Diabetologia (2019) 62:306–310
https://doi.org/10.1007/s00125-018-4775-z

SHORT COMMUNICATION

Gestational diabetes in young women predicts future risk of serious liver disease

Ravi Retnakaran[1,2,3] · Jin Luo[4] · Baiju R. Shah[3,4,5,6]

Received: 16 July 2018 / Accepted: 3 October 2018 / Published online: 13 November 2018

Abstract

Aims/hypothesis In common with type 2 diabetes, gestational diabetes mellitus (GDM) is associated with a propensity for hepatic fat deposition. We hypothesised that GDM predicts future lifetime risk of serious liver-disease outcomes, such as cirrhosis, liver failure and need for transplantation.

Methods From population-based administrative databases, we identified all women in Ontario, Canada, who had a pregnancy resulting in live birth between April 1994 and March 2002 ($N = 698{,}078$). This population was stratified into individuals with ($n = 17{,}932$) and without ($n = 680{,}146$) GDM, and both groups were further stratified according to subsequent development of type 2 diabetes in the years after delivery. The median follow-up for the development of serious liver disease (defined as hospitalisation for cirrhosis, liver failure or transplantation) was 14.0 years.

Results Women with GDM had a higher risk of serious liver disease than those without GDM ($n = 680{,}146$; HR = 1.40, 95% CI 1.01, 1.94). Compared with women who did not have GDM and did not develop diabetes ($n = 635{,}998$), those with GDM who subsequently developed type 2 diabetes ($n = 8567$) had a higher risk of serious liver disease (adjusted HR = 1.56, 95% CI 1.02, 2.39), as did those without GDM who developed type 2 diabetes ($n = 44{,}148$; adjusted HR = 2.48, 95% CI 2.10, 2.93), but not those with GDM who did not develop type 2 diabetes ($n = 9365$; adjusted HR = 1.15, 95% CI 0.69, 1.91).

Conclusion/interpretation GDM is associated with future risk of serious liver disease in young women, the development of which may be dependent upon progression to non-gestational diabetes.

Keywords Cirrhosis · Gestational diabetes · Liver disease · Liver failure · Transplantation

Abbreviations

CVD	Cardiovascular disease
GDM	Gestational diabetes mellitus
ODD	Ontario Diabetes Database

Introduction

A diagnosis of gestational diabetes mellitus (GDM) provides a unique opportunity to identify future risk of cardiometabolic disease in young women long before any clinical manifestation [1]. Indeed, women with GDM have a higher risk than those without GDM of ultimately developing type 2 diabetes and cardiovascular disease (CVD) [1]. In common with non-gestational diabetes, GDM is associated with a propensity for hepatic fat deposition [2–5]. However, it is not known whether GDM is associated with the risk of serious liver-disease

✉ Baiju R. Shah
baiju.shah@ices.on.ca

1 Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada

2 Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Toronto, ON, Canada

3 Division of Endocrinology, University of Toronto, Toronto, ON, Canada

4 Institute for Clinical and Evaluative Sciences, Toronto, ON, Canada

5 Department of Medicine, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Room G106, Toronto, ON M4N 3M5, Canada

6 Institute for Health Policy Management and Evaluation, University of Toronto, Toronto, ON, Canada

Research in context

What is already known about this subject?

- Women who develop gestational diabetes mellitus (GDM) have a propensity for hepatic fat deposition
- The relationship between GDM-associated hepatic fat deposition and serious liver-disease outcomes is yet to be determined

What is the key question?

- Do women with GDM have a risk of serious liver-disease outcomes (such as cirrhosis, liver failure and transplantation) later in life, and is the risk related to subsequent development of type 2 diabetes?

What are the new findings?

- Women with a history of GDM have a higher risk of serious liver disease later in life than women with pregnancies unaffected by GDM
- Among women with a history of GDM, an elevated risk of serious liver disease is only evident in those who subsequently progress to type 2 diabetes after pregnancy

How might this impact on clinical practice in the foreseeable future?

- A diagnosis of GDM may provide an opportunity to identify a risk of advanced liver disease in young women long before its clinical manifestation, thereby enabling risk modification and possible prevention of these serious outcomes

outcomes (such as cirrhosis, liver failure and transplantation) later in life. Thus, our objective was to evaluate the long-term risk of serious liver disease in women with a history of GDM and the potential role of subsequent progression to type 2 diabetes.

