglycemia in pregnancy were fresh recruits (2017 onwards), as our earlier cohort had no control group (women with normoglycemia in pregnancy). Study participants participated at least six months post-delivery.

Exclusion criteria included women with hyperglycemia other than GDM, such as overt diabetes in pregnancy or pre-existing diabetes mellitus. We excluded women who had diabetes at the time of study evaluation or were pregnant. We also excluded women with evidence of hepatitis B or hepatitis C infection (which were tested in each study participant with NAFLD), a known cause of liver disease, history of significant alcohol intake (>14 drinks/week; each drink: 10 g of alcohol) and a history of steroid intake in the past 1 year (except for the indication of fetal lung maturation during the antenatal period). Other exclusion criteria included a history of major organ impairment, chronic infections, connective tissue disorders, chronic inflammatory conditions and intake of other drugs known to cause fatty liver (Figure S1)[19].

Participant recruitment and procedure on the day of testing

Participants were recruited during their routine clinic visits or invited to participate through telephonic calls. We invited them to attend the center in a fasting state (minimum fast of 10 h). A detailed questionnaire was completed at the scheduled visit for all participants, documenting relevant personal and medical history. The details on anthropometric and biochemical parameters and their measurements including the method of oral glucose tolerance test administration and calculation of insulin indices, such as homeostasis model of assessment of insulin resistance (HOMA-IR; a marker of insulin resistance), insulinogenic index (a marker of insulin secretion) and disposition index (a marker of composite beta-cell function), were provided in our previous publication and as Appendix S1[17]. The Matsuda Index (a marker of insulin sensitivity) was calculated using an online web calculator[20]. Dietary assessment was carried out using a 24-h recall method. Physical activity was assessed using a validated global physical activity questionnaire (GPAQ)[21].

Definitions

Prediabetes and diabetes were defined by the American Diabetes Association criteria, overweight and obesity by the World Health Organization criteria, and metabolic syndrome by the International Diabetes Federation criteria (details provided in Appendix S1)[22–24]. Transaminitis was defined as aspartate aminotransferase or alanine aminotransferase level >40 IU/L[25].

Algorithm for the diagnosis of NAFLD

All study participants (cases and controls) underwent abdominal ultrasonography (USG) and FibroScan. Abdominal USG was carried out after a 10-h fast using the Supersonic Aixplorer Imagine (Supersonic, Aix-en-Provence, France) USG machine with a curvilinear probe (2–5 MHz). One of the two consultant radiologists (DK and AG) carried out the scan, and were blinded to the clinical data of study participants. Normal liver parenchyma has a homogeneous echotexture with echogenicity equal to or slightly higher than that of the renal cortex and spleen. Hepatic steatosis severity was graded as: grade 0, normal echogenicity; grade 1, diffusely increased hepatic echogenicity, but appreciable periportal and diaphragmatic echogenicity; grade 2, diffusely increased hepatic echogenicity obscuring periportal echogenicity, but appreciable diaphragmatic echogenicity; and grade 3, diffusely increased hepatic echogenicity obscuring periportal and diaphragmatic echogenicity[26].

FibroScan was carried out after a 10-h fast using FibroScan 502 Touch (Echosens, Paris, France) by trained personnel. The scan was carried out on the right lobe of the liver through an intercostal space; measurements were taken using the M/XL probe, as per the manufacturer's recommendations, and the XL probe was used for measurements in obese participants (BMI ≥30 kg/m^2). Controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) were estimated with FibroScan. A total of 10 successful acquisitions were carried out on each participant. The person who carried out the FibroScan was blinded to the clinical data of study participants. Hepatic steatosis was defined as CAP ≥270[27]. An LSM value of >6 kPa was defined as a marker of fibrosis[28].

Sample size calculation

With an anticipated NAFLD prevalence of 38 and 17%, respectively, among women with and without prior GDM[10], and accounting for a case : control enrolment ratio of 3:1, power of 80% and an alpha error of 0.05, 177 cases and 59 controls were required for the study.

