Published in final edited form as:

Obstet Gynecol. 2008 December ; 112(6): 1294–1302. doi:10.1097/AOG.0b013e31818da09b.

Long-Term Blood Pressure Changes Measured From Before to After Pregnancy Relative to Nonparous Women

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Abstract

Objective—To prospectively examine whether blood pressure changes persist after pregnancy among women of reproductive age.

Methods—Prospective, population-based, observational cohort of 2,304 (1,167 black, 1,137 white) women (aged 18–30) who were free of hypertension at baseline (1985–86) and reexamined up to six times at 2, 5, 7, 10, or 20 years later (2005–2006). We obtained standardized blood pressure measurements before and after pregnancies, and categorized women into time-dependent groups by the cumulative number of births since baseline within each time interval [0 births (referent); 1 interim birth and 2 or more interim births; non-hypertensive pregnancies]. The study assessed differences in systolic and diastolic blood pressures among interim birth groups using multivariable, repeated measures linear regression models stratified by baseline parity (nulliparous and parous) adjusted for time, age, race, baseline covariates (blood pressure, BMI, education, oral contraceptive use), and follow-up covariates (smoking, anti-hypertensive medications, oral contraceptive use, weight gain).

Results—Among nulliparas at baseline, mean (95%CI) fully adjusted systolic and diastolic blood pressures (mm Hg), respectively, were lower by -2.06 (-2.72 to -1.41) and -1.50 (-2.08 to -0.92) after one interim birth, and lower by -1.89 (-2.63 to -1.15) and -1.29 (-1.96 to -0.63) after 2 or more interim births compared with no births (all p -value <0.001). Among women already parous at baseline, adjusted mean blood pressure changes did not differ by number of subsequent births.

Conclusion—A first birth is accompanied by persistent lowering of blood pressure from preconception to years after delivery. Although the biologic mechanism is unclear, pregnancy may create enduring alterations in vascular endothelial function.

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Financial Disclosure: The authors have no potential conflicts of interest to disclose.

INTRODUCTION

Pregnancy produces marked alterations in vascular physiology; if these persist, pregnancy might provide insights into mechanisms of adult blood pressure regulation.(1) Hemodynamic adaptations during pregnancy include increases in cardiac output and blood volume, and decreases in perfusion pressure and total systemic vascular resistance, together elevating uteroplacental blood flow without compromising maternal circulation. Mean arterial pressure declines in the first trimester of pregnancy, likely due to a drop in systemic vascular reactivity to norepinephrine and nitric oxide-induced blunting of vascular reactivity to angiotensin II. (2–4) Angiogenic factors (vascular endothelial growth factor, VEGF and placental growth factor, PlGF) produced by placental trophoblast, signal the growth of placental and uterine spiral arteries.(5) This acutely contributes to reductions in maternal peripheral vascular resistance. But do these physiologic adaptations leave a lasting imprint on the postpartum mother?

Blood pressure is somewhat lower in parous, as compared to nulliparous women, according to several, but not all, previous epidemiologic studies.(6) The causality of this association, however, must be viewed with skepticism on several grounds. First, it is not clear whether women with previous births have lower blood pressure or whether women without any births have higher blood pressure. Second, studies of parity and blood pressure have generally been cross-sectional or retrospective, leaving temporality unclear. Third, not all results have been consistent. Finally, not all parity is equivalent with respect to cardiovascular effects; women with hypertensive disorders of pregnancy are at elevated risk for future hypertension.(7) Whether non-hypertensive births reduce blood pressure remote from pregnancy, therefore, remains unclear. A study of 30 women that measured preconception blood pressures reported a non-significant 2 mm Hg lower mean arterial blood pressure at one year postpartum.(8)

We sought to prospectively examine changes in blood pressure from the time before to after pregnancy relative to women who did not give birth within a large, population-based cohort of women of reproductive age from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. We hypothesize that delivery of a pregnancy uncomplicated by hypertension persistently lowers levels of both systolic and diastolic blood pressure compared with no births.

