

History of gestational diabetes and future cardiovascular disease: What have we learned?

It is well established that a history of gestational diabetes mellitus (GDM) will increase the risks of developing metabolic syndrome (MetS) and type 2 diabetes mellitus, and is often subsequently linked to a future risk of cardiovascular disease (CVD). Recommendations from The American Diabetes Association (ADA) indicate that GDM is one of the risk factors for future CVD in women based on previous evidence showing strong associations between GDM and CVD, such as myocardial infarction and stroke¹. However, most of those relationships were obtained from analysis of retrospective data. To date, very few studies have analyzed GDM cohorts with long-term follow up while carefully controlling for many common risk factors and lifestyle characteristics.

Tobias *et al.*² reported long-term CVD events in women with a previous history of GDM using the Nurses' Health Study II, and these findings are clearly valuable from a clinical perspective. The Nurses' Health Study II was a longitudinal prospective study that started in 1989 with a total of 116,430 nurses aged between 24 and 44 years in the USA. Questionnaires were carried out every 2 years to collect updated patterns of lifestyle as well as health-related information. Nurses were enrolled if they reported having a previous birth at age ≥ 18 years in the 1989 baseline data collection or an incident first birth during follow up until 2001. The last phase of the questionnaire collected was in year 2001, when incident GDM was ascertained. Those participants who reported a history of CVD, type 1 diabetes mellitus

or cancer before baseline or the first pregnancy were excluded from the analysis.

Among the 89,479 participants eligible for analysis (with a mean age at first birth of 26.6 years and a mean age of 34.9 years at study enrollment in 1989), 5,292 (5.9%) reported a history of GDM in at least one pregnancy either at baseline (58%) or during the follow-up period (42%). Those with a history of GDM were more likely to be older at pregnancy, had greater prevalence rates of overweight or obesity before pregnancy, pregnancy hypertensive disorders, a family history of type 2 diabetes mellitus, did less physical activity and consumed less alcohol.

Incident primary CVD events reported in 1,161 parous women during a median of 25.7 years of follow up (1.1 events per 1,000 person-years) included 612 myocardial infarctions (MI) and 553 strokes. Those women with a history of GDM had a 60% greater risk of developing CVD during follow up (hazard ratio [HR] 1.60, 95% confidence interval [CI] 1.26–2.04). Additional adjustment for potential confounding factors moderately attenuated the associations (HR 1.29, 95% CI: 1.01–1.65). A history of GDM was still positively associated with MI risk (HR 1.45, 95% CI: 1.05–1.99) in the fully adjusted model, but there was no positive correlation with stroke risk.

Interestingly, among those nurses with a history of GDM, 1,008 (19.0%) developed type 2 diabetes mellitus as compared with the 4,078 (4.8%) nurses without prior GDM. Compared with the reference group of parous women without GDM or type 2 diabetes mellitus, a more than threefold higher risk of CVD was found for women with both GDM and type 2 diabetes mellitus or type 2 diabetes mellitus only compared with women without diabetes mellitus (HR 3.71, 95% CI: 1.79–7.67 and HR 3.74, 95% CI: 1.85–7.53,

respectively) in the fully adjusted model. One critical issue is whether there were any protective effects on future CVD in the women who had a history of GDM without progression to type 2 diabetes mellitus, possibly as a result of the maintenance of healthy lifestyle habits. The findings of the present study clearly show that women with a history of GDM, but without progression to type 2 diabetes mellitus, did not have a higher CVD risk after adjusting for weight changes and other lifestyle factors. Similar trends were found for MI and stroke outcomes. These phenomena were further demonstrated by results showing that GDM was not associated with CVD risk during follow up among women who scored in the upper half of the cohort for dietary quality. Most of these women carried out at least 500 metabolic equivalent min/week of physical activity, were never smokers and had a body mass index of < 25.0 kg/m². Additionally, among women with at least three out of the four above-mentioned healthy lifestyle factors, a history of GDM was not associated with increased CVD risk.

Although the absolute risk difference was quite low (0.5 additional events per 1,000 person-years), the findings from this longitudinal study confirmed previous studies that found a history of GDM was associated with a modest higher risk of CVD compared with women without a history of GDM. It is interesting to note that adjusting for updated lifestyle risk factors for CVD explained some, but not all, of this relationship. Furthermore, it is encouraging that GDM was not shown to be associated with CVD risk among women who live with healthier behavior profiles (such as having a healthy diet, more physically active, never smoker, or not overweight or obese).

There are several concerns with respect to a history of GDM and outcomes

*Corresponding author. Wayne H-H Sheu
 Tel: +886-4-2374-1300
 Fax: +886-4-2374-1318
 E-mail address: whhsheu@vghtc.gov.tw
 Received 14 May 2018; revised 23 May 2018;
 accepted 28 May 2018

