

# Pregnancy Loss and Carotid Intima–Media Thickness in Mexican Women

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**Background**—Cardiovascular disease in women often develops without conventional risk factors. Prenatal loss is a common pregnancy outcome that may result in physiological changes that can increase the potential future risk of cardiovascular disease. Insufficient information exists regarding the impact of pregnancy loss on early markers of cardiovascular disease risk.

**Methods and Results**—Cross-sectional analysis of 1767 disease-free women from the MTC (Mexican Teachers' Cohort) who had been pregnant was used to evaluate the relationship between pregnancy loss and carotid intima–media thickness (IMT). Participants responded to a questionnaire regarding their reproductive history, risk factors, and medical conditions. We defined pregnancy loss as history of miscarriage and/or stillbirth. Trained neurologists measured IMT using ultrasound. We log-transformed IMT and defined subclinical carotid atherosclerosis (SCA) as  $IMT \geq 0.8$  mm and/or plaque. We used multivariable linear and logistic regression models to assess the relation of pregnancy loss, IMT, and SCA. The mean age of participants was  $49.8 \pm 5.1$  years. The prevalence of pregnancy loss was 22%, and we observed SCA in 23% of participants. Comparing participants who reported a pregnancy loss and those who did not, the multivariable-adjusted odds ratio for SCA was 1.52 (95% confidence interval, 1.12–2.06). Women who experienced a stillbirth had 2.32 higher odds (95% confidence interval, 1.03–5.21) of SCA than those who did not. Mean IMT appeared to be higher in women who reported a pregnancy loss relative to those who did not; nevertheless, this was not statistically significant.

**Conclusions**—Pregnancy loss could be linked to cardiovascular disease later in life. The key findings of our study await confirmation and further investigation of the potential underlying mechanisms for this association is required. (*J Am Heart Assoc.* 2018;7:e007582. DOI: 10.1161/JAHA.117.007582.)

**Key Words:** carotid intima–media thickness • pregnancy • subclinical atherosclerosis risk factor

Cardiovascular disease (CVD) continues to be the leading cause of death among women in the United States<sup>1</sup> and worldwide.<sup>2</sup> Significant advances have been made in our understanding of the impact that perimenopausal reproductive factors have on cardiovascular health in women.<sup>3</sup> However, there is a need to strengthen our knowledge regarding reproductive events occurring earlier in life to better predict lifetime risk of CVD in women.

Miscarriages are fairly common (lifetime prevalence ranges from 7% to 29%),<sup>4</sup> whereas stillbirth is an unusual occurrence (lifetime prevalence <1%).<sup>4</sup> Most miscarriages result from chromosomal abnormalities of the embryo. In contrast, stillbirth is often rooted in limited access to adequate prenatal care.<sup>5</sup> However, both miscarriage and stillbirth are considered to be highly stressful events that may produce lasting psychological effects such as posttraumatic stress

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Accompanying Tables S1 through S5 are available at <http://jaha.ahajournals.org/content/7/2/e007582/DC1/embed/inline-supplementary-material-1.pdf>

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## Clinical Perspective

### What Is New?

- As the mortality gap related to cardiovascular disease diminishes between men and women, careful evaluation of risk factors that affect only women is needed.
- In this study that relied on centralized measurement of carotid intima–media thickness in middle-aged Mexican women, a history of pregnancy loss was associated with increased risk of cardiovascular disease.
- The association with subclinical cardiovascular disease was stronger when women reported a history of stillbirth.

### What Are the Clinical Implications?

- Our findings underscore the importance of considering unconventional risk factors, such as reproductive history, when assessing cardiovascular risk in women.

symptoms.<sup>6,7</sup> Posttraumatic stress disorder along with other stress-related mental health disorders are associated with incident CVD.<sup>8</sup> Abnormal neuroendocrine responses and unhealthy behaviors triggered by highly stressful life events appear to underlie this relation.<sup>9–11</sup>

Some prospective studies<sup>12–14</sup> have found a direct relation between pregnancy loss and CVD, and a smaller cross-sectional study did not find a statistically significant association, after adjustment for risk factors, between stillbirth and carotid intima–media thickness (IMT).<sup>15</sup> Pregnancy loss may be a modifiable risk factor that could play an important role in future cardiovascular health, particularly for women living in communities with insufficient perinatal care services.<sup>16</sup> Consequently, we investigated the association between pregnancy loss and subclinical CVD in a population of women living in Mexico.

## Methods

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. These data will be made available by providing a user name to enter the MTC (Mexican Teachers' Cohort) databases.<sup>17</sup>

## Study Population

The MTC is a prospective cohort composed of 115 315 female teachers living throughout 12 economically diverse Mexican states. Data collection began in 2006–2008.<sup>18</sup> Women responded to a baseline questionnaire on their demographic characteristics, reproductive history, dietary habits, lifestyle, and known medical conditions. The

participants received a follow-up questionnaire every 3 years to update any new risk factors and/or medical conditions. From September 2012 to June 2016, a random subsample of 3536 MTC participants (aged  $\geq 40$  years and living within a 50-km radius from clinical sites) from 3 states ( $\approx 1200$  per state) were invited to take part in an ancillary study of subclinical CVD in which women would undergo a clinical assessment. Clinical evaluations took place in 6 clinical sites located in the 2 southern states of Chiapas and Yucatan and in the city of Monterrey, Nuevo León, located in the north. Close to 70% ( $n=2375$ ) of the women invited chose to participate in the clinical assessment after providing their written informed consent. The institutional review boards at the National Institute of Public Health and the Medical School of the Monterrey Institute of Technology and Advanced Studies both approved the project.

