Published in final edited form as:

Pregnancy Hypertens. 2017 October ; 10: 171–176. doi:10.1016/j.preghy.2017.08.001.

Pregnancy complications and later vascular ultrasound measures: A cohort study

Emily W. Harville^a, Markus Juonala^{b,c}, Jorma S. A. Viikari^b, Mika Kähönen^d, and Olli T. Raitakari^e

^aDepartment of Epidemiology, Tulane University School of Public Health, US ^bDepartment of Medicine, University of Turku and Division of Medicine, Turku University Hospital, Turku, Finland ^cMurdoch Childrens Research Institute, Parkville, Victoria, Australia ^dDepartment of Clinical Psychology, Tampere University Hospital and University of Tampere, Finland ^eThe Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku and Department of Clinical Physiology, Turku University Hospital, Finland

Abstract

Objectives—Pregnancy complications predict or even predispose to later cardiovascular disease in the mother. We examined whether pregnancy complications are associated with post-pregnancy measures of endothelial dysfunction and arterial stiffness.

Study design—Prospective cohort; Data for 847 women female participants in the Cardiovascular Risk in Young Finns Study were linked with the national birth registry. Preterm birth (<37 weeks), low birthweight (<2500 g), small-for-gestational-age (weight <10th percentile for gestational age), and hypertensive disorders of pregnancy were examined as predictors of later vascular measures.

Main outcome measures—Flow-mediated dilatation (FMD), carotid intima-media thickness (IMT), Young's elastic modulus (YEM), and carotid artery distensibility

Results—In some analyses, gestational hypertension and pre-eclampsia were associated with increased YEM. Low birthweight was also associated with an increase in IMT, and this increased risk was present prior to the pregnancy.

Address for correspondence: Dr. Emily Harville, Department of Epidemiology, Tulane School of Public Health and Tropical Medicine, 1440 Canal St. SL-18, New Orleans, LA 70112-2715, Tel. 504-988-7327, Fax. 504-988-1568, Harville@tulane.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Competing interests

The authors have no competing interests

Authors' contributions

EWI conceived and conducted the analysis and took the lead in writing the paper

JV, MJ: analysis and interpretation of the data, technical and material support, study supervisions

OR: obtaining funding and study supervision

MK: technical and material support, analysis and interpretation of the data

All authors: critical revision of the manuscript for important intellectual content

Conclusions—The increased cardiovascular risk in the mother observed after low birthweight and hypertensive disorders may be due to vascular changes, and some of this increased risk may be present before pregnancy.

Keywords

Brachial artery, ultrasonography; birth, premature; infant, low birth weight; pre-eclampsia

INTRODUCTION

A number of studies indicate that pregnancy complications predict or even predispose to later cardiovascular disease. Women who deliver a preterm or low birthweight infant have a higher risk of cardiovascular disease [1], elevated blood pressure, and insulin resistance later in life [2]. Women who develop pre-eclampsia have elevated blood pressure and lipids after pregnancy [3, 4] and are at higher risk of developing diabetes [4, 5], metabolic syndrome [6], and cardiovascular disease [7]. The pathways for these associations are less studied. It also is not clear whether these women are at higher baseline or genetic risk for cardiovascular disease, which is revealed during pregnancy, or whether pregnancy complications induce this higher cardiovascular risk [8].

Flow-mediated dilatation (FMD) is a marker of endothelial function. Ultrasound measurements of the brachial artery diameter are taken after a blood pressure cuff is inflated and deflated on the lower forearm.[9] Generally, healthier cardiovascular function is associated with increased FMD [10]. Young adults with low or declining FMD are more likely to develop hypertension and an adverse cardiovascular profile, independent of other known cardiovascular risk factors.[11] Several studies have linked pre-eclampsia, gestational hypertension, or delivery of a small-for-gestational-age baby with reduced FMD and endothelial dysfunction postpartum, at least in the short term [12–18].

Carotid intima-media thickness is a measure of the thickening of the artery walls, an indicator of atherosclerosis, and a subclinical marker of cardiovascular disease [19]. Few studies have correlated reproductive outcomes with carotid intima-media thickness. In one study, pre-eclampsia was associated with increased intima-media thickness (IMT) when studied approximately 7 months postpartum [20], and stillbirth was associated with risk of carotid plaque [21]. Among women aged 45 to 79, IMT was highest in nulliparous women, somewhat higher in women with multiple children, and lowest in women who had a single birth [22]. Another study found that carotid IMT was higher in those with higher parity, but this was largely due to associations with age [21]. In the Cardiovascular Risk in Young Finns study, FMD is inversely associated with carotid IMT [10], while other studies have found limited associations between the two markers [23, 24].