MATERIALS AND METHODS

The CARDIA Study is a multi-center, longitudinal, observational study designed to describe the development of risk factors for coronary heart disease in young black and white men and women. In 1985–1986, 5,115 participants (2,787 women; 52% black), aged 18 to 30, were recruited from four geographic areas: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California.(9;10) Retention rates were 91, 86, 81, 79, 74, and 72 percent of the surviving cohort 2, 5, 7, 10, 15 and 20 years (2005–2006) after baseline.(11; 12) Institutional Review Boards at each participating study center approved the study. Written, informed consent was obtained from subjects for all study procedures.

Sample Selection Criteria

Of 2,787 women, we excluded women reporting a hysterectomy or removal of both ovaries (n=25), history of hypertension (n=249) or current anti-hypertensive medication use (n=5), elevated systolic(≥ 140 mm Hg) and/or diastolic(≥ 90 mm Hg) blood pressure (n=14), past or current heart medication (n=34) or current asthma medication (n=58) at baseline. We also excluded women missing self-reported hypertension status (n=10) or non-pregnant systolic and diastolic blood pressures (n=88) at baseline and/or at all follow-up exams. Our analytic sample included 2,304 (1,167 black, 1,137 white) women, of whom 1,531 were nulliparous and 773 parous at baseline. Women excluded tended to be of black race, smokers, older, less

educated, have higher body mass index and larger waist girth at baseline than the analytic sample.

Data Collection Methods

Blood Pressure Measurements—After an initial 5-minute rest, blood pressure was measured three times at one minute intervals using the Hawksley random-zero (RZ) sphygmomanometer through year 15 and the OmRON HEM907XL oscillometer at year 20; the first and fifth phase Korotkoff sounds were recorded. The appropriate cuff size (small, medium, large, extra large) was based on the upper arm circumference, which was measured by the blood pressure technician at the midpoint between the acromion and the olecranon. The second and third measurements were averaged.

Among 200 CARDIA participants across 5-year age groups, we established calibration equations for transforming Omron levels to RZ levels. Blood pressure was measured three times using the Omron and RZ devices together simultaneously according to CARDIA protocol for RZ blood pressure measurements and the protocol developed by Dr. Ronald Prineas. The average of the 2nd and 3rd readings from the RZ device was regressed on Omron measurements for both Systolic (SBP) and Diastolic (DBP) blood pressures for the year 20:

$$\text{Calibrated RZ SBP} = 3.74 + 0.96 * \text{OMRON average SBP}, R^2 = 0.94$$

$$\text{Calibrated RZ DBP} = 1.30 + 0.97 * \text{OMRON average DBP}, R^2 = 0.91$$

Repeated Measures of Dependent Variable—Changes in blood pressure (systolic and diastolic) were computed for six time intervals each starting from baseline (0 to 2, 0 to 5, 0 to 7, 0 to 10, 0 to 15 and 0 to 20 years) by subtracting the baseline (year 0) from each follow-up measurement.

Anti-hypertensive Medication Use—Anti-hypertensive medication use was self-reported at baseline and in years 2, 5, 7, 10, 15 and 20. We dichotomized responses for all exams as one fixed variable; ever or never using anti-hypertensive medication during follow-up.

Baseline Parity, Interim Pregnancies and Births, and Hypertension—At each exam we asked each woman whether she was currently pregnant or breastfeeding, number of pregnancies since the last exam including abortions, miscarriages, and live or stillbirths, length of gestation and delivery dates. We classified pregnancies ending in miscarriages, abortions and/or less than 20 weeks gestation as pregnancy losses, and 20 weeks or longer as births. Women were asked at each exam whether they had developed “hypertension without toxemia” or “toxemia” in a pregnancy. Hypertension without toxemia was classified as gestational hypertension and toxemia was preeclampsia. Nulliparity at baseline was defined as no live births prior to baseline. Births after baseline are called “interim” births.

