ORIGINAL ARTICLE

# Uterine artery Doppler velocimetry and obstetric outcomes in connective tissue diseases diagnosed during the first trimester of pregnancy

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## ABSTRACT

**Objective** To evaluate the effect of connective tissue disease (CTD) diagnosed during the first trimester on uterine arteries (UtA) Doppler velocities and on pregnancy outcomes.

**Method** Pregnant women were screened for CTDs during the first trimester, using a questionnaire, testing for autoantibodies, rheumatologic examination and UtA Doppler evaluations.

**Results** Out of 3932 women screened, 491 (12.5%) were screened positive at the questionnaire; of them, 165(33.6%) tested positive for autoantibodies, including 66 eventually diagnosed with undifferentiated connective tissue disease (UCTD), 28 with a definite CTD and 71 with insufficient criteria for a diagnosis. Controls were 326 women screened negative for autoantibodies. In logistic analysis, women diagnosed with either UCTD (OR = 7.9, 95% CI = 2.3–27.3) or overt CTD (OR = 24.9, 95% CI = 6.7–92.4), had increased rates of first trimester bilateral UtA notches compared with controls. The rates of bilateral UtA notches persisting in the second (15/94 vs 0/326, $p < 0.001$) and third trimesters (7/94 vs 0/326, $p < .001$) were higher among women with CTDs than in controls. The risk of complications (preeclampsia, fetal growth restriction, prematurity, diabetes, fetal loss) was higher (OR = 7.8, 95% CI = 3.6-17.0) among women with CTDs than in controls.

**Conclusion** Women with undiagnosed CTDs have higher rates of bilateral UtA Doppler notches throughout pregnancy and increased rates of adverse pregnancy outcomes than controls. © 2012 John Wiley & Sons, Ltd.

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## INTRODUCTION

Connective tissue diseases (CTDs) are a group of heterogeneous disorders characterized by an immunological reaction against self antigens, autoantibody production and immuno-complex deposition onto sensitive tissues.[1] Women with systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), rheumatoid arthritis (RA) and systemic sclerosis (SSc) pre-existing pregnancy are at an increased risk of preeclampsia, pre-term delivery and fetal growth restriction (FGR).[2–4] Undifferentiated connective tissue disease (UCTD) may be associated with an increased risk of small for gestational age (SGA), pre-term delivery, preeclampsia and fetal loss.[5]

Uterine artery (UtA) Doppler examination can be used to indirectly assess trophoblast development and uteroplacental perfusion.[6,7] Uteroplacental circulation develops through trophoblast invasion starting at 8 to 10 weeks with endovascular plugging and destruction of the muscoloelastic media of intradecidual segments of the spiral arteries, subsequently involving also the inner third of their myometrial segments.[6,7] Abnormal uteroplacental circulation, as assessed with UtA Doppler velocimetry, has been linked to pregnancy complications such as hypertension, FGR and early pregnancy failure, both in women at high risk[8] and in the general population.[9,8,10,11] Complications of pregnancy such as FGR or preeclampsia are considered the results of an inadequate trophoblast invasion of spiral arteries and impaired perfusion through the fetal-placental unit.[12] In pregnancies complicated by preeclampsia or FGR, there is a superficial invasion of uterine spiral arteries with an increased resistance in Doppler flow velocity as early as 10 to 11 weeks of pregnancy.[13] In longitudinal studies, increased Doppler pulsatility of uterine arteries persisting through the second trimester of pregnancy was associated with an increased risk of preeclampsia, FGR and stillbirth.[7] In most cases, increased UtA resistance undergoes normalization as gestation advances. However, about 30% of women with persistently abnormal UtA Doppler findings in the early third

 

trimester are at an increased risk of pregnancy complications.[14] In pregnancies complicated by already established SLE and APS, abnormal UtA Doppler waveforms between 20 and 30 weeks predict later adverse events.[15–20] In previous studies, we have found that a two-step process using a screening questionnaire was a reliable method to screen for undiagnosed CTD during the first trimester of pregnancy.[5,21] In the present study, we have tested whether CTD diagnosed during the first trimester of pregnancy are associated with UtA Doppler findings suggesting inadequate trophoblastic invasion.