Arterial compliance – the degree to which the arteries are able to respond to and rebound from changes in arterial pressures – is associated with myocardial dysfunction [25]. Stiffening of the arteries with age is stronger in women compared to men [26], but women overall have better carotid compliance than men [27]. Arterial stiffness can be measured by a number of indicators, including carotid artery distensibility and Young's elastic modulus, which account for differences in vessel diameter as well. Higher arterial stiffness has been

found in women who have delivered a small-for-gestational-age [28] or preterm [29] infant, as well as those with hypertensive disorders during pregnancy [30].

In the Cardiovascular Risk in Young Finns study, several indices of endothelial function and carotid artery elasticity were examined in women at different points in pregnancy. FMD was not found to be different from non-pregnant controls, nor did it change significantly over time. Young's elastic modulus rose over pregnancy, while carotid artery distensibility declined [31]. Few studies have been able to study these cardiovascular risk indicators in the longer term after pregnancy complications, nor have many studied the effect of more common complications such as low birthweight and preterm birth. In addition, a previously-identified gap is studies with both pre-pregnancy and post-pregnancy data.[30] We hypothesized that pregnancy complications would be associated with reduced FMD, IMT, and carotid artery distensibility after pregnancy.

METHODS

Source population

The methods for the Cardiovascular Risk in Young Finns study have been described in detail previously [32]. Briefly, 3596 children and adolescents aged 3–18 years (1832 female), randomly chosen from population registers, were enrolled in 1980. Follow-up assessments were conducted every three years between 1980 and 1992, and then in 2001 and 2007. Retention rates for women were 81% in 1983, 72% in 1986, 68% for clinical examinations in 2001, and 66% for 2007. There was no difference in baseline cholesterol, blood pressure, or BMI between those lost to follow-up and those continuing to participate [32].

Data from the cardiovascular study cohort were merged with the Finnish national birth registry. The birth registry contains information on every birth in Finland since 1987 and includes data on health during the pregnancy. 1316 women had at least one singleton pregnancy in the registry. The study visit prior to the pregnancy was defined as the last visit before the recorded last menstrual period (LMP). (If no LMP was recorded [n=130], it was estimated as being 10 weeks prior to the first prenatal visit [the mean time for first prenatal visit in the data]).

Brachial artery FMD

FMD was measured as previously described.[10, 33] Briefly, the left (standard as non-dominant) brachial artery diameter was measured both at rest and during reactive hyperemia upon release of a pneumatic tourniquet which had been inflated to 250 mm Hg around the forearm for 4.5 minutes. The vessel diameter was measured. The average of 3 measurements at each time point was used to derive the maximum FMD (the greatest value between 40 and 80 seconds), as well as the area under the curve (AUC), for a summary across the time points. Two-hour between-study coefficient of variation of 9% and 3-month between-visit coefficient of variation of 26% for this technique have been found. [10, 34] The carotid intima-media thickness (IMT) was measured approximately 10 mm proximal to the carotid bifurcation [10]. Young's Elastic Modulus (YEM) is designed to estimate arterial stiffness independent of IMT [31]: $([\text{systolic blood pressure} - \text{diastolic blood pressure}] \times \text{diastolic}$

diameter)/([systolic diameter – diastolic diameter]/IMT). Carotid artery distensibility (Cdist) measures the ability of the arteries to expand in response to the pulse pressure, estimated as ([systolic diameter – diastolic diameter]/diastolic diameter)/(systolic blood pressure – diastolic blood pressure).

FMD measures were taken in 2001 and 2007, and data were limited to women not pregnant at the time of the ultrasound measure. 690 women had a pregnancy prior to the first FMD/IMT measures, while 842 women had a pregnancy prior to the last FMD/IMT measure. 283 women had both FMD measures and a pregnancy between the two. Descriptive statistics for each group are provided in table S1.

Pregnancy outcomes

The birth registry data include direct reports of some medical information, as well as up to 10 spaces to record diagnoses using ICD-9 and ICD-10 codes. We analyzed two pregnancy complications: overall hypertensive disorders of pregnancy and pre-eclampsia. Overall hypertensive disorders of pregnancy were defined as any hypertensive disorder specified as having begun during defined as a recorded diagnosis of eclampsia (n=1) as well as ICD-9 codes 6424–6427 and ICD-10 codes O11, O12, O14, and O15. Three birth outcomes were also examined: preterm birth was defined as birth at <37 weeks' gestation, low birthweight as weight <2500 g, and small-for-gestational-age as weight below the 10th percentile for gestational age, with percentiles based on this study population.

