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Association between Number of Live Births and Markers of Subclinical Atherosclerosis: The Dallas Heart Study

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Abstract

Aims—Higher parity has been associated with increased maternal risk of cardiovascular (CV) disease, but the mechanism is not well delineated. Whether the number of live births is associated with coronary and aortic subclinical atherosclerosis has not been fully evaluated.

Methods and Results—Women from the Dallas Heart Study, a multiethnic population-based cohort of subjects aged 30–65, were included if they had data on self-reported live births and coronary artery calcium (CAC) measured by computed tomography or aortic wall thickness (AWT) by MRI. CAC was positive if >10 Agatston Units, and AWT if greater than the 75th percentile reference point for age and gender. Among the 1644 women included in the study, the mean age was 45 years and 55% were black. Sequential multivariable models were done adjusting for age, race, traditional CV risk factors, body mass index, income, education, hormone replacement therapy, oral contraceptives, and physical activity. Using women with 2–3 live births as the reference, those with 4 or more live births had an increased prevalence of elevated CAC (OR 2.2, 95% CI 1.28–3.65) and AWT (OR 1.6, 95% CI 1.04–2.41). Women with 0–1 live births also had increased CAC (OR 1.9, 95% CI 1.16–3.03) and AWT (OR 1.5, 95% CI 1.05–2.09) after multivariable adjustment.

Conclusion—The number of live births is associated with subclinical coronary and aortic atherosclerosis, with an apparent U-shaped relationship. Further studies are needed to confirm this association and explore the biological underpinnings of these findings.

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Keywords

women; pregnancy; subclinical atherosclerosis; coronary artery calcification; cardiovascular disease; aortic wall thickness

Introduction

Cardiovascular (CV) disease remains the number one cause of death in women. There is increasing interest in the impact of childbearing, associated complications, and reproductive patterns on CV risk since pregnancy is a time of several physiologic changes which may unmask underlying cardiometabolic risk(1) or serve as an exposure that may have lasting consequences for cardiometabolic health. Multiple studies have demonstrated that pregnancy complications such as preeclampsia, gestational hypertension, and gestational diabetes are associated with increased CV risk (2–4) which has led to the recommendation of including a pregnancy history as part of a standard CV evaluation visit(5). Attention has extended beyond the role of pregnancy complications to consider the relationship of parity with the development of CV disease.

Higher parity (number of births) has been associated with increased maternal risk of CV disease in many (6–8), but not all studies(9). Some studies have shown a threshold effect for parity (6), above which the risk of CV disease increases, while others have demonstrated a J-shaped association with increased risk in nulliparous and grand multiparous women. Pregnancy complications,(10) adverse lifestyle risk factors (8) and child-rearing (11) explain some, but not all of the association for women. It is hypothesized that there may be specific pregnancy related changes, such as dyslipidemia(12), changes in fat distribution (13), or metabolic changes(14), that contribute to these risks and atherosclerosis may be an intermediary between these proposed mechanisms and clinical CV disease. However, the exact mechanism for the relationship between parity and CV disease has not been delineated.

Therefore, we investigated the association between the number of live births and subclinical atherosclerosis, as measured by coronary artery calcification (CAC) and aortic wall thickness (AWT), in the Dallas Heart Study. We used 2–3 births as the reference based on prior studies showing a nadir of risk at this number of births(8).

Methods

The Dallas Heart Study (DHS) is a multiethnic, probability-based, population study of Dallas County adults, with intentional oversampling of African Americans to compose approximately 50% of the cohort. Detailed methods of DHS phase 1 (DHS-1) have been described previously(15). The study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas, TX. Between 2000 and 2002, 3072 male and female participants completed all phases of DHS-1, including detailed survey, laboratory testing and multiple imaging studies. Among the 1695 women completing DHS-1, those who had CAC or AWT measurements and reported information regarding number of live births were included in the study (n=1644).