Women who had never been pregnant ( $n=376$ ) and those without a complete IMT measurement ( $n=220$ ) were excluded. Women with prevalent myocardial infarction (MI) or stroke ( $n=12$ ) were also excluded. Ultimately, the analysis was conducted using the remaining 1767 women.

## Assessment of Pregnancy and Pregnancy Loss

In 2008, participants were asked to respond to a comprehensive reproductive history questionnaire composed of questions asking for details regarding up to 10 pregnancies. In the questionnaire, women were asked to give information on their age at each pregnancy and the type of delivery (vaginal, cesarean, miscarriage, or ectopic pregnancy). Participants were also asked whether the pregnancy resulted in a live birth and whether they had been diagnosed with preeclampsia and/or gestational diabetes. In 2011, participants' reproductive history was updated based on responses to the following questions: "Have you been pregnant in the past 2 years?"; "How many pregnancies did you have?" (1, 2, 3, or more); "Number of pregnancies lasting less than 6 months?" (none, 1, 2, 3, or more); "Number of pregnancies lasting more than 6 months" (none, 1, 2, 3, or more); and, "Number of live births" (none, 1, 2, 3, or more). In 2011, when we evaluated the presence of preeclampsia, we clarified that this diagnosis was equivalent to hypertension in pregnancy.

We defined pregnancy loss as reporting at least 1 miscarriage or stillbirth during the participant's lifetime. Women who responded in 2008 to having had a miscarriage and those who reported in 2011 to having had a pregnancy of  $<6$  months were considered to have had a miscarriage. Women who reported in 2008 that they had a delivery that did not result in a live birth or who reported in 2011 that they had a pregnancy of  $>6$  months that did not result in a live birth were considered to have had a stillbirth.

## Subclinical CVD

Neurologists used SonoSite MicroMaxx ultrasound and M'AthStd Software on an Asus laptop to measure IMT and to identify atherosclerotic plaques. A senior neurologist and coauthor with extensive experience in measurement and interpretation of ultrasonography of carotid arteries trained all study neurologists. Measurements were performed on both common carotid arteries and followed the Mannheim Carotid Intima–Media Thickness and Plaque Consensus,<sup>19</sup> in which patients put themselves in a supine position and rotated their head 0° to 30°. Neurologists measured IMT between the lumen–intima and media–adventitia interfaces on the far wall of the common carotid arteries at least 5 mm below the bifurcation. The image was of a 10-mm arterial segment. We used the mean IMT for each common carotid artery to calculate the overall mean. For poor-quality images, a near-wall IMT measurement was retaken. Atherosclerotic plaques were defined as the presence of structures protruding into the arterial lumen by  $\geq 0.5$  mm or 50% of the surrounding IMT or IMT  $> 1.5$  mm. We determined the reproducibility of our IMT assessment by repeating measurements (one done by a vascular neurologist and one done by a vascular neurology resident) for 147 study participants (n=101 for Chiapas and n=46 for Yucatan). Reproducibility was high  $r=0.89$  (95% confidence interval [CI], 0.85–0.93) for Chiapas and  $r=0.92$  (95% CI, 0.85–0.93) for Yucatan. These investigators carried out a validation process including intra- and interobserver reproducibility.

## Covariates

Covariate information was obtained from self-reported information at baseline (2008) and was updated if possible using 2011 data. Marital status and education were provided by the baseline questionnaire. A question on whether the participant or her parents spoke an indigenous language was used to assess ethnicity. Total number of pregnancies and history of preeclampsia were determined using the 2008 comprehensive reproductive history questionnaire and updated in 2011. Alcohol intake was determined using a previously validated semiquantitative food frequency questionnaire.<sup>20</sup> Using 10 response categories ranging from *never* to *6 or more times a day*, women were asked to specify how often, on average, during the past year they consumed a standard serving size of 9 types of alcohol. Smoking status was defined as *never*, *past*, or *current smoker* based on self-reporting from 2008 and 2011. We assessed average time spent each week in the previous year on moderate (riding a bike, dancing, hiking) and vigorous (swimming, running) recreational physical activity, using a questionnaire that included 8 response categories ranging from none to  $> 10$  hours per week. During the clinical visit, standardized personnel measured weight to the nearest

0.1 kg using an electronic scale and height to the nearest millimeter using a wall stadiometer. When information on weight was not available, we relied on weight that was self-reported in 2008 or 2011, which is valid in this population.<sup>21</sup> We calculated body mass index as weight in kilograms divided by height in meters squared. We classified individuals as having diabetes mellitus if they reported having been diagnosed with diabetes mellitus on either questionnaire. We classified participants as having hypertension if they reported having had a medical diagnosis and/or were under treatment in 2008 and 2011.<sup>22</sup> We used treated hypercholesterolemia to identify hypercholesteremic women.

