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Associations of hypertensive disorders of pregnancy and gestational diabetes mellitus with menopausal symptoms at midlife in Project Viva

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Abstract

Objective.—To evaluate the associations of a lifetime history of hypertensive disorders of pregnancy (HDP) and gestational diabetes mellitus (GDM) with menopausal symptoms in midlife.

Methods.—Secondary analysis of women participating in Project Viva, an ongoing cohort enrolled during pregnancy. The exposure was lifetime history of HDP or GDM assessed for the

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index pregnancy by review of outpatient and hospital medical records and for all other pregnancies by interview or questionnaire at study entry (1999-2002) and the midlife visit (2017-2021). The primary outcome was the Menopause Rating Scale (MRS) applied at the midlife study visit. We used linear or logistic regression models adjusted for covariates such as baseline age, race/ethnicity, education, married/cohabiting, household income, baseline parity, age at menarche, and body mass index at midlife.

Results.—Of the 676 included participants, 120 (18%) had history of HDP, and 47 (7%) had history of GDM. The mean (SD) age was 52 (3.9) years at the midlife visit, and 48% of the participants had experienced menopause. There were no consistent differences in total symptoms, domain-specific or individual symptoms in women with history of HDP or GDM. A history of HDP and/or GDM was not associated with age at the onset of natural menopause.

Conclusions.—Our findings do not support an association of a history of HDP or GDM with the severity of menopausal symptoms or age at the onset of natural menopause. Larger studies of women with history of these pregnancy complications are needed to clarify their association with menopausal symptoms.

Keywords

Gestational Diabetes Mellitus; Hypertensive Disorders of Pregnancy; Menopause Rating Scale; Menopausal Symptoms; Project Viva

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) and gestational diabetes mellitus (GDM) are common complications that affect each around ~9% of pregnancies in the United States (US).[1,2] HDP and GDM may serve as early markers of future health risks.[3] Women with history of HDP or GDM exhibit persistent vascular and endothelial dysfunction and higher adiposity at midlife,[4,5] factors implicated in the etiology of symptoms that commonly manifest around menopause, such as vasomotor symptoms (VMS).[6-8] Therefore, it is possible that women with history of HDP or GDM are at higher risk of experiencing menopausal symptoms during the menopausal transition. Understanding these associations is essential considering the increasing burden of HDP and GDM in the US.[9,10]

To date, there is limited evidence regarding the association of HDP and GDM with menopausal symptoms. In retrospective studies, HDP have been linked to frequency, duration, and severity of subsequent menopausal symptoms – particularly VMS.[11,12] However, these studies have some methodological limitations. First, retrospective studies, particularly if they relied on self-reported data on pregnancy complications,[11] are subject to recall bias wherein women with no symptoms would be less likely to recall pregnancy complications.[13] Second, the published studies recruited women from clinical settings (i.e., cardiology clinic or women's health clinic), who may not be representative of all women undergoing the menopausal transition in terms of risk and burden of menopausal symptoms. To date, we are aware of only one prospective study that assessed self-reported history of HDP and/or GDM in relation to menopausal symptoms.[14] That analysis of US women found an association between HDP and/or GDM with the presence and frequency of

hot flashes, but the association was not independent of sociodemographic characteristics such as race/ethnicity, financial strain, and education. However, the aforementioned study combined HDP and GDM into one exposure even though they are different pathologies with distinct etiologies and consequences. In the present analysis, we sought to gain a greater understanding of the relationship between a lifetime history of HDP and GDM and menopausal symptoms among women participating in a longitudinal cohort for nearly two decades.