We formed time-dependent interim birth groups based on the cumulative number of interim births and pregnancy hypertension status. We assigned women to one of five groups for each interval: 0 births (referent), one birth and two or more (2+) births; non-hypertensive pregnancies, and one or more (1+) births with gestational hypertension, and one or more (1+) births with preeclampsia. Women remained in these categories for all subsequent intervals until the end of the follow-up regardless of future pregnancies.

The validation study of pregnancy hypertension included 290 (217 multiparas, 83 primiparas) CARDIA women whose medical records were obtained for 366 pregnancies in 1986–1996. We abstracted antepartum and intrapartum blood pressures, urinary protein levels, medication use, and ICD-9 codes. Preeclampsia was defined as elevated blood pressure (systolic ≥ 140 ,

diastolic ≥ 90 mm Hg) and 1+proteinuria on two or more occasions after 20 weeks of gestation, and/or a discharge diagnosis ICD9 codes:642.4–642.5, and/or medications specifically used to treat preeclampsia prior to or during labor. Gestational hypertension was defined as elevated blood pressure and absence of 1+proteinuria on two or more occasions after 20 weeks of gestation, and/or a discharge diagnosis ICD9 code:642.3. The sensitivity and specificity, respectively, for self-report of preeclampsia was 36 and 93 percent, and for gestational hypertension was 8 and 98 percent. Negative predictive values were 98 and 91 percent for preeclampsia and gestational hypertension, respectively. Because of substantial misclassification (i.e., over-reporting pregnancy hypertension) results for gestational hypertension and preeclampsia pregnancies are not presented.

Anthropometric Measurements and Other Covariates—Weight, height and waist circumference were measured by certified technicians according to a standardized protocol described previously.(13) Body weight was measured to the nearest 0.1kg using a calibrated balance beam scale in participants wearing light clothing. Height (without shoes) was measured to the nearest 0.5 cm using a vertical ruler. Waist circumference was measured to the nearest 0.5 cm at the minimal abdominal girth.(14) BMI was computed as weight in kilograms divided by squared height in meters. Weight gain was calculated by subtracting baseline weight from weights at each exam.

Socio-demographic and behavioral data were collected at each exam using self- and interviewer-administered questionnaires. Trained interviewers assessed dietary intake during the previous month using the CARDIA Dietary History at baseline, and daily physical activity scores using the CARDIA Physical Activity History at each exam.(15) Baseline categorical variables were smoking (never, former, or current), years of education (12 or less, 13–15, 16 or more), marital status (never married, widowed, divorced or separated, or married), OC use (never, past, current), alcohol intake quartiles, and physical activity scores (race-specific quartiles). Daily dietary nutrient estimates of total fat, protein, carbohydrate, and energy intake (kJ) were used to obtain the percentages of kilocalories from fat, protein, and carbohydrate, and crude fiber. Physical activity quartiles have been correlated positively with symptom-limited graded treadmill exercise test duration.(16) Time-dependent smoking and OC use groups were categorized as current, past or never for each exam.

Statistical Methods

Baseline characteristics by interim birth groups at the end of follow-up were assessed, including frequency distributions, means, standard deviations, medians and interquartile range. Multiple linear regression methods (analysis of variance) were used to assess baseline differences in continuous variables and weight gain during follow-up among interim birth groups. Chi-square statistics were used to examine differences among interim birth groups by race, baseline categorical variables (marital status, oral contraceptive use, education, smoking) and ever taking anti-hypertensive medication, oral contraceptive use, and smoking during follow-up. Wilcoxon rank sum and Kruskal Wallis one-way tests were used to assess differences in alcohol intake and physical activity (median, inter-quartile range) due to skewedness in the distributions. P-values were obtained from two-sided tests (significance < 0.05).

Longitudinal blood pressure changes—Systolic and diastolic blood pressure measurements from years 0, 2, 5, 7, 10, 15 and 20 were assembled along with fixed variables, race, and age, and time-dependent interim births groups over the six intervals. Repeated measures linear regression methods (SAS 9.1, PROC MIXED) were used to estimate unadjusted and adjusted differences in mean changes in systolic and diastolic blood pressures among interim births (0 births as referent).