Variable Definitions

Number of live births was self-reported on a questionnaire administered at study entry. Women who reported never being pregnant were included in the analysis as zero live births. Demographic information including race/ethnicity, household income and education level achieved were also determined by self-report. Ethnicity was self-identified by the participants as non-Hispanic black, non-Hispanic white, Hispanic or other. Body mass index (BMI) was calculated based on measured height and weight. Waist circumference was measured 1 cm above the iliac crest and hip circumference at the widest circumference of the buttocks at the area of the greater trochanters. Smoking status was determined by self-report. Diabetes mellitus (DM) was defined by one of the following: self-report accompanied by use of anti-hyperglycemic medication or by elevated serum glucose (fasting >126 mg/dl [7.0 mmol/l] or by nonfasting glucose >200 mg/dl [11.1 mmol/l]). Postmenopausal status was defined as those women who self-reported being postmenopausal, having their last menstrual period more than 12 months prior to enrollment, or having a bilateral salpingo-oophorectomy (BSO). Oral contraceptive pills (OCP) and hormone replacement therapy (HRT) use were determined by the current list of medications for each participant; preparations with just progesterone were excluded. Physical activity participation was assessed via questionnaire at study entry as previously described (16). The presence of polycystic ovarian syndrome (PCOS) was prospectively characterized in a nested cohort of premenopausal women within the Dallas Heart Study. PCOS was defined by Rotterdam consensus criteria, in which any two of the following had to be present: oligomenorrhea, hyperandrogenism, or polycystic ovarian morphology (17). Ovarian morphology was evaluated using Pelvic MRI.

Imaging Measurements of Subclinical Atherosclerosis

Coronary artery calcification—Electron beam computed tomography scanning was performed using an Imatron C-150XP EBCT scanner using a previously described protocol (18). Duplicate scans were performed within 1–2 minutes. CAC scores are expressed in Agatston units as averaged scores from the two consecutive scans. An Agatston score >10 was the data-derived threshold for the presence of calcium to maximize the signal-to-noise ratio and reproducibility among obese participants as previously described (18).

Aortic Wall Thickness—Details of the cardiovascular magnetic resonance imaging protocol have been previously described (19). AWT was calculated by subtracting the luminal radius from the total vessel radius, averaged, over 6 slices from measurements made on the infrarenal abdominal aorta. The sex – and age- specific (in 5-year increments) 75th percentile of AWT were calculated using data from all subjects in the DHS cohort with these measurements available (20).

Statistical Analyses

Continuous data are presented as median values with interquartile ranges and categorical variables are presented as proportions. Women were stratified based on the reported number of live births (0–1, 2–3, 4+). The reference group for the analyses was 2–3 births based on prior studies showing a nadir of risk in these women (8) and comparison with groups with 0–

1 and 4 live births were performed separately (8). Differences in baseline characteristics were analyzed using Pearson's chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Sequential multivariable logistic regression models with elevated CAC and AWT as the outcomes were used to assess independent associations of the number of live births and measures of subclinical atherosclerosis. Sensitivity analyses were performed restricting analysis to women over the age of 40 and postmenopausal women to eliminate women who may have additional child-bearing potential and thus may have not completed child-bearing. Women with PCOS were also excluded from the analysis to determine if this would attenuate the association between 0–1 live births and subclinical atherosclerosis.

Additional sensitivity analyses involved separating women who reported never being pregnant from those women who had been pregnant but reported no live births.

All statistical analyses were performed using SAS version 9.2. For all statistical testing, a 2-sided p value <0.05 was considered statistically significant.

Results

The baseline characteristics of the 1644 women are shown in Table 1. Women with 4 or more live births were older, had higher BMI and waist circumference, were more likely to be hypertensive and diabetic, and had higher triglycerides, total cholesterol, and LDL-C levels than women with 2–3 live births. The proportion of Caucasian women was lower in those with 4 or more births than 2–3 births (13% vs 27%, $p < 0.01$) and the inverse was seen with Hispanic women (29% vs 18%, $p < 0.01$). Women with 4 or more births were more likely to have less than a high school education (41% vs 18%, $p < 0.01$) and earn less than 16,000 dollars per year (35% vs 21%, $p < 0.01$). Women with 4 or more live births were less physically active compared to those women with 2–3 live births (0 vs 88 MET-minutes per week, $p < 0.01$).