METHODS

Study population

This study was a secondary analysis of a subset of women participating in Project Viva, an ongoing prospective cohort of women recruited during pregnancy (median 9.9 weeks of gestation) from a large multispecialty group practice, Atrius Harvard Vanguard Medical Associates, in eastern Massachusetts between 1999 and 2002. Details on recruitment and eligibility have been described elsewhere.[15] Of 2,100 women with singleton births, 772 remained in follow-up through the midlife visit, at approximately 18 years after delivery, and provided information on menopausal symptoms via the Menopause Rating Scale (MRS) (Supplemental figure 1). To restrict our analysis to women potentially undergoing the menopausal transition, we excluded 79 women younger than 45 years of age at the midlife visit who had not experienced menopause by the time of the visit, based on self-report. We did not exclude eight women younger than 45 years who reported having experienced menopause. Age 45 is a typical threshold for the onset of perimenopause in general settings.[16] We further excluded women with type 1 or type 2 diabetes (n=6) and chronic hypertension (n=11) at enrollment to the study, given our interest in identifying cases of HDP and GDM. Our analytic sample included 676 participants who responded to at least 10 (of the 11 total) items of the MRS and who had complete exposure data. As expected, given the inclusion criteria for the study, women in the analytic sample, compared to those excluded (n=1,424), were older at enrollment (mean age 33.7 vs. 30.9 years). Women in the analytic sample also had a lower pre-pregnancy body mass index (BMI) (mean 24.4 vs. 25.1 kg/m^2) and were also more likely to be white (73.7 vs. 62.9%), college-educated (79.2 vs. 57.5%), married or cohabiting (95.7 vs. 89.2%) and to have a household income>$70,000/year (67.4 vs. 57.4%). All participants provided written informed consent at enrollment and at each study visit. The institutional review board of Harvard Pilgrim Health Care approved all study protocols.

Exposure variables

Our primary exposures were lifetime history of HDP or GDM, assessed separately. We determined these exposures using four complementary sources of information. First, in the interview conducted in the 1^{st} trimester of pregnancy, participants were asked whether they had been diagnosed with diabetes, hypertension, or preeclampsia in any of their past pregnancies. Second, to determine whether a participant had an HDP for the index pregnancy, we reviewed outpatient and hospital medical records to screen for the presence of gestational hypertension or preeclampsia, as previously reported.[17] Similarly, we determined the presence of GDM for the index pregnancy using information from the clinical GDM

screening at 26-28 weeks of gestation.[18] Third, at the midlife study visit, participants were asked to complete a detailed reproductive history questionnaire where they reported each of their pregnancies and the occurrence of gestational hypertension, preeclampsia, or gestational diabetes. Finally, we identified additional cases of HDP or GDM from an interview also conducted at the midlife study visit. In this interview, we asked participants whether they had been diagnosed with hypertension or diabetes in any of their past pregnancies. We considered participants to have a history of HDP or GDM if their answer was positive to any of the questions mentioned above; otherwise, we considered them to have no history of pregnancy complications. The index pregnancy accounted for 51% of the cases of HDP and 64% of GDM. We evaluated the agreement between information on pregnancy complications self-reported at midlife in the reproductive history questionnaire vs. history of HDP and GDM obtained from the medical records for the index pregnancy, and observed substantial agreement between the two sources of information: GDM, Cohen's kappa=0.78; HDP, Cohen's kappa=0.63.[19]

Outcome variables

We assessed menopausal symptoms using the MRS administered at the midlife visit.[20] This scale queries the presence and severity of 11 menopausal symptoms over the past year, with response options ranging from 0=none to 4=very severe. The total score ranges from 0 to 44 points, with a higher score corresponding with more severe symptoms. In addition, the MRS classifies the 11 symptoms into three domains: somatic (hot flashes/sweating, heart discomfort, sleep problems, and joint and muscle discomfort), psychological (depressive mood, irritability, anxiety, and physical and mental exhaustion), and urogenital (sexual problems, bladder problems, and vaginal dryness). We studied the total MRS score and the domain-specific scores as continuous variables. For analyses of the individual items, we dichotomized them as any symptoms vs. none.

As a secondary outcome, we studied age at the onset of natural menopause in relation to history of pregnancy complications. At the midlife visit, participants reported whether their menstrual periods had stopped for at least 12 months, the reason for this (i.e., natural or secondary [surgical, radiation/chemotherapy]), and age at the onset of menopause.

Covariates

Participants at enrollment (index pregnancy) reported their age, race/ethnicity, education level, marital status, annual household income, parity, and prenatal smoking habits via a self-administered questionnaire. Race/ethnicity included white, black, Asian, Hispanic, more than one race/ethnicity, and other races/ethnicities. Due to the small samples in some categories, we combined Asian, Hispanic, more than one race/ethnicity, and other races/ethnicities into the ‘other’ category. We calculated pre-pregnancy BMI for the index pregnancy (kg/m^2) from self-reported pre-pregnancy weight and height. Women reported age at their first menstrual period at a study visit conducted ~13 years after enrollment. We calculated participants’ age at the midlife visit using their date of birth and the visit date and estimated their BMI using research measures of weight and height.