We assessed effect modification by time, race, baseline parity and BMI in the association of interim birth groups with blood pressure changes. Two-way interaction terms for race, baseline parity and BMI were examined simultaneously in the models to assess potential heterogeneity by including appropriate cross-product terms. We found evidence of significant two-way interaction terms for baseline parity ($p < 0.05$) and race ($p < 0.001$) with interim birth groups, but not for BMI ($p > 0.10$) for systolic blood pressure. Unadjusted and multivariable adjusted means for systolic and diastolic blood pressure changes were also contrasted among interim birth groups separately for each race. A three-way interaction term for baseline parity, race, and time-dependent interim births showed no evidence for effect modification by race and baseline parity ($p > 0.10$). We also examined heterogeneity in interim birth group effects over time via inclusion of appropriate cross-product terms for time of exams and time-dependent interim birth groups, and found no evidence of heterogeneity (all $p > 0.10$). Both baseline and time-dependent covariates included in models as confounders were selected based on their association with outcome measures independent of association with interim birth groups. Model fit was assessed by comparison of Akaike's Information Criteria (AIC), which is a measure of the goodness of fit of an estimated statistical model, assessing both precision and model complexity. (17)

Results are stratified by baseline parity (nulliparous and parous) for races combined. Unadjusted models included indicator variables for time (exam years). Next, Model 1 was adjusted for baseline covariates (relevant blood pressure measure, BMI, education, race, smoking, OC use, age) and time. Time-dependent pregnancy losses and asthma medication, and baseline covariates (dietary intake, physical activity) did not act as confounders. Next, we added anti-hypertensive medication use during follow-up and time-dependent variables (OC use, smoking) by stepwise addition. We examined study center as a fixed variable in all adjusted models, but it had little impact on the estimates. Lastly, we examined time-dependent weight gain as a potential mediator. Overall significant ($p < 0.05$) differences in mean blood pressure changes among time-dependent interim birth groups and pair-wise comparisons relative to 0 births were tested within baseline parity models.

RESULTS

Among 2,304 women (51% black, 49% white), mean (SD) age was 25 (3.7) years and 66 percent were nulliparous at baseline (60% white, 40% black). Of these, 635 nulliparas and 298 primi- or multiparas gave birth at least once after baseline (Table 1). Among 474 women who delivered 2+interim births, only 102 had three and 33 had four births. Among nulliparas, those with interim birth(s) (Table 1) tended to be younger and married; have smaller waist girth and lower BMI; and less likely to use oral contraceptives at baseline. Parous women with interim birth(s) were younger, more educated; had lower BMI and smaller waist girth; higher %Kcal CHO and lower %Kcal as saturated fat than those without births. Women with interim births were less likely to have taken anti-hypertensive medications or oral contraceptives, or to have smoked, but gained more weight (Table 2).

Among nulliparas at baseline, unadjusted systolic and diastolic blood pressures were 2 mm Hg lower for 1 interim birth and 2+interim births versus none (Table 3, Figure 1). Differences became slightly weaker with multivariate adjustment for both baseline and time-dependent covariates. Fully adjusted mean (95% CI) systolic and diastolic blood pressures (mm Hg), respectively, were lower by -2.06 (-2.72 to -1.41) and -1.50 (-2.08 to -0.92) for 1 interim birth and by -1.89 (-2.63 to -1.15) and -1.29 (-1.96 to -0.63) for 2 or more interim births compared with no births (all $p < 0.001$).

Among women parous at baseline, unadjusted systolic blood pressures were -1 mm Hg lower for one interim birth and -3 mm Hg lower for 2+interim births versus none, and diastolic blood

pressures were -1.60 mm Hg lower for 2+interim births versus none (Table 4, Figure 1). In fully adjusted models, systolic or diastolic blood pressures did not differ among interim birth groups for women parous at baseline.