Additional covariates

Covariates likely to be associated with exposure and outcome, based on prior literature, were chosen for adjustment. Data from the birth registry were used to calculate maternal age at delivery and parity. Body mass index (BMI) at study visit was used as a continuous variable unless otherwise indicated. Smoking was categorized as never, former, and current at 2007 as well as during pregnancy. A socioeconomic status variable was created, based on a combination of occupational status reports at 3 times: first, reported socioeconomic status based on occupational status in 2001 (manual/lower-grade non-manual/higher-grade non-manual); second, socioeconomic status in 2007; and third, socioeconomic status as a child, based on parent's occupation. Living status was categorized as married, living with a partner/engaged, and not living with a partner. Systolic blood pressure was measured in a sitting position after 5 minutes' rest, using a standard sphygmomanometer in 1980 and 1983 and a random-zero sphygmomanometer after 1983 (Hawksley & Sons Ltd, Lancin, UK). Fasting LDL-c and triglycerides were measured at each visit (details of the measurement protocols published previously [35, 36]). For covariates with multiple measures, covariates from 2007 were used in models that incorporated 2007 outcome measures, and covariates from 2001 were used in models that incorporated in 2001 outcome measures.

As the cardiovascular risk factors (blood pressure, lipids) are potentially along the causal pathway, models were run first with basic confounders (age, BMI, smoking, socioeconomic status [SES]), and then with the cardiovascular risk factors. In most cases, results were quite similar, and so the fully adjusted results are presented. If results differed, this is mentioned in the text (more details provided in supplementary material).

Statistical analysis

The relationship between pregnancy complications and outcomes was assessed in two ways: first, taking into account all pregnancies prior to the last outcome measure (n=842), and second, as the relationship between the pregnancy outcome at the pregnancy directly prior to the first CVD measure for the woman (n=690). For the first analysis, having the complication during any of the pregnancies was considered having a history of the outcome. Bivariate and multivariable linear modeling was used, with FMD/IMT/YEM/Cdist as the outcome measure and history of low birthweight, preterm birth, small-for-gestational-age, hypertensive disorders of pregnancy and pre-eclampsia as the exposures.

Median time between the pregnancy with complications and the first FMD measure was 9 years. Models were run adjusting for this time gap, as well as assessing interaction with this time gap, to see if measurements taken closer to the pregnancy were more strongly related to the outcome. Interactions with BMI were also assessed, using a product term.

Finally, we addressed the question of whether having a pregnancy complication changes the relationship with the outcome. For associations that were found in the initial analyses, the subset of women who had a pregnancy between the two CVD measures was examined (n=283). The relationship between complications at that pregnancy and CVD measures in both 2001 and 2007 was examined: if having a pregnancy complication increases risk, one would expect that the relationship with the 2007 measures would be stronger than that with the 2001 measures. Next, the relationship between those complications and the 2007 measures was examined, adjusted for 2001 levels: if relationships between pregnancy complications and later CVD measures are due to underlying risk, we would expect adjustment for baseline, pre-pregnancy measures would reduce the association between pregnancy complications and later CVD risk (i.e., baseline risk essentially acts as a confounder, so adjustment removes the association).

Multiple imputation using PROC MI and PROC MIANALYZE in SAS (SAS 9.2, Cary, NC) was used to impute missing covariate data in the final adjusted models.[37] Socioeconomic status was the variable missing most commonly. All p-values are two-sided.

The original study was approved by the local ethics committees. The data linkage and analysis were approved by the Medical Birth Register and the Institutional Review Board of Tulane University.

RESULTS

Study participants included in this analysis were largely in their 30s in 2001 (table 1). Between 20% and 30% were smokers, over 80% were married or living with a partner, 17% were obese (BMI ≥ 30) and final parity was most commonly 2.

Table 2 presents data for all pregnancies prior to the latest FMD measure. The associations between low birthweight and pre-eclampsia and FMD were in the direction of reductions in FMD. Low birthweight was also associated with an increase in IMT.

Considering the pregnancy closest in time to the measurement (table 3), gestational hypertension was associated with increased IMT ($p=0.01$) and YEM measure ($\beta=0.19$, $p=0.05$ for basic adjustment, $\beta=0.18$, $p=0.06$ after additional adjustment for cardiovascular factors). The gestational hypertension/log(YEM) association was stronger in women in higher-BMI women (adjusted $\beta=0.448$ for those with $BMI>25$ vs. 0.114 for those with $BMI \leq 25$; p for interaction= 0.01). Pre-eclampsia at this pregnancy was associated with increased YEM ($p<0.01$) and lower CDist ($\beta=-1.49$, $p=0.04$ for basic adjustment, $\beta=-1.36$, $p=0.06$ after adjustment for cardiovascular factors).