Rationale for determining sample size with an intended 3:1 case : control enrolment ratio

The study participants included a follow up of our previous cohort (2012–2016)[10], as well as fresh recruitments (2017 onwards). Our earlier cohort included only women with previous GDM (cases). Therefore, whereas the cases for this study were enrolled from 2012 to 2019, the controls could only be recruited from 2017 onwards. Thus, the study recruitment mandated a higher case : control enrolment ratio. This is similar to a study by Foghsgaard *et al.*[12] (Diabetes care, 2017), where cases (women with prior GDM) were nearly 10-fold that of controls.

Statistical analysis

We carried out statistical analysis using Stata 12.0 (StataCorp, College Station, TX, USA). Data are presented as the number (%), mean ± standard deviation or median (interquartile range [IQR]), as appropriate. For qualitative variables, Pearson's χ^2-test or Fisher's exact test were used as appropriate. Student's *t*-test was used for the normally distributed quantitative variables. For quantitative variables without normal distribution (time since index delivery, triglycerides, HOMA-IR, insulinogenic index, disposition index, Matsuda Index and physical activity [MET hours per week]), the Wilcoxon rank-sum test was used. Logistic regression analysis was used to evaluate factors associated with NAFLD, and results expressed as odds ratio (95% confidence interval [CI]). The significance level was set at $P < 0.05$. The association between GDM (exposure) and NAFLD (outcome) was evaluated after adjustment for various covariates. In model 1, the covariates adjusted were age, economic status, education and employment, and the number of live births. In model 2, we adjusted for various postpartum parameters, including time since the index delivery, exclusive breast-feeding for ≥6 months, and subclinical or overt hypothyroidism at the time of current evaluation. Model 3 involved adjustment for all covariates listed in models 1 and 2. The rationale for the selection of covariates and subgroup analysis is as follows: age and postpartum intervals were expected to differ between cases and controls considering the recruitment for the study. As both can have a bearing on the outcome, these were adjusted. Education, employment and economic status are surrogate markers reflecting socioeconomic status, and are known risk factors associated with NAFLD. Similarly, multiparity (history of ≥2 deliveries), the absence of exclusive breast-feeding and hypothyroidism have reported associations with various metabolic conditions, including NAFLD, and were, therefore, adjusted. All adjusted variables were categorical, except for the postpartum interval. Age and exclusive breast-feeding categories were defined as ≥35 years (yes or no) and ≥6 months (yes or no). Considering the recruitment process, we expected the postpartum interval to be different between two groups, and hence carried out a subgroup analysis of cases (women with prior GDM) with a postpartum interval of <2 and >2 years.

RESULTS

Baseline characteristics

We evaluated a total of 309 women (201 and 108 with and without previous history of GDM, respectively) at a mean age of 31.9 ± 5.0 years and a median 16 months (IQR 9–38 months) after childbirth. All women without a previous history of GDM (controls) were enrolled between 6 and 24 months postpartum (median 9 months [IQR 7–

13 months]). Cases were significantly older compared with controls (mean age 33.0 ± 5.0 vs 29.8 ± 4.3 years; $P < 0.001$), had higher live births and were more likely to be employed (Table 1). The two groups were similar regarding the level of education and exclusive breast-feeding status (Table 1).

Prevalence of NAFLD in women with and without a previous history of GDM

The prevalence of NAFLD based on abdominal USG was significantly higher in women with prior GDM compared with those without (overall 62.7% vs 50.0%; $P = 0.038$; grade 2 and 3 13.9% vs 6.5%; Table 2). Similarly, a higher proportion of women with previous GDM had NAFLD by FibroScan (CAP value ≥270) compared with women without previous GDM (50.3% vs 28.0%, $P < 0.001$). Participants with LSM ≥6 were nearly twofold higher in cases (18.1%) compared with controls (9.4%; Table 2).

