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# Vascular ultrasound measures before pregnancy and pregnancy complications: A prospective cohort study

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## Abstract

**Objectives—**To examine the relationship between pre-pregnancy indicators of cardiovascular risk and pregnancy complications and outcomes.

**Study design—**Data from 359 female participants in the Cardiovascular Risk in Young Finns Study were linked with the national birth registry. Flow-mediated dilatation (FMD; maximum change in the left brachial artery diameter after rest and hyperemia); carotid intima-media thickness (IMT); Young's elastic modulus (YEM); and carotid artery distensibility (Cdist) at the visit prior to the pregnancy were examined as predictors of hypertensive disorders, birthweight, and gestational age using multivariable linear regression with adjustment for confounders (age, BMI, smoking, and socioeconomic status).

**Results—**No relations were seen between FMD, IMT, or the stiffness indices, and hypertensive disorders. Higher pre-pregnancy FMD was associated with lower gestational age, while increased Cdist was associated with reduced birthweight-for-gestational-age.

**Conclusions—**Some cardiovascular ultrasound measures pre-pregnancy may predict pregnancy complications, but the association is likely to be small.

### MeSH headings

Brachial artery; ultrasonography; birth; premature; infant; low birth weight; hypertension; pregnancy-induced

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## 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], while women who develop pre-eclampsia and gestational diabetes are at higher risk of later cardiovascular disease [3, 4], also shown in Scandinavian studies [5, 6]. A number of cardiovascular risk indicators have been associated with pregnancy complications, both during and after pregnancy. Increased flow-mediated dilatation (FMD) is a marker of endothelial function and is generally associated with better cardiovascular health [7]. Change in FMD has been used to predict pre-eclampsia [8], and pre-eclampsia and gestational diabetes have been associated with lower FMD postpartum [9]. Carotid intima-media thickness (IMT) is a measure of the thickening of the artery walls, an indicator of atherosclerosis, and a subclinical marker of cardiovascular disease [7]. Pre-eclampsia and gestational diabetes have been associated with increased IMT postpartum [10], though not in every study [11, 12]. Finally, increased arterial stiffness leads to heart damage and is a predictor of cardiovascular events and mortality [13], and has been demonstrated in pregnancies with lower birthweight [14].

It is not clear whether women who develop pregnancy complications are at higher constitutional risk for cardiovascular disease, which is revealed during pregnancy, or whether pregnancy complications induce the later, higher cardiovascular risk. To our knowledge no studies have examined the relation between FMD, IMT, or arterial stiffness prior to the pregnancy and pregnancy complications. Such markers are of particular importance because they might indicate not only whether such a relationship exists, but suggest possible mechanisms of effects (such as endothelial dysfunction and arterial stiffness in the mother or in the placenta). We hypothesized that reduced pre-pregnancy FMD and IMT and greater arterial stiffness would be associated with increased risk of hypertensive disorders and lower birthweight and gestational age.

## Material and methods

### Source population

The methods for the Cardiovascular Risk in Young Finns study have been described in detail previously [15]. 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 [15].

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]).

## Cardiovascular risk indicator measures

FMD was measured as previously described [7]. 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), both in absolute terms and as a percentage of baseline. 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. [7] The carotid intima-media thickness (IMT) was measured approximately 10 mm proximal to the carotid bifurcation; a minimum of four measurements were taken and the mean was used [7]. The common carotid artery diameter was measured in end-diastole and end-systole at least twice [16]; the mean of the measurements was used. Young's Elastic Modulus (YEM) is designed to estimate arterial stiffness independent of IMT [17]: ([systolic blood pressure − diastolic blood pressure] × 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 and carotid measures were first taken in 2001. 359 women had a pregnancy after the 2001 visit; analysis was limited to the first pregnancy after this visit.

In a previous analysis, several indices of endothelial function (FMD) and carotid artery elasticity (Young's elastic modulus, coronary artery distensibility) 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 coronary artery distensibility declined [18].

## 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. Complications were defined as overall hypertensive disorders of pregnancy were defined as any hypertensive disorder specified as having begun during pregnancy, or an eclamptic disorder (there were too few cases to examine pre-eclampsia separately). Birthweight, gestational age, and birthweight-for-gestational-age were also modeled as continuous outcomes.

