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# Altered vascular function in healthy normotensive pregnant women with bilateral uterine artery notches

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**Objectives** To assess endothelial function and vascular mechanical properties in normotensive pregnant women with high resistance in the uteroplacental circulation.

**Design** Cross-sectional prospective study.

**Setting** Doppler ultrasound laboratory at university department of obstetrics and gynaecology referral centre for high risk pregnancies.

**Participants** Forty-two caucasian normotensive pregnant women: 23 with uncomplicated pregnancies and 19 with bilateral uterine artery notches.

**Methods** Flow-mediated dilatation of the brachial artery was measured by ultrasonography at 25 gestational weeks. Concentrations of nitrite and nitrate in the plasma were established at 25 and 32 gestational weeks. The elastic properties of the common carotid artery, abdominal aorta and popliteal artery were measured with an ultrasonic echo-tracking system.

**Results** Flow-mediated dilatation at two minutes after cuff deflation was significantly lower in the bilateral notch group compared with the control group, 8.3% and 13.7%, respectively ($P = 0.0007$). The ability to sustain vasodilatation was reduced in the bilateral notch group ($P = 0.02$). Lower values of nitrite and nitrate in the plasma were found at 32 gestational weeks in the bilateral notch group than in the control group (mean 24.76 μM/L (SD 5.6) and 30.93 μM/L (8.2), respectively; $P = 0.008$). Nitrite and nitrate levels tended to be lower in the bilateral notch group even at 25 gestational weeks (29.45 μM/L (8.3) and 35.73 μM/L (11.0) in the bilateral notch and control group, respectively; $P = 0.09$). There was no difference in aortic, carotid or popliteal elasticity between the two groups.

**Conclusions** Healthy normotensive pregnant women with bilateral uterine artery notches show impaired endothelial function, but no differences in vascular mechanical properties.

## INTRODUCTION

Pregnancy is associated with profound maternal haemodynamic changes. Systemic vascular tone falls leading to profound vasodilatation[1]. One of the crucial mechanisms of adaptation to meet the increased needs of the growing fetus is the decrease of resistance in the uteroplacental circulation with gestation. The initial decrease until 24 to 25 gestational weeks is thought to be caused by trophoblastic invasion into decidual and myometrial segments of spiral arteries[2]. Failure of trophoblastic invasion leads to persisting high resistance to flow and an insufficient uteroplacental circulation[3].

Uterine artery blood flow velocity can be assessed with Doppler ultrasound. An abnormal uterine artery velocity waveform is characterised by decreased diastolic flow (i.e. high pulsatility or resistance index) and/or the presence of an early diastolic notch, a result of the reflected pressure wave from a high resistance uteroplacental bed[4]. Pregnant women with bilateral uterine artery notches are particularly at risk of developing complications later in pregnancy such as pregnancy-induced hypertension, pre-eclampsia or intrauterine growth restriction[5].

Whether high resistance is also present in other vascular beds of normotensive pregnant women with bilateral uterine artery notches is not known. Resistance in a vascular bed is influenced by mechanical properties of the vessels; increased stiffness would lead to higher resistance. Mechanical properties of arteries, such as stiffness, can be studied by echo-tracking ultrasonography[6]. The behaviour of a vascular bed is influenced not only by the structure of the vessels, but also by the presence of vasoactive substances. The endothelium is a source of a potent vasoactive substance, the endothelium derived nitric oxide, and its function is therefore of special interest. Recent data suggest that nitric oxide is likely to be one of the primary mediators responsible for the fall in vascular resistance during pregnancy[7]. Endothelial function and the production of endothelial nitric oxide can be indirectly assessed by a non-invasive ultrasound technique described in 1992 by Celermajer *et al.*[8] Measuring serum nitrate, a stable end-metabolite of nitric

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oxide[9] is another method of assessing the production of nitric oxide by the endothelium.

The aim of this study was to establish whether otherwise healthy normotensive pregnant women with bilateral uterine artery notches have altered vascular mechanical properties and endothelial function in general.

