# Early, Incomplete, or Preclinical Autoimmune Systemic Rheumatic Diseases and Pregnancy Outcome

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*Objective.* To evaluate the impact of preclinical systemic autoimmune rheumatic disorders on pregnancy outcome.

*Methods.* In this longitudinal cohort study, patients were enrolled during the first trimester of pregnancy if they reported having had connective tissue disorder symptoms, were found to be positive for circulating autoantibodies, and on clinical evaluation were judged to have a preclinical or incomplete rheumatic disorder. The incidence of fetal growth restriction (FGR), preeclampsia, and adverse pregnancy outcomes in patients with preclinical rheumatic disorders was compared with that in selected controls, after adjustment for confounders by penalized logistic regression. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated.

*Results.* Of 5,232 women screened, 150 (2.9%) were initially diagnosed as having a suspected rheumatic disorder. After a mean ± SD postpartum follow-up of 16.7 ± 5.5 months, 64 of these women (42.7%) had no clinically apparent rheumatic disease and 86 (57.3%) had persistent symptoms and positive autoantibody results, including 10 (6.7%) who developed a definitive rheumatic disease. The incidences of preeclampsia/FGR and of small for gestational age (SGA) infants were 5.1% (23 of 450) and 9.3% (42 of 450), respectively, among controls, 12.5% (8 of 640) (OR 2.7 [95% CI 1.1–6.4]) and 18.8% (12 of 64) (OR 2.2 [95% CI 1.1–4.5]), respectively, among women with no clinically apparent disease, and 16.3% (14 of 86) (OR 3.8 [95%

CI 1.9–7.7]) and 18.6% (16 of 86) (OR 2.3 [95% CI 1.2–4.3]), respectively, among those with persisting symptoms at follow-up. Mean ± SD umbilical artery Doppler pulsatility indices were higher among women with no clinically apparent disease (0.95 ± 0.2) and those with persisting symptoms (0.96 ± 0.21) than in controls (0.89 ± 0.12) ($P = 0.01$ and $P < 0.001$, respectively).

*Conclusion.* In our study population, preclinical rheumatic disorders were associated with an increased risk of FGR/preeclampsia and SGA. The impact of these findings and their utility in screening for FGR/preeclampsia need to be confirmed in population studies.

Systemic autoimmune rheumatic diseases are associated with increased rates of adverse pregnancy outcomes, including spontaneous abortion, preeclampsia, fetal growth restriction (FGR), and prematurity (1). Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), undifferentiated connective tissue disease (UCTD), and other systemic autoimmune diseases are chronic diseases that progress over many years and are preceded by a long period of time with detectable autoantibodies but few symptoms (2,3). Final diagnosis of these diseases requires the presence of several signs and symptoms according to internationally validated classification schema (4). Most affected subjects, at least in the first stages of these diseases, have a limited number of laboratory abnormalities and clinical symptoms and usually do not meet classification criteria (4,5). There is a growing body of evidence that these preclinical phases can be associated with up-regulation of inflammatory cytokines and endothelial dysfunction leading to systemic adverse effects, such as accelerated atherosclerosis and cardiovascular and lung diseases (6,7).

Although retrospective epidemiologic data suggest that adverse pregnancy outcomes often antedate the subsequent development of SLE, RA, SSc, or antiphospholipid syndrome (APS), the effect of preclinical autoimmune

systemic diseases on pregnancy outcome has not been well studied. In a previous cohort study, using a 2-step approach with a self-reported questionnaire and autoantibody detection, we evaluated the effects of well-defined rheumatic diseases diagnosed during the first trimester on pregnancy outcome (8). The purpose of the present study, carried out using a similar approach, was to evaluate the effects of preclinical or incomplete autoimmune systemic rheumatic disorders detected during the first trimester of pregnancy on pregnancy outcome.