If having a pregnancy complication increases risk of later cardiovascular disease, one would expect the relationship with the later measures to be stronger than the earlier measures. In our sample, the low birthweight (LBW)-IMT association was stronger in the 2001 than 2007; no other results were precise enough to provide information (low number of cases and too much overlap in confidence intervals to draw conclusions one way or another: supplementary materials). Another hypothesis is that any relationships found between pregnancy complications and later CVD measures are due to underlying risk. In that case, we would expect adjustment for baseline, pre-pregnancy measures to reduce the association between pregnancy complications and later CVD risk. The data were consistent with this hypothesis for the LBW-IMT association, which was reduced after adjustment for baseline measures (Initial $\beta=0.42$, $p=0.06$; after adjustment, 0.03 , $p=0.08$; supplementary materials), but not for any others.

DISCUSSION

Our analysis indicated a few possible associations between pregnancy complications and vascular parameters. Giving birth to a low birthweight baby was associated with increased IMT, and the data were most consistent with the idea that this increased risk was present prior to the pregnancy. To our knowledge, no one has examined this precise question, although a person's own birthweight has been associated with adult IMT [38, 39]. Our results are therefore consistent with a familial (due to environment or genetics) predisposition to both LBW and atherosclerotic disease. Hypertensive disorders were associated with increased YEM in some analyses, consistent with some previous research on arterial stiffness[30], and some indicating women with pre-eclampsia have been have stiffer umbilical arteries [40] and ascending aorta [41] during pregnancy. Previous work in this cohort has demonstrated a stiffening of the carotid artery during pregnancy but no correlations with endothelial function in other arteries.[31]

The lack of association between pre-eclampsia and later FMD is inconsistent with some previous studies, and may reflect the fact that much of previous research has been conducted shortly after pregnancy, often within 12 months postpartum [12, 14, 16, 17], and may indicate that women return to endothelial health post-pregnancy, for the most part. Alternately, it may simply be an issue of statistical power. Also, pre-eclampsia is a heterogeneous disease, and early-onset cases are usually more severe and associated with worse health post-pregnancy.[42] The number of early-onset cases in this cohort is likely quite small, and we are not able to distinguish between term and preterm cases.

Strengths of our study include the prospective design and ability to link to the national birth registry, allowing essentially complete follow-up and independent data collection for those who have given birth. In addition, ours is one of the few studies to have pre- and post-pregnancy data on a sample. However, the small number of cases limits our study power, especially for pre-eclampsia. Registry studies do not record all cases of pre-eclampsia [43] and even taking that into account, the reported incidence of complications among our study population was very low (although our population was fairly young, healthy, and lean).[44] In addition, there is no standardized time between the pregnancy and the measurements. It is also possible that residual confounding—for example, by socioeconomic status or weight gain during or after pregnancy—might be present in these results.

This analysis did not indicate strong relationships between history of pregnancy complications and indicators of cardiovascular risk, but there were a few hints of possible relationships. Future research should further explore the pathways between lifetime endothelial function, arterial function, and complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Cardiovascular Risk in Young Finns study was supported financially by the Academy of Finland (grants 117797, 126925, and 121584), Social Insurance Institution of Finland, Turku University Foundation, special federal grants for Turku University Central Hospital, Juho Vainio Foundation, Finnish Foundation of Cardiovascular Research, Finnish Cultural Foundation, and Orion Farnos Research Foundation.

The data linkage was supported by the National Institute of Child Health And Human Development (K12HD043451 to EWH).

The funding body had no influence on the analysis or interpretation of data, or on the decision to publish.

Abbreviations

FMD	flow-mediated dilatation
IMT	intima-media thickness
YEM	Young's elastic modulus
BMI	body mass index
LMP	last menstrual period
LDL-c	low density lipoprotein

References

1. Catov JM, Newman AB, Roberts JM, Kelsey SF, Sutton-Tyrrell K, Harris TB, Colbert L, Rubin SM, Satterfield S, Ness RB. Preterm delivery and later maternal cardiovascular disease risk. *Epidemiology*. 2007; 18(6):733–9. [PubMed: 17917602]
2. Catov JM, Newman AB, Roberts JM, Sutton-Tyrrell KC, Kelsey SF, Harris T, Jackson R, Colbert LH, Satterfield S, Ayonayon HN, Ness RB. Association between infant birth weight and maternal