## METHODS

Forty-two caucasian pregnant women participated in the study: 23 controls with uncomplicated pregnancies and normal Doppler velocimetry of uterine arteries, and 22 normotensive women with risk pregnancies with bilateral uterine artery notches. All women of the latter group were regularly followed at the Doppler ultrasound laboratory with assessment of fetoplacental circulation until the delivery. The control and the study groups were comparable with regard to parity: median zero (range 0–1) and zero (0–3), respectively, and gestational age at vessel examination: median 178 days (161–187) and 176 days (136–194), respectively. The mean (standard deviation) age of the women in the control group was 29 years (3) and in the bilateral notch group 32 years (4). There were no smokers among the women in the control group and two smokers in the bilateral notch group. Adverse outcomes were defined as: intrauterine growth restriction (fetal weight deviation below the mean − two standard deviations of the reference population[10]), preterm delivery (gestational age at delivery $<37$ completed gestational weeks), placental abruption or stillbirth.

All women in the study group were recruited during the period from March 1999 to June 2000 at the Doppler ultrasound laboratory, where they were referred for assessment of fetoplacental circulation. The inclusion criteria for recruitment to the study group were: bilateral uterine artery notches, singleton pregnancy, gestational age $\leq$28 completed gestational weeks, normotensivity, absence of bleeding and a negative history for cardiovascular disease, renal disease or type I or II diabetes. Out of 99 pregnant women with bilateral uterine artery notches and appropriate gestational age who were referred to the Doppler laboratory, 70 had pre-eclampsia, four bleeding and 25 were eligible for the study. Twenty-two women gave their informed consent, three declined to participate in the study. Three women who had entered into the study and later in pregnancy developed pre-eclampsia (blood pressure $\geq$140/90 mmHg and proteinuria $\geq$0.03 g/L or rise of diastolic blood pressure $>$20 mmHg) or pregnancy-induced hypertension were excluded. Thus, the notch group comprised 19 women.

The controls were recruited at the routine ultrasound scan for fetal anomalies at 18 to 20 gestational weeks. During the period of March 1999 to November 1999, twenty-six healthy pregnant women with a singleton pregnancy were randomly asked to participate in the study. Two women declined. Women who gave their informed consent had the uterine artery flow examined with Doppler ultrasound after the ultrasound scan and were scheduled for a second uterine artery Doppler examination at 25 to 27 gestational weeks when the maternal vascular function also was assessed and the first blood sampling took place. One woman who had entered into the study developed subsequently pre-eclampsia and was excluded. Thus, the control group consisted of 23 women. The study was approved by the local ethics committee.

### Doppler velocimetry

Uterine artery Doppler velocimetry was performed using an Aspen Acuson system fitted with a 3.5 MHz abdominal transducer (Acuson, Mountain View, California, USA). The high-pass filter was set at 125 Hz. The uterine artery was visualised with colour Doppler imaging on each side at the level of crossing with the external iliac artery. The Doppler gate was placed over the uterine artery with an insonation angle of less than 50° and flow velocity waveforms during at least six heart cycles were recorded. The pulsatility index was calculated automatically by the system. The presence or absence of an early diastolic notch in the waveform was assessed visually.

### Examination of the mechanical properties of vessels

For non-invasive assessment of vessel diameter and pulsatile diameter changes, an electronic echo-tracking instrument (Diamove, Teltec, Lund, Sweden) was used. The Diamove is interphased with a Hitachi EUB 240 (Hitachi Medical Corporation, Tokyo, Japan) real-time scanner and equipped with a 3.5 MHz and 5 MHz linear array ultrasound probes. Two electronic markers representing the electronic gates automatically lock on the echoes from the posterior interface of the anterior vessel wall and the anterior interface of the posterior wall. The markers are displayed in real-time image to indicate the level at which the recording is performed. The echo-tracking instrument measures the instant distance between vessel walls perpendicular to the longitudinal axis of the vessel[11]. The pulse repetition frequency is 868 Hz, which results in a maximum tracking velocity of 95 mm/s (at 3.5 MHz ultrasound frequency) and a time resolution of 1.15 ms. The smallest detectable vessel wall movement is 7.8 $\mu$m[12]. The variabilities for repeated measurements of the pulsatile diameter changes are 10%–15% (coefficient of variation) for the vessels investigated[6]. All measurements were performed by two experienced investigators. A personal computer was used for storage and evaluation of the pulse waveform signals.