On logistic regression analysis, women with a previous history of GDM had 1.68-fold higher odds (95% CI 1.05–2.70) of having NAFLD than women without such history (Table 3). The odds ratios were found to increase further after adjustment for various covariates, being 2.11-fold higher (95% CI 1.16–3.85) in the fully adjusted model 3. On a subgroup analysis involving women with GDM matched for the postpartum duration with controls (6–24 months), the unadjusted odds ratio for NAFLD was even higher (1.93, 95% CI 1.07–3.47), and the results remained significant after adjustment in models 1 and 2. In women with GDM and postpartum duration >24 months, although the effect size remained >1.0 across unadjusted and adjusted models, the results were not statistically significant.

Burden of cardiometabolic risk factors

Women with prior GDM and NAFLD on USG ($n = 126$) had a higher burden of cardiometabolic risk factors than women with prior GDM and no NAFLD on USG ($n = 75$). The prevalence of prediabetes, overweight/obesity and metabolic syndrome was 64.3, 72.2 and 34.1%, respectively, in women with GDM and NAFLD compared with 44% ($P = 0.005$), 44% ($P < 0.001$) and 20% ($P = 0.033$) in women with GDM and no NAFLD. HOMA-IR was significantly higher (3.1 [1.8–4.3] vs 2.2 [1.6–3.1]; $P < 0.001$), whereas the Matsuda Index was significantly lower (3.0 [2.0–4.9] vs 4.2 [3.0–6.1]; $P < 0.001$) in women with GDM and NAFLD compared with women with GDM and no NAFLD (Table 4).

Women with GDM and NAFLD on USG and elevated CAP (>270) on FibroScan had significantly higher odds of having prediabetes (OR 4.4, 95% CI 2.5–8.0) and metabolic syndrome (OR 5.8, 95% CI 2.7–12.5) compared with those with GDM and no NAFLD on USG and CAP value <270 on FibroScan.

Factors associated with NAFLD in women with GDM

On logistic regression analysis, being overweight/obese at the time of testing (OR 3.31, 95% CI 1.82–6.03), having prediabetes

Table 1 | Baseline characteristics of the study population

Variable	Total ($n = 309$)	Women with previous GDM (cases) ($n = 201$)	Women without previous GDM (controls) ($n = 108$)	*P*-value
Demographic				
Age at current testing (years)	31.9 ± 5.0	33.0 ± 5.0	29.8 ± 4.3	<0.001
BMI at time of testing (kg/m^2)	26.3 ± 4.6	26.9 ± 4.7	25.0 ± 4.3	<0.001
Annual economic status[†]				
<INR 20,000	63 (22.2)	37 (19.5)	26 (27.7)	0.118
Working status (employed)	60 (19.4)	47 (23.4)	13 (12.0)	0.016
Education (graduate or above)	207 (67.0)	137 (68.2)	70 (64.8)	0.551
Antenatal				
No. live births ≥2	135 (43.7)	104 (51.7)	31(28.7)	<0.001
No. previous pregnancies ≥1	231 (74.8)	164 (81.6)	67 (62.0)	<0.001
Postpartum				
Time since last delivery (months)	16 (9–38)	32 (12–51)	9 (7–13)	<0.001
Exclusive breast-feeding for ≥6 months[‡]	220 (71.4)	142 (71.0)	78 (72.2)	0.821
Hypothyroidism (subclinical/overt)[§]	98 (32.1)	58 (29.4)	40 (37.0)	0.174
Present OGTT 0 min value (mmol/L)	5.0 ± 0.5	5.2 ± 0.6	4.8 ± 0.5	<0.001
Present OGTT 30min value (mmol/L)[‡]	8.2 ± 1.7	8.6 ± 1.7	7.4 ± 1.5	<0.001
Present OGTT 120 min value (mmol/L)	6.3 ± 1.5	6.6 ± 1.6	5.8 ± 1.3	<0.001
HbA1c (mmol/mol)	36.1 ± 4.5	36.9 ± 4.6	34.6 ± 4.1	<0.001
HbA1c (%)	5.5 ± 0.4	5.5 ± 0.4	5.3 ± 0.4	<0.001

Data are presented as the mean ± standard deviation, median (25th–75th quartile) or *n* (%). BMI, body mass index; GDM, gestational diabetes mellitus; HbA1c, hemoglobin A1c; INR, Indian rupees; OGTT, oral glucose tolerance test. [†]$n = 284$ (190 and 94 respectively for columns 3 and 4). [‡]$n = 308$ (200 for column 3). [§]$n = 305$ (197 for column 3).