Risk factor profiles were similar among women with 0–1 live births compared with those with 2–3 live births with the exception of DM, which was more common in those with 0–1 births (12% vs 9%, $p < 0.05$). BMI and WHR, were lower in women with 0–1 births than 2–3 births. There were fewer African American women in the group with 0–1 live births (46% vs 54%, $p < 0.01$) and more Caucasian women (40% vs 27%, $p < 0.01$). Women with 0–1 births were more likely to have completed college (31% vs. 17%, $p < 0.01$) and earn more than 50,000 dollars per year (33% vs 27%, $p < 0.05$). Women with 0–1 live births were more likely to be taking OCPs (8% vs 4.8%, $p < 0.05$).

Subclinical Atherosclerosis

Coronary artery calcification—CAC prevalence was 11% in those with 2–3 births, 27% in those with 4+ births, and 15% in those with 0–1 births (Figure 1) with a p value <0.0001 for trend. After multivariable adjustment for age, race, systolic blood pressure (SBP), antihypertensive medications, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides, statin use, DM, smoking, BMI, income, education, OCP, HRT and physical activity, both 4+ births (odds ratio (OR) 2.2, 95% confidence interval (CI) (1.28–

3.65)), and 0–1 births (OR 1.9, 95% CI, 1.16–3.03) were independently associated with CAC when using 2–3 live births as the reference group (Table 2). A sub-analysis dividing the number of live births into integer groups demonstrated a similar trend in association, with a nadir seen at 3 live births (Figure 3).

Aortic Wall Thickness—Women with 4+ or 0–1 live births had a higher prevalence of AWT >75thile, 33% and 25% respectively, than those with 2–3 live births, 22% (Figure 2). Using 2–3 live births as the reference, women with 4 or more and 0–1 live births had a significantly higher multivariable adjusted prevalence of AWT >75thile (OR 1.6, 95% CI 1.04–2.41 and OR 1.5, 95% CI 1.05–2.09, respectively) (Table 2). Sub-analysis further separating number of live births into integer subgroups also demonstrated a similar trend in association with a nadir of 3 live births (Figure 4).

Sensitivity Analyses—Sensitivity analyses restricting the cohort to women older than 40 years of age and postmenopausal women demonstrated similar trends as the original analysis for both measures of subclinical atherosclerosis, although the association in postmenopausal women was no longer significant with the reduction in sample size (Table 3). Removing women with PCOS from the analysis did not attenuate the association for those women with 0–1 births as seen in Table 3. Similarly, excluding those women who had never been pregnant (n=222) did not attenuate the increased odds of CAC or AWT in those with 0–1 live births.

Discussion

Among women in the DHS, we observed a U-shaped association between the number of live births and two measures of subclinical atherosclerosis, coronary artery calcium and aortic wall thickness, with a nadir at 3 live births. These relationships were consistent when restricting to older age groups and women who had likely completed child bearing. These results provide potential mechanistic underpinnings for the previously reported bimodal relationship between parity and clinical CV events (7, 8).

Several prior studies have investigated the relationship between parity and clinical CV disease outcomes with varied findings. Ness et al, using data from the Framingham Heart Study and the National Health and Nutrition Examination Survey National Epidemiologic Follow-up Study, noted an increased CV disease risk after 6 or more pregnancies suggesting a threshold effect of increased risk(6). Similarly, Catov et al noted increased risk of cardiovascular disease in parous women (women having one or more births) when compared to nulliparous women (10). In contrast, Colditz et al reported a trend toward slightly increased risk in nulliparous versus parous women (9). More recently, in a study by Parikh et al evaluating the association between parity and CV disease events defined by first hospitalization or death due to CHD, stroke or heart failure, the authors reported a J shaped association for the composite outcome as well as each component outcome (7). Lawlor et al also demonstrated a J shaped association between CHD, defined as self-reported or chart diagnosis of myocardial infarction, angina, or heart failure and number of children. These studies reported a nadir of risk at 2 or between 2–3 births while we report a nadir of risk closer to 3 births. It is possible that this slight difference is due to the higher number of

average births in black and Hispanic minority groups, which comprise 75 percent of the DHS, whereas these prior studies were done in homogenous non-Hispanic white populations. In a prospective cohort study, Dior et al found a U shaped association between live births and death (including cardiovascular and circulatory death) using 2–4 live births (multiparous women) as the reference group. This study included a more diverse cohort including Europeans, Israelis and women of north and west African descent (21)