The maternal abdominal aorta was insonated from the epigastrium and measurements were performed approximately 2 cm under the processus xyphoideus. The maternal

common carotid was insonated from behind the sternocleidomastoid muscle and measurements were performed 2 cm distal from the bifurcation. Measurements of the popliteal artery were performed in the central part of the popliteal fossa. All three vessels were visualised in the longitudinal section.

Arterial blood pressure was obtained by auscultation with a sphygmomanometer on the right arm. Blood pressure was measured as well on the left arm to exclude differences in blood pressure between the left and right arm.

Strain, or fractional diameter change was defined as:

$$\text{Strain} = \frac{\text{Dsyst} - \text{Ddiast}}{\text{Ddiast}}$$

Pressure strain elastic modulus (Ep)[13] was defined as:

$$\text{Ep} = \text{K} \times \frac{P\text{syst} - P\text{diast}}{(\text{Dsyst} - \text{Ddiast})/\text{Ddiast}}$$

Stiffness ($\beta$)[14] was defined as:

$$\beta = \frac{\text{Ln}(P\text{syst}/P\text{diast})}{(\text{Dsyst} - \text{Ddiast})/\text{Ddiast}}$$

In the formulae, *P* syst and *P* diast are the maximum systolic and diastolic pressures, Dsyst and Ddiast are the corresponding vessel diameters in mm, Ep is measured in $N/m^2$, K is the factor for converting mmHg into $N/m^2$ and equals 133.3. The main outcome variable: 'stiffness' ($\beta$), is pressure independent and it characterises the vessel wall mechanics in the physiologic pressure range. Stiffness is inverse to the distensibility or compliance. A high value of $\beta$ denotes a stiffened arterial wall.

Three consecutive recordings of pulsatile diameter changes were obtained from the abdominal aorta, the common carotid artery and the popliteal artery. Strain, Ep and $\beta$ were calculated off-line from the diameter curves.

## Assessment of the endothelial function

Endothelial function was assessed using high resolution ultrasonography on the brachial artery as described by Celermajer *et al.*[8] Changes in the brachial artery diameter in response to reactive hyperaemia were measured using a 7.0 MHz linear array transducer and an Aspen Acuson system (Acuson, Mountain View, California, USA). The women rested for 10 minutes in a room with stable temperature before a baseline scan was obtained. The right brachial artery was identified 3–5 cm above the antecubital crease and scanned in the longitudinal view. The image depth was set at 3 cm, and gain was adjusted to optimally visualise the arterial wall interface. Images were recorded continuously on video-tape for off-line analysis. After obtaining a one-minute baseline brachial artery scan, the exact location of the transducer was marked on the patients overarm. Thereafter a blood pressure cuff was placed over the patient's upper arm and inflated to 200 mmHg. The inflation pressure was maintained for four minutes. After sudden deflation of the cuff, the transducer was immediately placed over the marked area and the brachial artery was scanned continuously for three minutes after deflation. Off-line, maximum vessel diameter was measured from the anterior interface to the posterior interface between media and adventitia. Brachial artery diameter was measured from the baseline scan and at 20 seconds, one minute and two minutes after cuff deflation. Flow-mediated dilatation was derived from the brachial artery diameter increase at the respective time interval in relation to the baseline diameter and expressed as percentage.

## Plasma nitrite and nitrate concentrations

Production of nitric oxide can be determined indirectly by measuring concentrations of nitrite and nitrate in the plasma. Blood samples were obtained from fasting subjects (12 hours) with controlled dietary intake of nitric oxide on two occasions: at gestational weeks 25–27 and 32–34. The two smokers were asked not to smoke 12 hours before blood sampling. For the measurement of nitrite ($NO_2^-$), 5 mL venous blood was drawn into a tube containing EDTA, which was immediately cooled on ice. Plasma was separated by centrifugation at 3000 *g* for 15 minutes and stored at −70°C.