## Additional covariates

Covariates likely to be associated with exposure and outcome, based on prior literature, were chosen for adjustment, with the assistance of directed acyclic graphs. 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 reported, former, and current at 2007 as well as during pregnancy. A



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socioeconomic status variable was created, based on a combination of occupational status reports at three 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. In addition, three biological covariates were chosen for additional adjustment: systolic blood pressure, total cholesterol, and triglycerides. In our previous work, all three were associated with birth outcomes [19].

### Statistical analysis

The relation between pre-pregnancy risk factors and subsequent pregnancy outcome was assessed using multiple linear (for continuous outcomes) and logistic (for dichotomous outcomes) regression. Predictors were examined as continuous variables as well as divided into tertiles (tertiles were chosen as providing some indication of shape of trend but providing sufficient numbers in each category). Results were similar, so the tertiles are provided for ease of presentation (alternate specifications in supplementary material). For the birthweight and gestational age data, an additional analysis was run, removing those who experienced hypertensive disorders or gestational diabetes.

Median time between the FMD measure and the pregnancy was 2 years. Models were run assessing interaction with this time gap, to see if measurements taken closer to the pregnancy were more strongly related to the outcome.

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. 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 in their late 20s and early 30s in 2001 (table 1). Approximately 20% were smokers, approximately 80% were married or living with a partner, 8% were obese (BMI≥30) and the population was fairly evenly split among those with one, two, or three+ children. Since the analysis design required the women to have had a pregnancy subsequent to 2001, they tended to be younger than the overall study population and have an older age at first pregnancy. At the included pregnancy, there were 22 cases of hypertensive disorders (3 of pre-eclampsia), and 28 cases of gestational diabetes. Mean birthweight was 3506 g and mean gestational age was 278 days (39.7 weeks).

No relations were seen between FMD, IMT, or the stiffness indices, and hypertensive disorders (table 2). We found an inverse relation between FMD before pregnancy and gestational age, so that higher FMD associated with lower gestational age (table 3). Birthweight was also lower with higher FMD in some analyses. No associations were seen between preconception FMD and birthweight-for-gestational-age; there was a tendency for

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there to be higher bwt-for-ga in the middle tertile. The middle tertile of IMT was associated with the lowest gestational age; no association was seen with birthweight. Gestational age was lower in the higher tertiles of YEM. The highest tertile of Cdist was associated with higher gestational age, but lower birthweight-for-gestational-age. Results were similar with women with complications removed, and with continuous measures (tables S1 and S2).

## Discussion

Endothelial dysfunction and arterial stiffness have been associated with adverse pregnancy outcome, as has adverse pre-pregnancy cardiovascular profile [20, 21]. Based on this research, we would expect pre-pregnancy worsened cardiovascular risk factors to be associated with higher risk of pregnancy-related hypertensive disorders and worse birth outcomes. Some of the associations that were found supported a link between poor cardiovascular health and adverse birth outcomes: for instance, higher Young's elastic modulus (an indicator of arterial stiffness) was associated with lower gestational age, though perhaps not beyond that explained by other cardiovascular risk factors. Other associations found did not support this idea: pre-eclampsia has been associated with increased IMT postpartum [10]; our results were imprecise, but in the opposite direction. Higher FMD prior to the pregnancy was associated with lower birthweight and gestational age, and increasing Cdist was associated with reduced birthweight-for-gestational-age. To our knowledge, these specific questions have not been analyzed before, though several studies have found associations between other pre-pregnancy cardiovascular risk factors and birth outcomes [19, 22]. One previous study found that pregnancies with lower birthweight for gestational age had higher arterial stiffness, independent of blood pressure; our results are in the same direction, though not precise enough to be definitive [14]. Preterm birth was associated with slightly higher IMT later in life, though not after adjustment for confounders, in a single study [23], while we found the lowest gestational age in the middle tertile of IMT. Many risk factors have a curvilinear association with pregnancy outcomes – for instance, both low and high BMI are associated with increased risks of complications. Overall, however, associations between the cardiovascular risk factors and birth outcomes were not strong.