Race-specific blood pressure changes showed that among white women, mean changes (95% CI) in systolic blood pressure (mm Hg) for primiparas and multiparas, respectively, versus nulliparas were more pronounced; -2.26 (-3.01 to -1.52) and -2.51 (-3.31 to -1.72); $p < 0.001$, and more modest among black women, -1.27 (-2.45 to -0.08); $p < 0.05$ and -0.45 (-1.09 to 1.98). Moreover, diastolic blood pressures were also significantly lower for white primiparas; -1.79 (-2.47 to -1.10) and multiparas; -1.67 (-2.40 to -0.94) versus nulliparas; all $p < 0.001$. In black women, diastolic blood pressures did not differ significantly for primiparas, -0.68 (-1.70 to 0.33), and multiparas, $+0.33$ (-0.99 to 1.65) versus nulliparas.

CONCLUSION

Several unique strengths of our study enhance its validity. First, blood pressure was measured using research methodology both before and after pregnancy, allowing us to look at prospective changes in blood pressure as a result of pregnancy. Standardized blood pressure measurements were available before conception for 100 percent of women in our analysis and 89 percent had at least four measurements after baseline (2 to 5-year intervals) up to 20 years, and 92% of births occurred prior to year 2001. Other strengths include the 72% retention rate at 20 years of follow-up and the internal comparison group of non-parous women.

The second, unique strength was our ability to segregate out pregnancies with hypertension. Blood pressure and vascular resistance are higher before, during, and well after pregnancy among women with preeclampsia or gestational hypertension. Our study benefited from being able to examine such pregnancies separately. Our focus was on how non-hypertensive pregnancies related to future blood pressure. A high negative predictive value (above 90%) for self-report of hypertension in pregnancy allowed us to precisely identify women without such conditions. Moreover, by excluding women with pre-existing hypertension, and controlling for treatment of hypertension during follow-up, we further enhanced the focus on women with non-hypertensive pregnancies in relation to blood pressure. Our validation study found a very low true -positive rate for self-report of gestational hypertension and preeclampsia, suggesting that self-report alone does not accurately identify those diagnosed with these specific complications. Women tended to over-report pregnancy hypertension. Whenever possible, physicians should try to confirm patient self-reports of blood pressure conditions with medical records.

Limitations of our study include variable timing of blood pressure measurements before conception and after delivery, and lack of blood pressure measurements during pregnancy. Self-reported hypertensive medication use outside of pregnancy is also a limitation, although we adjusted for this factor in our models. Self-reports are not entirely accurate measures of actual hypertensive medication use. Nonetheless, non-differential misclassification would have biased our results toward the null. Moreover, hypertensive medications were more common among women with no interim births, and their exclusion likely further biased our result toward the null.

To our knowledge, only one previous study examined blood pressure changes from before to after pregnancy.(8), and found a non-significant, 2 mm HG lower mean arterial pressure of 2 mm Hg at one year postpartum among 30 primi- and multiparas combined.(8) An analysis of the Medical Research Council National Survey of Health that collected reproductive history data prior to later life blood pressure assessments,(18) found lower adjusted systolic and diastolic blood pressures of 2.9 and 1.5 mm Hg among women aged 36 with any versus no

children. The magnitude of these mid-life associations is similar to ours, and, like our finding, additional children beyond one did not further lower blood pressure. Another study measured blood pressure prior to an index pregnancy, but all measurements were during pregnancy. Mean arterial pressure was significantly lower in the index as compared to the first (preceding) pregnancy.(19) This suggests either that blood pressure declined after the first pregnancy or that first versus other pregnancies have differential impact on blood pressure.

Several cross-sectional studies examined the relationship between reproductive history and blood pressure or hypertension, with conflicting results.(6) Some showed no significant association or a clinically small negative relationship.(20–22), and another (23) found lower blood pressure by 0.47 mm Hg with each additional pregnancy among pre-menopausal women and modestly lower, by 0.39 mm Hg among post-menopausal women. These data suggest that parity may be inversely associated with blood pressure at mid-life, but this may resolve with age.