It is unclear whether the associations of parity with CV disease events and death are due to the burden of atherosclerotic disease, increase in plaque vulnerability, or to prothrombotic effects. Pregnancy has been considered a proatherogenic state associated with increased weight, insulin resistance, and dyslipidemia(12, 14). Some changes, such as a decrease in HDL (22, 23) and increased visceral adiposity (24), persist or occur after parturition suggesting an impact of pregnancy that extends beyond the pregnancy itself. Recently, Kews et al reported that an adverse cardiometabolic profile can emerge as early as one year postpartum in women who do not lose their pregnancy weight within twelve months after delivery(25).

The association between the number of live births and measures of subclinical atherosclerosis in our study supports the hypothesis that multiple pregnancies increase exposure time to the atherogenic milieu, increasing the risk of atherosclerotic heart disease. Although this risk does not appear to be mediated by weight alone since the association was independent of BMI. It is possible that this association is due to residual confounding, as those with multiple births also have an increased risk factor burden. However, adjustment for traditional risk factors and measures of socioeconomic status did not attenuate the strong associations observed in our age and race adjusted models suggesting that physiologic changes during pregnancy itself may be implicated. A change in body fat distribution with an increase in visceral deposition of adipose tissue at the end of pregnancy(26) and postpartum(27) may be another mechanism for the increased cardiovascular risk. Visceral adipose tissue (VAT) has recently been shown to be associated with incident hypertension (28) and diabetes(29), and abdominal obesity has been associated with early atherosclerosis as measured by CAC in young multiethnic adults(30).

In contrast to associations in multiparous women, the increased prevalence of subclinical atherosclerosis in women with 0–1 live births is not consistent with this paradigm of repetitive exposure to the atherogenic milieu of pregnancy, suggesting a secondary pathophysiologic process. It is possible that women who are unable to complete multiple pregnancies or have difficulty getting pregnant have another pathophysiologic process that increases their risk. This was explored by Parikh et al in a paper demonstrating that subfertility, defined as a duration of 1 year or more of involuntary childlessness, was associated with increased CVD risk when subfertility lasted five or more years (31). Another possible explanation is PCOS, as this syndrome is associated with metabolic derangements and increased CV risk, as well as infertility. A prior study evaluating women with PCOS noted an increased association with CAC compared to age matched controls without PCOS (32). However, within the DHS cohort, this association was not previously observed (17). In addition, excluding women with PCOS in our study did not impact our findings.

Other systemic factors limiting fertility may also share associations with CV disease, such as hypercoagulable states and rheumatologic illness. Although excluding subjects who had never been pregnant did not alter our findings, our survey instrument did not differentiate between those who had never attempted pregnancy vs. those who were unable to conceive. One other possibility for the U-shaped association of pregnancy and atherosclerosis is that pregnancy may initially be protective, but with repeated exposure there is increased risk similar to the relationship seen with alcohol consumption and cardiovascular risk(33, 34). It should be noted that some studies have only found an association between CV risk and multiparity, suggesting possible residual confounding in women with 0–1 births. Additional studies and more granular information regarding prior history of miscarriages are needed to validate and better understand the potentially increased risk in women with 0–1 live births.

Few prior studies have examined the association between parity and subclinical atherosclerosis measures. One study demonstrated augmented CIMT progression in women who gave birth during the study period compared to controls(35). Another small study evaluated the association with parity and CAC, and reported an increase in CAC prevalence in older postmenopausal women with four or more live births(36). Our study is unique in that it examined the association between the number of live births and subclinical atherosclerosis in two different vascular beds. In addition, women in our study were examined at a relatively young age which allows for evaluation of atherosclerotic changes prior to the increase in atherosclerotic burden associated with older age and increased risk factor burden.