Plasma samples (200 μL) were deproteinised by adding 400 μL ZnSO4 (5%) and 500 μL NaOH (215 mM). The samples were mixed and, after 10 minutes centrifuged at 1000 *g* at 4°C. Nitrate ($NO_3^-$) in the supernatants was reduced to nitrite ($NO_2^-$) with copper-coated granules of cadmium. 300 μL supernatant and 100 μL glycin–NaOH buffer (1.5%) together with 0.2–0.3 activated cadmium were mixed gently for exactly 90 minutes. The concentration of $NO_2^-$ in the reduced plasma supernatants was determined after reaction with Greiss reagent consisting of 0.5% sulphanilamide, 0.05% naphthylethylene–diamine–dihydrochloride and 2.5% $H_3PO_4$. Equal volumes (100 μL) of reduced samples and Greiss reagent were mixed and incubated for 10 minutes at room temperature. $NO_2^-$ concentration proportional to $OD_{550}$ was determined using a microtiterplate reader (Elx808 Bio-Tek Instruments Inc) and expressed in micromoles/L (μM/L).

## Statistics

The results were evaluated using the Mann–Whitney *U* test, Wilcoxon signed rank test, Fisher's exact test or $\chi^2$ test, as appropriate. A significant difference was considered present if $P < 0.05$.

**Table 1.** Demographic and clinical data of pregnant women with bilateral uterine artery notches and controls. The values are given as mean [SD]. SBP and DBP = systolic and diastolic blood pressure, respectively.

| | Bilateral notch $n = 19$ | Controls $n = 23$ | $P$ |
|---|---|---|---|
| Age (years) | 32 [4] | 29 [3] | 0.02 |
| Height (cm) | 166.7 [3.3] | 167.2 [5.7] | |
| SBP (mmHg)* | 111 [13] | 107 [10] | |
| DBP (mmHg)* | 68 [6] | 59 [6] | 0.003 |
| Mean arterial pressure (mmHg) | 82 [10] | 75 [5] | 0.01 |

* Blood pressure values at the time of vascular examination (25–27 gestational weeks).

**Table 3.** Adverse outcome of pregnancy.

| | Bilateral notch* ($n = 18$) | Controls* ($n = 22$) |
|---|---|---|
| Preterm delivery | 3 | 3 |
| IUGR | 3 | — |
| Preterm delivery + IUGR | 4 | — |
| Placental abruption | 1 | — |
| Stillbirth | 1 | — |
| Total | 12 | 3 |

* Data not available in 1 patient from the bilateral notch group and 1 patient in the control group.

## RESULTS

Demographic data, clinical outcome variables and adverse outcomes are given in Tables 1, 2 and 3. Twelve women (63%) with bilateral notches as compared with three controls (13%) had adverse outcome of pregnancy ($P = 0.03$). In the notch group, six women (32%) were delivered by acute caesarean section and two (10%) by elective caesarean section. In the control group, three women (13%) were delivered by acute caesarean section.

No significant differences in β and Ep of the abdominal aorta, common carotid artery and popliteal artery between the two groups were found (Table 4). Strain was lower in all three vessels in the notch group, but the difference reached statistical significance only in common carotid artery ($P = 0.04$). There was no significant difference between the two groups in systolic or diastolic blood pressure at the time of the first visit at the antenatal care unit at 7–10 weeks of gestation. At the time of the assessment of vascular function, women with bilateral uterine notches had significantly higher diastolic blood pressure than controls (68 mmHg *vs* 59 mmHg, $P = 0.003$) (Table 1). Between the first visit at the antenatal care unit and the time of assessment of vascular function, diastolic blood pressure decreased in controls (−6.5 mmHg (6.4)), while an increase was noted in the notch group (3.5 mmHg (9.2)) ($P = 0.001$).