## Statistical Analyses

We categorized participants according to any record of pregnancy loss and used the group without reported pregnancy loss as the reference category. Continuous variables were summarized as mean $\pm$ SD, and categorical variables are reported as percentages to compare distributions among women with and without history of pregnancy loss. Because IMT was positively skewed, we used log transformation to normalize its distribution. We evaluated the statistical significance ( $P < 0.05$ ) between exposed and unexposed groups by using a *t* test for continuous variables and the  $\chi^2$  test for categorical variables. We used age- and multivariable-adjusted linear regression models to estimate the percentage difference in mean IMT and corresponding 95% CIs comparing women who had experienced pregnancy loss and women who had not. We defined subclinical carotid atherosclerosis (SCA) disease as mean IMT  $\geq 0.8$  mm or the presence of plaque on either common carotid artery. As a sensitivity analysis, we evaluated IMT without log-transforming this variable. We used logistic regression to estimate age and multivariable-adjusted odds ratios (ORs) and 95% CIs for SCA. Multivariable models included age (in years), state of residence (Chiapas, Yucatan, Nuevo León), marital status (married, not married), graduate education (yes, no), indigenous ethnicity (yes, no), total pregnancies (continuous), preeclampsia, diabetes mellitus, hypertension, and hypercholesterolemia. We conducted additional analyses to explore the impact of further adjustment for potential mediators (alcohol [nondrinker, drinker], smoking [never, past, current], recreational physical activity [continuous in h/wk], and body mass index [continuous in kg/m<sup>2</sup>]) and to evaluate stillbirth independent of miscarriage (women who had had a miscarriage were excluded). We conducted several sensitivity analyses. First, we excluded women who self-reported a diagnosis of lupus or rheumatoid arthritis. These autoimmune conditions are strong predictors of pregnancy loss and are associated with increased cardiovascular risk.<sup>23</sup> Second, we repeated analyses comparing women with a history of

stillbirth only and women with no history of pregnancy loss. Third, we evaluated 2 alternative definitions of SCA: (1) IMT  $\geq 1.0$  mm or plaque and (2) only plaque. Finally, because preeclampsia may affect cardiovascular risk through hypertension later in life, we evaluated the relationship only among women with and without a history of preeclampsia. All analyses were performed using SAS version 9.4 (SAS Institute).

## Results

Mean age of participants was  $49.8 \pm 5.1$  years, and the prevalence of pregnancy loss was 22% ( $n=394$ ). The mean IMT was  $0.688 \pm 0.094$  mm, and the prevalence of SCA was 23% ( $n=405$ ). Characteristics of women according to history of pregnancy loss are shown in Table 1. Relative to women who never experienced pregnancy loss, women who did were less educated; most resided in Chiapas and had a higher total

**Table 1.** Characteristics of 1767 Mexican Women According to Pregnancy Loss

	No Pregnancy Loss (n=1373)	Pregnancy Loss (n=394)*	P Value
Age, y	49.8 (5.2)	49.9 (5.0)	0.78
State of residence			
Chiapas	34.4	38.6	0.06
Yucatán	30.0	29.6	0.85
Nuevo León	35.6	31.8	0.09
Married	76.5	76.6	0.94
Graduate education	16.7	13.2	0.22
Ethnicity	15.9	16.2	0.86
Total pregnancies	2.5 (0.9)	3.7 (1.3)	<0.0001 <sup>†</sup>
Preeclampsia	7.6	11.9	0.008 <sup>†</sup>
Alcohol consumption, yes	16.2	18.5	0.22
Smoking			
Never	79.3	76.4	0.20
Past	12.3	17.3	0.009 <sup>†</sup>
Current	7.6	6.1	0.29
Physical activity, h/wk	2.8 (4.7)	2.5 (4.5)	0.42
BMI, kg/m <sup>2</sup>	29.3 (5.2)	29.3 (5.6)	0.86
Diabetes mellitus	3.1	4.3	0.22
Hypertension	14.0	15.2	0.56
Hypercholesterolemia	19.2	20.1	0.72

\*Pregnancy loss: history of miscarriage and/or stillbirth.

<sup>†</sup>Statistically significant differences ( $P < 0.05$ ) between exposed and unexposed groups. Calculated using  $t$  test for continuous variables and  $\chi^2$  test for categorical variables.

number of pregnancies ( $3.7 \pm 1.3$ ). The prevalence of preeclampsia, diabetes mellitus, and hypertension was higher among women who experienced pregnancy loss compared with women who did not. Regular consumption of alcohol and smoking appeared to be more common among women with pregnancy loss. We excluded 12% of women without an IMT evaluation. When comparing women with and without IMT measurements, we observed minor differences in age (48.8 versus 49.9 years) and prevalence of previously diagnosed hypertension (14.7% versus 17.7%); however, women included in the current analysis who were teachers were more likely to have a graduate education than those who were not teachers (15.9% versus 7.7%).