Table 2 | Comparison of non-alcoholic fatty liver disease prevalence and liver parameters in women with and without previous gestational diabetes mellitus

Variable	Total (n = 309)	Women with GDM (cases) (n = 201)*	Women with GDM (<2 years) (n = 85)	Women with GDM (>2 years) (n = 116)	Women without GDM (controls) (n = 108)*	P-value*
NAFLD (any grade)	180 (58.3)	126 (62.7)	56 (65.9)	70 (60.3)	54 (50.0)	0.038
Grade 1 NAFLD	145 (46.9)	98 (48.8)	42 (49.4)	56 (48.3)	47 (43.5)	
Grade ≥2 NAFLD	35 (11.3)	28 (13.9)	14 (16.5)	14 (12.1)	7 (6.5)	
CAP ≥270[†]	127 (42.3)	97 (50.3)	43 (53.1)	54 (48.2)	30 (28.0)	<0.001
LSM ≥6[†]	45 (15.0)	35 (18.1)	6 (7.4)	29 (25.9)	10 (9.4)	0.041
AST >40 IU/L[‡]	15 (4.9)	9 (4.5)	4 (4.7)	5 (4.4)	6 (5.6)	0.681
ALT >40 IU/L[‡]	40 (13.0)	26 (13.0)	10 (11.8)	16 (13.9)	14 (13.0)	0.993

Data are presented as n (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; NAFLD, non-alcoholic fatty liver disease. *P-value for comparison of parameters between women with and without gestational diabetes mellitus (GDM) in previous pregnancy (columns 3 and 6, respectively); P-value not provided for subgroup analysis. [†]n = 300 (193,81, 112 and 107, respectively for columns 3, 4, 5 and 6). [‡]n = 308 (200 and 115, respectively for columns 3 and 5).

Table 3 | Unadjusted and adjusted odds ratios (95% confidence intervals) for the association between prior gestational diabetes status and non-alcoholic fatty liver disease

Variable	Unadjusted OR	Model 1[†]	Model 2[‡]	Model 3[§]
Exposure variable: gestational diabetes mellitus				
NAFLD	1.68 (1.05–2.70)	1.76 (1.04–3.00)	2.03 (1.16–3.56)	2.11 (1.16–3.85)
P-value	0.032	0.036	0.013	0.014
Exposure variable: gestational diabetes mellitus (<2 years)				
NAFLD	1.93 (1.07–3.47)	2.03 (1.07–3.86)	1.91 (1.06–3.46)	2.01 (1.05–3.83)
P-value	0.028	0.031	0.032	0.035
Exposure variable: gestational diabetes mellitus (>2 years)				
NAFLD	1.52 (0.90–2.58)	1.32 (0.71–2.46)	2.40 (0.86–6.70)	2.72 (0.92–8.09)
P-value	0.120	0.385	0.096	0.072

Reference category for comparisons being women with normoglycemia in pregnancy. NAFLD, non-alcoholic fatty liver disease; OR, odds ratio. [†]Model 1: Adjusted for age (≥35 years), economic status, occupation, education and live birth. [‡]Model 2: Adjusted for time since last delivery, exclusive breast feeding for ≥6 months and hypothyroidism. [§]Model 3: model 1 + model 2.

(OR 2.29, 95% CI 1.28–4.11) and having metabolic syndrome (OR 2.07, 95% CI 1.06–4.07) were positively associated with the presence of NAFLD. A significant association was observed for per unit increase in HOMA-IR (OR 1.54, 95% CI 1.23–1.93) and Matsuda Index (OR 0.78, 95% CI 0.69–0.90; Table 5).