- cardiovascular risk factors in the health, aging, and body composition study. *Ann Epidemiol.* 2007; 17(1):36–43. [PubMed: 16843009]
3. Barden AE, Beilin LJ, Ritchie J, Walters BN, Michael C. Does a predisposition to the metabolic syndrome sensitize women to develop pre-eclampsia? *J Hypertens.* 1999; 17(9):1307–15. [PubMed: 10489109]
 4. Magnussen EB, Vatten LJ, Smith GD, Romundstad PR. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. *Obstet Gynecol.* 2009; 114(5):961–70. [PubMed: 20168095]
 5. McDonald SD, Yusuf S, Sheridan P, Anand SS, Gerstein HC. Dysglycemia and a history of reproductive risk factors. *Diabetes Care.* 2008; 31(8):1635–8. [PubMed: 18458144]
 6. Stekkinger E, Zandstra M, Peeters LL, Spaanderman ME. Early-onset preeclampsia and the prevalence of postpartum metabolic syndrome. *Obstet Gynecol.* 2009; 114(5):1076–84. [PubMed: 20168110]
 7. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. *Lancet.* 2005; 366(9499): 1797–803. [PubMed: 16298217]
 8. Craici I, Wagner S, Garovic VD. Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test? *Ther Adv Cardiovasc Dis.* 2008; 2(4):249–59. [PubMed: 19124425]
 9. Charakida M, Masi S, Luscher TF, Kastelein JJ, Deanfield JE. Assessment of atherosclerosis: the role of flow-mediated dilatation. *Eur Heart J.* 2010; 31(23):2854–61. [PubMed: 20864485]
 10. Juonala M, Viikari JS, Laitinen T, Marniemi J, Helenius H, Ronnema T, Raitakari OT. Interrelations between brachial endothelial function and carotid intima-media thickness in young adults: the cardiovascular risk in young Finns study. *Circulation.* 2004; 110(18):2918–23. [PubMed: 15505080]
 11. Lazdam M, Lewandowski AJ, Kyliantiras I, Cunningham C, Diesch J, Francis J, Trevitt C, Neubauer S, Singhal A, Leeson P. Impaired endothelial responses in apparently healthy young people associated with subclinical variation in blood pressure and cardiovascular phenotype. *Am J Hypertens.* 2012; 25(1):46–53. [PubMed: 21976278]
 12. Yinon Y, Kingdom JC, Odutayo A, Moineddin R, Drewlo S, Lai V, Cherney DZ, Hladunewich MA. Vascular dysfunction in women with a history of preeclampsia and intrauterine growth restriction: insights into future vascular risk. *Circulation.* 2012; 122(18):1846–53.
 13. Paradisi G, Biaggi A, Savone R, Ianniello F, Tomei C, Caforio L, Caruso A. Cardiovascular risk factors in healthy women with previous gestational hypertension. *J Clin Endocrinol Metab.* 2006; 91(4):1233–8. [PubMed: 16434462]
 14. Chambers JC, Fusi L, Malik IS, Haskard DO, De Swiet M, Kooner JS. Association of maternal endothelial dysfunction with preeclampsia. *JAMA.* 2001; 285(12):1607–12. [PubMed: 11268269]
 15. Hamad RR, Eriksson MJ, Silveira A, Hamsten A, Bremme K. Decreased flow-mediated dilation is present 1 year after a pre-eclamptic pregnancy. *J Hypertens.* 2007; 25(11):2301–7. [PubMed: 17921826]
 16. Agatista PK, Ness RB, Roberts JM, Costantino JP, Kuller LH, McLaughlin MK. Impairment of endothelial function in women with a history of preeclampsia: an indicator of cardiovascular risk. *Am J Physiol Heart Circ Physiol.* 2004; 286(4):H1389–93. [PubMed: 15020302]
 17. Kanagalingam MG, Nelson SM, Freeman DJ, Ferrell WR, Cherry L, Lowe GD, Greer IA, Sattar N. Vascular dysfunction and alteration of novel and classic cardiovascular risk factors in mothers of growth restricted offspring. *Atherosclerosis.* 2009; 205(1):244–50. [PubMed: 19022445]
 18. Paradisi G, Mattoli MV, Tomei C, Zuppi C, Lulli P, Quagliozzi L, Caruso A. Cardiovascular risk factors in healthy women with previous small for gestational age infants. *J Obstet Gynaecol Res.* 2011; 37(10):1397–404. [PubMed: 21599807]
 19. de Groot E, van Leuven SI, Duivenvoorden R, Meuwese MC, Akdim F, Bots ML, Kastelein JJ. Measurement of carotid intima-media thickness to assess progression and regression of atherosclerosis. *Nat Clin Pract Cardiovasc Med.* 2008; 5(5):280–8. [PubMed: 18332891]
 20. Blaauw J, van Pampus MG, Van Doormaal JJ, Fokkema MR, Fidler V, Smit AJ, Aarnoudse JG. Increased intima-media thickness after early-onset preeclampsia. *Obstet Gynecol.* 2006; 107(6): 1345–51. [PubMed: 16738162]

