



<http://dx.doi.org/10.1016/j.ultrasmedbio.2014.02.018>

● *Original Contribution*

## INTIMA-MEDIA THICKNESS MEASUREMENTS IN THE FETUS AND MOTHER DURING PREGNANCY: A FEASIBILITY STUDY

SANDER GALJAARD,\* SUZANNE A. PASMAN,\* LIEVEKE AMEYE,† DIRK TIMMERMAN,\*  
 and ROLAND DEVLIEGER\*

\*KU Leuven Department of Development and Regeneration: Pregnancy, Fetus and Neonate, Gynaecology and Obstetrics, University Hospitals Leuven, Leuven, Belgium; and †KU Leuven Department of Development and Regeneration: Pregnancy, Fetus and Neonate, Gynaecology and Obstetrics, Leuven, Belgium

(Received 31 May 2013; revised 7 February 2014; in final form 12 February 2014)

**Abstract**—Fetal intima-media thickness (IMT) has been suggested as a marker of pre-clinical atherosclerosis, and maternal IMT could be altered through dynamic circumstances related to pregnancy. We investigated the feasibility of measurement of IMT at four pre-defined fetal and four pre-defined maternal arterial locations to determine vascular changes that could be associated with impaired vascular function. IMT was measured from the first to third trimester (12–34 wk), in 38 low-risk pregnancies. We imaged a 10-mm region of interest using a Mindray (Shenzhen, China) high-resolution ultrasound machine with automated IMT measurement software. Fetal abdominal aorta IMT was measurable during the second trimester in 71% and during the third trimester in 100% of the cases, and umbilical artery IMT was measurable in 50% and 82% of cases during the second and third trimesters, respectively. Fetal IMT measurements were not possible during the first trimester. It was not often feasible to measure the IMT of the fetal common carotid artery, fetal renal artery and maternal iliac artery (maximal 20% of cases). Maternal common carotid artery, abdominal aorta and uterine artery IMTs were measurable throughout pregnancy. There was a significant relation between gestational age and IMT in the umbilical artery ( $p = 0.03$ ) and a significant relation between body mass index and IMT in the maternal common carotid artery ( $p = 0.01$ ). IMT measurements are feasible in some maternal and fetal vessels of interest. Further studies are underway to obtain more insight into vascular development during normal and pathologic pregnancies. (E-mail: [roland.devlieger@uzleuven.be](mailto:roland.devlieger@uzleuven.be)) © 2014 World Federation for Ultrasound in Medicine & Biology.

**Key Words:** Intima-media thickness, Fetus, Fetal programming, Arterial wall properties, Maternal medicine, Body mass index, Obesity.

### INTRODUCTION

The fetal environment has been found to be at the origin of conditions that present during adulthood. Low birth weight or intra-uterine growth restriction (IUGR) is associated with cardiovascular disease (CVD), type 2 diabetes mellitus and hypertension in adult life (Barker et al. 1989). This “fetal origin of adult disease” theory was also proposed by Law et al. (1993). In these studies adults who were small at birth had higher blood pressure and an increased prevalence of CVD. It has been suggested that relative fetal undernourishment causes alterations that

involve cardiovascular development, especially at the arterial level (Crispi et al. 2012).

Arteries are composed of three concentric layers. The intima is composed of endothelium; the media is a distinct layered structure of smooth muscle cells, collagen and elastic fibers; and the outer part of the vessel is the adventitia, which also comprises collagen and elastic fibers. In pathology studies, intima-media thickness (IMT) in the abdominal artery is reported to be the first site involved in the process of atherosclerosis in adults (McGill et al. 2000). Histology of the abdominal aorta wall of an intra-uterine growth-restricted stillborn infant with a prenatally increased IMT revealed inflammation of the thickened intima layer. Lo Vasco et al. (2011) suggested that this is a very early sign of future adult lesions. The assessment of pre-clinical IMT changes may be an important predictor of future

Address correspondence to: Roland Devlieger, Fetal Medicine Unit, University Hospitals Leuven, Herestraat 49, B-3000 Leuven, Belgium. E-mail: [roland.devlieger@uzleuven.be](mailto:roland.devlieger@uzleuven.be)

atherosclerosis and cardiovascular risk. Ultrasonography has the potential to detect these vascular changes.

Few studies have measured IMT in fetuses during pregnancy. [Cosmi et al. \(2009\)](#) measured the IMT of the abdominal aorta in 38 fetuses with IUGR and 32 appropriate-for-gestational-age (AGA) fetuses. The measurements were performed around 33 wk of gestational age (range: 30–34 wk). They focused on a single fetal vessel, the fetal abdominal aorta, and found that the IMT in the IUGR group was increased compared with that in the AGA group. Their consecutive studies represent the first on the sole use of a sonographic technique to investigate IMT in the fetus ([Zanardo et al. 2011, 2013](#)). IMT in mothers has also been poorly investigated so far. Existing studies have been performed on the common carotid artery (CCA) only. Furthermore, studies were performed only in late pregnancy and compared these values with those of non-pregnant groups and hypertensive versus non-hypertensive groups. These reports are inconsistent on whether the CCA IMT is increased in pregnancy ([Sator et al. 1999](#)). There are also some reports suggesting that the intima/media ratio is increased as a result of the inflammation and recruitment of inflammatory cells that occur in the atherosclerotic process, primarily in the intima layer ([Akhter et al. 2013](#)). It has been hypothesized that the pregnancy-related increased hemodynamic load causes adaptations of elastic arteries, which could be gestational age dependent ([Yuan et al. 2013b](#)). Also, acute changes in IMT in response to acute blood pressure and vascular tone modifications have been reported ([Thijssen et al. 2011](#)).