## MATERIALS AND METHODS

This prospective cohort study was conducted on pregnant women at the time of screening for Down syndrome at 11 to 13 + 6 weeks from May 2005 to April 2011. Because this was a pilot study involving only few members of the staff, we restricted the enrolment only to women attending the clinic each Friday during a 6-year period. The study was approved by the local Institutional Review Board of our Department. Women with known autoimmune rheumatic disease, inherited thrombophilia or pregestational diabetes were excluded from the study.

Prior to the medical evaluation, each woman was asked to complete the screening questionnaire, taking into account the most common symptoms of CTD according to commonly used classification criteria for SLE, RA, primary Sjogren's syndrome (SS), SSc, APS and UCTD.[21]The screening questionnaire includes ten items and takes between 5 and 7 min to complete (Table 1). Women who answered positively to one or more of the questions were tested for the presence of circulating autoantibodies including anti-nuclear antibody (ANA), anti-double-stranded DNA (dsDNA), anti-extractable nuclear antigen (ENA), anticardiolipin antibody (aCL), anti-β2 glycoprotein I antibodies (aβ2GPI) and lupus anticoagulant (LA) according to standardized methods.[22]

To ensure random sampling, the first four consecutive women with negative responses each month were tested for autoantibodies and served as controls. Cases and controls were referred to the Rheumatology Unit of our hospital for further clinical assessment including a careful history and a physical examination. Both cases and controls were followed for prenatal care and delivered at our institution.

Table 1 Questionnaire to screen for connective tissue disorders. Women answer yes or no to all of the questions

| |
|---|
| 1. Have you ever had generalized or localized reddening of your skin after exposure to sunlight? |
| 2. Have you ever had an obvious or prominent rash on your cheeks or nose? |
| 3. Do your hands or feet become white in the cold and then blue or pink? |
| 4. (a) Have you ever had painful and swollen joints? |
| (b) Do you suffer from stiffness lasting 1 h or more in the morning? |
| 5. Have you ever had pericarditis or pleuritis? |
| 6. Do you have a dry mouth? |
| 7. Do you feel like you have sand in your eyes? |
| 8. Have you ever had painful white mouth ulcers? |
| 9. Have you ever had thrombophlebitis? |
| 10. Have you had two or more miscarriages or stillbirths? |

First trimester ultrasound evaluation was performed at enrolment, before the results of anti-antibody testing was known. Doppler velocimetry of UtA was evaluated using 3.5 to 5 Mhz curvilinear transabdominal probe, and the size of the sampling gate was set to 2 mm. A mid-sagittal section of the uterus was examined and the cervical canal was identified. The probe was moved laterally until the para-cervical vascular plexus was seen. Color Doppler was turned on, and the UtA was identified as it turned cranially to make its ascent to the uterine body. Measurements were taken at this point, before the UtA branched into the arcuate arteries. Once it was ensured that the angle of insonation was $<60°$, the pulsed Doppler gate was placed over the vessel, and the signal was recorded until at least three consecutive flow velocity waveforms of good quality were obtained. The mean pulsatility index (PI) and resistance index (RI) for left and right UtA were obtained by averaging the value of three consecutive measurements. The presence of diastolic notching (defined as a dip in UtA waveform in early diastole) was also recorded. Abnormal UtA Doppler was defined by the presence of bilateral notching or by mean RI and PI above the 95th percentile 22 to 23. Doppler velocimetry of UtA and, in the third trimester, of umbilical arteries, were performed at 19 to 21 and 29 to 32 weeks of pregnancy.