21. Kharazmi E, Moilanen L, Fallah M, Kaaja R, Kattainen A, Kahonen M, Jula A, Kesaniemi A, Luoto R. Reproductive history and carotid intima-media thickness. *Acta Obstet Gynecol Scand*. 2007; 86(8):995–1002. [PubMed: 17653887]
22. Wolff B, Volzke H, Robinson D, Schwahn C, Ludemann J, Kessler C, John U, Felix SB. Relation of parity with common carotid intima-media thickness among women of the Study of Health in Pomerania. *Stroke*. 2005; 36(5):938–43. [PubMed: 15845891]
23. Yeboah J, Burke GL, Crouse JR, Herrington DM. Relationship between brachial flow-mediated dilation and carotid intima-media thickness in an elderly cohort: the Cardiovascular Health Study. *Atherosclerosis*. 2008; 197(2):840–5. [PubMed: 17804000]
24. Irace C, Fiaschi E, Cortese C, Gnasso A. Flow-mediated vasodilatation of the brachial artery and intima-media thickness of carotid artery in never-treated subjects. *Int Angiol*. 2006; 25(3):274–9. [PubMed: 16878076]
25. Fernandes VR, Polak JF, Cheng S, Rosen BD, Carvalho B, Nasir K, McClelland R, Hundley G, Pearson G, O'Leary DH, Bluemke DA, Lima JA. Arterial stiffness is associated with regional ventricular systolic and diastolic dysfunction: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2008; 28(1):194–201. [PubMed: 17962621]
26. Vaidya D, Heckbert SR, Wasserman BA, Ouyang P. Sex-specific association of age with carotid artery distensibility: multi-ethnic study of atherosclerosis. *J Womens Health (Larchmt)*. 2012; 21(5):516–20. [PubMed: 22393881]
27. Marlatt KL, Kelly AS, Steinberger J, Dengel DR. The influence of gender on carotid artery compliance and distensibility in children and adults. *J Clin Ultrasound*. 2013; 41(6):340–6. [PubMed: 23233368]
28. Hooijschuur MC, Ghossein-Doha C, Al-Nasiry S, Spaanderman ME. Maternal metabolic syndrome, preeclampsia, and small for gestational age infancy. *Am J Obstet Gynecol*. 2015; 213(3):e1–7.
29. Catov JM, Dodge R, Barinas-Mitchell E, Sutton-Tyrrell K, Yamal JM, Piller LB, Ness RB. Prior preterm birth and maternal subclinical cardiovascular disease 4 to 12 years after pregnancy. *J Womens Health (Larchmt)*. 2013; 22(10):835–43. [PubMed: 24033091]
30. Ehrenthal DB, Goldstein ND, Wu P, Rogers S, Townsend RR, Edwards DG. Arterial stiffness and wave reflection 1 year after a pregnancy complicated by hypertension. *J Clin Hypertens (Greenwich)*. 2014; 16(10):695–9. [PubMed: 25116457]
31. Karkkainen H, Saarelainen H, Valtonen P, Laitinen T, Raitakari OT, Juonala M, Kahonen M, Hutri-Kahonen N, Heinonen S. Carotid artery elasticity decreases during pregnancy - the Cardiovascular Risk in Young Finns study. *BMC Pregnancy Childbirth*. 2014; 14:98. [PubMed: 24602149]
32. Raitakari OT, Juonala M, Ronnema T, Keltikangas-Jarvinen L, Rasanen L, Pietikainen M, Hutri-Kahonen N, Taittonen L, Jokinen E, Marniemi J, Jula A, Telama R, Kahonen M, Lehtimäki T, Akerblom HK, Viikari JS. Cohort profile: The Cardiovascular Risk in Young Finns Study. *Int J Epidemiol*. 2008; 37(6):1220–6. [PubMed: 18263651]
33. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet*. 1992; 340(8828):1111–5. [PubMed: 1359209]
34. Jarvisalo MJ, Jartti L, Karvonen MK, Pesonen U, Koulou M, Marniemi J, Hammar N, Kaprio J, Paakkunainen U, Simell O, Raitakari OT, Ronnema T. Enhanced endothelium-dependent vasodilation in subjects with Proline7 substitution in the signal peptide of neuropeptide Y. *Atherosclerosis*. 2003; 167(2):319–26. [PubMed: 12818415]
35. Porkka KV, Raitakari OT, Leino A, Laitinen S, Rasanen L, Ronnema T, Marniemi J, Lehtimäki T, Taimela S, Dahl M, Uhari M, Akerblom HK, Viikari JS. Trends in serum lipid levels during 1980–1992 in children and young adults. The Cardiovascular Risk in Young Finns Study. *Am J Epidemiol*. 1997; 146(1):64–77. [PubMed: 9215224]
36. Raiko JR, Viikari JS, Ilmanen A, Hutri-Kahonen N, Taittonen L, Jokinen E, Pietikainen M, Jula A, Loo BM, Marniemi J, Lehtimäki T, Kahonen M, Ronnema T, Raitakari OT, Juonala M. Follow-ups of the Cardiovascular Risk in Young Finns Study in 2001 and 2007: Levels and 6-year changes in risk factors. *J Int Med*. 2010; 267(4):370–84.

37. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009; 338:b2393. [PubMed: 19564179]
38. Hovi P, Turanlahti M, Strang-Karlsson S, Wehkalampi K, Jarvenpaa AL, Eriksson JG, Kajantie E, Andersson S. Intima-media thickness and flow-mediated dilatation in the Helsinki study of very low birth weight adults. *Pediatrics*. 2011; 127(2):e304–11. [PubMed: 21262880]
39. Valente MH, da Silva Gomes FM, Bensenor IJ, Brentani AV, de Ulhoa Escobar AM, Grisi SJ. Relation between birth weight, growth, and subclinical atherosclerosis in adulthood. *Biomed Res Int*. 2015; 2015:926912. [PubMed: 25648854]
40. Dodson RB, Martin JT, Hunter KS, Ferguson VL. Determination of hyperelastic properties for umbilical artery in preeclampsia from uniaxial extension tests. *Eur J Obstet Gynecol Reprod Biol*. 2013; 169(2):207–12. [PubMed: 23548660]
41. Orabona R, Sciatti E, Vizzardi E, Bonadei I, Valcamonico A, Metra M, Frusca T. Elastic properties of ascending aorta in patients with a previous pregnancy complicated by early or late preeclampsia. *Ultrasound Obstet Gynecol*. 2016; 47(3):316–323. [PubMed: 25754870]
42. Cirillo PM, Cohn BA. Pregnancy complications and cardiovascular disease death: 50-year follow-up of the Child Health and Development Studies pregnancy cohort. *Circulation*. 2015; 132(13):1234–42. [PubMed: 26391409]
43. Teperi J. Multi method approach to the assessment of data quality in the Finnish Medical Birth Registry. *J Epidemiol Community Health*. 1993; 47(3):242–7. [PubMed: 8350040]
44. Heinonen S, Saarikoski S. Reproductive risk factors, pregnancy characteristics and obstetric outcome in female doctors. *BJOG*. 2002; 109(3):261–4. [PubMed: 11950180]

Highlights

- Pregnancy complications predict or even predispose to later cardiovascular disease in the mother.
- Gestational hypertension and pre-eclampsia were associated with increased arterial stiffness post-pregnancy.
- Low birthweight was also associated with an increase in carotid intima-media thickness, and this increased risk was present prior to the pregnancy
- Pregnancy complications may lead to vascular changes in some cases, and reveal existing risk in others.

Table 1

Female Participants in the Cardiovascular Risk in Young Finns Study, 2001–2007

		Participants with a pregnancy prior to the last FMD measure (n=842)	
		N	% [†]
Age in 2001	24–27	186	22.1
	30–33	320	38.0
	36	176	20.9
	39	160	19.0
Total births across entire study period	1	189	22.5
	2	381	45.3
	3+	272	32.3
average socioeconomic status	lower	215	25.7
	middle	452	54.1
	higher	169	20.2
Relationship status in 2001	married	514	61.8
	living with partner, engaged	212	25.5
	not living with partner	106	12.7
Smoking in 2001	Never	421	51.5
	prior	172	21.0
	current	225	27.5
Body mass index in 2001	<20	86	10.3
	20–<25	437	52.3
	25–<30	215	25.8
	30+	97	11.6
Pregnancy complications	low birthweight	44 [*]	5.2
	preterm birth	66	7.8
	small-for-gestational-age	60	7.2
	hypertensive disorders of pregnancy	14	1.7
	pre-eclampsia	6	0.7
	gestational diabetes	29	3.4
		Mean	SD
	Max FMD, mm [§]	0.27	0.14