Mean IMT was higher in women with pregnancy loss ( $0.696 \pm 0.097$  mm) compared with those without ( $0.687 \pm 0.093$  mm). However, after adjusting for age, demographic characteristics, number of pregnancies, preeclampsia, diabetes mellitus, and hypertension, we observed no association between pregnancy loss and IMT (Table 2). The adjusted percentage difference in IMT comparing women with and without pregnancy loss was 1.0% (95% CI,  $-0.5$  to  $2.5$ ). Additional adjustments of potential mediators (alcohol, smoking, physical activity, and body mass index) resulted in a percentage difference of 0.9% (95% CI,  $-1.5$  to  $2.4$ ) comparing women with and without pregnancy loss.

We observed a higher prevalence of SCA in women who experienced pregnancy loss compared with those who did not (27% versus 22%; Figure). After adjusting for demographic characteristics and risk factors common to pregnancy loss and CVD, women who had previously experienced pregnancy loss had 52% higher odds of SCA compared with those with no pregnancy loss (OR: 1.52; 95% CI, 1.12–2.06; Table 3). When we adjusted for other lifestyle factors that could affect the impact of pregnancy loss on cardiovascular health, the estimate changed only slightly (OR: 1.54; 95% CI, 1.14–2.10).

In the sensitivity analyses, when we repeated analyses excluding women with self-reported lupus or rheumatoid arthritis, we found very similar results (OR: 1.56; 95% CI, 1.14–2.13; Tables S1 and S2).

We further explored the relationship between pregnancy loss and CVD by conducting analyses that compared women who had stillbirth with women with no pregnancy loss. Women who had experienced stillbirth more often were obese and indigenous and had a higher total number of pregnancies than women who had not had a stillbirth. We also found that women experiencing stillbirth had a higher prevalence of preeclampsia (17.2%) and hypertension (20.7%) than women who had not (7.6% and 14%, respectively). We observed a significantly higher IMT in women with stillbirth ( $0.709 \pm 0.092$  mm) relative to those who had not experienced pregnancy loss ( $0.687 \pm 0.093$  mm). In multivariate analyses, the adjusted percentage difference comparing women who had

**Table 2.** Adjusted Percentage Differences (95% CI) in Mean IMT Comparing Women With and Without Pregnancy Loss

	n	Mean IMT (SD)	Age-Adjusted	Multivariable 1	Multivariable 2
No pregnancy loss	1373	0.687 (0.093)	Ref	Ref	Ref
Pregnancy loss	394	0.695 (0.097)	1.2 (–0.2 to 2.6)	0.8 (–0.5 to 2.2)	1.0 (–0.5 to 2.6)

Multivariable model 1: Age, indigenous language, graduate education, clinical site, and married. Multivariable model 2: Model 1 plus preeclampsia, total pregnancies, diabetes mellitus, hypertension, and hypercholesterolemia. CI indicates confidence interval; IMT, intima–media thickness; Ref, reference.

stillbirth with those who did not was 1.6% (95% CI, –2.8 to 6.2) after adjusting for age, demographic characteristics, the number of pregnancies, preeclampsia, diabetes mellitus, and hypertension. Results were minimally affected by inclusion of behavioral mediators in the model. The prevalence of SCA was 38% in women with stillbirth (Figure). The multivariable adjusted OR for SCA comparing women who had stillbirth with those who had no pregnancy loss was 2.32 (95% CI, 1.03–5.21). Further adjustments for behavioral intermediates yielded a very similar estimate (OR: 2.31; 95% CI 1.01–5.26).

When we repeated analyses without log-transforming the outcome variable, we did not observe significant changes in our results. The multivariable-adjusted differences in mean IMT comparing women with and without pregnancy loss was 0.008 (95% CI, –0.003 to 0.019; Table S3). In addition, using an alternative definition of SCA (IMT  $\geq$ 1.0 mm or plaque) or analyzing only carotid plaque as the outcome for women with and without pregnancy loss, the multivariable adjusted OR for SCA was 1.01 (95% CI, 0.53–1.91; Table S4) and for carotid plaque only was 1.26 (95% CI, 0.59–2.68; Table S5).

Finally, we repeated these analyses by stratifying the history of preeclampsia and observed no evidence that the association was different for these subgroups. The corresponding multivariable OR for women with pregnancy loss and no history of preeclampsia compared with women with preeclampsia was 1.52 (95% CI, 1.10–2.10), whereas the

OR for women with pregnancy loss and history of preeclampsia compared with women without a history of preeclampsia was 1.49 (95% CI, 0.59–3.77).

## Discussion

In this sample of Mexican women, pregnancy loss was directly associated with SCA even after adjusting for risk factors for CVD. Our results suggest that women with a history of stillbirth may be at a higher risk for CVD later in life relative to women with miscarriage.