Statistical analyses

We first compared the distributions of participants' characteristics and menopausal symptoms by lifetime history of HDP or GDM using frequencies and percentages for categorical variables and mean and standard deviation (SD) for numerical variables.

In our primary analysis, we assessed history of HDP or GDM as separate exposures in relation to menopausal symptoms. We analyzed the total MRS and domain-specific scores as continuous outcomes using linear regression models (results presented as β coefficients and 95% confidence intervals [CI]). Given the skewed distribution of the individual items of the MRS, we dichotomized them as any symptoms vs. none (reference) and used logistic regression for analysis (results presented as odds ratios [OR] and 95% CI). For all exposure/outcome associations, we implemented a series of models adjusted for potential confounders. Model 1 included maternal age at enrollment (18-29 years, 30-34 years, 35-45 years), and race/ethnicity (white, black, other). Model 2 was additionally adjusted for college education (yes, no), married/cohabiting (yes, no), annual household income>$70,000 (yes, no), parity at enrollment (nulliparous: yes, no), and age at menarche (<12 years, 12-15 years, ≥15 years). The last model additionally included BMI at the midlife visit (kg/m^2). Additional adjustment for age at the midlife visit or smoking habits at enrollment yielded identical results; hence these variables were not included in the final models. Adjusting for BMI before the index pregnancy instead of BMI at midlife yielded consistent results.

As a secondary analysis, we stratified lifetime history of HDP into a three-level variable: 1) lifetime history of gestational hypertension only; 2) lifetime history of any preeclampsia, with or without gestational hypertension in a different pregnancy; or 3) neither. The results of this analysis were consistent with those of the primary analysis. Therefore, we present only the results for the two conditions combined as HDP.

We conducted a survival analysis using a Cox proportional-hazard model to study the relationship between history of either HDP or GDM (combined into one exposure for the sake of statistical power) and time-to-natural menopause (results presented as hazard ratios [HR] and 95% CI). We included only the 659 participants with complete exposure-event data for this analysis. The event of interest was the occurrence of natural menopause, and age was the time scale for the model. Women who had not experienced menopause by the midlife visit or who had experienced secondary menopause (i.e., surgery, radiation/chemotherapy) were censored at the age of the midlife visit or age at secondary menopause. We adjusted this analysis for the aforementioned confounders.

Since HDP and GDM were not mutually exclusive, we conducted sensitivity analyses restricting the non-exposed groups to 527 women with a history of neither HDP nor GDM. With these analyses, we ruled out that our findings were related to the contamination of the reference groups. To reduce bias due to missing values for covariates, we conducted chained equation multiple imputation to generate 50 imputed data sets using an imputation model that included the exposures, outcomes, and covariates of interest (we only used multiple imputed values for covariates). BMI at the midlife visit was the covariate with the highest proportion of missing values (11%). The imputed data sets were combined and analyzed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

RESULTS

At the midlife visit, approximately 18 years after delivery, women's mean (SD) age was 52.0 (3.9) years. Women in our study were predominantly white (73.7%), college-educated (79.2%), married (95.7%), high income (67.4%), never smokers (72.0%), and had a pre-pregnancy BMI <25 kg/m^2 (65.5%) (Table 1). The study population included 120 women (17.8%) with history of HDP and 47 women (7.0%) with history of GDM. Women with history of HDP or GDM, vs. their counterparts, were less likely to have a normal weight before the index pregnancy and at the midlife visit. Women with history of GDM were also less likely to be white, college-educated, and married. There were minor, non-significant differences in the proportion of women who had experienced menopause at the midlife assessment among those with history of HDP (51.3 vs. 46.8%) or GDM (39.1 vs. 48.2%) compared to women without history of these conditions.

We did not observe differences in total symptoms or domain-specific symptoms in women with history of HDP vs. those with no history (Table 2, Supplemental table 1). When we analyzed menopausal symptoms individually, we noted higher, non-significant odds of vaginal dryness in women with history of HDP (Model 3: OR 1.48, 95% CI 0.96 to 2.27) (Table 3). We did not observe consistent associations between history of GDM and menopausal symptoms in either bivariate or multivariable analyses (Table 2 and 3, and Supplemental table 1). Our results were consistent in direction, magnitude, and precision, after restricting the non-exposed groups to women with a history of neither HDP nor GDM in sensitivity analyses (Supplemental tables 2 and 3). In survival analysis, history of HDP and/or GDM was not associated with age at natural menopause in unadjusted (HR 0.91, 95% CI 0.68 to 1.22) or adjusted (HR 0.92, 95% CI 0.66 to 1.30) models.