No direct maternal influences on vascular wall property changes in the fetus have been reported yet. One possible factor could be the hyper-estrogenic state of the mother, which may affect the fetus through transplacental passage ([Crispi et al. 2012](#); [Sator et al. 1999](#)). Also, pre-gestational maternal body mass index (BMI) could be an identifiable metabolic risk factor ([Raitakari et al. 2003](#)).

There seems to be a lack of research on other vascular sites and vascular wall properties, in both the fetus and the mother. Therefore, we wanted to investigate the feasibility of performing IMT measurements at pre-defined vessel locations using automated software in the fetus and mother during pregnancy. Furthermore, the IMT measurements were investigated in relation to gestational age, BMI and distance from the ultrasound probe to the target vessel (depth).

## METHODS

We performed a cross-sectional study between March and August 2011 in pregnant women with a low risk of CVD: no known maternal hypercholesterolemia,

diabetes, pre-existing hypertension, pregnancy-induced hypertension or pre-eclampsia. The study was performed in the context of the pilot phase of the DALI (Vitamin D and Lifestyle Intervention) study to prevent gestational diabetes, a 7th Framework Program of the European Community (FP7, Grant Agreement 242187). Patients who came for their routine ultrasound scans at the prenatal care unit at the University Hospital Leuven were recruited. The scans are planned at about 12, 20 and 30 wk of gestation; gestational age was confirmed during the first trimester. Additional patients were included from admissions at the maternal intensive care unit for threatened premature birth but in the absence of cardiovascular compromise (hypertension, pre-eclampsia or hemolysis, elevated liver enzymes, low platelet count syndrome). Pre-conception BMI (in kg/m<sup>2</sup>) was calculated using height measurements at the first antenatal visit and the self-reported weight before conception. Approval by the medical ethics committee was given, and informed consent was obtained at inclusion.

Intima-media thickness was measured by a single experienced operator (S.G.) with the M7 high-resolution real-time B-mode ultrasound machine (Mindray, Shenzhen, China), equipped with 6.0- to 14.0-MHz, 4.0- to 7.0-MHz and 3.0- to 7.0-MHz linear array transducers and automated and validated IMT measurement software ([Figs. 1 and 2](#)). The probe was chosen on the basis of the

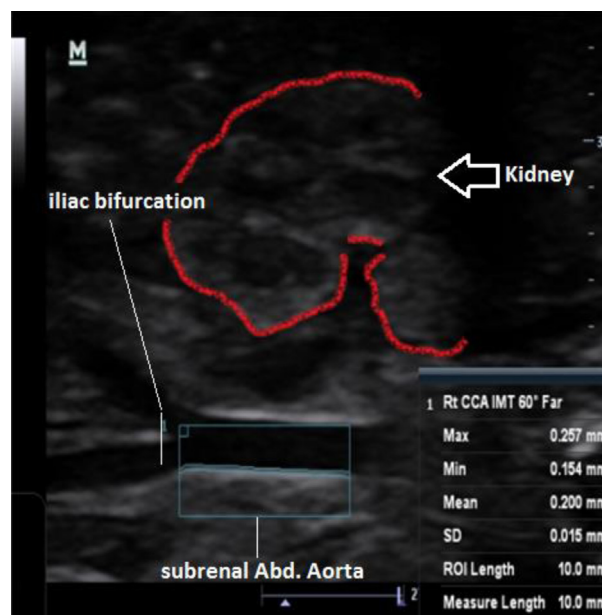


Fig. 1. Ultrasound coronal view of the fetal lower abdominal region. Intima-media thickness was measured in the fetal abdominal aorta, below the renal artery and above the iliac bifurcation, at gestational age 20 wk 2 d, with a 3.0- to 7.0-MHz linear transducer. CCA = common carotid artery, IMT = intima-media thickness, ROI = region of interest, SD = standard deviation.

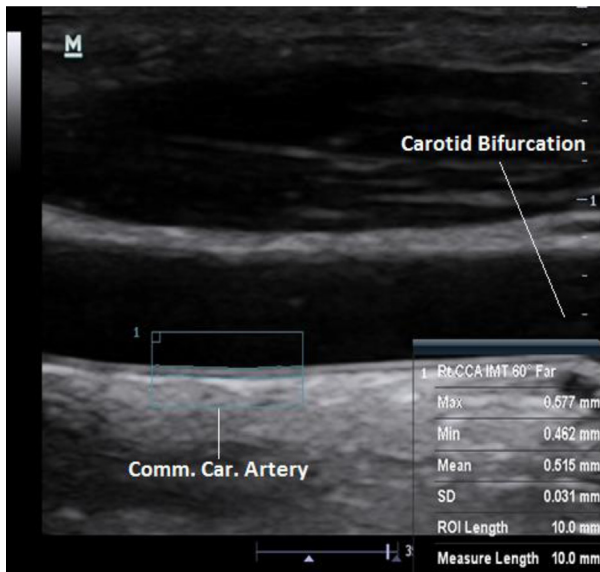


Fig. 2. Ultrasound measurement of intima-media thickness in the maternal common carotid artery, proximal to the carotid bulb (bifurcation of the external-internal carotid artery), at 20 wk 2 d of gestation using a 3.0- to 7.0-MHz linear transducer. CCA = common carotid artery, IMT = intima-media thickness, ROI = region of interest, SD = standard deviation.

depth of penetration required. In the majority of cases ( $n = 35$ ), we used the high-frequency (3.0–7.0 MHz) probe. In all measurements, both fetal and maternal, we used a minimum region of interest (ROI) window of 10 mm, an angle of insonation of  $60^{\circ}$ – $90^{\circ}$  in a coronal or sagittal view and the vessel in end-diastolic cardiac phase, as determined on the B-mode image. The IMT was defined as the distance between the leading edge of the blood-intima interface and the leading edge of the media-adventitia interface on the far wall of the vessel and was measured in micrometers. The automated IMT wall tracking software allowed online measurement of the target vessel: Minimum, maximum and mean IMT values were outlined immediately. Hereby a feedback mechanism was available for the relationship of IMT to vessel lumen properties. If the maximum IMT measurement crossed the anatomic delineation of the vessel and hence created a large discrepancy with the minimum IMT value, a large standard deviation (SD) resulted. For fetal vessels, a  $SD \leq 100 \mu\text{m}$ , and for maternal vessels a  $SD \leq 130 \mu\text{m}$ , was considered a valid measurement and otherwise rejected for recording. These cutoff points were chosen to obtain realistic values for IMT as a quality control for the innovative IMT measurements. Vessel depth was measured in a straight angle from the center of the ultrasound probe surface to the far end of the target vessel wall.