Flow-mediated dilatation of the brachial artery was significantly lower in the bilateral notch group at all three measurements (20s, $P = 0.01$; one minute, $P = 0.01$ and two minutes, $P = 0.0007$) (Fig. 1). Flow-mediated dilatation in the bilateral notch group was 6.3% at 20s, 9.5% at one minute and 8.3% at two minutes compared with 9.2%, 13.4% and 13.7%, respectively, in the control group. The resting mean vessel diameter was 3.57 mm (0.43) in the group with bilateral uterine artery notch and 3.45 mm (0.31) in the controls ($P = 0.15$). Lower values of nitrite and nitrate in the plasma were found at 32 gestational weeks in the bilateral notch group than in the control group (24.76 μM/L (5.6)) and 30.93 μM/L (8.2)), respectively; $P = 0.008$). Nitrite and nitrate levels tended to be lower in the bilateral notch group even at 25 gestational weeks (29.45 μM/L (8.3) and 35.73 μM/L (11.0) in the bilateral notch and control group, respectively; $P = 0.09$) (Fig. 2).

## DISCUSSION

Very little attention has been paid to possible structural changes in the human arterial tree as one of the mechanisms of haemodynamic adaptation during pregnancy. In large arteries of the rat a marked increase in the expression of actin, a major contractile structural protein of the muscle cells and decrease in stiffness, has been observed during pregnancy[15,16]. Furthermore, structural alteration of

**Table 2.** Outcome variables in the bilateral notch group and control group. IUGR = intrauterine growth restriction defined as birthweight < mean − 2 SD of the normal population.

| | Bilateral notch+ | | | | Controls+ | | | | $P$ |
|---|---|---|---|---|---|---|---|---|---|
| | $n$ | Mean [SD] | Median | Range | $n$ | Mean [SD] | Median | Range | |
| Gestational age at delivery (days) | 18 | 258 [19] | 263 | 219–284 | 22 | 278 [12] | 278 | 250–297 | 0.0008 |
| Birthweight (g) | 18 | 2371 [783] | 2397 | 1075–3850 | 22 | 3640 [535] | 3590 | 2620–4550 | <0.0001 |
| Birthweight deviation* (%) | 18 | −21.2 [16.0] | −19.3 | −47.9–+4.4 | 22 | 3.9 [13.2] | 1.8 | −18.6–+28.5 | 0.0001 |
| IUGR | 8 | — | — | — | 0 | — | — | — | |
| Placental weight (g) | 18 | 435 [126] | 412 | 220–650 | 22 | 674 [135] | 670 | 360–880 | <0.0001 |
| pH umbilical artery | 16 | 7.21 [0.12] | 7.24 | 6.83–7.32 | 20 | 7.23 [0.06] | 7.22 | 7.10–7.36 | ns |
| pH umbilical vein | 16 | 7.28 [0.13] | 7.30 | 6.85–7.37 | 20 | 7.31 [0.07] | 7.31 | 7.12–7.43 | ns |
| Apgar score at 5 min | 18 | — | 9 | 4–10 | 22 | — | 10 | 8–10 | ns |

* Deviation from the expected gestational age related birthweight.
+ Data not available in 1 patient from the bilateral notch group and 1 patient in the control group.

**Table 4.** Vascular data in pregnant women with bilateral uterine artery notches ($n = 19$) and in controls ($n = 23$). Values are mean [SD]. Dmax = maximum vessel diameter in systole; Dmin = minimum vessel diameter in diastole; Ep = pressure strain elastic modulus.

| | Aorta | | Common carotid artery | | Popliteal artery | |
|---|---|---|---|---|---|---|
| | Bilateral notch | Controls | Bilateral notch | Controls | Bilateral notch | Controls |
| Dmax (mm) | 17.57 [1.27] | 17.26 [1.76] | 7.51 [0.52] | 7.50 [0.49] | 5.8 [0.84] | 6.04 [0.71] |
| Dmin (mm) | 15.20 [1.02] | 14.71 [1.59] | 6.83 [0.51] | 6.68 [0.53] | 5.60 [0.83] | 5.81 [0.73] |
| Dmean (mm) | 16.35 [1.05] | 15.64 [1.98] | 7.17 [0.50] | 7.00 [0.62] | 5.68 [0.85] | 5.92 [0.73] |
| Ep | 0.38 [0.18] | 0.36 [0.08] | 0.62 [0.24] | 0.56 [0.16] | 2.0 [1.0] | 1.8 [0.8] |
| Stiffness | 3.4 [1.5] | 3.4 [0.7] | 5.1 [1.6] | 5.70 [2.3] | 17.8 [9.7] | 17.3 [7.5] |
| Strain | 0.16 [0.05] | 0.17 [0.04] | 0.10 [0.03]* | 0.13 [0.04]* | 0.03 [0.02] | 0.04 [0.02] |