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. However, the small number of cases limits our study power. Registry studies do not record all cases of pre-eclampsia and diabetes, and even taking that into account, the reported incidence of these complications among our study population was low. In addition, there is no standardized time between the pregnancy and the measurements. All of these issues may have increased measurement error and limited our ability to detect small associations. We cannot distinguish between spontaneous and medically indicated preterm births, though removing women with reported complications, which likely excludes many of the medically indicated preterm births, left our results unchanged. It is also possible that residual confounding—for example, by socioeconomic status or weight gain during pregnancy—might be present in these results. The study population is Scandinavian, and results might not be the same in other populations.

Our results suggest a degree of association between endothelial dysfunction, arterial stiffness, and pregnancy complications, but that the mechanisms involved are unclear and perhaps not linear. Future research should further explore these relations and pathways between lifetime endothelial function, hypertensive disorders, gestational age, and birthweight. Studies of cardiovascular risk factors in young people should consider follow-up for pregnancies and pregnancy health. In addition, studies examining the effect of pregnancy complications on later cardiovascular markers should consider that the women with complications may enter the pregnancy with already altered levels of those markers.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

| | |
|---|---|
| **FMD** | flow-mediated dilatation |
| **BMI** | body mass index |
| **IMT** | intima-media thickness |
| **YEM** | Young's elastic modulus |
| **CDist** | coronary artery distensibility |

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**Table 1**

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

| | Participants with a FMD measure prior to pregnancy (n=359) | | All participants in the Young Finns study with at least one pregnancy and one FMD measure (n=922) | |
|---|---|---|---|---|
| | N | % | N | % |
| Age in 2001 | | | | |
| ≤24 | 76 | 21.2 | 88 | 9.5 |
| 27 | 105 | 29.2 | 146 | 16.0 |
| 30–33 | 139 | 38.7 | 343 | 37.2 |
| ≥36 | 39 | 10.9 | 345 | 37.3 |
| Total births | | | | |
| 1 | 107 | 29.8 | 248 | 26.9 |
| 2 | 138 | 38.4 | 415 | 45.0 |
| 3+ | 114 | 31.8 | 259 | 28.1 |
| average socioeconomic status | | | | |
| lower | 74 | 20.9 | 233 | 25.5 |
| middle | 184 | 51.8 | 486 | 53.2 |
| higher | 97 | 27.3 | 195 | 21.3 |
| Relationship status in 2001 | | | | |
| married | 155 | 44.0 | 530 | 58.2 |
| living with partner, engaged | 125 | 35.5 | 242 | 26.6 |
| not living with partner | 72 | 20.5 | 139 | 15.3 |
| Smoking in 2001 | | | | |
| Never | 200 | 57.0 | 464 | 51.0 |
| prior | 67 | 19.1 | 186 | 21.0 |
| current | 84 | 23.9 | 246 | 28.0 |
| Body mass index in 2001 | | | | |
| <20 | 42 | 11.8 | 99 | 10.8 |
| 20–<25 | 197 | 55.2 | 477 | 52.2 |
| 25–<30 | 90 | 25.2 | 235 | 25.7 |
| 30+ | 28 | 7.8 | 103 | 11.3 |
| Pregnancy complications at any pregnancy | | | | |
| low birthweight | 18 | 5.1 | 49 | 5.3 |
| preterm birth | 30 | 8.3 | 71 | 7.7 |
| hypertensive disorders of pregnancy | 15 | 4.2 | 18 | 2.0 |
| pre-eclampsia | 6 | 1.7 | 8 | 0.9 |
| gestational diabetes | 44 | 12.3 | 46 | 5.0 |
| age at first pregnancy | 31.9 | 4.1 | 27.2 | 4.5 |
| Max FMD, mm, 2001 | 0.27 | 0.1 | 0.27 | 0.14 |
| FMD area under the curve, 2001 | 9.10 | 5.3 | 9.14 | 5.32 |
| IMT, mm | 0.59 | 0.1 | 0.58 | 0.08 |
| Young’s elastic modulus, mmHg/mm | 257.8 | 101.6 | 299.4 | 179.9 |

| | Participants with a FMD measure prior to pregnancy (n=359) | | All participants in the Young Finns study with at least one pregnancy and one FMD measure (n=922) | |
|---|---|---|---|---|
| | **N** | **%** | **N** | **%** |
| carotid compliance %/10mmHg | 2.43 | 0.8 | 2.27 | 0.76 |