ANAs were tested by a standard indirect immunofluorescence technique using a BX 51 Olympus fluorescence microscope at $\times 40$ magnification. Serum was first diluted 1:80 in phosphate-buffered saline (PBS) and overlaid onto fixed Hep-2 cell slides (Immuno Concept, Sacramento, CA, USA) in a moist chamber for 30 min at room temperature. Slides were then rinsed and washed twice in PBS for 10 min. A fluorescent-labeled antibody specifically directed towards human immunoglobulin G (IgG) (g chains) (Delta Biologicals, Pomezia, Italy) was used as the fluorescent conjugate. The positive samples (titre $\geq$ 1:80) were evaluated at increasing dilutions in PBS up to 1:640. Anti-dsDNAs were determined by both indirect immunofluorescence and a quantitative enzyme-linked immunosorbent assay (ELISA). The immunofluorescence assay was performed at 1:10 serum dilution in PBS using Crithidialuciliae as the substrate (INOVA, San Diego, CA, USA) and fluorescent-labeled anti-human IgG (g-chain specific) as the fluorescent conjugate. ELISA was performed using a commercially available kit (Axis-Shield, Dundee, UK). Alkaline phosphatase-labeled murine monoclonal antibodies to both human IgG and IgM (heavy and light chains) were used. The absorbance was read at 550 nm. Serum samples were evaluated in triplicate, and the median value was considered. The upper limit of normal was 30 UI/mL. ENA antibodies were evaluated in triplicate by commercially available ELISA kits. Single ENA specificities were investigated: Sm, RNP, Ro/SSA, La/SSB, Scl-70 and Jo1. Commercially available ELISA kits (OrgentecDiagnostika, Mainz, Germany) were used to detect aCL (IgG and IgM) and aβ2GPI (IgG and IgM) by means of a peroxidase-conjugated solution of either polyclonal rabbit anti-human IgG (heavy and light chains) or polyclonal rabbit anti-human IgM (heavy and light chains). The absorbance was read at 450 nm. Serum samples were evaluated in triplicate; the upper limits of normal were 10 U/mL for IgGaCL, 7 U/mL for IgMaCL and 8 U/mL for both aβ2GPI IgG and IgM. LA was assayed by activated partial thromboplastin

 

time, diluted Russell's viper venom time and kaolin clotting time according to published guidelines.[23]

A complete follow-up of pregnancy was obtained in all patients, with the following variables recorded: gestational age at delivery, birth weight, FGR, SGA infant, preeclampsia (PE) or gestational hypertension (GH), fetal loss, pre-term delivery and rate of Cesarean section. FGR was defined as fetal abdominal circumference below the 10th percentile of our local intrauterine growth curve. SGA was defined as a sex-adjusted birth weight below the 10th percentile of the Italian population.[24] GH was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg on at least two occasions at least 6 h apart, occurring after 20 weeks of gestation.[25] PE was defined as hypertension plus proteinuria (300 mg or more in a 24-h period).

Statistical analyses were carried out with the Mann–Whitney *U*-test and chi-square analysis to compare continuous and categorical variables, respectively. One-way ANOVA with post hoc Bonferroni tests were used to compare differences of normally distributed variables between the groups. Spearman Rho was used to test for a linear trend. Partitioning of chi-square statistics with Bonferroni correction for multiple comparisons was used to evaluate statistical significance of pairwise comparisons in $2 \times K$ tables. Multinomial logistic regression analysis was used to test for the association between clinical categories of patients and perinatal variables adjusting for potential confounders (maternal age and parity, smoking during pregnancy, fetal gender).

## RESULTS

During the study period, we enrolled 4091 women; 159 (3.9%) did not complete the questionnaire and were excluded from the study, leaving 3932 subjects for the final analysis. A total of 491 (12.5%) patients answered positively to one or more items of the questionnaire and were tested for autoantibodies, which were positive in 165of them (33.6%). After a careful rheumatologic evaluation and follow-up for 6 months to 1 year, 28 of the 491 subjects with a positive questionnaire (5.7%) were diagnosed with an overt CTD (SLE, RA, SS, SSc, polymiosites/dermatomiosites, mixed connective tissue diseases, APS; group D), 66 (13.4%) were diagnosed with UCTD (group C), and 71 (14.4%) had insufficient criteria for a diagnosis of CTD (group B). All these patients were positive for one or more of the autoantibodies tested. The remaining 326 women with a positive questionnaire tested negative for autoantibodies and rheumatologic examination and were excluded from the study. Out of the 362 asymptomatic control subjects recruited, 36 (9.9%) refused to be tested for autoantibodies and were excluded from the study, leaving 326 subjects for final analysis (group A). The overall prevalence was 0.18% for SLE (7/3932), 0.23% for SS (9/3932), 0.15% for RA (6/3932), 0.13% for APS (5/3932) and 0.03% for SSc (1/3932). UCTD was the most frequent rheumatologic condition with a prevalence of 1.7% (66/3932).

The frequency of the symptoms in the three groups of cases (insufficient criteria for diagnosis, previously undiagnosed UCTD or undiagnosed overt CTD) is reported in Table 2. Partitioning of chi-square indicated that painful joints ($p < .001$) and dry mouth ($p < .001$) were significantly more frequent among subjects with a definite diagnosis as compared with those with rheumatologic symptoms but without a definite rheumatic diagnosis. Photosensitivity ($p = 0.009$), erythema ($p = 0.014$) and Raynaud's phenomenon ($p = 0.002$) were more frequent among women with UCTD than in subject without a definite rheumatic diagnosis.