	Participants with a pregnancy prior to the last FMD measure (n=842)	
	N	% [‡]
Intima-media thickness	0.58	0.09
Young's elastic modulus	291.3	138.7
Carotid artery distensibility	2.26	0.76

FMD, flow mediated dilatation

^{**}
at any prior pregnancy

[‡]
proportions may not add to 100 due to rounding

[§]
2001 measures

Table 2
Relationship Between Pregnancy Complications (in any pregnancy) and Subsequent Cardiovascular Ultrasound measures in the Cardiovascular Risk in Young Finns

	Flow-mediated dilatation (n=838)						Intima-media thickness (n=842)						YEM (log) (n=842)						Coronary artery distensibility					
	unadjusted			adjusted*			unadjusted			adjusted*			unadjusted			adjusted*			unadjusted			adjusted*		
	beta	SD	p	beta	SD	p	beta	SD	p	beta	SD	p	beta	SD	p	beta	SD	p	beta	SD	p	beta	SD	p
low birthweight	-0.050	0.020	0.02	-0.038	0.020	0.06	0.017	0.013	0.02	0.025	0.012	0.04	0.011	0.071	0.87	0.074	0.064	0.24	0.023	0.110	0.84	-0.056	0.107	0.60
preterm birth	-0.024	0.017	0.17	-0.017	0.017	0.30	0.010	0.010	0.30	0.013	0.010	0.20	0.065	0.059	0.27	0.077	0.053	0.15	-0.110	0.090	0.23	-0.125	0.088	0.16
small-for-gestational-age	-0.025	0.018	0.17	-0.022	0.018	0.21	0.006	0.011	0.63	0.004	0.010	0.68	-0.027	0.062	0.66	-0.042	0.056	0.45	0.086	0.099	0.38	0.109	0.092	0.24
gestational hypertension	-0.039	0.036	0.29	-0.034	0.036	0.34	-0.015	0.022	0.50	-0.011	0.021	0.61	0.093	0.124	0.45	0.125	0.112	0.27	-0.210	0.200	0.29	-0.244	0.186	0.19
pre-eclampsia	-0.090	0.055	0.09	-0.092	0.055	0.09	0.023	0.035	0.50	0.002	0.032	0.95	0.137	0.189	0.47	0.008	0.170	0.96	-0.160	0.300	0.59	0.036	0.283	0.90

* adjusted for age, BMI, smoking, and socioeconomic status, systolic blood pressure, total cholesterol, and triglycerides

** log-transformed

Table 3

Relationship Between Pregnancy complications (in pregnancy prior to measure) and Subsequent Cardiovascular Ultrasound measures in the Cardiovascular Risk in Young Finns

	Flow-mediated dilatation (n=645)						Intima-media thickness (n=689)						YEM (log) (n=687)						coronary artery distensibility (n=688)					
	unadjusted			adjusted*			unadjusted			adjusted*			unadjusted			adjusted*			unadjusted			adjusted*		
	beta	SD	p	beta	SD	p	beta	SD	p	beta	SD	p	beta	SD	p	beta	SD	p	beta	SD	p	beta	SD	p
low birthweight	-0.029	0.035	0.40	-0.009	0.034	0.80	0.010	0.022	0.65	0.018	0.022	0.39	0.060	0.098	0.54	0.115	0.095	0.23	-0.115	0.189	0.54	-0.200	0.185	0.28
preterm birth	-0.021	0.028	0.45	-0.008	0.028	0.77	-0.025	0.017	0.15	-0.019	0.017	0.28	0.046	0.079	0.56	0.067	0.076	0.38	-0.206	0.152	0.18	-0.226	0.148	0.13
small-for-gestational-age	0.001	0.022	0.98	-0.003	0.021	0.91	-0.006	0.131	0.62	-0.006	0.013	0.64	-0.061	0.059	0.30	-0.055	0.057	0.33	0.097	0.114	0.39	0.080	0.111	0.47
gestational hypertension	-0.031	0.380	0.42	-0.040	0.038	0.29	0.054	0.021	0.01	0.052	0.021	0.01	0.186	0.097	0.06	0.180	0.094	0.06	-0.130	0.189	0.49	-0.133	0.184	0.47
pre-eclampsia	...	...	...	...	...	...	0.084	0.086	0.33	0.080	0.085	0.34	1.362	0.383	<0.01	1.236	0.369	<0.01	-1.604	0.744	0.03	-1.364	0.723	0.06

* adjusted for age, BMI, smoking, socioeconomic status, systolic blood pressure, total cholesterol, and triglycerides