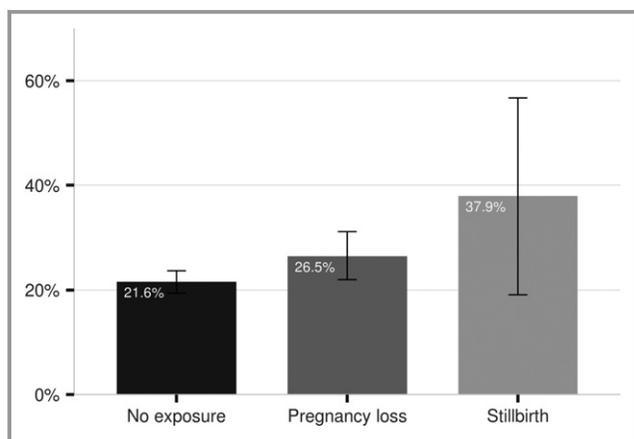
Pregnancy is associated with profound physiological changes, some of which could affect multiple CVD pathways (hormonal changes, fat and glucose metabolism, low-grade inflammation, and oxidative stress).<sup>24</sup> Psychological stress, as a consequence of pregnancy loss, activates sympathetic nervous system and hypothalamic–pituitary–adrenal axis responses.<sup>25</sup> Continual activation of these pathways often results from highly stressful life events and has been associated with markers of cardiovascular risk and CVD.<sup>26</sup>

Miscarriages result mainly from embryonic anomalies, whereas stillbirths are attributed to obstetric conditions and placental abnormalities.<sup>27,28</sup> However, both conditions appear to have similar risk for posttraumatic stress disorder (25% for miscarriage and 21% for stillbirth).<sup>6,7</sup> In cross-sectional studies, posttraumatic stress disorder has been associated with inflammatory markers and alterations in circulating lipids.<sup>29</sup> In addition, individuals who endure highly stressful life events often alter their lifestyle choices in a way that would affect cardiovascular health.<sup>30</sup> Traumatic life events have been associated with higher chances of smoking, gaining weight, physical inactivity, and elevated CVD risk.<sup>10,11,31,32</sup>

**Table 3.** Adjusted OR for Subclinical Carotid Atherosclerosis (95% CI) According to History of Pregnancy Loss

	No Pregnancy Loss	Pregnancy Loss
Cases/noncases	296/1077	108/286
Age-adjusted	1	1.39 (1.07–1.82)
Multivariable model 1	1	1.38 (1.05–1.80)
Multivariable model 2	1	1.51 (1.12–2.05)

CI indicates confidence interval; OR odds ratio.

**Figure.** Prevalence and 95% confidence intervals for subclinical carotid atherosclerosis.

Pregnancy loss and CVD could also be potentially linked by shared risk factors. Hypertension, for example, might occur after preeclampsia,<sup>33</sup> so we adjusted for history of preeclampsia. We excluded women with preeclampsia in a sensitivity analysis, and the results were similar to what was observed among all participants. Endothelial dysfunction has also been linked to pregnancy loss and adverse placental outcomes,<sup>34</sup> so we cannot exclude the possibility that this common cause of pregnancy loss and CVD might explain the relationship found in our results.

The relation between pregnancy loss and incident CVD has been evaluated using several study designs.<sup>35</sup> Even though the prevalence of posttraumatic stress disorder after miscarriage and stillbirth is similar,<sup>6,7</sup> several studies suggest that CVD may have a stronger association with stillbirth than with miscarriage. A prospective population-based cohort study in Denmark<sup>12</sup> that included close to 1 million women and studied them for >15 years found that those who experienced pregnancy loss were at increased risk of CVD, predominantly among those who had experienced a stillbirth. The likelihood of MI was close to 3 times higher in women who had previously experienced a stillbirth (relative risk: 2.69; 95% CI, 2.06–3.50). The association appeared to be weaker for miscarriages; however, relative to women who had not experienced pregnancy loss, women who had experienced  $\geq 4$  miscarriages appeared to have the same risk as women who had a previous stillbirth. Another cohort study also observed this dose-response relationship,<sup>13</sup> and incident MIs were found to be 9 times more common among women who had experienced >3 miscarriages compared with women who had not experienced pregnancy loss (hazard ratio: 8.90; 95% CI, 3.18–24.9). In that study, the incidence of MI doubled for each stillbirth (hazard ratio: 2.32; 95% CI, 1.19–4.50). In the Women's Health Initiative,<sup>14</sup> women with a history of  $\geq 1$  stillbirths were more likely to have an MI relative to women without stillbirth. Our results are consistent with these observations and with a cross-sectional study conducted in Finland that used IMT as the outcome.<sup>15</sup> We also observed that stillbirth may have a stronger impact on CVD. Surprisingly, both our study and the Finnish study found that pregnancy loss was associated with SCA but not with IMT. The Finnish study may have been limited by a smaller sample size (n=746). After adjustment for multiple risk factors, the association between stillbirth and atherosclerotic plaque was no longer significant (OR: 3.61; 95% CI, 0.86–15.23). In our study, a history of stillbirth more than doubled the odds of SCA (OR: 2.32; 95% CI, 1.03–5.21). Interestingly, a large population-based Japanese cohort<sup>36</sup> observed an inverse relation between the number of pregnancy losses and CVD. This difference could be attributed to differences between Western and Asian populations in behavioral responses to stressful events or obstetric care.