There were 36/491 patients (7.9%) treated during pregnancy: 18/66 (27.7%) UCTD, 6/9 (66.6%) SS, 5/5 (100%) APS, 4/7 (57, 14%) systemic lupus erythematosus (LES) and 3/6 (50%) AR. Patients affected by APS or UCTD with antiphospholipid autoantibodies were treated with acetilsalicilic acid (ASA) and low-molecular weight heparin (LMWH), at the diagnosis of APS or at the detection of antiphospholipid autoantibodies, so not before 14 to 16 weeks of gestation. Patients with rheumatologic symptoms were treated with corticosteroids alone or in association with ASA or Hydrossychloroquine, as in AR or in LES or in SS.

The main characteristics of our population are reported in Tables 3 and 4. Maternal age was higher among women with an overt rheumatic disease than in negative controls (Bonferroni post hoc test = 0.016). Gestational age, birth weight and birth

Table 2 **Rates of symptoms among women with insufficient criteria for a diagnosis of rheumatic disease (Group B), previously undiagnosed undifferentiated connective tissue diseases (Group C) and undiagnosed over rheumatic diseases (Group D)**

| | Group B *N* = 71 (%) | Group C *N* = 66 (%) | Group D *N* = 28 (%) | *P*-value * Group D + C versus B | *P*-value * Group C versus B |
|---|---|---|---|---|---|
| Photosensitivity | 23 (32.4) | 38 (57.6) | 13 (46.4) | 0.008. | 0.012 |
| Erythema/malar rash | 11 (15.5) | 24 (36.4) | 8 (28.6) | 0.012 | 0.02 |
| Raynaud's phenomenon | 14 (19.7) | 31 (50.0) | 8 (28.6) | 0.005 | 0.003 |
| Tender/swollen joints | 4 (5.6) | 17 (25.7) | 13 (46.4) | <0.001 | 0.002 |
| Serositis | 1 (1.4) | 1 (1.5) | 1 (3.6) | 0.75 | 1.0 |
| Dry mouth | 6 (8.4) | 12 (18.2) | 19 (67.8) | <0.001 | 0.13 |
| Dry eyes | 6 (8.4) | 10 (15.1) | 5 (17.8) | 0.34 | 0.34 |
| Painful mouth ulcers | 5 (7.0) | 9 (13.6) | 2 (7.1) | 0.38 | 0.32 |
| Thrombophlebitis | 1 (1.4) | 2 (3.0) | 2 (7.1) | 0.32 | 1.0 |
| Pregnancy loss (≥2) | 12 (16.9) | 6 (9.1) | 4 (14.3) | 0.69 | 0.27 |

* *P*-values are corrected for multiple comparisons by Bonferroni method.

Table 3 **Rates of maternal features and pregnancy outcomes in the study population**