Methods

A population-based cohort study was conducted using healthcare administrative databases from the Ministry of Health and Long-Term Care of Ontario, Canada. These databases include discharge abstracts from all hospitalisations in the province, physician service claims for reimbursement for virtually all consultations, procedures and visits, and demographic data for all residents eligible for healthcare in Ontario. The Ontario Diabetes Database (ODD) is a validated registry of physician-diagnosed non-gestational diabetes that is derived from these data [6]. The MOMBABY database is derived from hospitalisation data, and links hospitalisation records of delivering mothers with their neonates. Individuals are linked across data sources through a unique and reproducibly-encrypted health-card number. The use of data in this study was authorised under section 45 of Ontario's *Personal Health Information Protection Act*, which does not require review by a Research Ethics Board.

The study population consisted of all women aged 15–54 years who had a live-birth delivery between April 1994 and March 2002. Individuals who died or emigrated prior to March 2002 were excluded. Women with pre-gestational diabetes (identified through ODD) were excluded, as were those who had liver-disease comorbidity encoded on their delivery hospitalisation records. For women with multiple eligible pregnancies, the most recent was selected. Baseline characteristics that were recorded for each woman were age at index delivery, socioeconomic status (ascertained from the neighbourhood household-income quintile), rurality of residence, hypertension and dyslipidaemia. Individuals with South Asian or Chinese ethnicity were identified, as previously described [7].

The presence or absence of GDM in the index pregnancy was ascertained from diagnostic codes associated with the delivery hospitalisation. Each group was further divided into those who did or did not develop incident diabetes during follow-up, based on postpartum entry into the ODD.

All women were followed for outcome events from April 2002 until March 2016; the available data did not permit outcome ascertainment prior to this window. The primary outcome was serious liver disease, defined as hospitalisation for cirrhosis, liver failure or liver transplantation. The crude incidence of serious liver disease during follow-up was ascertained for GDM and non-GDM groups, and for the four groups that were obtained by further stratification according to the development of diabetes. Baseline characteristics were compared using *t* tests for continuous variables and χ^2 tests for categorical variables. Cox proportional hazards regression with left truncation to April 2002 was used for modelling of the independent association of GDM and/or subsequent diabetes with serious liver-disease outcomes. Data were censored for death, end of healthcare eligibility or end of follow-up.

Models were constructed unadjusted or with adjustment for age, income, rurality, hypertension and dyslipidaemia. Because Asian ethnicity is associated with both GDM and liver-disease outcomes, a third model was constructed with further adjustment for ethnicity. Analyses were performed using SAS Enterprise Guide version 6.1 (Cary, NC, USA).

Results

The study population ($N = 698,078$) consisted of 17,932 women who had GDM and 680,146 who did not have GDM (Table 1). Consistent with known risk factors, women with GDM had a higher mean age than women without GDM, and were more likely to be of Chinese or South Asian ethnicity, more likely to be living in an urban setting, and more likely to have a low income (all $p < 0.001$). Diagnoses of hypertension and dyslipidaemia were also more common in women with GDM (both $p < 0.001$). Development of type 2 diabetes in the years after pregnancy was far more common in women with GDM than in those without GDM (47.8% vs 6.5%, $p < 0.001$).

Outcome ascertainment began in April 2002 (a mean of 3.6 years after delivery) and continued for 14.0 years. Women who had GDM had an elevated risk of serious liver disease compared with those without GDM (HR = 1.40, 95% CI 1.01, 1.94), although the absolute event rates were modest in both groups (15 and 11 events per 100,000 person-years, respectively). The groups were further stratified on the basis of incident diabetes. Among women with GDM, the event rate was higher in those who subsequently developed diabetes than in those who did not (19 and 12 events per 100,000 person-years, respectively). Similarly, among women who did not have GDM, the event rate was higher in those who developed diabetes than in those who did not (29 and 10 events per 100,000 person-years, respectively).

To explore the relationship between GDM and postgestational diabetes in the development of serious liver disease, we determined the HRs (relative to a reference group of women with neither GDM nor type 2 diabetes) in (i) women with GDM who later developed type 2 diabetes, (ii) women with GDM who did not develop type 2 diabetes and (iii) women without GDM who later developed type 2 diabetes (Table 2). The risk of serious liver disease was elevated in both groups of women who went on to develop diabetes: HR = 1.88, 95% CI 1.23, 2.87, $p = 0.004$ in women with GDM; and HR = 2.76, 95% CI 2.35, 3.25, $p < 0.0001$ in women without GDM (model I). The risk was not elevated in women with GDM who did not develop diabetes (HR = 1.26, 95% CI 0.76, 2.09, $p = 0.38$). This pattern remained after adjustment for age, income, region of residence, hypertension and dyslipidaemia (model II) and after further adjustment for ethnicity (model III), as shown in Table 2.