We aimed to obtain one image per pre-defined location of the vessel at three consecutive time points and analyzed these immediately, bedside. Maternal measure-

ments were performed after completion of fetal measurements, allowing the mothers to reach a state of relative rest.

Fetal and maternal arteries were measured at pre-defined locations:

- Fetal abdominal aorta: below the renal artery junction and above the iliac bifurcation (Fig. 1).
- Fetal umbilical artery: in a longitudinal plane, a horizontal trajectory part of the vessel.
- Fetal common carotid artery (fetal CCA): on the left or right side (depending on fetal position), proximal to the junction of the carotid bulb.
- Fetal renal artery: in the left or right renal artery (depending on position of the fetus).
- Maternal common carotid artery (maternal CCA): patient in supine position, head tilted slightly left laterally (angle of  $45^{\circ}$ ), probe approximately 6 cm above the clavicle; measurement 1–2 cm proximal to the junction of the internal-external carotid artery, the carotid artery bulb (Fig. 2), as described by Willekes *et al.* (1999).
- Maternal abdominal aorta: right lateral tilted position, identification of left kidney and renal artery; measurement below the junction of the renal artery and above the iliac bifurcation.
- Maternal uterine artery: Median of the cross point of the uterine artery and external iliac artery, preferably on the ipsilateral side of the placental location.
- Maternal external iliac artery: probe positioning by movement laterally from the uterus and identification of the external iliac artery from the vein by Doppler signal.

Statistical analysis was performed with SPSS software Version 20.1 (IBM, Armonk, NY, USA). Categorical values were compared using the Fisher exact test. The relationship between BMI and feasibility or non-feasibility of measurement of IMT was tested with an independent sample *t*-test because BMI was distributed normally. Repeated measurements were compared with an intra-class correlation coefficient (two-way random effects). The relationships between IMT, gestational age and BMI, and also that between the coefficient of variation and depth, were tested with Spearman's bivariate correlation. A  $p$ -value  $< 0.05$  was considered to indicate significance. All tests were two-tailed.

## RESULTS

### Study population

During the study period, 38 pregnant women were recruited; there were 36 Caucasians and 2 Africans. Median age was  $31 \pm 2.3$  y (range: 17–38 y). Two women were measured at a different gestational age; in one

mother, both twins were measured, resulting in a total of 41 ultrasound examinations.

Gestational age (GA) ranged from 12 wk to 33 wk 5 d, with a median of 29 wk. Five ultrasound examinations were performed during the first trimester (GA <14 wk), 14 ultrasound examinations during the second trimester (GA  $\geq$ 14 and <28 wk) and 22 ultrasound examinations during the third trimester (GA  $\geq$ 28 wk). Mean arterial pressure measured after the ultrasound scan was  $103.8 \pm 8.2$  mm Hg (range: 85.7–123 mm Hg).

Pre-pregnancy BMI of the women ranged from 18 to  $30 \text{ kg/m}^2$  (median:  $23 \text{ kg/m}^2$ ). There were two ultrasound examinations in underweight women (BMI <18.5  $\text{kg/m}^2$ ), 27 ultrasound examinations in normal-weight women (BMI  $\geq$ 18.5 and <25  $\text{kg/m}^2$ ), 10 ultrasound examinations in overweight women (BMI  $\geq$ 25 and <30  $\text{kg/m}^2$ ) and 2 ultrasound examinations in obese women (BMI  $\geq$ 30  $\text{kg/m}^2$ ) (World Health Organization classification of body mass index, 1995,  $\text{kg/m}^2$ ).

Six twin pregnancies were included in the study: 2 ultrasound examinations were performed in dichorionic di-amniotic twins, 4 ultrasound examinations in mono-chorionic di-amniotic twins and 2 in mono-chorionic mono-amniotic twins.

Seven women smoked during pregnancy and seven women received medication (1 tenofovir/emtricitabine, lopinavir/ritonavir and levetiracetam; 3 atosiban in combination with betamethasone; 1 aspirin cardio; 1 levothyroxine; 1 calcitriol; and 1 calcium carbonate).

The majority of the examinations (n = 35) were performed with the high-frequency 3.0- to 7.0-MHz linear ultrasound transducer.

#### Feasibility of measurement of IMT

Intima-media thickness was measurable in the fetal abdominal aorta (Fig. 1) in the second (71%) and third (100%) trimesters of pregnancy. IMT in the umbilical artery was measurable in the second (50%) and third (82%) trimesters of pregnancy, as outlined in Table 1. However,

these measurements were not feasible during the first trimester. It was not feasible to measure the fetal common carotid artery and fetal renal artery in any trimester in our study. The maternal common carotid artery (Fig. 2) was measurable in all examinations (100%) in all trimesters (Table 1). Throughout pregnancy, the maternal abdominal aorta and the uterine artery were measurable in half of the cases (40%–60%). For the maternal external iliac artery, IMT measurements were not feasible at any gestational age in our study.