DISCUSSION

We observed a high prevalence of NAFLD in Indian women with a history of GDM diagnosed using the IADPSG criteria. Women with prior GDM and NAFLD had a higher burden of cardiometabolic risk factors than those with prior GDM and no NAFLD. Overweight/obesity, metabolic syndrome, prediabetes and HOMA-IR were positively associated with NAFLD, whereas the Matsuda Index showed a negative association with NAFLD.

The prevalence of NAFLD in women with prior GDM was 62.7%. This estimate is higher than that reported in previous studies (Table 6)[10–13]. Importantly, the current study reported a higher prevalence of NAFLD, despite the study participants being younger and leaner (lower BMI) compared with previous studies. However, these results are not surprising, given that South Asian people are known to develop a high burden of CVD risk factors at a younger age and lower BMI than white people. The study by Ajmera *et al.*[11] reported a NAFLD prevalence of 14%, which is lower compared with the current study and other studies. This difference could be attributed to the use of computed tomography to determine NAFLD in their study compared with USG in other studies. We know that computed tomography has limited sensitivity for the diagnosis of mild hepatic steatosis compared with USG[29].

We also used FibroScan in the present study for the documentation of hepatic steatosis. FibroScan has been validated for the assessment of hepatic steatosis and fibrosis in NAFLD[30]. The prevalence of NAFLD by FibroScan was significantly high, at 50.3% in women with prior GDM, compared with 28.0% in

Table 4 | Comparison of cardiometabolic risk factors and insulin-related parameters among women with prior gestational diabetes mellitus with and without non-alcoholic fatty liver disease

Variable	GDM with NAFLD (n = 126)	GDM without NAFLD (n = 75)	P-value
Prediabetes	81 (64.3)	33 (44.0)	0.005
Systolic BP (mmHg)	108.3 ± 12.1	105.6 ± 9.6	0.102
Systolic BP ≥140 mmHg	2 (1.6)	0 (0.0)	0.530
Diastolic BP (mmHg)	73.3 ± 9.7	70.6 ± 8.8	0.0502
Diastolic BP ≥90 mmHg	6 (4.8)	2 (2.7)	0.713
Metabolic syndrome	43 (34.1)	15 (20.0)	0.033
BMI (kg/m^2)	27.9 ± 4.6	25.3 ± 4.4	<0.001
BMI ≥25 kg/m^2	91 (72.2)	33 (44.0)	<0.001
Waist circumference (cm)	94.3 ± 10.7	87.8 ± 10.9	<0.001
Waist circumference ≥80 cm	114 (90.5)	58 (77.3)	0.010
Total cholesterol (mmol/L)[†]	4.4 ± 0.8	4.4 ± 0.9	0.960
Total cholesterol ≥5.2 mmol/L[†]	27 (21.4)	12 (16.2)	0.369
LDL-C (mmol/L)[†]	2.6 ± 0.7	2.7 ± 0.8	0.784
LDL-C ≥2.6 mmol/L[†]	61 (48.4)	38 (51.4)	0.688
HDL-C (mmol/L)[†]	1.2 ± 0.3	1.2 ± 0.2	0.429
HDL-C <1.29 mmol/L[†]	85 (67.5)	41 (55.4)	0.088
Triglyceride (mmol/L)[†]	1.2 (0.9–1.6)	1.1 (0.9–1.3)	0.044
Triglyceride ≥1.7 mmol/L[†]	26 (20.6)	9 (12.2)	0.128
HOMA-IR[†]	3.1(1.8–4.3)	2.2 (1.6–3.1)	<0.001
Insulinogenic index ($pmol_{ins}/mmol_{glu}$)[‡]	148.6 (105.2–229.2)	157.4 (85.6–288.2)	0.798
Disposition index ($L/mmol_{glu}$)[‡]	1.7 (1.1–2.9)	2.4 (1.4–3.9)	0.010
Matsuda Index[‡]	3.0 (2.0–4.9)	4.2 (3.0–6.1)	<0.001
Physical activity (MET hours per week)[‡]	51.7 (32.3–70.0)	50.2 (22–74)	0.438
Physical activity (MET hours per week) ≥20[‡]	18 (14.5)	18 (24.3)	0.083
Calories from carbohydrates (kcal/day)	1012.6 ± 262.3	1062.6 ± 250.2	0.185
Calories from fats (kcal/day)	390.1 ± 151.6	413.8 ± 162.0	0.299
Calories from proteins (kcal/day)	210.6 ± 59.5	221.7 ± 62.6	0.208
Fiber (g/day)	22.2 ± 6.6	23.9 ± 8.5	0.112
Total calorie intake (kcal/day)	1613.2 ± 390.8	1700.4 ± 399.1	0.132