Table 1 Characteristics of the study population according to the presence or absence of GDM

Variable	No GDM (n = 680,146)	GDM (n = 17,932)	p value[a]
Age (years), mean ± SD	29.7 ± 5.5	32.0 ± 5.1	<0.001
Ethnicity, n (%)			<0.001
Chinese	26,047 (3.8)	1056 (5.9)	
South Asian	22,632 (3.3)	1279 (7.1)	
Other	631,467 (92.8)	15,597 (87.0)	
Income quintile, n (%)			<0.001
Lowest	155,291 (22.8)	4939 (27.5)	
Second	139,598 (20.5)	3825 (21.3)	
Third	135,894 (20.0)	3599 (20.1)	
Fourth	134,143 (19.7)	3181 (17.7)	
Highest	112,159 (16.5)	2239 (12.5)	
Missing	3061 (0.5)	149 (0.8)	
Residency, n (%)			<0.001
Urban	505,575 (74.3)	14,387 (80.2)	
Semi-urban	123,790 (18.2)	2373 (13.2)	
Rural	43,310 (6.4)	797 (4.4)	
Missing	7471 (1.1)	375 (2.1)	
Hypertension, n (%)	11,066 (1.6)	769 (4.3)	<0.001
Dyslipidaemia, n (%)	8430 (1.2)	511 (2.8)	<0.001
Subsequent diabetes, n (%)	44,148 (6.5)	8567 (47.8)	<0.001

[a] p values calculated from t tests for age and from χ^2 tests for other variables

Table 2 Cox proportional hazards regression modelling of the association of GDM and/or subsequent diabetes with serious liver-disease outcomes

Model	HR	95% CI	p value
Model I			
GDM with subsequent diabetes	1.88	1.23, 2.87	0.004
GDM without subsequent diabetes	1.26	0.76, 2.09	0.38
No GDM, with subsequent diabetes	2.76	2.35, 3.25	<0.0001
Model II			
GDM with subsequent diabetes	1.54	1.01, 2.36	0.047
GDM without subsequent diabetes	1.11	0.67, 1.86	0.68
No GDM, with subsequent diabetes	2.47	2.09, 2.91	<0.0001
Model III			
GDM with subsequent diabetes	1.56	1.02, 2.39	0.04
GDM without subsequent diabetes	1.15	0.69, 1.91	0.60
No GDM, with subsequent diabetes	2.48	2.11, 2.93	<0.0001

For HRs, the reference group was women who had neither GDM nor subsequent diabetes. HRs were adjusted for the following covariates: model I, unadjusted; model II, adjusted for age, income, region of residence, hypertension and dyslipidaemia; model III, adjusted for covariates in model II and also for ethnicity

Discussion

Results from several studies have indicated that women with previous GDM have a higher prevalence of fatty liver than those without GDM [2–5, 8]. Liver fat identified by ultrasonography in early pregnancy can predict subsequent gestational dysglycaemia, suggesting that hepatic steatosis precedes the development of GDM [9]. In addition, pre-gravid serum levels of γ-glutamyl transferase can predict the risk of GDM in a subsequent pregnancy [10]. Altogether, these data suggest that women who develop GDM have a chronic predisposition to hepatic fat deposition that is present both before and after pregnancy. However, it is not known whether these women ultimately progress to the serious clinical outcomes of advanced liver disease.

The results of the current study extend our knowledge by demonstrating that GDM is associated with the risk for future development of serious liver outcomes. Although absolute event rates in our population were modest, these hepatic outcomes are very serious, and are associated with considerable morbidity and mortality. We identified a GDM-associated risk of serious outcomes over a 14.0 year median follow-up in a population with a mean age at baseline of 32.0 years, and it is possible that this risk will increase as the population progresses into middle age.

Among women with GDM, we only identified a significant risk of serious liver disease in the subgroup of those who progressed to post-gestational diabetes. Notably, in a similar population, significant HRs for microvascular pathologies requiring vitrectomy/photocoagulation or renal dialysis were only found to occur in the subgroup of women with GDM who developed type 2 diabetes, whereas significant HRs for macrovascular CVD outcomes occurred in women with GDM with or without subsequent development of diabetes [1]. The clinical implications of these relationships are that although the propensity for hepatic fat accumulation in women with a history of GDM suggests that there may be benefits to some degree of clinical monitoring of this group, efforts that focus on the prevention of post-gestational diabetes in this population could contribute to mitigation of the risk of serious liver-disease outcomes.