Another important issue raised by our findings is the clinical significance of a 2 mm Hg reduction in mean blood pressure for women's long-term health. Based on intervention trials, a reduction in the mean blood pressure by 2 mm Hg would result in a reduction in stroke mortality of 6%, coronary heart disease mortality of 4%, and a reduction in total mortality of 3% for the population. Therefore, our findings provide evidence for a clinically significant impact on health among the population of women who have pregnancies uncomplicated by hypertension. (24)

What might mediate the decline in blood pressure after a first pregnancy? There may be no direct effect of pregnancy. Instead passage through the stress of pregnancy without hypertensive complications may simply define a group of women who have more healthy vascular function. On the other hand, pregnancy may have a direct, lasting impact on blood pressure. Vascular resistance falls substantially early in pregnancy, accompanied by reductions in blood pressure.

Mechanisms likely involved in the pregnancy-related decline in vascular resistance include resistance to pressors such as angiotensin II, angiogenesis and weight change. Angiotensin II resistance is demonstrable as early as the tenth week of pregnancy.(25) It is more pronounced among women with pregnancies uncomplicated by hypertension than in women with pregnancy-induced hypertension. Secondly, angiogenesis may help regulate blood pressure during pregnancy.(26) VEGF inhibitors, used to treat cancer patients, can induce hypertension. (27) During pregnancy, proangiogenic proteins, including VEGF and PlGF, are markedly upregulated.(5) Indeed, preeclampsia has been proposed to result from lack of angiogenic endothelial signaling. Preeclamptic pregnancies have high concentrations of soluble fms-like tyrosine kinase 1 (sFlt1), which negatively correlate with blood pressure. Lastly, weight change may affect blood pressure. Gestational weight gain is highly variable, but on average about 1 kg is retained by 12 months postpartum or longer (28), although 15–20 percent of women retain at least 5 kg.(29) Weight loss is associated with blood pressure decline, although this is not linear: large weight reductions after surgery have similar effects to much smaller reductions after lifestyle modification.(30) Weight loss alone is an unlikely explanation for our findings because lower blood pressure remained after adjusting for BMI and weight gain; thus blood pressure declines pre- versus post-partum despite weight gain.

What remains unknown is whether and how physiologic alterations during pregnancy impact physiology after pregnancy. Does vascular reactivity remain suppressed after pregnancy? Does angiogenesis remain up-regulated or do pregnancy-related alterations in endothelial function or vascular bed size remain post-partum? Another important issue that requires further study

is whether blood pressure lowering after a first birth may be weaker in black women than white women because of other risk factors.

A first birth may be accompanied by persistent lower levels of blood pressure from preconception to years after delivery, accounting for preconception levels, weight gain, secular trends and behaviors. Few lifestyle modifications persistently lower blood pressure. Thus, pregnancy is a natural model that may provide insights into the pathophysiology of hypertension. Although the biologic mechanism for blood pressure reduction is unclear, pregnancy may create enduring alterations in endothelial function.

Acknowledgments

Disclosure of Funding: Supported by contracts # N01-HC-48047, N01-HC-48048, N01-HC-48049, N01-HC-48050, and N01-HC-95095, from the National Heart, Lung, and Blood Institute, and Career Development Award, Grant number K01 DK059944 from the National Institute of Diabetes, Digestive and Kidney Diseases.

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Figure 1.

Unadjusted average systolic and diastolic blood pressure levels at each exam year (time) among interim birth groups (0, 1 interim birth and 2+ interim births; non-hypertensive pregnancies) during the 20-year study stratified by parity at baseline (nulliparous and parous). A: Systolic blood pressure of women nulliparous at baseline; B: Diastolic blood pressure of women nulliparous at baseline; C: Systolic blood pressure of women parous at baseline; D: Diastolic blood pressure of women parous at baseline.

Table 1
Baseline Characteristics for Women by Interim Birth Groups (Non-Hypertensive Pregnancies) Stratified by Parity Groups at Baseline.