Our analysis has some strengths including a population-based sample; collection of detailed information on participants' reproductive histories; and a centralized, high-quality assessment of subclinical CVD.

There are also some limitations to consider in interpreting these results. The cross-sectional nature of our study limits our ability to discern the directionality of the observed association; however, because the study group was composed of middle-aged women, pregnancies occurred mostly in early adulthood, a time when established CVD is unlikely to have been present. Women were also unaware of their IMT measurements, thus limiting the likelihood that participants' reporting of pregnancy loss was affected by their cardiovascular risk. Unmeasured and residual confounding due to common causes of pregnancy loss and CVD cannot be excluded; for example, we were unable to assess endothelial dysfunction, which has been linked to pregnancy loss and adverse placental outcomes.<sup>34</sup> In addition, socioeconomic status is a risk factor associated with CVD and pregnancy loss.<sup>5,37</sup> We cannot exclude the possibility of residual confounding by socioeconomic status; however, all participants have a stable job and healthcare coverage. In this study, our capacity to evaluate miscarriages independent of stillbirth was limited given potential underreporting or misreporting of pregnancy loss. We found that some women had difficulty distinguishing between miscarriage and stillbirth because they reported having both for the same pregnancy. Moreover, we assessed miscarriage using slightly different definitions in the self-administered questionnaires (miscarriage versus having had a pregnancy of <6 months). There is a possibility of misclassification for the exposure, particularly for the 2008 questionnaire, as some women may have considered miscarriage (*aborto* in Spanish) to mean induced abortion. Furthermore, we were unable to make a distinction between induced abortion and spontaneous miscarriage; however, induced abortion is illegal in the Mexican states where the study was performed and was legalized in some states in Mexico only recently. Even though our study included an important number of women, we could not evaluate recurrent miscarriages due to sample size. Finally, our participants were mostly educated Mexican women. Psychological stress varies across populations and socioeconomic groups<sup>38</sup>; therefore, the association we observed may not be generalizable to the general Mexican population. Nevertheless, educated women represent an important and growing proportion of the Mexican population.

## Conclusions

This study suggests that pregnancy loss may be related to subclinical atherosclerosis in later life, but confirmative evidence is required for future studies. We hypothesize that this relation may result from a complex interaction of stress-

induced physiological alterations and/or behavioral change. Further research on these underlying mechanisms is needed. Women with a history of pregnancy loss should be closely monitored for cardiovascular risk. Strengthening perinatal care services not only prevents poor reproductive outcomes but also could potentially affect women's future cardiovascular health.