| | Group A *N*=326 mean ± SD | Group B *N*=71 mean ± SD | Group C *N*=66 mean ± SD | Group D *N*=28 mean ± SD | *P*-value * Group D versus A | *P*-value Group C versus A | *P*-value Group C+D versus A | *P*-value Group C+D versus B |
|---|---|---|---|---|---|---|---|---|
| Maternal age (years) | 32.4 ± 4.5 | 32.7 ± 4.0 | 32.5 ± 4.6 | 34.0 ± 4.0 | 0.28 | 1.0 | 0.72 | 0.98 |
| Gestational age (weeks) | 38.9 ± 2.2 | 39.3 ± 1.5 | 37.9 ± 3.8 | 36.7 ± 5.8 | 0.001 | 0.004 | <0.0001 | <0.0001 |
| Birth weight (g) | 3278.6 ± 490.8 | 3220.3 ± 479.0 | 3035.6 ± 671.4 | 2918.2 ± 684.4 | 0.001 | 0.015 | <0.0001 | 0.05 |
| Z-score birth weight | 0.2 ± 1.0 | −0.2718 ± 1.04 | −0.2798 ± 1.0 | −0.4439 ± 0.89 | 0.038 | 0.033 | 0.021 | 0.12 |
| Z-score third trimester abdominal circumference | 0.1474 ± 0.84 | 0.0570 ± 0.87 | −0.1221 ± 1.05 | −0.0086 ± 0.94 | 1.0 | 0.18 | 0.09 | 0.94 |
| | *N* (%) | *N* (%) | *N* (%) | *N* (%) | | | | |
| Nulliparity | 160 (49) | 44 (61.9) | 42 (63.6) | 18 (64.3) | 0.72 | 0.18 | 0.016 | 0.81 |
| Smoking | 35 (10.7) | 7 (9.9) | 5 (7.6) | 3 (10.7) | 1.0 | 1.0 | 1.0 | 1.0 |
| Spontaneous abortion | 2 (0.6) | 3 (4.2) | 3 (4.5) | 3 (10.7) | 0.015 | 0.17 | 0.015 | 0.73 |
| Preeclampsia | 7 (2.14) | 0 | 8 (12.1) | 3 (10.7) | 1.0 | 0.7 | <0.0001 | 0.003 |
| Fetal growth restriction | 3 (0.92) | 0 | 4 (6.0) | 2 (7.1) | 0.025 | 0.09 | 0.001 | 0.037 |
| Small for gestational age | 25 (7.6) | 9 (12.6) | 10 (15.15) | 4 (14.3) | 1.0 | 0.41 | 0.05 | 0.86 |
| Prematurity < 34 weeks | 7 (2.15) | 0 | 4 (6.06) | 15 (53.6) | <0.0001 | 0.68 | <0.0001 | 0.001 |
| Cesarean section | 80 (24.5) | 18 (25.3) | 32 (48.48) | 12 (42.8) | 0.26 | 0.001 | <.0001 | 0.001 |
| Z-score AC < 2 SD | 1 (0.31) | 0 | 4 (6.06) | 1 (3.5) | 0.69 | 0.01 | 0.003 | 0.07 |
| Overall complications | 15 (4.6) | 5 (7.0) | 16 (24.24) | 10 (35.7) | 0.25 | <0.0001 | <0.0001 | 0.004 |

A = controls; B = insufficient criteria for a diagnosis; C = undifferentiated connective tissue diseases; D = overt rheumatic diseases.
* *P*-values are corrected for multiple comparisons by Bonferroni method.

Table 4 **Rates of uterine artery and umbilical artery Doppler findings in the study population**

| | Group A *N* = 326 mean ± SD | Group B *N* = 71 mean ± SD | Group C *N* = 66 mean ± SD | Group D *N* = 28 mean ± SD | *P*-value * Group D versus A | *P*-value * Group C versus A | *P*-value * Group C + D versus A | *P*-value * Group C + D versus B |
|---|---|---|---|---|---|---|---|---|
| PI UtA mean first trimester | 1.38 ± 0.19 | 1.35 ± 0.22 | 1.42 ± 0.31 | 1.65 ± 0.46 | 0.008 | 0.005 | <0.0001 | 0.001 |
| PI UtA mean second trimester | 0.97 ± 0.40 | 1.02 ± 0.35 | 1.16 ± 0.18 | 1.25 ± 0.22 | <0.0001 | <0.0001 | <0.0001 | 0.02 |
| PI UtA mean third trimester | 0.85 ± 0.35 | 0.79 ± 0.17 | 0.87 ± 0.12 | 0.91 ± 0.12 | 0.37 | 0.95 | 1.0 | 0.41 |
| RI UtA mean first trimester | 0.56 ± 0.09 | 0.59 ± 0.10 | 0.64 ± 0.12 | 0.77 ± 0.16 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| RI UA mean second trimester | 0.55 ± 0.12 | 0.54 ± 0.12 | 0.62 ± 0.09 | 0.69 ± 0.12 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| RI UA mean third trimester | 0.54 ± 0.11 | 0.53 ± 0.10 | 0.61 ± 0.08 | 0.68 ± 0.09 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| | *N* (%) | *N* (%) | *N* (%) | *N* (%) | | | | |
| UA bilateral notch first trimester | 8 (2.4) | 3 (4.2) | 9 (13.6) | 11 (39.3) | <0.0001 | 0.003 | <0.0001 | 0.002 |
| UA bilateral notch second trimester | 12 (3.6) | 5 (7.0) | 11 (16.6) | 8 (28.6) | <0.0001 | 0.002 | <0.0001 | 0.024 |
| UA bilateral notch third trimester | 8 (2.45) | 0 | 7 (10.6) | 3 (10.7) | 0.007 | 0.036 | 0.001 | 0.005 |
| PI Umb Art > 2 SD | 12 (3.6) | 2 (2.8) | 8 (12.12) | 4 (14.3) | 0.004 | 0.05 | 0.002 | 0.02 |