Baseline Risk Factors	Nulliparous at Baseline				Parous at Baseline			
	Interim Birth Groups (1373 women)				Interim Birth Groups (707 women)			
	0 Births (n=738)	1 Birth (n=261)	2+ Births (n=374)	p-value	0 Births (n=404)	1 Birth (n=203)	2+ Births (n=100)	p-value
Race (Black)	304 (41.0)	120 (46.0)	113 (30.2)	<.001	292 (72.3)	140 (69.0)	65 (65.0)	0.32
Education (high school or less)	196 (26.6)	86 (33.0)	89 (23.8)	0.01	236 (58.4)	97 (47.8)	48 (48.0)	0.008
Marital Status (married)	71 (9.6)	45 (17.2)	71 (19.0)	<.001	161 (39.9)	94 (46.3)	45 (45.0)	0.04
Smoker (current)	191 (25.9)	62 (23.8)	75 (20.1)	0.24	167 (41.3)	67 (33.0)	35 (35.0)	0.07
OC use (current)	268 (36.3)	60 (23.0)	105 (28.1)	<.001	71 (17.6)	26 (12.8)	20 (20.0)	<.001
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	mean (SD)				mean (SD)			
Age (y)	24.8 (3.6)	23.8 (3.8)	23.7 (3.6)	<.001	26.8 (3.1)	25.5 (3.5)	23.9 (3.4)	<.001
BMI (kg/m ²)	24.4 (5.6)	23.2 (4.5)	22.6 (4.0)	<.001	25.5 (6.1)	24.0 (5.3)	24.0 (5.2)	<.01
Waist girth (cm)	73.9 (11.8)	71.1 (8.9)	69.9 (7.9)	<.001	76.9 (11.5)	73.6 (10.5)	73.9 (9.7)	<.001
% Kcal as CHO	47.6 (7.5)	46.4 (7.3)	47.3 (7.3)	0.07	48.0 (7.9)	46.4 (7.1)	45.8 (7.1)	<.01
% Kcal as Fat	36.6 (6.2)	37.6 (6.3)	36.6 (6.2)	0.05	37.2 (6.6)	38.4 (5.7)	38.4 (6.1)	0.05
% Kcal as Saturated Fat	13.6 (3.0)	14.0 (3.1)	13.8 (3.0)	0.16	14.1 (3.2)	14.5 (3.1)	14.8 (3.1)	0.06
Fiber (g)/100 Kcal	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.21	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.95
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	median (interquartile range)				median (interquartile range)			
Alcohol Intake(ml/d) [‡]	2.4 (9.7)	2.4 (9.6)	2.4 (10.9)	0.33	0.0 (7.6)	0.0 (5.5)	2.4 (10.0)	0.50
Physical activity score [‡]	320.5 (337.0)	333.0 (340.0)	326.0 (335.0)	0.17	221.5 (276.0)	236.0 (301.0)	234.0 (252.5)	0.60

[‡] Wilcoxon-Rank Sum Test

[‡] Kruskal Wallis Test

Table 2

Potential Confounders or Mediators of Blood Pressure Changes during 20-Year follow-up among Interim Birth Groups (Non-Hypertensive Pregnancies) Stratified by Parity Groups at Baseline (Nulliparous and Parous)

Characteristics during 20- Years of Follow-up	Nulliparous at baseline				Parous at baseline			
	Interim Births Groups (1373 women)			p-value	Interim Births Groups (707 women)			p-value
	0 Interim Births (n=738)	1 Interim Birth (n=261) n (%)	2+ Interim Births (n=374)		0 Interim Births (n=404)	1 Interim Births (n=203) n (%)	2+ Interim Births (n=100)	
Ever taking anti-hypertensive medications	69 (9.4)	18 (6.9)	28 (7.5)	<0.001	102 (25.3)	25 (12.3)	10 (10.0)	<0.001
Ever current OC use	233 (31.6)	49 (18.8)	69 (18.5)	<0.001	79 (19.6)	24 (11.8)	21 (21.0)	0.04
Ever smoker	348 (47.2)	109 (41.8)	158 (42.3)	0.16	261 (64.6)	111 (54.7)	57 (57.0)	0.04
Weight gain (kg) [†]	11.3 (13.7)	14.3 (14.0)	12.2 (11.9)	0.006	14.3 (12.9)	15.3 (13.4)	16.8 (14.3)	0.23

[†]22 women are missing weight gain at the end of follow up.