* $P = 0.04$.

non-contractile matrix proteins of the artery has been reported in rabbits[17]. Thus, it is possible, that the human arterial tree may also undergo structural changes to meet the volume changes that occur during pregnancy. Structural changes of the vessel wall will influence the mechanical properties of the vascular tree. Since the possibility to histologically study vascular structure and vessel properties in human pregnancy is limited, indirect methods have to be used.

Mechanical properties of major arteries in humans can be studied non-invasively by magnetic resonance imaging[18] or ultrasonography with either M-mode or echo-tracking techniques. The echo-tracking technique is easy to use in clinical settings, has good resolution and gives reproducible results[19]. This technique has been successfully used to assess gender differences in the mechanical properties of arteries in the human[20], the influence of age on vascular stiffness[21] and to study the behaviour of vessels in vascular disease, such as Marfan's syndrome[22] or diabetes mellitus[23]. Because of the non-invasive nature of this technique, it is suitable for studies in pregnancy. Lower arterial distensibility was found in the aorta of small-for-gestational age fetuses[24,25]. Mechanical properties of large arteries in the mother and fetus during normal and diabetic pregnancy were studied by Hu *et al.*[26], who reported a decreased stiffness in the aorta of healthy pregnant women at the end of the first trimester. The authors concluded that the reduction of aortic stiffness might be the consequence of structural remodelling of arterial walls or the result of an alteration of smooth muscle tone, or both[26].

We hypothesised that normotensive patients with bilateral uterine artery notching had increased vessel wall stiffness, as compared with healthy controls due to an altered cardiovascular adaptation to pregnancy. Patients with pre-eclampsia or pregnancy induced hypertension were excluded to avoid the effect of elevated blood pressure on the mechanical properties of vessels. No differences in the stiffness of the aorta and common carotid artery were found between the two groups. Since both vessels are elastic arteries with a large proportion of elastic components, a major contribution of smooth muscle to the mechanical properties can be excluded. Thus our findings suggest that there are no major differences in the vessel wall properties of larger arteries between patients with bilateral uterine artery notches and controls.

When compared with pregnant controls with normal uterine artery blood flow, pregnant women with high resistance in the uteroplacental circulation had a significantly reduced flow-mediated dilatation of the brachial artery. In arteries that have an intact endothelium, increased flow causes a dilatation of the vessels[27,28]. Flow-mediated dilatation can be induced by reactive hyperaemia following the occlusion of the upper arm by a blood-pressure cuff and is the basis of the non-invasive assessment of endothelial function[8]. This test can be used as a reliable indicator of the