#### Effect of gestational age and BMI on feasibility

The proportion of patients in whom it was feasible to measure IMT at the level of the fetal abdominal aorta increased significantly with increasing gestational age. It increased from 0% in the first trimester to 71% in the second trimester ( $p = 0.01$ ), and further increased from 71% to 100% between the second and third trimesters ( $p = 0.02$ ). The feasibility of measurement of IMT at the level of the fetal umbilical artery was also significantly related to gestational age, with a significant increase between the first and third trimesters (0% to 82%,  $p = 0.002$ ), although the difference between the second and third trimesters was not significant (50% to 82%,  $p = 0.067$ ). The feasibility of measurement of IMT in the fetal CCA was not related to gestational age, with an insignificant difference between the second and third trimesters (18% vs. 10%,  $p = 0.14$ ). IMT of the fetal renal artery was never measurable (Table 1).

The feasibility of measurement of IMT in the maternal arteries studied was independent of gestational age. The IMT in the maternal external iliac artery was difficult to measure in all trimesters of pregnancy (Table 1).

No relationship was found between maternal BMI and the feasibility of measurement of IMT for any fetal or maternal blood vessel studied: fetal abdominal aorta ( $p = 0.18$ ), umbilical artery ( $p = 0.19$ ), fetal CCA ( $p = 0.19$ ), maternal CCA ( $p = 0.50$ ), maternal abdominal

Table 1. Feasibility of at least one good-quality intima-media thickness measurement in pre-defined regions of fetal and maternal arteries in the first, second and third trimesters of pregnancy

Vessel assessed	Number (%) of measurements			
	First trimester (n = 5)	Second trimester (n = 14)	Third trimester (n = 22)	Total (n = 41)
<b>Fetus</b>				
Abdominal aorta	0	10 (71%)	22 (100%)	32 (76%)
Umbilical artery	0	7 (50%)	18 (82%)	25 (61%)
Common carotid artery	0	0	4 (18%)	4 (10%)
Renal artery	0	0	0	0
<b>Mother</b>				
Common carotid artery	4 (100%)	11 (100%)	16 (100%)	31 (100%)*
Abdominal aorta	2 (40%)	7 (50%)	9 (41%)	18 (44%)
Uterine artery	2 (40%)	7 (50%)	13 (59%)	22 (54%)
External iliac artery	1 (20%)	1 (7%)	0	2 (5%)

\* The common carotid artery intima-media thickness measurement was examined in respectively 4 of 5, 11 of 14 and 16 of 22 women.



aorta ( $p = 0.69$ ), maternal uterine artery ( $p = 0.64$ ) and maternal external iliac artery ( $p = 0.51$ ).

#### *Intra-observer agreement*

For each blood vessel measured, there was no significant difference between the first and second measurements, or between second and third and first and third repeated measurements. This was determined with the inter-class correlation coefficient: 0.965 for fetal abdominal aorta, 0.975 for fetal umbilical artery, 0.946 for maternal CCA, 0.999 for maternal abdominal aorta and 0.747 for maternal uterine artery.

#### *Range of IMT values throughout pregnancy and effect of BMI and depth*

The IMT range and median for each vessel are outlined per trimester in Table 2. In our small population, no relationship was evident between IMT and gestational age in the fetal abdominal aorta ( $p = 0.13$ ), fetal CCA ( $p = 0.20$ ), maternal CCA ( $p = 0.92$ ), maternal abdominal aorta ( $p = 0.54$ ) and maternal uterine artery ( $p = 0.77$ ). However, we did find a significant relationship between IMT and gestational age in the fetal umbilical artery ( $p = 0.03$ ), with median IMTs of 289  $\mu\text{m}$  in the second trimester and 301  $\mu\text{m}$  in third trimester.

We did not find a significant relationship between IMT and maternal BMI in the fetal abdominal aorta ( $p = 0.18$ ), fetal umbilical artery ( $p = 0.78$ ), fetal CCA ( $p = 0.20$ ), maternal abdominal aorta ( $p = 0.24$ ) or maternal uterine artery ( $p = 0.86$ ). However, there was a significant relationship between the IMT and BMI in the maternal CCA ( $p = 0.01$ ), with an IMT of 445  $\mu\text{m}$  in one underweight woman; medians of 510  $\mu\text{m}$  in normal-weight women and 540  $\mu\text{m}$  in overweight women; and an IMT of 507  $\mu\text{m}$  in one obese woman.

The mean coefficient of variation (SD/mean, SD and mean as reported by the Mindray software per measurement) and the mean with 95% confidence interval (CI)

of the IMT values are reported (in  $\mu\text{m}$ ) in Table 3. For the dispersion of the range of IMT values, the minimum, maximum and median IMT values (in  $\mu\text{m}$ ) are also listed in Table 3, as are the mean depth and range of depths (in cm) of the vessels. The coefficient of variation was found to be the lowest for IMT in the fetal umbilical artery and was also low in the fetal abdominal aorta, maternal CCA and maternal abdominal aorta.

There was a significant positive relationship between vessel depth and coefficient of variation for the IMT value in the maternal CCA ( $\rho = 0.27$ ,  $p = 0.019$ ) and maternal uterine artery ( $\rho = 0.45$ ,  $p = 0.014$ ). However, there was no significant relationship in the fetal abdominal aorta ( $p = 0.67$ ), fetal umbilical artery ( $p = 0.33$ ), fetal CCA ( $p = 0.60$ ) or maternal abdominal aorta ( $p = 0.40$ ).