Table 3

Multivariable Adjusted Differences (mean, 95% CI) in Blood Pressure Changes for interim birth groups (Non-hypertensive pregnancies) relative to 0 interim birth group (referent) among 1373 Women Nulliparous at baseline.

Time Dependent Interim Birth Groups	Unadjusted	Model 1: baseline BP, smoking, race, age, BMI, education, OC use	Δ Systolic Blood Pressure (mm Hg)			Δ Diastolic Blood Pressure (mm Hg)		
			Model 1+ ever taking anti- hypertensive medication			Model 1+ ever taking anti- hypertensive medication + time dependent: smoking, OC use		
			Mean (95%CI) Difference Relative to 0 interim births			Mean (95%CI) Difference Relative to 0 interim births		
1 birth (n=261 primiparas)	-1.99*** (-2.68, -1.31)	-1.94*** (-2.61, -1.28)	-1.96*** (-2.62, -1.31)	-1.88*** (-2.54, -1.22)	-2.06*** (-2.72, -1.41)	-1.25*** (-1.83, -0.66)	-1.31*** (-1.90, -0.72)	-1.50*** (-2.08, -0.92)
2+ births (n=374 multiparas, 871 births)	-2.25*** (-3.05, -1.45)	-1.99*** (-2.75, -1.22)	-1.99*** (-2.74, -1.24)	-1.83*** (-2.59, -1.08)	-1.89*** (-2.63, -1.15)	-1.23*** (-1.90, -0.56)	-1.24*** (-1.91, -0.56)	-1.29*** (-1.96, -0.63)

* p-value < 0.05,

** p-value < 0.01,

*** p-value < 0.001. Δ = change, BP = blood pressure, OC = oral contraceptives Difference in mean Δ in blood pressure relative to referent group (0 interim birth group, n=738 nulliparas at end of follow-up)

Table 4

Multivariable Adjusted Differences (mean, 95% CI) in Blood Pressure changes for interim birth groups (Non-hypertensive pregnancies) relative to the 0 interim birth group (referent) among 707 Women already Parous at baseline.

Time-Dependent Interim Birth Groups	Unadjusted	Model 1: baseline BP, smoking, race, age, BMI, education, OC use	Model 1+ ever taking anti- hypertensive medication	Model 1+ ever taking anti- hypertensive medication + time dependent: smoking, OC use	Model 1+ ever taking anti- hypertensive medication, time dependent: smoking, OC use + weight gain
Δ Systolic Blood Pressure (mm Hg)					
Mean (95%CI) Difference Relative to 0 Births					
1 birth (n=203 multiparas)	-1.24* (-2.34, -0.14)	-0.87 (-1.95, 0.21)	-0.41 (-1.45, 0.64)	-0.19 (-1.24, 0.85)	-0.34 (-1.38, 0.70)
2+ births (n=100 multiparas, 259 births)	-3.14*** (-4.77, -1.50)	-2.37*** (-4.00, -0.74)	-1.68* (-3.26, -0.10)	-1.29 (-2.87, 0.30)	-1.49 (-3.07, 0.09)
Δ Diastolic Blood Pressure (mm Hg)					
Mean (95%CI) Difference Relative to 0 Births					
1 birth (n=203 multiparas)	-0.69 (-1.68, 0.29)	-0.58 (-1.49, 0.34)	-0.16 (-1.04, 0.73)	-0.09 (-0.98, 0.80)	-0.24 (-1.12, 0.64)
2+ births (n=100 multiparas, 259 births)	-1.60* (-3.05, -0.15)	-1.31 (-2.69, 0.07)	-0.77 (-2.12, 0.57)	-0.57 (-1.92, 0.78)	-0.77 (-2.10, 0.57)

* p-value < 0.05,

** p-value < 0.01,

*** p-value < 0.001, Δ = change, BP= blood pressure, OC = oral contraceptives

Difference in mean Δ relative to referent group. (0 interim birth group, n=404 primi- or multiparas)