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## References

- Garcia M, Mulvagh S, Bairey Merz C, Buring J, Manson J. Cardiovascular disease in women. *Circ Res*. 2016;118:1273–1293.
- Mexico, Institute for Health Metrics and Evaluation [Internet]. Healthdata.org. 2017. Available at: <http://www.healthdata.org/mexico>. Accessed July 10, 2017.
- Colditz G, Willett W, Stampfer M, Rosner B, Speizer F, Hennekens C. Menopause and the risk of coronary heart disease in women. *N Engl J Med*. 1987;316:1105–1110.
- (INEGI) I. Encuesta Nacional de la Dinámica Demográfica 2014. Beta.inegi.org.mx. 2017. Available from: <http://www.beta.inegi.org.mx/proyectos/enchogares/especiales/enadid/2014/>. Accessed July 10, 2017.
- Lawn J, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, Gardosi J, Day L, Stanton C. Stillbirths: Where? When? Why? How to make the data count? *Lancet*. 2011;377:1448–1463.
- Farren J, Jalmbrant M, Amey L, Joash K, Mitchell-Jones N, Tapp S, Timmerman D, Bourne T. Post-traumatic stress, anxiety and depression following miscarriage or ectopic pregnancy: a prospective cohort study. *BMJ Open*. 2016;6:e011864.
- Hughes P, Turton P, Hopper E, Evans C. Assessment of guidelines for good practice in psychosocial care of mothers after stillbirth: a cohort study. *Lancet*. 2002;360:114–118.
- Sumner J, Kubzansky L, Elkind M, Roberts A, Agnew-Blais J, Chen Q, Cerdá M, Rexrode K, Rich-Edwards J, Spiegelman D, Suglia S, Rimm E, Koenen K. Trauma exposure and posttraumatic stress disorder symptoms predict onset of cardiovascular events in women. *Circulation*. 2015;132:251–259.
- Steptoe A, Kivimäki M. Stress and cardiovascular disease: an update on current knowledge. *Annu Rev Public Health*. 2013;34:337–354.
- Chwastiak L, Rosenheck R, Kazis L. Association of psychiatric illness and obesity, physical inactivity, and smoking among a national sample of veterans. *Psychosomatics*. 2011;52:230–236.
- LeardMann C, Woodall K, Littman A, Jacobson I, Boyko E, Smith B, Wells T, Crum-Cianflone N. Post-traumatic stress disorder predicts future weight change in the Millennium Cohort Study. *Obesity*. 2015;23:886–892.
- Ranthe M, Andersen E, Wohlfahrt J, Bundgaard H, Melbye M, Boyd H. Pregnancy loss and later risk of atherosclerotic disease. *Circulation*. 2013;127:1775–1782.
- Kharazmi E, Dossus L, Rohrmann S, Kaaks R. Pregnancy loss and risk of cardiovascular disease: a prospective population-based cohort study (EPIC-Heidelberg). *Heart*. 2010;97:49–54.
- Parker D, Lu B, Sands-Lincoln M, Kroenke C, Lee C, O'Sullivan M, Park H, Parikh N, Schenken R, Eaton C. Risk of cardiovascular disease among postmenopausal women with prior pregnancy loss: the women's health initiative. *Ann Fam Med*. 2014;12:302–309.
- Kharazmi E, Moilanen L, Fallah M, Kaaja R, Kattainen A, Kähönen M, Jula A, Kesaniemi A, Luoto R. Reproductive history and carotid intima-media thickness. *Acta Obstet Gynecol Scand*. 2007;86:995–1002.
- Bronfman-Pertsovsky M, López-Moreno S, Magis-Rodríguez C, Moreno-Altamirano A, Rutstein S. Atención prenatal en el primer nivel de atención: características de los proveedores que influyen en la satisfacción de las usuarias. *Salud Pública Mex*. 2003;45:445–454.
- Hartasanchez SA. Pregnancy Loss and Carotid Intima Media Thickness. Mexican Teachers' Cohort. 2017 Available at: [http://www.home/mario.flores/sasuser.v94/Pregloss\\_CIMT\\_Aug2017.sas](http://www.home/mario.flores/sasuser.v94/Pregloss_CIMT_Aug2017.sas). Accessed November 26, 2017.
- Lajous M, Ortiz-Panozo E, Monge A, Santoyo-Vistrain R, García-Anaya A, Yunes-Díaz E, Rice M, Blanco M, Hernández-Avila M, Willett W, Romieu I, López-Ridaura R. Cohort Profile: The Mexican Teachers' Cohort (MTC). *Int J Epidemiol*. 2015;44:e10. <https://doi.org/10.1093/ije/dyv123>
- Touboul P, Hennerici M, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Hernandez Hernandez R, Jaff M, Kownator S, Naqvi T, Prati P, Rundek T, Sitzer M, Schminke U, Tardif J, Taylor A, Vicaud E, Woo KS. Mannheim carotid intima-media thickness and plaque consensus (2004–2006–2011). *Cerebrovasc Dis*. 2012;34:290–296.
- Hernandez-Avila M, Romieu I, Parra S, Hernandez-Avila J, Madrigal H, Willett W. Validity and reproducibility of a food frequency questionnaire to assess dietary intake of women living in Mexico City. *Salud Pública Mex*. 1998;40:133–140.
- Ortiz-Panozo E, Yunes-Díaz E, Lajous M, Romieu I, Monge A, López-Ridaura R. Validity of self-reported anthropometry in adult Mexican women. *Salud Pública Mex*. 2017;59:266–275.
- Catzín-Kuhlmann A, Juárez-Armenta A, Ortiz-Panozo E, Monge-Urrea A, Puchner K, Cantú-Brito C, López-Ridaura R, Rice M, Kurth T, Lajous M. Restless legs syndrome and hypertension in Mexican women. *Movmnt Disords Clinl Practice*. 2015;2:274–279.
- Phansenee S, Sekararithi R, Jatavan P, Tongsong T. Pregnancy outcomes among women with systemic lupus erythematosus: a retrospective cohort study from Thailand. *Lupus*. 2018;27:158–164.
- Soma-Pillay P, Nelson-Piercy C, Tolppanen H, Mebazaa A. Physiological changes in pregnancy. *Cardiovasc J Afr*. 2016;27:89–94.
- McEwen B. Allostatics and the epigenetics of brain and body health over the life course. *JAMA Psychiatry*. 2017;74:551.
- Fishta A, Backé E. Psychosocial stress at work and cardiovascular diseases: an overview of systematic reviews. *Int Arch Occup Environ Health*. 2015;88:997–1014.
- Massalska D, Zimowski J, Bijok J, Pawelec M, Czubak-Barlik M, Jakiel G, Roszkowski T. First trimester pregnancy loss: clinical implications of genetic testing. *J Obstet Gynaecol Res*. 2016;43:23–29.
- The Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. *JAMA*. 2011;306:2459.
- Passos I, Vasconcelos-Moreno M, Costa L, Kunz M, Brietzke E, Quevedo J, Salum G, Magalhaes PV, Kapczinski F, Kauer-Sant'Anna M. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. *Lancet Psychiatry*. 2015;2:1002–1012.
- Rozanski A. Behavioral cardiology: current advances and future directions. *J Am Coll Cardiol*. 2014;64:100–110.
- Koenen K, Stellman S, Sommer J, Stellman J. Persisting posttraumatic stress disorder symptoms and their relationship to functioning in Vietnam veterans: a 14-year follow-up. *J Trauma Stress*. 2008;21:49–57.
- Kubzansky L, Bordenlois P, Jun H, Roberts A, Cerda M, Bluestone N, Koenen K. The weight of traumatic stress: a prospective study of posttraumatic stress disorder symptoms and weight status in women. *JAMA Psychiatry*. 2014;71:44.