A = controls; B = insufficient criteria for a diagnosis; C = undifferentiated connective tissue diseases; D = overt rheumatic diseases.
* *P*-values are corrected for multiple comparisons by Bonferroni method.

weight *Z*-score were lower among women with either UCTD (Bonferroni post hoc test = 0.004, 0.015 and 0.033, respectively) or other definite rheumatic disease (Bonferroni post hoc test = <.001, <.001 and 0.038, respectively) compared with asymptomatic controls. There was a significant trend for reduced gestational age (Spearman Rho = −0.15, $p = 0.005$), birth weight (Spearman Rho = −0.167, $p = 0.002$) and birth weight Z-score (Spearman Rho = −0.13, $p = 0.02$) with respect to increasing severity of rheumatic disease (from asymptomatic to overt disease). Mean UtA PI and RI values were significantly higher among women with undiagnosed CTDs compared with control group ($p < 0.01$ for PI, $p < 0.05$ for RI in overt rheumatic diseases; $p < 0.001$ for PI and $p < 0.01$ in UCTD).

The detection of UtA bilateral notching at first trimester Doppler evaluation was more frequent in women with undiagnosed UCTD or overt rheumatic diseases than in asymptomatic controls ($p = 0.003$ and $p < 0.001$, respectively). In addition, compared with asymptomatic controls, subjects with UCTD or a definite diagnosis of rheumatic diseases had increased persistence of UtA bilateral notches throughout the second ($p = 0.002$ and $p < 0.001$) and third trimesters of pregnancy ($p = 0.036$ and $p = 0.007$, respectively).

Partitioning of chi-square statistics indicated that the prevalence of spontaneous abortions ($p = 0.015$) and overall pregnancy complications ($p < 0.001$) were significantly more frequent in women with previously undiagnosed rheumatic disease as compared with asymptomatic controls. The rates of pre-term delivery less than 34 weeks of gestation ($p = 0.001$) and overall complications ($p = 0.004$) were also higher among women with overt rheumatic diseases than in those without a definite diagnosis.

Compared with asymptomatic controls, patients with previously undiagnosed UCTD had higher rates of preeclampsia ($p = 0.006$), FGR ($p = 0.01$), increased (>2 SD) umbilical artery PI ($p = 0.05$) and overall pregnancy complications ($p < .001$). The rates of preeclampsia and overall obstetric complications were higher among UCTD patients even when compared with subjects without a definite diagnosis of rheumatic disease ($p = 0.003$ and $p = 0.027$, respectively).

Irrespective of the groups studied, the prevalence of preeclampsia (5/31 vs 13/460, OR = 6.6, 95% CI = 1.7–21.6), FGR (6/31 vs 30/460, OR = 3.4, 95% CI = 1.1–9.5) and overall complications (14/31 vs 32/460, OR = 11, 95% CI = 4.5–26) were significantly higher among women with UtA bilateral notches recorded during the first trimester as compared with those with either absent ($n = 388$) or unilateral ($n = 72$) notch. Statistically significant increased risks of preeclampsia (9/36 vs 9/455, OR = 16.5, 95% CI = 5.3–50.6), FGR (6/36 vs 30/455, OR = 2.8, 95% CI = 1–7.1) and overall adverse outcomes (18/36 vs 28/455, OR = 15.3, 95% CI = 7–32.5) were also found among

 

women with UtA notches persistent throughout the second trimester. Finally, among the 94 patients with either UCTD or other CTD, the risk of adverse pregnancy outcome was significantly higher among those with bilateral UtA notches recorded during the first (13/20 vs 13/75, OR = 8.9, 95% CI = 2.6–31.0) and second trimesters (13/20 vs 13/74, OR = 8.7, 95% CI = 2.6–30.5) or persisting through the second trimester (9/15 vs 6/79, OR = 18.3, 95% CI = 4.6–70.8) than among those with normal measurements. Interestingly, all seven cases with bilateral notches persisting through the third trimester had a CTD (four UCTD and three an overt rheumatic disease) and developed a pregnancy complication (five preeclampsia and two FGR). The corresponding prevalence of adverse outcome among the 87 subjects without third trimester UtA notches was 9.2% (8/87, $p < .001$ compared with those with bilateral notches).