Data are presented as the mean ± standard deviation, median (q25–q75) or n (%). BMI, body mass index; BP, blood pressure; GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model of assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; LSM, liver stiffness measurement; MET, metabolic equivalent; NAFLD, non-alcoholic fatty liver disease. [†]n = 74 for column 3. [‡]n = 121 and 74, respectively for columns 2 and 3. [§]n = 124 and 74, respectively for columns 2 and 3.

women without prior GDM. In addition, 18.1% of women in the prior GDM group had LSM values ≥6 (suggestive of any grade of hepatic fibrosis) compared with just 9.4% of women in the control group.

On logistic regression analysis, overweight/obesity (BMI ≥25 kg/m^2), metabolic syndrome and prediabetes showed a significant positive association with NAFLD. In addition, HOMA-IR and the Matsuda Index showed significant positive and negative associations, respectively. These findings are consistent with the reported literature and highlight the role of insulin resistance in the pathophysiology of NAFLD[10,12]. We also found a high burden of cardiometabolic risk factors in women with prior GDM and NAFLD. In addition, the odds of having prediabetes and metabolic syndrome were four- to six-fold higher in women with prior GDM and NAFLD on both modalities, compared with those with prior GDM and no NAFLD.

Notably, the prevalence of NAFLD was unusually high in our control group; that is, 50%, compared with that reported in the general population; that is, 17–32%. It is difficult to comment on the difference in the absence of previous data from the South Asian region in this subpopulation. It could be speculated that these women had adverse fat accumulation during pregnancy, which persisted or further increased in the postpartum period. A study involving longitudinal follow up and serial assessments of liver fat in the postpartum period among women with normoglycemia in pregnancy would be useful.

The present study suggests that the prevalence of NAFLD is high in women with prior GDM. The presence of NAFLD is associated with higher insulin resistance and lower β-cell function, and a high burden of CVD risk factors at a relatively young age. From a clinical and research perspective, it will be of interest to longitudinally follow these high-risk women to evaluate the accumulation of new CVD risk factors and the

Table 5 | Factors associated with non-alcoholic fatty liver disease among women with gestational diabetes mellitus on univariate regression analysis

Variable	No. participants	Bivariate OR (95% CI)	*P*-value
Age ≥35 years	201	0.76 (0.42–1.37)	0.364
Occupation	201	0.75 (0.39–1.46)	0.397
Education	201	0.83 (0.45–1.54)	0.556
Economic status	190	0.76 (0.36–1.64)	0.490
Use of insulin and/or OAD during pregnancy	200	2.09 (0.98–4.43)	0.056
Subclinical/overt hypothyroidism	197	1.17 (0.62–2.22)	0.629
Exclusively breast-fed for 6 months or more	200	0.85 (0.46–1.60)	0.619
BMI ≥25 kg/m^2	201	3.31 (1.82–6.03)	<0.001
Hypertension	201	2.81 (0.59–13.36)	0.195
Prediabetes	201	2.29 (1.28–4.11)	0.005
Metabolic syndrome	201	2.07 (1.06–4.07)	0.034
Physical activity (MET hours per week) ≥20	198	0.53 (0.25–1.10)	0.086
Total calorie intake (per 100 kcal)	201	0.95 (0.88–1.02)	0.133
HOMA-IR	200	1.54 (1.23–1.93)	<0.001
Matsuda index	198	0.78 (0.69–0.90)	<0.001

BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; HOMA-IR, homeostasis model of assessment of insulin resistance; MET, metabolic equivalent; NAFLD, non-alcoholic fatty liver disease; OAD, oral antidiabetic agent; OR, odds ratio.