## PATIENTS AND METHODS

The study was approved by the local ethics committee. Subjects were recruited from among unselected pregnant women enrolled for prenatal care at our department during the first trimester of pregnancy. As this was a pilot cohort study conducted by only a few staff members, we restricted the enrollment to all women seen at the clinic for prenatal care on 1 day per week only (Mondays), during a 5-year period (May 2009 to June 2014). The criteria for enrollment were as follows: 1) singleton pregnancy, 2) prenatal care and delivery at our department, 3) fluency in the Italian language, 4) no previous diagnosis of or treatment for a CTD, and 5) absence of fetal malformations or chromosomal anomalies.

The characteristics of the study and the validation of the methods used have been reported elsewhere (8). Briefly, after informed consent was obtained and before the medical evaluation was conducted, each woman was asked to complete a screening questionnaire addressing symptoms of CTDs (Table 1). Women who answered "yes" to 1 or more of the questions were tested for the presence of circulating autoantibodies, including antinuclear antibody (ANA), anti–double-stranded DNA (anti-dsDNA), anti–extractable nuclear antigen (anti-ENA), anti-cardiolipin antibody (aCL), anti–$\beta_2$-glycoprotein I (anti–$\beta_2$GPI), and lupus anticoagulant (LAC), according to standardized methods as previously described (9). ANA was considered positive if the titer was $\geq$1:80. Rheumatoid factor and anti–citrullinated protein antibodies were not included in the screening autoantibody profile, but rather were tested only in patients with symptoms of arthritis found in the rheumatologic evaluation. Subjects with a positive questionnaire response (at least 1 item) and with a positive autoantibody test result constituted the initial population of cases. They were referred to the rheumatology unit of our hospital for further clinical assessment including careful history-taking and physical examination. Rheumatologists were unaware of the questionnaire results. Rheumatic diseases were classified according to widely used criteria for UCTD (10), RA (11), SLE (12), APS (13), Sjögren's syndrome (SS) (14), SSc (15), polymyositis/dermatomyositis (16), and mixed CTD (MCTD) (17).

The final population of cases for this study consisted of only patients with a suspected rheumatic disease (symptoms plus autoantibodies) who did not fulfill the above-mentioned criteria for a definite rheumatic disorder. In order to monitor for the evolution of rheumatic disorders during pregnancy, cases were followed up with clinical rheumatologic and laboratory evaluations every 1–2 months during pregnancy and every 6–12 months after delivery, depending on the severity of symptoms.

**Table 1.** Ten-item screening questionnaire for symptoms of a rheumatologic disorder

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 your 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 hour 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 2 or more miscarriages or stillbirths?

To ensure random sampling, the first 3 subjects after each index case who were without rheumatologic symptoms as assessed by questionnaire and were willing to participate in the study were tested for autoantibodies and served as the control group. After enrollment, cases and controls were followed up with monthly obstetric, clinical, and ultrasound evaluations. The mean uterine artery pulsatility index in the first and second trimester was evaluated according to standard methods (18). Pulsatility indices of uterine or umbilical arteries were considered abnormal when the values were higher than the 95th percentile of reference curves (18). FGR was diagnosed when the abdominal fetal circumference on ultrasonographic examination fell below the 10th percentile of the local reference curves, confirmed on at least 2 consecutive measurements obtained 2 weeks apart after the standard ultrasonography performed at 18–22 weeks of pregnancy, and the pulsatility index of the umbilical artery was higher than the 95th percentile of reference curves, signaling reduced perfusion of the fetal placental unit. Preeclampsia was diagnosed according to standard criteria (19). Small for gestational age (SGA) infants were diagnosed when birth weight was below the 10th percentile of customized Italian growth curves (20). Moderate-to-severe pregnancy complications included spontaneous abortion, preeclampsia, FGR, and delivery before 34 weeks' gestation.