## DISCUSSION

This is the first study to investigate the feasibility of arterial IMT measurement in mother and fetus throughout pregnancy using ultrasound. We were able to measure IMT in the fetal abdominal aorta and the umbilical artery during the second and third trimesters. Furthermore, we found a positive relationship between IMT and gestational age in the umbilical artery. No relationship between IMT value and gestational age was evident in any of the other fetal and maternal blood vessels. The maternal CCA IMT could be measured throughout pregnancy and exhibited a positive association with pre-gestational BMI. Maternal abdominal aorta and uterine artery IMT measurements were feasible, although more difficult than measurement of maternal CCA IMT.

Cardiovascular disease generally becomes apparent in older patients; however, the intra-uterine environment has been postulated as having a crucial role in programming the fetus for short-term survival in the early postnatal period, but with impaired consequences for

Table 2. Medians and ranges of intima-media thickness measurements in pre-defined regions of fetal and maternal arteries in the first, second and third trimesters of pregnancy

Vessel assessed	Intima-media thickness ( $\mu\text{m}$ )					
	First trimester		Second trimester		Third trimester	
	Median	Range	Median	Range	Median	Range
<b>Fetus</b>						
Abdominal aorta	—	—	330	181–431	342	201–586
Umbilical artery	—	—	289	225–572	301	212–417
Common carotid artery	—	—	—	—	295	185–367
Renal artery	—	—	—	—	—	—
<b>Mother</b>						
Common carotid artery	452	400–539	545	440–712	504	378–740
Abdominal aorta	580	523–616	561	367–680	652	495–735
Uterine artery	229	163–415	246	195–351	238	160–535
External iliac artery	—	582	—	601	—	—

Table 3. Mean and 95% CI; minimum, median and maximum intima-media thickness per measured fetal/maternal artery throughout pregnancy; and vessel depth

	Intima-media thickness ( $\mu\text{m}$ )						
	Fetus*			Mother			
	Abdominal aorta	Umbilical artery	Common carotid artery	Common carotid artery	Abdominal aorta	Uterine artery	External iliac artery
Mean	334	314	286	517	575	264	592
95% CI	313–354	294–334	165–406	498–537	534–616	231–296	471–712
Minimum	181	212	185	378	367	160	582
Median	335	301	295	511	578	236	592
Maximum	586	572	367	740	735	535	601
CV	0.12	0.09	0.17	0.13	0.11	0.15	0.18
Vessel depth (cm) <sup>†</sup>							
Mean	5.8	5.0	5.2	2.2	10.4	3.1	5.9
Range	3.9–9.2	3.1–8.4	4.4–6.0	1.5–2.7	7.5–14.2	1.6–4.9	4.7–7.0

CI = confidence interval, CV = coefficient of variation.

\* Data on the fetal renal artery were scarce.

<sup>†</sup> To the far end of the vessel wall.

cardiovascular function and metabolic changes in later adult life when intra-uterine life is unfavorable (Barker et al. 1989; Galjaard et al. 2013; Law et al. 1993). Pathology and histology studies indicate that IMT thickening is caused by inflammation and that the abdominal aorta artery is the first location of increasing IMT as a sign of atherosclerosis (Jarvisalo et al. 2001; Lo Vasco et al. 2011; McGill et al. 2000). Therefore, assessment of pre-clinical IMT changes may be used to predict future atherosclerosis and cardiovascular risk.

In newborns, the association between birth weight, abnormal growth and increased IMT in the abdominal aortic artery and development of atherosclerosis later in life is supported by several studies (Jarvisalo et al. 2001; Koklu et al. 2007; Satoru et al. 2012; Skilton et al. 2005). In early childhood, Crispi et al. (2012) reported early signs of cardiovascular dysfunction at 3–6 y of age in children with IUGR and small-for-gestational-age (SGA) children as compared with AGA children. Not only was their cardiac function affected, but the CCA IMT was also increased in both children with IUGR and SGA children. In a recent study, Dratva et al. (2013) reported an increased CCA IMT at the age of 11 y to be associated with increased birth weight.

Very few studies, however, have measured IMT in fetuses and mothers during pregnancy. Cosmi et al. (2009) measured IMT in the abdominal aorta of 38 fetuses with IUGR and 32 AGA children. They found the IMT to be higher in fetuses with IUGR than in AGA fetuses (1.9 mm vs 1.15 mm,  $p < 0.001$ ). The measurements were performed around 33 wk of gestational age (range: 30–34 wk), and this study represents the first sonographic investigation of IMT in fetuses. Sarikabadayi et al. (2012) measured umbilical wall thick-

ness in the third trimester with routine obstetric ultrasound equipment, but did not measure umbilical IMT. IMT in the carotid arteries in pregnant women was found to differ from IMT in the non-pregnant fertile female population. This was largely related to the increase in carotid media and decrease in carotid intima that supposedly occurs because of the different estrogen levels in the two groups (Sator et al. 1999). There is lack of research on other vascular sites in pregnant women. Furthermore, relationships between IMT development and pre-gestational weight (underweight, normal-weight, overweight and obese mothers), excessive gestational weight gain or gestational and type I/II diabetes mellitus have not yet been reported during pregnancy.

Our study employed a clear IMT measurement protocol to study the feasibility in relevant maternal and fetal arterial vessels at different gestational ages, using a cross-sectional design. The automated IMT wall tracking software allowed instantaneous measurement of the target vessel, and therefore, immediate feedback on the relationship of IMT to vessel lumen properties was available. If the maximum IMT measurement crossed the anatomic delineation of the vessel and hence created a large discrepancy with the minimum IMT value, a large standard deviation resulted. These cutoff values were used to define a successful measurement as a quality control for the innovative IMT measurements. Furthermore, through bedside analysis of three different consecutive images of the identical pre-defined vessel location instead of simply three off-line analyses of the same image, we could take the image acquisition process into account, being a large source of intra-observer variability.