DISCUSSION

In this racially diverse sample of 676 peri- and postmenopausal women in the Project Viva longitudinal cohort study, we did not find consistent associations of a history of HDP or GDM with menopausal symptoms at midlife assessed by the Menopause Rating Scale. Also, we did not detect associations between HDP and/or GDM and age at natural menopause.

In this study, we did not observe differences in the frequency or severity of menopausal symptoms assessed by the total MRS score or the domain-specific scores in women with history of HDP. We did not find associations between history of HDP and menopausal symptoms when we assessed them individually, except for a marginally significant association with vaginal dryness. Our finding of a null association between HDP and VMS is in line with an analysis of over 2,000 participants in the Study of Women's Health Across the Nation (SWAN). In this study, Cortés *et al.* observed higher odds of reporting any hot flashes (OR 1.27, 95% CI 1.05 to 1.53) among women with history of HDP and/or GDM in age-adjusted models.[14] However, the estimates were attenuated after accounting for sociodemographic characteristics (i.e., race/ethnicity, education, financial strain). Contrary to our findings, a study by Drost *et al.* showed that Dutch women with history of HDP had higher odds of VMS (OR 1.62, 95% CI 1.00 to 2.63) and higher odds of experiencing VMS for more than one year (OR 2.05, 95% CI 1.08 to 3.89).[11] Similarly, Faubion *et al.*

reported a higher total MRS score among US women with history of HDP using hormone therapy (β 2.28, 95% CI 0.12 to 4.44), compared to those without history of HDP.[12] The retrospective design and selection criteria of these two studies might, to some extent, explain the difference in findings compared with our results. Specifically, Drost *et al.* studied women at high cardiovascular risk who were recruited from a cardiology clinic. This approach may have led to an overrepresentation of women with a lifetime history of HDP (n=274 out of 853 (32%) in that study vs. n=120 out of 676 (18%) in ours)[11] and potentially, greater statistical power to detect associations with VMS. Faubion *et al.* studied women referred to a women's health clinic for menopause or sexual health consultation, who may not be representative of the general population of women undergoing the menopausal transition.[12] It is also possible that lack of adjustment for important confounders in prior studies by Drost et al., and Faubion et al., such as race/ethnicity, education, and income, explains the difference in findings. Considering these characteristics as confounders is essential as they precede adverse pregnancy outcomes and are potential determinants of a higher burden of menopausal symptoms.[21,22]

The association between history of GDM and total menopausal symptoms was in the expected direction but non-significant. The same was true for the estimates of the somatic and psychological domains and some of the individual items. The wide confidence intervals and null findings could be related, to some extent, to the low number of women with history of GDM in our sample (n=47). Only one study has evaluated menopausal symptoms in relation to history of GDM.[14] As previously mentioned, that study by Cortés *et al.* found higher odds of reporting any hot flashes among women with history of HDP and/or GDM in the age-adjusted model. However, only 27 women in their exposure group had history of GDM, and the remaining had history of HDP. Since ours represents the first study that has assessed GDM as an independent exposure, additional studies are needed to clarify the relationship between GDM and menopausal symptoms.

We did not observe differences in the timing of natural menopause by history of HDP and/or GDM. To the best of our knowledge, ours is the first report on the timing of menopause and history of these pregnancy complications. Although not directly comparable to our study, there are reports of an earlier age at menopause among US women with chronic hypertension and diabetes.[23,24] If there is a relation between HDP and/or GDM and timing of menopause, it is possible that we did not have statistical power to detect it since there were only 45 women who had experienced natural menopause by the time of our outcome assessment among those with HDP and/or GDM. Nevertheless, this represents an important question that needs to be addressed in future, adequately powered studies.

Strengths of this study include the prospective design and the fact that most cases of HDP or GDM were related to the index pregnancy, hence identified through medical records as opposed to self-report. By identifying most cases of HDP or GDM early in the study, years before the assessment of menopausal symptoms, we minimized reporting bias. Additional strengths include the racially/ethnically diverse study sample recruited in a general-risk setting, thus, more likely to be representative of women with history of HDP or GDM undergoing the menopausal transition. The use of a validated scale to assess menopausal

symptoms and adjustment for a wide range of confounders in the statistical analysis are also strengths.