These findings add to the growing body of literature suggesting that pregnancy and its associated changes and complications may increase a woman's risk for future CV disease. More information is needed to confirm these findings and fully understand the clinical implications for cardiovascular risk assessment. A pregnancy history should be an important component of a comprehensive complete CV risk history in women and may help clinicians target young women at higher risk for CV disease for more aggressive risk factor modification. Since pregnancy occurs relatively early in a woman's life, consideration of the CV risks associated with multiple (or no) pregnancies may provide opportunities for earlier intervention to decrease lifetime risk.

Limitations

The limitations of our study include a retrospective cohort design that limits our ability to assess for causality. In addition, there remains the possibility that there are other biological or socioeconomic confounders that are not accounted for in our multivariable models. The questionnaire did not have information regarding total number of pregnancies or the number of miscarriages/live births. We do not have information on and thus are unable to adjust for preeclampsia, gestational diabetes, and other pregnancy complications that are known to be associated with increased CV risk. However, prior studies have shown that the association of parity with CV disease is independent of pregnancy complications (7, 10, 21). Lastly, our cohort includes women in their 30's who may not have completed childbirth. However, the findings were insensitive to exclusion of women who could still remain in their child-bearing years.

Conclusions

This study demonstrates a U-shaped association between the number of live births and measures of subclinical atherosclerosis. Additional research is needed to confirm these results and better delineate the increased risk observed in women with 0–1 live births.

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Translational Perspective

The number of live births a woman has may be associated with subclinical atherosclerosis. Additional studies are needed to evaluate causation and understand the clinical implications for risk assessment and counseling.

Figure 1.
Coronary Artery Calcification Prevalence by Number of Live Births

Figure 2.
Aortic Wall Thickness >75% Prevalence by Number of Live Births

Figure 3.

Odds of CAC>10 Stratified by Number of Live Births

* All analyses used fully adjusted model (Model 3)

Figure 4.

Odds of AWT>75% Stratified by Number of Live Births

* All analyses used fully adjusted model (Model 3)

Table 1**Baseline Characteristics of the Study Cohort**

		Number of Live Births		
		0–1	2–3	4+
N		559	787	298
Age		42 [35, 50]	43 [36, 51]	51 [39, 57] [‡]
Race				
	Caucasian	225 (40%) [‡]	216 (27%)	40 (13%) [‡]
	African American	258 (46%) [‡]	424 (54%)	170 (57%)
	Hispanic	63 (11%) [‡]	139 (18%)	85 (29%) [‡]
	Other	13 (2%)	8 (1%)	3 (1%)
Risk Factors				
	Diabetes	69 (12%) [‡]	68 (9%)	54 (18%) [‡]
	Smoking	130 (23%)	202 (26%)	69 (23%)
	Hypertension	168 (30%)	267 (34%)	139 (47%) [‡]
	Systolic BP	122 [111, 135]	123 [112, 136]	127 [115, 144] [‡]
	Diastolic BP	78 [72, 85]	79 [73, 85]	80 [74, 87]
	TC	176 [153, 199]	176 [153, 202]	183 [158, 213] [‡]
	LDL-C	101 [80, 122]	103 [81, 125]	109 [86, 129] [‡]
	HDL-C	52 [44, 62]	51 [43, 61]	50 [42, 60]
	Triglycerides	88 [64, 128]	90 [64, 127]	99 [69, 146] [‡]
	CRP	3.30 [1.5, 8.1]	3.7 [1.5, 8.45]	5.10 [2.20, 11] [‡]
	BMI	28 [24, 34] [‡]	30 [25, 35]	30 [26, 36] [‡]
	WHR	0.85 [0.80, 0.90] [‡]	0.86 [0.81, 0.91]	0.88 [0.83, 0.92] [‡]
Education				
	<High School	60 (11%) [‡]	145 (18%)	122 (41%) [‡]
	High School	148 (26%) [‡]	275 (35%)	94 (32%)
	Some College	179 (32%)	236 (30%)	62 (21%) [‡]
	College +	172 (31%) [‡]	130 (17%)	20 (7%) [‡]
Income				
	<16K	89 (19%)	141 (21%)	88 (35%) [‡]
	16–30K	90 (19%) [‡]	180 (27%)	86 (34%)
	30–50K	140 (30%) [‡]	157 (24%)	55 (22%)
	>50K	155 (33%) [‡]	178 (27%)	22 (9%) [‡]
	HRT	80 (14%)	121 (15.4%)	38 (12.8%)
	OCP	46 (8%) [‡]	38 (4.8%)	16 (5.4%)
	PCOS	51 (9%)	73 (9%)	18 (6%)
	Physical Activity	159 [0, 495]	88 [0, 480]	0 [0, 300] [‡]