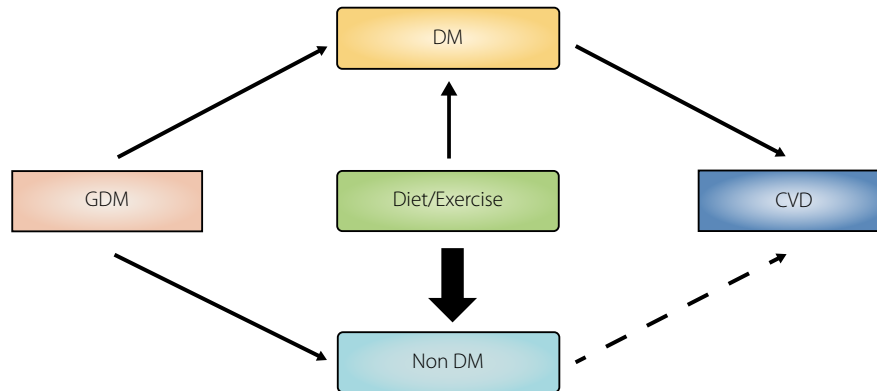


Figure 1 | Women who had history of gestational diabetes mellitus (GDM) had a lower chance of developing future cardiovascular disease (CVD) if they maintained physical activity, had increased dietary quality and had lower weight gain. Dot line denotes less chance. DM, diabetes mellitus; Non DM, without diabetes mellitus.

(incident non-fatal and outcomes of fatal MI and stroke), as some of the patients' information was self-reported. As such, some data might have been misclassified. However, the authors stated that self-reported GDM was previously validated against medical records in a subgroup of the Nurses' Health Study II participants in a 1991 questionnaire, with 94% of cases confirmed³. The outcomes of diagnosis were either ascertained by review of medical records with participants' consent or by examining death certificates and autopsy reports. We do not know how many outcomes were confirmed by those measures. In addition, both physical activities and dietary records were assessed once every 4 years and converted into metabolic equivalent tasks, so the healthy dietary pattern adherence scores were relatively arbitrary. Furthermore, we do not know how genetic determinants might interact with lifestyle patterns and influence the development of MetS, diabetes mellitus or even CVD risks in those women with a history of GDM. The nurses who participated in this study were mainly white women (89% of those with GDM, 92% of those without GDM), which might preclude generalizing the results to other races. However, a recent study in which nearly half of the female participants were black reported a very similar finding⁴. In the Coronary Artery Risk Development in Young Adults study, investigators

enrolled 898 young women (age 10–30 years, among them, 47% were black) who did not have diabetes mellitus and heart disease at baseline (1985–1986), delivered one or more post-baseline births, reported a history of GDM and had common carotid intima media thickness (ccIMT; mm) measured in the years 2005–2006. A total of 119 (13%) reported GDM (7.6/100 deliveries), with an average age of 31 years at the last birth during the 20-year follow-up period. In 777 women without subsequent development of MetS or diabetes mellitus, the mean ccIMT was 0.023 mm higher for GDM vs non-GDM groups after controlling for race, age, parity and pre-pregnancy body mass index (0.784 vs 0.761, $P = 0.039$). Addition of the pre-pregnancy insulin resistance index had a minor impact on the adjusted mean net ccIMT difference (0.22 mm). The mean ccIMT did not differ by GDM status among 121 women who developed diabetes mellitus or MetS ($P = 0.58$). The authors concluded that a history of GDM might be a marker for early atherosclerosis independent of pre-pregnancy obesity. Additionally, investigators from the Coronary Artery Risk Development in Young Adults study recently found that a history of GDM among black women was associated with the subsequent development of chronic kidney disease (defined by an estimated glomerular filtration rate <60 mL/min/1.73 m² or a urine albumin:creatinine

ratio ≥ 25 mg/g), with a mean follow up of 20.8 years⁵.

The main message is that GDM is possibly related to future CVD risk, but only in women with a sustained unhealthy lifestyle after pregnancy. Those women who maintained physical activity with at least 500 metabolic equivalents min/week, were never smokers, increased dietary quality with less weight gain and kept a body mass index of <25.0 kg/m² had a lower chance of developing future CVD, despite having GDM before (Figure 1). Further studies to evaluate long-term health interventions in women with a history of GDM among different races are clearly warranted.

DISCLOSURE

The authors declare no conflict of interest.

Cherng-Lan Hsu¹,

Wayne H-H Sheu^{2,3,4,5*} 

¹Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, Taipei, ²Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, ³School of Medicine, National Yang-Ming University, ⁴School of Medicine, National Defense Medical Center, Taipei, and ⁵College of Life Sciences, National Chung Hsing University, Taichung, Taiwan

REFERENCES

1. Mosca L, Benjamin EJ, Berra K, *et al.* Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol* 2011; 57: 1404–1423.
2. Tobias DK, Stuart JJ, Li S, *et al.* Association of history of gestational diabetes with long-term cardiovascular disease risk in a large prospective cohort of US women. *JAMA Intern Med* 2017; 177: 1735–1742.
3. Solomon CG, Willett WC, Rich-Edwards J, *et al.* Variability in diagnostic evaluation and criteria for gestational diabetes. *Diabetes Care* 1996; 19: 12–16.
4. Gunderson EP, Chiang V, Pletcher MJ, *et al.* History of gestational diabetes mellitus and future risk of atherosclerosis in mid-life: the Coronary Artery Risk Development in Young Adults study. *J Am Heart Assoc* 2014; 3: e000490.
5. Dehmer EW, Phadnis MA, Gunderson EP, *et al.* Association between gestational diabetes and incident maternal CKD: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Kidney Dis* 2018; 71: 112–122.

Doi: 10.1111/jdi.12874