The present study revealed several impediments to measurement of IMT in fetal arteries. In the first

trimester, it was not possible to obtain a ROI window of 10 mm for all fetal vessels because of their small size. In the second and third trimesters, because of fetal movements, the position and distance of the target vessel from the ultrasound probe (“depth”) could impair measurement of IMT. In the umbilical artery, the coiling of the cord could prevent acquisition of a straight ROI window of at least 10 mm. The fetal CCA was often not visualized because of fetal position (anterior flexing of the fetal neck); hence a ROI window of 10 mm could not be defined. The main obstacle to obtaining reliable IMT measurements in the fetal renal artery was the limited angle of insonation ( $<60^\circ$  or  $>90^\circ$ ) at which the vessel could be visualized.

The impediments to measuring IMT in maternal arteries generally were limited examination time and maternal discomfort, making it sometimes impossible to complete all measurements. Because its trajectory is superficial, the maternal CCA is, at each attempt, reachable for ultrasound examination. During pregnancy it was more difficult to reach the abdominal aorta because of the interposition of the fetus and uterus, and the “depth” sometimes prevented successful measurement. The uterine artery is characterized by a very curly trajectory, making it hard to obtain a ROI window of 10 mm in the correct angle of insonation ( $<60^\circ$  or  $>90^\circ$ ). The correct angle was also the main obstacle to successful measurement of maternal external iliac artery IMT in pregnancy.

It is not easy to compare our quantitative IMT data with those of other studies as the available information relies mostly on histopathology or postnatal IMT studies, including the fetal-to-infancy transition period in IMT development. The median IMTs in the fetal CCA and abdominal aorta in our study were 295 and 335  $\mu\text{m}$ , respectively, which are comparable to the results obtained by [Jarvisalo et al. \(2001\)](#). They performed an ultrasound study in 11-y-old children with a high risk (hypercholesterolemia/diabetes) and a low risk for atherosclerosis. In the control group they obtained IMTs in the CCA and abdominal aorta of 420 and 440  $\mu\text{m}$ , respectively. In the high-risk group, both carotid IMT and abdominal aorta IMT were increased compared with values for the low-risk group. Abdominal aorta IMT was higher than CCA IMT, indicative of the predilection of the abdominal aorta as the first location of IMT changes related to atherosclerosis. The small variation with our study could be related to the different time frame (fetuses vs. children) in which the IMT was measured by [Jarvisalo et al. \(2001\)](#). But globally, the studies support the robustness of our findings ([Dratva et al. 2013](#)).

In preterm neonates, abdominal aorta IMT was found to increase from 316 to 348  $\mu\text{m}$  for children born at respectively 25 and 37 wk of gestation ([Koklu et al. 2007](#)). This is very similar to our results (335  $\mu\text{m}$ ),

although we could not report a significant positive relationship between IMT and gestational age in our study, probably because of our small study population. Furthermore, it is unknown whether birth has an effect on vessel properties, for example, as a result of a change in blood pressure and hence different distention of arteries after birth. In their ultrasound study, [Cosmi et al. \(2009\)](#) reported an IMT of 1150  $\mu\text{m}$  in third-trimester fetuses, which can probably partly be explained by the fact that the authors studied a growth-restricted population. Also, they used different equipment and ultrasound resolution in their elegant studies ([Zanardo et al. 2011, 2013](#)).

The median IMT of the umbilical artery in our study was 301  $\mu\text{m}$  in the third trimester. In their histopathology study, [Junek et al. \(2000\)](#) reported an IMT of about 30  $\mu\text{m}$  in umbilical cords, measured after birth. They compared the evolution of IMT in umbilical arteries and veins after birth from fetuses with IUGR (controls) and fetuses born of mothers with pre-eclampsia (PE). They found that the total IMT increased with advancing gestational age at birth, because the increase in the intima was larger than the observed decrease in the media. Between the two groups the IMT was 15% thicker in the umbilical arteries from fetuses of mothers with PE than in the controls. Of course, the umbilical cord changes significantly after birth with contraction of Wharton’s jelly, the umbilical vein and arteries. We can only speculate if this may explain the difference in IMTs between our study and that of [Junek et al. \(2000\)](#). [Sarikabadayi et al. \(2012\)](#) measured umbilical wall thickness in the third trimester with standard obstetric ultrasound and umbilical IMT and wall thickness in postnatal pathology specimens. Although there was a positive correlation between prenatal and postnatal findings, the absolute values cannot be compared between these two time frames because of the different structures examined.

Maternal CCA IMT was, on average, 517  $\mu\text{m}$  in our study. This is comparable to the result obtained by [Sator et al. \(1999\)](#), who reported 560  $\mu\text{m}$  in pregnant women. We did not find a correlation with gestational age, but our study was designed to study feasibility at different time points in gestation and not gestational age-related effects.

Interestingly, we found a positive relationship between maternal CCA IMT and maternal preconception BMI. This is in accordance with the study of [Dick et al. \(2013\)](#), who found a positive relationship between IMT and obesity, although their study was conducted in male and non-pregnant female patients. [Yuan et al. \(2013a\)](#) found very recently, in late third-trimester pregnancy, a difference in maternal CCA IMT between normotensive and pre-eclamptic pregnancies (351  $\pm$  85  $\mu\text{m}$  vs. 459  $\pm$  95  $\mu\text{m}$ ).