Statistical analyses were carried out with one-way analysis of variance and the Bonferroni post hoc test to compare continuous variables between groups. Log-transformed data were used when the normality assumption was not met. Categorical variables were compared by Pearson's chi-square test. Partitioning of chi-square statistics with Bonferroni correction for multiple comparisons was used to evaluate the statistical significance of pairwise comparisons in $2 \times K$ tables. Associations between the diagnostic category of the rheumatic disorder and pregnancy outcomes were evaluated using penalized logistic regression analysis with odds ratios (ORs) and 95% confidence intervals (95% CIs), adjusted for potential confounders (Stata 13.0 for Windows). Penalized maximum likelihood estimation has been proposed as a suitable method of regression analysis for uncommon events (21). Logistic equations included complications of pregnancy (preeclampsia, FGR, SGA, other moderate or severe pregnancy complications) as outcome variables and first-trimester smoking (yes/no), previous history of a low-birth-weight (<2,500-gm) infant, and the diagnostic category of the

**Table 2.** Associations between rheumatologic symptoms and autoantibody results*

| Symptom | Autoantibody | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | ANA (n = 119) | Anti-dsDNA (n = 2) | IgG aCL (n = 9) | IgM aCL (n = 22) | IgG anti-$\beta_2$GPI (n = 8) | IgM anti-$\beta_2$GPI (n = 15) |
| Photosensitivity (n = 85) | 63 (52.9) | 2 (100) | 4 (44.4) | 12 (54.5) | 4 (50) | 8 (53.3) |
| Erythema/malar rash (n = 81) | 63 (52.9) | 2 (100) | 7 (77.8) | 16 (72.7) | 3 (37.5) | 8 (53.3) |
| RP (n = 78) | 60 (50.4) | 1 (50) | 5 (55.6) | 13 (59.1) | 5 (62.5) | 10 (66.7) |
| Tender/swollen joints (n = 49) | 41 (34.5) | – | – | 3 (13.6) | 3 (37.5) | 4 (26.7) |
| Serositis (n = 5) | 5 (4.2) | – | – | – | – | – |
| Dry mouth (n = 14) | 9 (7.6) | – | 1 (11.1) | 3 (13.6) | – | 2 (13.3) |
| Dry eyes (n = 22) | 18 (15.1) | – | 1 (11.1) | 1 (4.5) | | 1 (6.7) |
| Mouth ulcers (n = 27) | 22 (18.5) | – | 1 (11.1) | 3 (13.6) | 2 (25) | 1 (6.7) |
| Thrombophlebitis (n = 5) | 4 (3.4) | – | – | 1 (4.5) | – | 1 (6.7) |
| Pregnancy loss (≥2) (n = 8) | 6 (5) | – | – | 1 (4.5) | 3 (37.5) | 3 (20) |
| >2 symptoms (n = 63) | 47 (39.5) | 2 (50) | 2 (22.2) | 8 (36.4) | 4 (50) | 5 (33) |

* Values are the number (%). ANA = antinuclear antibody; anti-dsDNA = anti−double-stranded DNA; aCL = anticardiolipin antibody; anti-$\beta_2$GPI = anti−$\beta_2$-glycoprotein I; RP = Raynaud's phenomenon.

autoimmune rheumatic disease (control/no clinically apparent disease/persisting rheumatic disorder) as explanatory variables. Finally, to evaluate the predictors of persistence of rheumatic disorders during follow-up among women with a suspected rheumatic disorder at enrollment, we used stepwise logistic regression analysis. Symptoms as depicted by questionnaire and autoantibody testing (ANA, anti-dsDNA, aCL, and anti-$\beta_2$GPI antibodies) were inserted into the logistic model as initial explanatory variables, and persistence of rheumatic disorders during follow-up as the outcome measure.