This study also has some limitations. First, our sample of exposed participants was relatively small; this limited our ability to stratify our exposures further and consider, for example, cases of gestational hypertension and preeclampsia in separate categories as primary exposures. Second, we had only one assessment of the MRS during midlife (mean of 52 years of age), which did not reflect menopausal symptoms across the entire menopausal transition. Third, around half of the participants in the analytic sample were postmenopausal, based on self-reported menopausal status. We did not have information to determine the specific stage in the menopausal transition for the participants who were not postmenopausal. However, by restricting the analytic sample to women over 45 years of age, we captured those more likely to be undergoing the menopausal transition, more likely to experience menopausal symptoms, and more relevant to our research question. Fourth, some cases of HDP or GDM were identified through self-report at the midlife study visit, concurrently with outcome assessment, which could result in misclassification of exposure status. However, since there was a substantial agreement between cases of HDP or GDM for the index pregnancy identified by self-report at midlife vs. medical records, we believe the probability of misclassification would be negligible. If misclassification were present, it would likely be non-differential with respect to the outcome and, thus, unlikely to bias the results. Lastly, our findings may only be generalizable to young midlife women of a similar sociodemographic background undergoing the menopausal transition.

CONCLUSIONS

Our findings in this cohort of peri- and postmenopausal women contradict those of previously published studies,[11,12] and do not support an association of a history of HDP or GDM and the severity of menopausal symptoms or the age at the onset of natural menopause. Additional prospective studies with larger samples of women with history of HDP or GDM are needed to clarify the associations between these pregnancy complications and menopausal symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Butwick AJ, Druzin ML, Shaw GM, Guo N. Evaluation of US State-Level Variation in Hypertensive Disorders of Pregnancy. JAMA Netw open 2020;3:e2018741. doi:10.1001/jamanetworkopen.2020.18741 [PubMed: 33001203]
2. Centers for Disease Control and Prevention. Diabetes During Pregnancy. Published 2018. Accessed September 15, 2021. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/diabetes-during-pregnancy.htm
3. Rich-Edwards JW, Fraser A, Lawlor DA, Catov JM. Pregnancy characteristics and women's future cardiovascular health: an underused opportunity to improve women's health? Epidemiol Rev 2014;36:57–70. doi:10.1093/epirev/mxt006 [PubMed: 24025350]
4. McElwain CJ, Tuboly E, McCarthy FP, McCarthy CM. Mechanisms of Endothelial Dysfunction in Pre-eclampsia and Gestational Diabetes Mellitus: Windows Into Future Cardiometabolic Health? Front Endocrinol (Lausanne) 2020;11:655. doi:10.3389/fendo.2020.00655 [PubMed: 33042016]
5. Fraser A, Nelson SM, Macdonald-Wallis C, et al. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the Avon Longitudinal Study of Parents and Children. Circulation 2012;125:1367–1380. doi:10.1161/CIRCULATIONAHA.111.044784 [PubMed: 22344039]
6. Thurston RC, Chang Y, Barinas-Mitchell E, et al. Physiologically assessed hot flashes and endothelial function among midlife women. Menopause 2018;25:1354–1361. doi:10.1097/GME.0000000000001239 [PubMed: 30358732]
7. Thurston RC, Chang Y, Mancuso P, Matthews KA. Adipokines, adiposity, and vasomotor symptoms during the menopause transition: findings from the Study of Women's Health Across the Nation. Fertil Steril 2013;100:793–800. doi:10.1016/j.fertnstert.2013.05.005 [PubMed: 23755948]
8. Thurston RC, Chang Y, Barinas-Mitchell E, et al. Menopausal Hot Flashes and Carotid Intima Media Thickness Among Midlife Women. Stroke 2016;47:2910–2915. doi:10.1161/STROKEAHA.116.014674 [PubMed: 27834746]
9. Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987-2004. Am J Hypertens 2008;21:521–526. doi:10.1038/ajh.2008.20 [PubMed: 18437143]
10. Shah NS, Wang MC, Freaney PM, et al. Trends in Gestational Diabetes at First Live Birth by Race and Ethnicity in the US, 2011-2019. JAMA 2021;326:660–669. doi:10.1001/jama.2021.7217 [PubMed: 34402831]
11. Drost JT, van der Schouw YT, Herber-Gast GCM, Maas AHEM. More vasomotor symptoms in menopause among women with a history of hypertensive pregnancy diseases compared with women with normotensive pregnancies. Menopause 2013;20:1006–1011. doi:10.1097/GME.0b013e3182886093 [PubMed: 23549443]
12. Faubion SS, King A, Kattah AG, et al. Hypertensive disorders of pregnancy and menopausal symptoms: a cross-sectional study from the data registry on experiences of aging, menopause, and sexuality. Menopause 2020;28:25–31. doi:10.1097/GME.0000000000001638 [PubMed: 32810078]
13. Coughlin SS. Recall bias in epidemiologic studies. J Clin Epidemiol 1990;43:87–91. doi:10.1016/0895-4356(90)90060-3 [PubMed: 2319285]
14. Cortés YI, Conant R, Catov JM, et al. Impact of nulliparity, hypertensive disorders of pregnancy, and gestational diabetes on vasomotor symptoms in midlife women. Menopause 2020;27:1363–1370. doi:10.1097/GME.0000000000001628 [PubMed: 32796290]
15. Oken E, Baccarelli AA, Gold DR, et al. Cohort profile: project viva. Int J Epidemiol 2015;44:37–48. doi:10.1093/ije/dyu008 [PubMed: 24639442]
16. Gold EB. The timing of the age at which natural menopause occurs. Obstet Gynecol Clin North Am 2011;38:425–440. doi:10.1016/j.ogc.2011.05.002 [PubMed: 21961711]
17. Perng W, Stuart J, Rifas-Shiman SL, Rich-Edwards JW, Stuebe A, Oken E. Preterm birth and long-term maternal cardiovascular health. Ann Epidemiol 2015;25:40–45. doi:10.1016/j.annepidem.2014.10.012 [PubMed: 25459086]