Table 6 | Comparison of studies evaluating the burden of non-alcoholic fatty liver disease in women with history of gestational diabetes mellitus

Study, country, year, reference	Criteria for GDM diagnosis	Sample size	Controls	Modality for liver fat assessment	Age (years)	BMI (kg/m^2)	Prevalence of NAFLD (%)
Forbes *et al.*, UK, 2010[10]	WHO criteria	110	Yes	USG	39.0 ± 1.0	28.9 ± 0.6	38
Ajmera *et al.*, USA, 2016[11]	Self-reported	124	Yes	CT	51.0 ± 8.0	31.1 (12.3)	14
Foghsgaard *et al.*, Denmark, 2017[12]	Danish criteria	100	Yes	USG	36.9 ± 5.6 (GDM, NAFLD) 39.0 ± 5.6 (GDM, no NAFLD)	34.6 ± 4.7 (GDM, NAFLD) 29.9 ± 4.7 (GDM, no NAFLD)	24
Mahmood *et al.*, Canada, 2018[13]	NDDG criteria	97	Yes	USG	NA	NA	48.4
Present study, India, 2020	IADPSG	201	Yes	USG	33.0 ± 5.0	27.9 ± 4.6 (GDM, NAFLD) 25.3 ± 4.4 (GDM, no NAFLD)	62.7

Data expressed as the mean ± standard deviation or median (25th–75th quartile). BMI, body mass index; CT, computed tomography; GDM, gestational diabetes mellitus; IADPSG, International Association of Diabetes and Pregnancy Study Groups; NAFLD, non-alcoholic fatty liver disease; NDDG, National Diabetes Data Group; USG, ultrasonography; WHO, World Health Organization.

progression of the existing risk factors. The long-term development of CVD and NAFLD-related liver diseases, such as cirrhosis and hepatocellular carcinoma, also need to be studied. Enrolling such high-risk women in an intensive lifestyle intervention program might be beneficial in reducing future hepatic and cardiovascular risk. However, these benefits need formal demonstration in a randomized controlled trial.

The strengths of the present study include a high-risk South Asian population where no previous data exist, large sample size, use of both USG and FibroScan to document hepatic steatosis, and comprehensive evaluation of CVD risk factors. In addition, this is the first study to document the burden of NAFLD in women with a history of GDM diagnosed by the IADPSG criteria – previous studies based the diagnosis of GDM on criteria other than these. With the increasing recognition and acceptability of the IADPSG criteria globally, the results of the present study assume further significance.

We acknowledge certain limitations of the present study. Cases and controls enrolled in the study were not matched for postpartum interval and age. However, these were adjusted appropriately in the analysis. We found that the prevalence of NAFLD in cases matched for the postpartum interval with controls; that is, 6–24 months was not different for those with the postpartum interval of >24 months. We did not carry out a

liver biopsy or magnetic resonance imaging derived proton-density-fat-fraction imaging, a modality known to provide accurate and reproducible quantification of liver fat[31]. However, liver biopsy is invasive, and magnetic resonance imaging derived proton-density-fat-fraction has limitations in terms of availability, cost and patient compliance.

The prevalence of NAFLD is very high in Indian women with a history of GDM diagnosed using the IADPSG criteria. Such women also have a high burden of cardiometabolic risk factors. Future studies should evaluate the intermediate and long-term hepatic and cardiovascular risk, and the impact of lifestyle interventions in reducing morbidity in such women.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Figure showing recruitment of participants.
Appendix S1 | Measurement details and definitions.