The associations between clinical categories of rheumatic diseases and perinatal variables were adjusted for maternal age and parity, smoking during pregnancy (yes vs no) and fetal gender by the use of multinominal logistic regression analysis (Table 5). Compared with asymptomatic controls, women diagnosed with either UCTD or overt rheumatic diseases had lower gestational age and birth weight, increasing rates of first and second trimesters UtA bilateral notching, FGR, preeclampsia and overall complications of pregnancy. The risk of overall complications among women with any rheumatic diseases (UCTD and overt rheumatic diseases) diagnosed during the first trimester was 7.8 (95% CI = 3.6–17.0).

## DISCUSSION

In our study, we found that women with previously undiagnosed rheumatic diseases identified in the first trimester of pregnancy had higher rates of bilateral Ua notches through pregnancy and increased rates of adverse pregnancy outcome compared with asymptomatic controls.

In previous studies, we found that a first trimester screening approach including a self-reported questionnaire, autoantibody testing and rheumatologic evaluation was able to detect women with previously undiagnosed rheumatic diseases.[5,21] The main difference of this study compared with those of other authors[2,4,15,18] involves the type of population studied. The subjects recruited had previously undiagnosed CTDs, and they had been unidentified or identified later, without a specific screening study. Pregnancy complicated by symptomatic pre-existing CTDs are at increased risk of pregnancy loss, prematurity, preeclampsia and FGR.[1] Our study suggests that also women diagnosed with a CTD during the first trimester of pregnancy are at increased risk of abnormal placentation as evaluated by a longitudinal study of UtA Doppler PI.

Because of the inclusion criteria (ability to comprehend and compile the questionnaire, willingness to participate in a study with supplemental visits and blood drawings), women included in the study were relatively well-educated white Italian women. Because this group of women is at low-intermediate risk of adverse pregnancy outcome, results cannot be generalized to other populations. However, the prevalences of main pregnancy complications such as preeclampsia, FGR, prematurity and cesarean section were similar to those reported in other Italian studies among women attending obstetric ultrasonographic clinics.[7,11,26]

Second trimester bilateral Ua notches are significantly predictive of adverse pregnancy outcome among women with APS (14), SLE (13,15,27,29) or SS (30) pre-existing pregnancy. The rates of bilateral UtA notches persisting during second trimester among women with SLE or APS pre-existing pregnancy are between 15 and 26%.[15,17] In our series, the prevalence of

Table 5 **Associations between clinical variables, uterine artery (UtA) pulsatility index (PI) and categories of rheumatic diseases**

| | Group A<br>*N* = 326 | Group B<br>*N* = 71 | Group C<br>*N* = 66 | Group D<br>*N* = 28 |
|---|---|---|---|---|
| Gestational age | Reference | 1.1 (0.9–1.4) | **0.8 (0.7–0.96)** | **0.8 (0.7–0.96)** |
| Weight | Reference | 0.9 (0.9–1.0) | **0.9 (0.9–0.97)** | **0.9 (0.8–0.96)** |
| Z-score weight | Reference | 0.78 (0.58–1.05) | 0.78 (0.58–1.06) | 0.63 (0.40–0.98) |
| Preeclampsia | Reference | Undefined | 19.38 (3.87–17.0) | 12.51 (1.90–82.24) |
| Fetal growth restriction | Reference | Undefined | 8.0 (1.40–45.64) | 9.94 (1.28–77.4) |
| Prematurity less than 34 weeks | Reference | Undefined | 2.23 (0.51–1.72) | 6.15 (1.60–23.7) |
| UtA Notch first trimester | Reference | 2.78 (0.60–12.83) | 7.88 (2.28–27.25) | 24.91 (6.71–92.42) |
| UtA PI first trimester | Reference | 0.69 (0.18–2.66) | 3.15 (0.97–10.32) | 24.5 (5.91–101.32) |
| UtA Notch second trimester | Reference | 1.58 (0.53–4.70) | 3.74 (1.54–9.04) | 6.45 (2.22–18.73) |
| UtA PI second trimester | Reference | 1.53 (0.69–3.38) | 2.91 (1.38–6.10) | 4.62 (1.73–12.36) |
| UtA Notch third trimester | Reference | Undefined | 3.49 (1.20–10.17) | 3.62 (0.87–14.95) |
| UtA PI third trimester | Reference | 0.44 (0.13–0.49) | 1.12 (0.44–2.87) | 1.55 (0.46–5.181) |
| PI umbilical artery >95th centile | Reference | Undefined | 3.15 (1.45–11.4) | 4.82 (1.0–18.2) |
| Overall perinatal complications | Reference | 0.83 (0.17–4.08) | 8.55 (3.31–22.02) | 9.53 (3.0–30.24) |