18. Regnault N, Gillman MW, Rifas-Shiman SL, Eggleston E, Oken E. Sex-specific associations of gestational glucose tolerance with childhood body composition. Diabetes Care 2013;36:3045–3053. doi:10.2337/dc13-0333 [PubMed: 23877978]

19. Ranganathan P, Pramesh CS, Aggarwal R. Common pitfalls in statistical analysis: Measures of agreement. Perspect Clin Res 2017;8:187–191. doi:10.4103/picr.PICR_123_17 [PubMed: 29109937]

20. Heinemann K, Ruebig A, Potthoff P, et al. The Menopause Rating Scale (MRS) scale: a methodological review. Health Qual Life Outcomes 2004;2:45. doi:10.1186/1477-7525-2-45 [PubMed: 15345062]

21. Bornstein E, Eliner Y, Chervenak FA, Grünebaum A. Racial Disparity in Pregnancy Risks and Complications in the US: Temporal Changes during 2007-2018. J Clin Med 2020;9. doi:10.3390/jcm9051414

22. Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. Am J Public Health 2006;96:1226–1235. doi:10.2105/AJPH.2005.066936 [PubMed: 16735636]

23. Khalil N, Sutton-Tyrrell K, Strotmeyer ES, et al. Menopausal bone changes and incident fractures in diabetic women: a cohort study. Osteoporos Int 2011;22:1367–1376. doi:10.1007/s00198-010-1357-4 [PubMed: 20658126]

24. Costanian C, McCague H, Edgell H, Ardern CI, Tamim H. Changes in adiposity and other factors in relation to age at natural menopause: analyses from the coronary artery risk development (CARDIA) study. Menopause 2019;26:162–171. doi:10.1097/GME.0000000000001196 [PubMed: 30153216]

Table 1.