FMD, flow mediated dilatation

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**Table 2**

Relation Between Preconception Vascular Ultrasound Measures and Subsequent Hypertensive Disorders in Finnish Women, 2001–2007.

| | unadjusted | | adjusted[a] | | adjusted for cardiovascular risk factors[b] | |
|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | **OR** | **95% CI** | **OR** | **95% CI** |
| Maximum flow-mediated dilatation (mm) | | | | | | |
| <0.21 | | | | | | |
| 0.21–0.3 | 0.70 | 0.22–2.28 | 0.53 | 0.16–1.83 | 0.50 | 0.14–1.75 |
| >0.3 | 1.31 | 0.47–3.65 | 1.01 | 0.35–2.93 | 1.10 | 0.36–3.30 |
| Intima-medial thickness (mm) | | | | | | |
| <0.52 | | | | | | |
| 0.52–0.58 | 1.17 | 0.41–2.35 | 0.98 | 0.34–2.88 | 0.96 | 0.32–2.86 |
| ≥0.59 | 1.02 | 0.35–3.00 | 0.75 | 0.24–2.36 | 0.69 | 0.21–2.23 |
| Young's elastic modulus (mmHg/mm) | | | | | | |
| <198.7 | | | | | | |
| 198.8–278 | 1.43 | 0.44–4.62 | 1.35 | 0.41–4.45 | 1.21 | 0.35–4.16 |
| >278 | 2.09 | 0.69–6.32 | 1.45 | 0.44–4.74 | 1.39 | 0.40–4.89 |
| Coronary artery distensibility (%/10 mmHg) | | | | | | |
| <1.99 | | | | | | |
| 1.995–2.73 | 0.52 | 0.19–1.46 | 0.72 | 0.24–2.15 | 0.70 | 0.23–2.16 |
| >2.73 | 0.43 | 0.15–1.28 | 0.57 | 0.18–1.77 | 0.58 | 0.17–1.93 |

[a] adjusted for age, BMI, smoking, and socioeconomic status

[b] additionally adjusted for systolic blood pressure, total cholesterol, and triglycerides

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## Table 3

Relation Between Preconception Vascular Ultrasound Measures and Subsequent Pregnancy Outcomes in Finnish Women, 2001–2007 (n=349).

| | birthweight | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | unadjusted | | | adjusted[a] | | | adjusted for cardiovascular risk factors[b] | | |
| | beta | SD | p | beta | SD | p | beta | SD | p |
| Maximum flow-mediated dilatation (mm) | | | | | | | | | |
| <0.21 | ref | | | | | | | | |
| 0.21–0.3 | 5 | 70 | 0.94 | −29 | 70 | 0.68 | −26 | 70 | 0.71 |
| >0.3 | −89 | 70 | 0.20 | −119 | 70 | 0.09 | −132 | 71 | 0.06 |
| Intima-medial thickness (mm) | | | | | | | | | |
| <0.52 | ref | | | | | | | | |
| 0.52–0.58 | 12 | 66 | 0.85 | 2 | 66 | 0.98 | −6 | 66 | 0.93 |
| ≥0.59 | 39 | 66 | 0.56 | 43 | 69 | 0.53 | 51 | 68 | 0.46 |
| Young's elastic modulus (mmHg/mm) | | | | | | | | | |
| <198.7 | ref | | | | | | | | |
| 198.8–278 | 36 | 67 | 0.59 | 44 | 67 | 0.52 | 73 | 68 | 0.28 |
| >278 | −15 | 67 | 0.82 | −25 | 70 | 0.72 | 18 | 73 | 0.81 |
| Coronary artery distensibility (%/10 mmHg) | | | | | | | | | |
| <1.99 | | | | | | | | | |
| 1.995–2.73 | 1 | 67 | 0.98 | 23 | 68 | 0.74 | 2 | 69 | 0.98 |
| >2.73 | 30 | 67 | 0.65 | 36 | 69 | 0.60 | −10 | 72 | 0.89 |