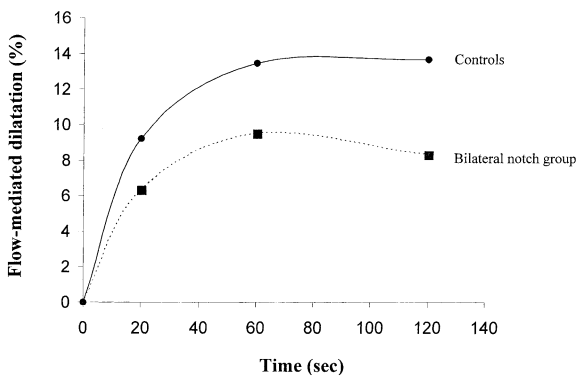


**Fig. 1.** Flow-mediated vasodilatation in pregnant women with bilateral uterine artery notches and in controls.

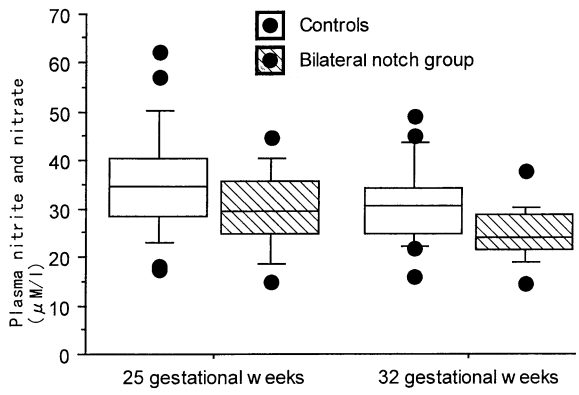


**Fig. 2.** Plasma nitrite and nitrate in pregnant women with bilateral uterine artery notches and in controls.

ability of endothelial cells to release nitric oxide[29]. It has been demonstrated that flow-mediated dilatation relies on the ability of the endothelium to release nitric oxide probably due to shear stress, since it can be partially blocked by $N^G$-monomethyl-L-arginine (L-NMMA), a specific inhibitor of nitric oxide synthase[30]. During normal pregnancy, flow-mediated dilatation and vascular nitric oxide activity in humans are enhanced[31,32]. The most likely explanation for this finding is the increased production of nitric oxide, rather than enhanced responsiveness to nitric oxide[33]. A significant correlation between flow-mediated dilatation in pregnant women and the gestational age was found in a study by Savvidou *et al.*[32] Flow-mediated dilatation was substantially increased from at least 10 weeks of gestation until 30 weeks.

Our finding of decreased flow-mediated dilatation in normotensive pregnant women with high resistance in the uteroplacental circulation indicates a certain degree of endothelial dysfunction in these patients. Furthermore, whereas in controls the flow-mediated dilatation rose continuously until two minutes after cuff deflation, in women with bilateral uterine artery notches the flow-mediated dilatation reached a peak at one minute after cuff deflation and than decreased ($P = 0.02$) (Fig. 1). Women of the bilateral notch group were not able to sustain the vasodilatation induced by reactive hyperaemia. This observation further supports the hypothesis of endothelial dysfunction in normotensive pregnant women with bilateral uterine artery notching, since nitric oxide appears to influence the time course of reactive hyperaemia. In the presence of nitric oxide, forearm blood flow is maintained at higher levels for a longer period after ischemia[34]. An important question is whether this dysfunction of endothelium was present before the women became pregnant and whether it prevailed after pregnancy. Besides the failure of trophoblastic invasion into spiral arteries, the reduced capacity of endothelial cells to release nitric oxide might contribute to the development of an abnormal uteroplacental circulation with high resistance to flow.

Our finding of lower blood levels of $NO_3^-$ and $NO_2^-$ in the women of the bilateral notch group seem to support the hypothesis of endothelial dysfunction. Similar findings were reported by Hata *et al.*[35] who found that maternal nitrate and nitrite blood concentrations were significantly lower in pregnancies with small for gestational age fetuses than those in pregnancies with AGA fetuses. There is also evidence for abnormal production of nitric oxide in pregnancies complicated by pre-eclampsia. However, the data on blood levels of nitrite and nitrate in women with pre-eclampsia are conflicting. There have been reports of either decrease[36], increase[37–39] or no change[40] in blood levels of nitrite and nitrate. The possible explanations for these discrepancies are differences in dietary precautions, sample preparation, study population, gestational age at sampling, use of antihypertensive drugs and shear stress.

In conclusion, there were no differences in mechanical properties of the vessel walls between healthy normotensive pregnant women with bilateral uterine artery notches and controls. In pregnant women with high resistance in the uteroplacental circulation, the flow-mediated dilatation and the ability to sustain vasodilatation was significantly reduced. This finding was supported by the lower plasma levels of nitrite, an indicator of systemic nitric oxide production, and further suggests that endothelial nitric oxide may play a significant role in maintaining low vascular resistance during pregnancy. Thus, healthy normotensive pregnant women with bilateral uterine artery notches have an altered vascular function. Whether the endothelial dysfunction is associated with pregnancy only, or it is present before and/or after pregnancy remains to be determined.

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