We cannot exclude the possibility that women with GDM who did not progress to type 2 diabetes during this study could still be at risk of developing serious liver disease in the future, particularly as the population was fairly young. In addition, it is possible that some women in our population may have developed liver disease in the time between delivery and the onset of outcome ascertainment in April 2002 (a mean of 3.6 years postpartum). However, given the infrequency of the outcome, very few women are likely to have been affected by this possibility. Another limitation of our study is that the administrative databases we used did not track some potentially important clinical risk factors, such as alcohol intake and body weight. Notably, obesity is a risk factor for GDM, type 2 diabetes and liver disease, and could therefore be an important factor in the relationships that we have described. Conversely, however, our use of population-based data made it possible to study the effects of both GDM and post-gestational diabetes in all parous women in the population, and to demonstrate the long-term risk of serious liver outcomes following GDM.

Acknowledgements The authors wish to thank P. Austin, Institute for Clinical Evaluative Sciences, for his assistance with statistical analyses. RR holds the Boehringer Ingelheim Chair in Beta-cell Preservation, Function and Regeneration at Mount Sinai Hospital and his research programme is supported by the Sun Life Financial Program to Prevent Diabetes in Women. The Institute for Clinical Evaluative Sciences (ICES) is a not-for-profit research institute funded by the Ontario Ministry of Health and Long-Term Care (MOHLTC). Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information (CIHI). No endorsement by ICES, the MOHLTC or CIHI is intended, or should be inferred. The opinions, results and conclusions reported in this study are those of the authors, and are independent of the funding sources. Some of the data were presented in an abstract at the 78th Scientific Sessions of the ADA, Orlando, in 2018.

Data availability The datasets analysed during the study are not publicly available.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement RR conceived the hypothesis and wrote the manuscript. RR and BRS designed the analysis plan. JL performed the statistical analyses. All authors interpreted the data and critically revised the manuscript for important intellectual content. All authors approved the final manuscript. BRS had full access to all of the data in the study and is responsible for the integrity of the work as a whole.

References

1. Retnakaran R, Shah BR (2017) Role of type 2 diabetes in determining retinal, renal, and cardiovascular outcomes in women with previous gestational diabetes mellitus. Diabetes Care 40(1):101–108. https://doi.org/10.2337/dc16-1400
2. Prikoszovich T, Winzer C, Schmid AI et al (2011) Body and liver fat mass rather than muscle mitochondrial function determine glucose metabolism in women with a history of gestational diabetes mellitus. Diabetes Care 34(2):430–436. https://doi.org/10.2337/dc10-1002
3. Forbes S, Taylor-Robinson SD, Patel N, Allan P, Walker BR, Johnston DG (2011) Increased prevalence of non-alcoholic fatty liver disease in European women with a history of gestational diabetes. Diabetologia 54(3):641–647. https://doi.org/10.1007/s00125-010-2009-0
4. Foghsgaard S, Andreasen C, Vedtofte L et al (2017) Nonalcoholic fatty liver disease is prevalent in women with prior gestational diabetes mellitus and independently associated with insulin resistance and waist circumference. Diabetes Care 40(1):109–116. https://doi.org/10.2337/dc16-1017

5. Ajmera VH, Gunderson EP, VanWagner LB, Lewis CE, Carr JJ, Terrault NA (2016) Gestational diabetes mellitus is strongly associated with non-alcoholic fatty liver disease. Am J Gastroenterol 111(5):658–664. https://doi.org/10.1038/ajg.2016.57
6. Hux JE, Ivis F, Flintoft V, Bica A (2002) Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. Diabetes Care 25(3):512–516. https://doi.org/10.2337/diacare.25.3.512
7. Shah BR, Chiu M, Amin S, Ramani M, Sadry S, Tu JV (2010) Surname lists to identify south Asian and Chinese ethnicity from secondary data in Ontario, Canada: a validation study. BMC Med Res Methodol 10(1):42. https://doi.org/10.1186/1471-2288-10-42
8. Tiikkainen M, Tamminen M, Häkkinen A-M et al (2002) Liver-fat accumulation and insulin resistance in obese women with previous gestational diabetes. Obes Res 10:859–867
9. De Souza LR, Berger H, Retnakaran R et al (2016) Non-alcoholic fatty liver disease in early pregnancy predicts dysglycemia in mid-pregnancy: prospective study. Am J Gastroenterol 111(5):665–670. https://doi.org/10.1038/ajg.2016.43
10. Sridhar SB, Xu F, Darbinian J, Quesenberry CP, Ferrara A, Hedderson MM (2014) Pregravid liver enzyme levels and risk of gestational diabetes mellitus during a subsequent pregnancy. Diabetes Care 37(7):1878–1884. https://doi.org/10.2337/dc13-2229