| | gestational age | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | unadjusted | | | adjusted[a] | | | adjusted for cardiovascular risk factors[b] | | |
| | beta | SD | p | beta | SD | p | beta | SD | p |
| Maximum flow-mediated dilatation (mm) | | | | | | | | | |
| <0.21 | | | | | | | | | |
| 0.21–0.3 | −2.6 | 1.6 | 0.11 | −2.8 | 1.6 | 0.08 | −2.8 | 1.6 | 0.08 |
| >0.3 | −3.4 | 1.6 | 0.04 | −3.3 | 1.6 | 0.04 | −3.5 | 1.6 | 0.03 |
| Intima-medial thickness (mm) | | | | | | | | | |
| <0.52 | | | | | | | | | |
| 0.52–0.58 | −3.3 | 1.5 | 0.03 | −3.1 | 1.5 | 0.04 | −3.2 | 1.5 | 0.03 |

| | gestational age | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | unadjusted | | | adjusted[a] | | | adjusted for cardiovascular risk factors[b] | | |
| | beta | SD | p | beta | SD | p | beta | SD | p |
| ≥0.59 | −1.4 | 1.5 | 0.36 | −0.2 | 1.6 | 0.92 | 0.1 | 1.6 | 0.94 |
| Young's elastic modulus (mmHg/mm) | | | | | | | | | |
| <198.7 | | | | | | | | | |
| 198.8–278 | −3.2 | 1.5 | 0.04 | −2.9 | 1.5 | 0.06 | −2.2 | 1.6 | 0.16 |
| >278 | −4.2 | 1.5 | 0.01 | −3.3 | 1.6 | 0.04 | −2.1 | 1.7 | 0.22 |
| Coronary artery distensibility (%/10 mmHg) | | | | | | | | | |
| <1.99 | | | | | | | | | |
| 1.995–2.73 | 1.9 | 1.5 | 0.22 | 1.3 | 1.6 | 0.41 | 0.6 | 1.6 | 0.71 |
| >2.73 | 4.1 | 1.5 | 0.01 | 3.3 | 1.6 | 0.04 | 1.9 | 1.7 | 0.25 |

| | birthweight-for-gestational-age | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | unadjusted | | | adjusted[a] | | | adjusted for cardiovascular risk factors[b] | | |
| | beta | SD | p | beta | SD | p | beta | SD | p |
| Maximum flow-mediated dilatation (mm) | | | | | | | | | |
| <0.21 | | | | | | | | | |
| 0.21–0.3 | 0.28 | 0.13 | 0.03 | 0.25 | 0.13 | 0.06 | 0.25 | 0.13 | 0.06 |
| >0.3 | 0.01 | 0.13 | 0.94 | −0.03 | 0.13 | 0.83 | −0.05 | 0.13 | 0.71 |
| Intima-medial thickness (mm) | | | | | | | | | |
| <0.52 | | | | | | | | | |
| 0.52–0.58 | 0.00 | 0.12 | 0.99 | −0.03 | 0.13 | 0.84 | −0.03 | 0.13 | 0.81 |
| ≥0.59 | −0.06 | 0.13 | 0.63 | −0.11 | 0.13 | 0.39 | −0.11 | 0.13 | 0.41 |
| Young's elastic modulus (mmHg/mm) | | | | | | | | | |
| <198.7 | | | | | | | | | |
| 198.8–278 | 0.11 | 0.13 | 0.38 | 0.11 | 0.13 | 0.37 | 0.13 | 0.13 | 0.31 |
| >278 | 0.17 | 0.13 | 0.17 | 0.14 | 0.13 | 0.30 | 0.18 | 0.14 | 0.20 |
| Coronary artery distensibility (%/10 mmHg) | | | | | | | | | |
| <1.99 | | | | | | | | | |
| 1.995–2.73 | −0.25 | 0.12 | 0.04 | −0.22 | 0.13 | 0.09 | −0.25 | 0.13 | 0.06 |
| >2.73 | −0.27 | 0.12 | 0.03 | −0.25 | 0.13 | 0.05 | −0.31 | 0.14 | 0.02 |

[a]adjusted for age, BMI, smoking, and socioeconomic status



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[b]additionally adjusted for systolic blood pressure, total cholesterol, and triglycerides