Several limitations to our present study have to be addressed. The number of patients studied was relatively

small and comprised a heterogeneous, although cardiovascular low-risk, obstetric population. Our study also compiled some longitudinal data with mostly cross-sectional measurements. Although significant relations were observed, the study may have been underpowered to show other correlations such as for gestational age or smoking. Furthermore, by defining a limitation in restricting the SD range for successful fetal and maternal IMT measurements, there is the possibility of underestimating the IMT measurements and hence probable first signs of inflammation or atherosclerosis. With respect to methodology, we chose to focus on the arterial vessel wall and a ROI of 10 mm. Another possibility is to include the lumen diameter of the vessel of interest in the measurements. Satoru et al. (2012) combined the lumen diameter of the abdominal aorta and IMT into an adjusted IMT (aIMT in mm/mm) measurement in newborns. For first-trimester measurements, consideration should be given to choosing a ROI window smaller than 10 mm to be able to measure fetal IMT or measure IMT in such tortuous vessels as the umbilical artery and uterine artery. Finally, more information on the plasticity of the vessel can be acquired if the automated software would take into account the influence of blood pressure, blood velocity and wall velocity from the vessels. The shear stress or arterial stiffness could thereby be defined through different cardiac cycles (Rossi et al. 2009; Yuan et al. 2013a, b). A longitudinal study would be required to observe intra-individual changes in IMT in selected blood vessels during gestation.

## CONCLUSIONS

This is the first study to investigate the possibility of measuring IMT during pregnancy in both fetal and maternal blood vessels. The study proves the feasibility of reliably measuring IMT with automated software in the fetal abdominal aorta and umbilical artery in the second and third trimesters of gestation. Strong correlations between our findings on fetal abdominal aorta IMT and those from the study by Koklu et al. (2007) on newborns of different gestational ages, support the robustness of our findings. Obesity of the mother did not hamper measurement of IMT in fetal arteries. The positive relationship between maternal CCA IMT and BMI invites further investigation into abnormal pregnancy. Furthermore, fetal IMT development in abnormal pregnancy is of interest, as it could contribute to elucidating the mechanisms of intra-uterine fetal programming and the prediction of the origin of adult metabolic diseases.

*Acknowledgments*—The research leading to these results has received funding from the European Community's 7th Framework Programme (FP7/2007-2013) under Grant Agreement 242187.

## THE AUTHORS SERVE ON BEHALF OF THE DALI CORE INVESTIGATOR GROUP:

- GERNOT DESOYE, PROJECT COORDINATOR, AUSTRIA<sup>1</sup>  
 DAVID SIMMONS, TRIAL COORDINATOR, UK<sup>2</sup>  
 ROSA CORCOY, SPAIN<sup>3,4</sup>  
 ALEXANDRA KAUTZKY-WILLER, AUSTRIA<sup>5</sup>  
 ANDRE VAN ASSCHE, BELGIUM<sup>6</sup>  
 PETER DAMM, DENMARK<sup>7</sup>  
 ELIZABETH R. MATHIESEN, DENMARK<sup>7</sup>  
 DORTE MØLLER JENSEN, DENMARK<sup>8</sup>  
 LISELOTTE ANDERSEN, DENMARK<sup>8</sup>  
 FIDELMA DUNNE, IRELAND<sup>9</sup>  
 ANNUNZIATA LAPOLLA, ITALY<sup>10</sup>  
 GRAZIANO DI CIANNI, ITALY<sup>11</sup>  
 FRANK SNOEK, NETHERLANDS<sup>12</sup>  
 MIREILLE VAN POPPEL, COORDINATING SPONSOR, NETHERLANDS<sup>13</sup>  
 EWA WENDER-OZEGOWSKA, POLAND<sup>14</sup>  
 AGNIESZKA ZAWIEJSKA, POLAND<sup>14</sup>  
 DAVID HILL, LAWSON SWITZERLAND<sup>15</sup>  
 PABLO REBOLLO, SPAIN<sup>16</sup>  
 ROLAND DEVLIEGER, BELGIUM<sup>6</sup>  
 and DIRK TIMMERMAN, BELGIUM<sup>6</sup>
- <sup>1</sup>Department of Obstetrics and Gynecology, Medizinische Universitaet Graz, Graz, Austria;  
<sup>2</sup>Institute of Metabolic Science, Addenbrookes Hospital, Cambridge, England;  
<sup>3</sup>Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;  
<sup>4</sup>CIBER Bioengineering, Biomaterials and Nanotechnology, Instituto de Salud Carlos III, Madrid, Spain;  
<sup>5</sup>Medical University of Vienna, Vienna City, Austria;  
<sup>6</sup>KU Leuven Department of Development and Regeneration: Pregnancy, Fetus and Neonate, Gynaecology and Obstetrics, University Hospitals Leuven, Leuven, Belgium;  
<sup>7</sup>Center for Pregnant Women with Diabetes, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;  
<sup>8</sup>Odense University Hospital, Odense, Denmark;  
<sup>9</sup>National University of Ireland, Galway, Ireland;  
<sup>10</sup>Universita Degli Studi di Padova, Padua, Italy;  
<sup>11</sup>Università di Pisa, Pisa, Italy;  
<sup>12</sup>Department of Medical Psychology, EMGO+—Institute for Health and Care Research, VU University Medical Centre, Amsterdam, the Netherlands;  
<sup>13</sup>Department of Public and Occupational Health, EMGO+—Institute for Health and Care Research, VU University Medical Centre, Amsterdam, the Netherlands;  
<sup>14</sup>Uniwersytet Medyczny im Karola Marcinkowskiego W. Poznaniu, Poznan, Poland;  
<sup>15</sup>Recherche en Santé Lawson SA, Bronschhofen, Switzerland; and  
<sup>16</sup>BAP Health Outcomes Research SL, Oviedo, Spain