33. Bellamy L, Casas J, Hingorani A, Williams D. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007;335:974.
34. Germain A, Romanik M, Guerra I, Solari S, Reyes M, Johnson R, Price K, Ananth Karumanchi S, Valdes G. Endothelial dysfunction: a link among preeclampsia, recurrent pregnancy loss, and future cardiovascular events? *Hypertension*. 2006;49:90–95.
35. Oliver-Williams C, Heydon E, Smith G, Wood A. Miscarriage and future maternal cardiovascular disease: a systematic review and meta-analysis. *Heart*. 2013;99:1636–1644.
36. Yamada K, Iso H, Cui R, Tamakoshi A. Recurrent pregnancy loss and cardiovascular disease mortality in Japanese women: a population-based, prospective cohort study. *J Stroke Cerebrovasc Dis*. 2017;26:1047–1054.
37. Centers for Disease Control and Prevention. Surveillance of health status in minority communities—Racial and Ethnic Approaches to Community Health Across the U.S. (REACH U.S.) Risk Factor Survey, United States, 2009. *Morb Mortal Wkly Rep*. 2011;60:1–44.
38. Anderson N, Bulatao R, Cohen B. National Research Council (US) Panel on Race & Race/Ethnicity, Socioeconomic Status, and Health. 2017. <https://www.ncbi.nlm.nih.gov/books/NBK25526/>. Accessed July 17, 2017.

# SUPPLEMENTAL MATERIAL

**Table S1. Adjusted OR for Subclinical Carotid Atherosclerosis (95% CI) according to history of pregnancy loss and excluding women with history of autoimmune disorders (RA and Lupus n=75)**

	No pregnancy loss 280/1034	Pregnancy loss 104/274
Cases/non-cases		
Age-adjusted	1	1.41(1.08,1.86)
Multivariable 1	1	1.40(1.07,1.84)
Multivariable 2	1	1.56(1.14,2.13)

Multivariable<sup>1</sup>: Age + indigenous language+ graduate education +clinical site +married

Multivariable<sup>2</sup>: 1 + preeclampsia + total pregnancies + diabetes + hypertension + hypercholesterolemia

**Table S2. Adjusted % differences (95% CI) in mean IMT comparing women with and without pregnancy loss. Excluding women with history of autoimmune disorders (RA and Lupus n=75)**

	N	Mean IMT (SD)	Age- adjusted	Multivariable <sup>1</sup>	Multivariable <sup>2</sup>
No Pregnancy loss	1,314	0.687mm	Ref	Ref	Ref
Pregnancy loss	378	0.697mm	1.1(-0.3,2.6)	0.8(-0.7,2.2)	1.1(-0.4,2.7)

Multivariable<sup>1</sup>: Age + indigenous language+ graduate education +clinical site  
+married

Multivariable<sup>2</sup>: 1 + preeclampsia + total pregnancies + diabetes +  
hypertension+hypercholesterolemia

**Table S3. Adjusted differences (95% CI) in mean IMT comparing women with and without pregnancy loss**

	N	Mean IMT (SD)	Age-adjusted	Multivariable <sup>1</sup>	Multivariable <sup>2</sup>
No Pregnancy loss	1,373	0.687 (0.093)	Ref	Ref	Ref
Pregnancy loss	394	0.695 (0.097)	0.009 (-0.001, 0.019)	0.006 (-0.004, 0.0160)	0.008 (-0.003, 0.01)

Multivariable<sup>1</sup>: Age + indigenous language+ graduate education +clinical site +married

Multivariable<sup>2</sup>: 1 + preeclampsia + total pregnancies + diabetes + hypertension + hypercholesterolemia

**Table S4. Adjusted OR for IMT ge 1.0mm or plaque (95% CI) according to history of pregnancy loss**

	No pregnancy loss	Pregnancy loss
Cases/non-cases		
Age-adjusted	1	1.01 (0.58,1.76)
Multivariable 1	1	0.98 (0.56,1.71)
Multivariable 2	1	1.01 (0.53,1.91)

Multivariable<sup>1</sup>: Age + indigenous language+ graduate education +clinical site

+married

Multivariable<sup>2</sup>: 1 + preeclampsia + total pregnancies + diabetes + hypertension +

hypercholesterolemia

**Table S5. Adjusted OR for carotid plaque (95% CI) according to history of pregnancy loss**

	No pregnancy loss	Pregnancy loss
Cases/non-cases		
Age-adjusted	1	1.34 (0.70,2.58)
Multivariable 1	1	1.25 (0.65,2.41)
Multivariable 2	1	1.26 (0.59,2.68)
Multivariable <sup>1</sup> : Age + indigenous language+ graduate education +clinical site +married		
Multivariable <sup>2</sup> : 1 + preeclampsia + total pregnancies + diabetes + hypertension + hypercholesterolemia		

## **Pregnancy Loss and Carotid Intima–Media Thickness in Mexican Women**

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