A = controls; B = insufficient criteria for a diagnosis; C = undifferentiated connective tissue diseases; D = overt rheumatic diseases.
Odds ratios (OR) and 95% confidence intervals were obtained by multinomial logistic regression analysis including terms for categories of rheumatic disease as dependent variable and maternal age, parity, smoking (yes, no) and fetal gender as confounders.

bilateral UtA notches persisting from first to second trimester of pregnancy among subjects with either UCTD or other rheumatic diseases was 16% and was a significant risk factor for adverse pregnancy outcome despite early initiation of treatments such as aspirin or LMWH. This finding suggests that even when undiagnosed or in their early paucisymptomatic stages, CTDs cause a negative effect on placentation. These results are supported by a large population study which found that the rates of adverse pregnancy outcome such as stillbirth, prematurity, preeclampsia or FGR are increased in SLE subjects compared with unaffected controls, even before clinical appearance of disease, supporting a pre-disease state which could adversely influence pregnancy outcome.[27]

Many authors have studied the predictive role of first trimester UtA Doppler velocimetry both in high risk and unselected populations.[12,26,28–30] Plasencia *et al.*[31] found that UtA PI at 11 to 13 + 6 weeks' gestation provides sensitive prediction of the development of preeclampsia. Melchiorre *et al.*[32] investigated the relationship between first trimester UtA RI and subsequent delivery of SGA neonates or FGR, and they found that the sensitivity of first trimester UtA Doppler is greater for SGA with preeclampsia than it is for FGR alone. In high risk populations, the predictive role of first trimester UtA Doppler on the development of preeclampsia, although confirmed, seems lower than in unselected populations.[33,34] Because this is not a population study, we cannot compute a reliable predictive value of first trimester UtA Doppler, but the rate of first trimester bilateral notches was more than ten times higher among women with undiagnosed CTD than in asymptomatic controls. In addition, the rates of pregnancy complications among subjects with CTDs were significantly higher among women with first and second trimester UtA Doppler notches than in those without notches.

Increased resistance in UtA flow persisting through the second and third trimesters has been already studied both in unselected and high risk populations.[35,36] A recent study[36] in high risk pregnant patients suggests that subjects with persistently increased UtA resistance in the first half of pregnancy has the highest risk (10 to 20-fold increase) of developing early preeclampsia. Our data confirm these findings, suggesting that in a high risk population persistently increased UtA resistance during the first half of pregnancy is associated with an increased risk of early preeclampsia and FGR, and of adverse pregnancy outcome. From a biological point of view, it is possible that persistently elevated UtA resistance during the first half of pregnancy could reflect a severe and persistent impairment in trophoblast invasion of spiral arteries.[35]

As for the predicting role of increased UtA resistance persisting through the third trimester, Ghi *et al.*[37] reported that it is a marker of an increased risk of adverse pregnancy outcome in a low risk population, when compared with late normalization. The significance of this finding in high risk pregnancies has not been clearly defined, but our data suggest that at least among patients with CTDs, a persistence of bilateral notches through second and third trimester indicates a very high risk of adverse pregnancy outcome. In conclusion, in our study, women with previously undiagnosed rheumatic diseases identified in the first trimester of pregnancy had higher rates of bilateral uterine arteries notches through pregnancy and increased rates of adverse pregnancy outcome compared with asymptomatic controls. These results suggest that inadequate invasion of trophoblast leading to complications such as preeclampsia, prematurity and FGR are common among women with misdiagnosed or paucisymptomatic CTDs.

### WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Many authors have studied the predictive role of first trimester uterine artery Doppler velocimetry both in high risk and in unselected populations to predict adverse pregnancy outcomes.

### WHAT DOES THIS STUDY ADD?

- Our study suggests that women diagnosed with a connective tissue disease during the first trimester are at increased risk of adverse outcomes associated with abnormal placentation, as witnessed by abnormal findings at uterine artery Doppler at first, second and third trimesters, as well as higher rates of preeclampsia and FGR.

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