## REFERENCES

- Akhter T, Wikstrom AK, Larsson M, Naessen T. Individual common carotid artery wall layer dimensions, but not carotid-IMT, indicate increased cardiovascular risk in women with preeclampsia: An investigation using non-invasive high-frequency ultrasound. *Circ Cardiovasc Imaging* 2013; <http://dx.doi.org/10.1161/CIRCIMAGING.113.000295>.
- Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischemic heart disease. *Lancet* 1989;2:577–580.
- Cosmi E, Visentin S, Fanelli T, Mautone AJ, Zanardo V. Aortic intima media thickness in fetuses and children with intrauterine growth restriction. *Obstet Gynecol* 2009;114:1109–1114.
- Crispi F, Figueras F, Cruz-Lemini M, Bartrons B, Bijns B, Gratacos E. Cardiovascular programming in children born small for gestational age and relationship with prenatal signs of severity. *Am J Obstet Gynecol* 2012;207:121.e1–121.e9.
- Dick TJ, Lesser IA, Leipsic JA, Mancini GB, Lear SA. The effect of obesity on the association between liver fat and carotid atherosclerosis in a multi-ethnic cohort. *Atherosclerosis* 2013;226:208–213.
- Dratva J, Breton CV, Hodis HN, Mack WJ, Salam MT, Zemp E, Gilliland F, Kuenzli N, Avol E. Birth weight and carotid artery intima-media thickness. *J Pediatr* 2013;162:906–911.
- Galjaard S, Devlieger R, Van Assche FA. Fetal growth and developmental programming. *J Perinat Med* 2013;41:101–105.
- Jarvisalo M, Jartti L, Nanto-Salonen, Irjala K, Ronnema T, Hartiala JJ, Celermajer DS, Raitakari OT. Increased aortic intima-media thickness: A marker of preclinical atherosclerosis in high risk children. *Circulation* 2001;104:2943–2947.
- Junek T, Baum O, Lauter H, Vetter K, Matejevic D, Graf R. Preeclampsia associated alterations of the elastic fibre system in umbilical cord vessels. *Anat Embryol* 2000;201:291–303.
- Koklu E, Kurtoglu S, Akcakus M, Yikilmaz A, Coskun A, Gunes T. Intima-media thickness of the abdominal aorta of neonate with different gestational ages. *J Clin Ultrasound* 2007;35:491–497.
- Law CM, de Swiet M, Osmond C, Fayers PM, Barker DJ, Cruddas AM, Fall CH. Initiation of hypertension in utero and its amplification throughout life. *Br Med J* 1993;306:24–27.
- Lo Vasco VR, Salmaso R, Zanardo V, Businaro R, Visentin S, Trevisanuto D, Cosmi E. Fetal aorta wall inflammation in ultrasound-detected aortic intima/media thickness and growth retardation. *J Reprod Immunol* 2011;91:103–107.
- McGill HC, McMahon CA, Herderick EE, Tracy RE, Malcom GT, Zieske AW, Strong JP. Effect of coronary heart disease risk factors on atherosclerosis of selected regions of the aorta and right coronary artery. PDAY research group. *Pathobiologic determinants of atherosclerosis in youth. Arterioscler Thromb Vasc Biol* 2000;20:836–845.
- Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, Jarvisalo MJ, Uhari M, Jokinen E, Ronnema T, Akerblom HK, Viikari JS. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: The Cardiovascular Risk in Young Finns Study. *JAMA* 2003;290:2277–2283.
- Rossi AC, Brands PJ, Hoeks APG. Nonlinear processing in B-mode ultrasound affects carotid diameter assessment. *Ultrasound Med Biol* 2009;35:736–747.
- Sarikabadayi YU, Aydemir O, Kanmaz G, Aydemir C, Oguz SS, Erdev O, Eyi EG, Zergeroglu S, Dilmen U. Umbilical artery intima-media and wall thickness in infants of diabetic mothers. *Neonatology* 2012;102:157–162.
- Sator MO, Joura EA, Gruber DM, Obruca A, Zeisler H, Egarter C, Huber JC. Non-invasive detection of alterations of the carotid artery in pregnant women with high frequency ultrasound. *Ultrasound Obstet Gynecol* 1999;13:260–262.
- Satoru I, Takamichi I, Ohishi A, Hiroaki I. Associations of abdominal aortic wall thickness in the newborn with maternal factors. *Am J Perinatol* 2012;29:441–448.
- Skilton MR, Evans N, Griffiths KA, Harmer JA, Celermajer DS. Aortic wall thickness in newborns with intrauterine growth restriction. *Lancet* 2005;365:1484–1486.
- Thijssen D, Scholten RR, van den Munckhof I, Benda N, Green DJ, Hopman M. Acute change in vascular tone alters intima-media thickness. *Hypertension* 2011;58:240–246.
- Willekes C, Brands PJ, Willegers JM, Hoeks APG, Reneman RS. Assessment of local differences in intima-media thickness in the human carotid artery. *J Vasc Res* 1999;36:222–228.
- Yuan LJ, Xue D, Duan YY, Cao TS, Yang HG, Zhou N. Carotid intima-media thickness and arterial stiffness in pre-eclampsia by analysis with a radio-frequency ultrasound technique. *Ultrasound Obstet Gynecol* 2013a;42:644–652.
- Yuan LJ, Xue D, Duan YY, Cao TS, Zhou N. Maternal carotid remodeling and increased carotid arterial stiffness in normal late-gestational pregnancy as assessed by radio-frequency ultrasound technique. *BMC Pregnancy Childbirth* 2013b;13:122.
- Zanardo V, Fanelli T, Weiner G, Fanos V, Zaninotto M, Visentin S, Cavallin F, Trevisanuto D, Cosmi E. Intrauterine growth restriction is associated with persistent aortic wall thickening and glomerular proteinuria during infancy. *Kidney Int* 2011;80:119–123.
- Zanardo V, Visentin S, Trevisanuto D, Bertin M, Cavallin F, Cosmi E. Fetal aortic wall thickness: A marker of hypertension in IUGR children? *Hypertens Res* 2013;36:440–443. <http://dx.doi.org/10.1038/hr.2012.219>.