Distribution of characteristics at enrollment into a pregnancy cohort (mean age 33.7 years) and in midlife (mean age 52.0 years) by lifetime history of HDP or GDM among 676 peri- and postmenopausal women [a]

	Overall	Lifetime history of HDP	Lifetime history of GDM
	n=676	Yes n=120 (17.8%)	Yes n=47 (7.0%)
Baseline characteristics	**N (%)**	**N (%)**	**N (%)**
Age at enrollment			
18-29 years	116 (17.2)	23 (19.2)	9 (19.1)
30-34 years	318 (47.0)	56 (46.7)	26 (55.3)
35-45 years	242 (35.8)	41 (34.2)	12 (25.5)
Race/ethnicity			
White	497 (73.7)	82 (68.3)	25 (53.2)
Black	80 (11.9)	21 (17.5)	11 (23.4)
Other	97 (14.4)	17 (14.2)	11 (23.4)
College graduate			
Yes	534 (79.2)	91 (75.8)	31 (66.0)
Married/cohabiting			
Yes	644 (95.7)	112 (93.3)	42 (89.4)
Annual household income >$70,000			
Yes	427 (67.4)	70 (64.8)	27 (62.8)
Pre-pregnancy BMI status			
Underweight/normal weight	443 (65.5)	58 (48.3)	18 (38.3)
Overweight	149 (22.0)	39 (32.5)	17 (36.2)
Obese	84 (12.4)	23 (19.2)	12 (25.5)
Prenatal smoking status			
Ever smoker	189 (28.0)	38 (31.7)	13 (27.7)
Age at the first menstrual period			
<12 years	98 (15.4)	25 (21.7)	11 (23.9)
12-14 years	470 (73.7)	81 (70.4)	31 (67.4)
≥15 years	70 (11.0)	9 (7.8)	4 (8.7)
Nulliparous			
Yes	311 (46.0)	52 (43.3)	25 (53.2)
Midlife characteristics			
Menopause			
Yes	318 (47.6)	60 (51.3)	18 (39.1)
Age at menopause			
<45 years	45 (6.8)	12 (10.5)	4 (8.7)
45-54 years	242 (36.6)	41 (36.0)	11 (23.9)
≥55 years	24 (3.6)	4 (3.5)	3 (6.5)
Has not reached menopause	350 (53.0)	57 (50.0)	28 (60.9)
Age at midlife visit			

	Overall	Lifetime history of HDP	Lifetime history of GDM
	n=676	Yes n=120 (17.8%)	Yes n=47 (7.0%)
<52 years	352 (52.1)	71 (59.2)	28 (59.6)
≥52 years	324 (47.9)	49 (40.8)	19 (40.4)
BMI status at midlife visit			
Underweight/normal weight	241 (41.3)	28 (28.0)	7 (16.7)
Overweight	172 (29.5)	27 (27.0)	14 (33.3)
Obese	171 (29.3)	45 (45.0)	21 (50.0)

BMI, body mass index; GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy.

[a]Description conducted in the non-multiple imputed dataset, the sample may not add up to 676 due to missing covariate values.

Table 2.

Associations of HDP or GDM with total and domain-specific menopausal symptoms among 676 peri- and postmenopausal women [a]

	Model 1	Model 2 β (95% CI)	Model 3
Lifetime history of HDP (no history of HDP *[ref]*)			
Total MRS score	0.44 (−0.70 to 1.59)	0.32 (−0.83 to 1.46)	0.13 (−1.02 to 1.27)
Somatic	0.24 (−0.25 to 0.73)	0.19 (−0.30 to 0.67)	0.10 (−0.39 to 0.58)
Psychological	−0.05 (−0.59 to 0.48)	−0.10 (−0.64 to 0.43)	−0.18 (−0.71 to 0.36)
Urogenital	0.26 (−0.13 to 0.64)	0.23 (−0.16 to 0.62)	0.20 (−0.19 to 0.60)
Lifetime history of GDM (no history of GDM *[ref]*)			
Total MRS score	0.95 (−0.77 to 2.68)	0.90 (−0.83 to 2.63)	0.50 (−1.24 to 2.25)
Somatic	0.57 (−0.17 to 1.31)	0.54 (−0.20 to 1.28)	0.35 (−0.39 to 1.09)
Psychological	0.34 (−0.47 to 1.14)	0.32 (−0.49 to 1.13)	0.18 (−0.64 to 0.99)
Urogenital	0.05 (−0.54 to 0.63)	0.04 (−0.55 to 0.63)	−0.03 (−0.62 to 0.57)

GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy; MRS, menopause rating scale.

[a]Estimates obtained from linear regression models.

Model 1: maternal age at enrollment (18-29 years, 30-34 years, 35-45 years), race/ethnicity (white, black, other).