		Number of Live Births		
		0–1	2–3	4+
Medications				
	ACE-I/ARBs	58 (11%)	79 (10%)	47 (16%) [†]
	Beta-Blockers	23 (4%)	44 (6%)	19 (7%)
	CCB	31 (6%)	51 (7%)	40 (14%) [‡]
	Diuretics	57 (11%)	69 (9%)	40 (14%) [†]
	Hypoglycemics	45 (8%) [†]	38 (5%)	27 (9%) [†]
	Aspirin	41 (8%)	57 (7%)	28 (20%)
	Statins	32 (6%)	41 (5%)	29 (10%) [†]

* Continuous variables listed as median [interquartile range]

[†] p < 0.05 (vs 2–3 live births)

[‡] p < 0.01 (vs 2–3 live births)

Abbreviations: BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; HRT, hormone replacement therapy; LDL-C, low-density lipoprotein cholesterol; OCP, oral contraceptive pill; PCOS, polycystic ovarian syndrome; TC, total cholesterol; WHR, waist-to-hip ratio; ACE-I, Angiotensin Converting Enzyme Inhibitors; ARBs, Angiotensin Receptor Blockers; CCB, Calcium Channel Blockers

Table 2**Multivariable Association of Number of Live Births with Subclinical Atherosclerosis**

Odds Ratio of CAC>10 per Number of Live Births (95% CI)			
Model	0–1	2–3	4+
Model 1- age, race	1.5 (1.01–2.11)	Referent	1.7 (1.17–2.60)
Model 2	1.5 (1.01–2.29)	Referent	1.9 (1.24–2.97)
Model 3	1.9 (1.16–3.03)	Referent	2.2 (1.28–3.65)
Odds Ratio of AWT>75%ile per Number of Live Births (95% CI)			
Model	0–1	2–3	4+
Model 1- age, race	1.2 (0.90–1.58)	Referent	1.9 (1.36–2.69)
Model 2	1.2 (0.91–1.65)	Referent	1.8 (1.27–2.60)
Model 3	1.5 (1.05–2.09)	Referent	1.6 (1.04–2.41)

Model 2 = Model 1 + SBP, Anti-Hypertensive Meds, TC, HDL, Trig, Statin, Smoking, DM, and BMI

Model 3 = Model 2 + Income, Education, OCP use, HRT use, Physical Activity

Table 3

Sensitivity Analyses of the Association of Number of Live Births with Subclinical Atherosclerosis

Odds of CAC>10 per Number of Live Births (95% CI)			
Restrictions	0–1	2–3	4+
Age > 40 years	1.9 (1.15–3.07)	Referent	2.3 (1.35–3.95)
Postmenopausal Status	1.7 (0.95–2.94)	Referent	2.2 (1.20–3.92)
Women without PCOS	1.9 (1.16–3.09)	Referent	2.1 (1.22–3.56)
Excluding women never pregnant	1.9 (1.11–3.26)	Referent	2.4 (1.38–3.99)
Odds of AWT>75%ile per Number of Live Births (95% CI)			
Restrictions	0–1	2–3	4+
Age > 40 years	1.6 (1.05–2.53)	Referent	1.5 (0.89–2.56)
Postmenopausal Status	1.7 (0.94–2.90)	Referent	1.7 (0.91–3.30)
Women without PCOS	1.5 (1.05–2.15)	Referent	1.7 (1.10–2.60)
Excluding women never pregnant	1.6 (1.08–2.36)	Referent	1.6 (1.06–2.48)

* All analyses used fully adjusted model (Model 3)