Model 2: model 1 + college education (yes, no), married/cohabiting (yes, no), annual household income>$70,000 (yes, no), parity at enrollment (nulliparous: yes, no), age at menarche (<12 years, 12-15 years, ≥15 years).

Model 3: model 2 + BMI at midlife (kg/m^2).

Table 3.

Associations of HDP or GDM with individual menopausal symptoms among 676 peri- and postmenopausal women [a]

Individual items by domain (any symptoms vs. none [ref])	Model 1	Model 2 OR (95% CI)	Model 3
Lifetime history of HDP (no history of HDP *[ref]*)			
Somatic domain			
Hot flashes/sweating	1.19 (0.78 to 1.80)	1.15 (0.75 to 1.75)	1.15 (0.75 to 1.77)
Heart discomfort	1.39 (0.91 to 2.13)	1.35 (0.88 to 2.08)	1.36 (0.88 to 2.10)
Sleep problems	1.14 (0.73 to 1.77)	1.10 (0.71 to 1.71)	1.07 (0.69 to 1.67)
Joint and muscular discomfort	0.97 (0.65 to 1.44)	0.96 (0.64 to 1.44)	0.88 (0.58 to 1.33)
Psychological domain			
Depressive mood	1.12 (0.75 to 1.66)	1.11 (0.74 to 1.65)	1.07 (0.72 to 1.60)
Irritability	1.14 (0.77 to 1.70)	1.10 (0.73 to 1.64)	1.08 (0.72 to 1.63)
Anxiety	0.80 (0.54 to 1.20)	0.79 (0.53 to 1.18)	0.78 (0.52 to 1.17)
Physical and mental exhaustion	1.07 (0.71 to 1.62)	1.00 (0.66 to 1.51)	0.99 (0.65 to 1.50)
Urogenital domain			
Sexual problems	1.16 (0.77 to 1.73)	1.16 (0.77 to 1.74)	1.15 (0.76 to 1.74)
Bladder problems	1.10 (0.73 to 1.67)	1.08 (0.71 to 1.64)	0.96 (0.62 to 1.47)
Vaginal dryness	1.42 (0.93 to 2.16)	1.39 (0.91 to 2.13)	1.48 (0.96 to 2.27)
Lifetime history of GDM (no history of GDM *[ref]*)			
Somatic domain			
Hot flashes/sweating	1.14 (0.61 to 2.12)	1.09 (0.57 to 2.06)	1.10 (0.57 to 2.10)
Heart discomfort	1.12 (0.58 to 2.16)	1.05 (0.53 to 2.06)	1.06 (0.53 to 2.09)
Sleep problems	1.21 (0.62 to 2.33)	1.17 (0.60 to 2.29)	1.12 (0.57 to 2.20)
Joint and muscular discomfort	1.45 (0.78 to 2.67)	1.48 (0.79 to 2.78)	1.27 (0.67 to 2.42)
Psychological domain			
Depressive mood	1.39 (0.76 to 2.54)	1.42 (0.78 to 2.61)	1.34 (0.72 to 2.48)
Irritability	0.95 (0.52 to 1.74)	0.90 (0.49 to 1.66)	0.87 (0.47 to 1.62)
Anxiety	1.13 (0.62 to 2.06)	1.12 (0.61 to 2.05)	1.09 (0.59 to 2.02)
Physical and mental exhaustion	1.30 (0.69 to 2.45)	1.19 (0.62 to 2.28)	1.17 (0.61 to 2.25)
Urogenital domain			
Sexual problems	0.87 (0.47 to 1.62)	0.91 (0.48 to 1.70)	0.89 (0.47 to 1.69)
Bladder problems	1.33 (0.71 to 2.50)	1.32 (0.70 to 2.50)	1.05 (0.55 to 2.04)
Vaginal dryness	0.79 (0.39 to 1.58)	0.76 (0.38 to 1.54)	0.85 (0.42 to 1.73)

GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy.

[a]Estimates obtained from logistic regression models.

Model 1: maternal age at enrollment (18-29 years, 30-34 years, 35-45 years), race/ethnicity (white, black, other).

Model 2: model 1 + college education (yes, no), married/cohabiting (yes, no), annual household income>$70,000 (yes, no), parity at enrollment (nulliparous: yes, no), age at menarche (<12 years, 12-15 years, ≥15 years).

Model 3: model 2 + BMI at midlife (kg/m^2).