## RESULTS

During the study period, of 5,451 women enrolled for prenatal care, 5,232 (96%) provided consent to participate in the study and completed the questionnaire. The proportion of subjects with rheumatologic symptoms according to the questionnaire responses was 9.8% (511 of 5,232). Of the 511 subjects with symptoms, 349 (68.3%) tested positive for autoantibodies and were sent to the rheumatology unit for evaluation and follow-up. The 162 subjects who had symptoms but were negative for autoantibodies were, after clinical evaluation, judged to be negative for a preclinical rheumatic disorder and were discharged from the study. The majority of subjects in this subgroup (86 of 162 [53.1%]) reported only 1 symptom; in most cases this was an ocular symptom (57 of 162 [35.2%]) or photosensitivity (39 of 162 [24.1%]).

Of the 349 women with symptoms who tested positive for autoantibodies, 199 (57%) were diagnosed as having a well-defined rheumatic disorder. Among the entire initial group of 5,232 subjects, the prevalence of the different rheumatic diseases diagnosed was 0.4% for RA (19 women), 0.31% for SS (16 women), 0.27% for primary APS (14 women), 0.25% for SLE (13 women), and 0.08% for other miscellaneous disorders (1 subject

with SSc, 1 with MCTD, 1 with granulomatosis with polyangiitis [Wegener's], and 1 with monoarticular arthritis). UCTD was diagnosed in an additional 2.5% of the subjects (131 women). Since the purpose of the study was to evaluate the effect of preclinical or incomplete rheumatic disorders on pregnancy outcome, these subjects with a well-defined rheumatic disease were excluded from further analyses. The final population of cases used in the study was thus composed of the remaining 150 subjects who had symptoms and were positive for autoantibodies but did not meet criteria for definite diagnosis of a specific rheumatic disease.

The distribution of the type of antibodies detected among cases, according to symptoms, is reported in Table 2. Eighty-seven (58%) of the cases reported 2 symptoms and the remaining 63 (42%) reported >2. None of the cases tested positive for anti-ENA or LAC. One hundred nineteen cases (79.3%) were positive for ANA: 82 (54.7%) at a titer of ≥1:80 and 37 (24.7%) at a titer of ≥1:160. Among the 450 controls, 25 subjects (5.6%) tested positive for ANA: 19 at a titer of ≥80 and 6 at a titer of ≥160. After a mean ± SD follow-up of 22.8 ± 4.8 months from entry into the study (median number of rheumatologic visits 7 [range 4–11]) and 16.7 ± 5.5 months postpartum, 64 of the cases (42.7%) had no symptoms and were classified as the no clinically apparent disease group, 10 (6.7%) were diagnosed as having a definite autoimmune rheumatic disease (4 with RA, 4 with stable UCTD, and 2 with primary APS), and 76 (50.7%) had persistent rheumatic symptoms and positive autoantibody results but still did not meet criteria for a definite rheumatic disease. Sixty-seven of the women in the latter group were classified as having "early" UCTD and 9 as having "non-criteria APS" (a disorder resembling APS but not fully meeting clinical and

**Table 3.** Sociodemographic variables in the cases and controls*

| | | Cases | | |
| | Controls (n = 450) | No clinically apparent disease (n = 64) | Persistence of symptoms (n = 86) | Overall (n = 150) |
| --- | --- | --- | --- | --- |
| Maternal age, mean ± SD years | 33.49 ± 4.22 | 33.39 ± 4.03 | 33.54 ± 4.77 | 33.47 ± 4.45 |
| BMI, mean ± SD kg/m$^2$ | 23.07 ± 3.44 | 22.75 ± 3.17 | 22.74 ± 3.12 | 22.74 ± 3.13 |
| Nulliparous | 315 (70) | 42 (65.6) | 54 (62.8) | 96 (64) |
| First-trimester smoking | 61 (13.6) | 14 (21.9) | 15 (17.4) | 29 (19.3) |
| Education | | | | |
|   <5 years | 3 (0.7) | 1 (1.6) | 2 (2.3) | 3 (2) |
|   6−8 years | 73 (16.2) | 8 (12.5) | 11 (12.8) | 19 (12.7) |
|   9−13 years | 244 (54.2) | 36 (56.2) | 40 (46.5) | 76 (50.7) |
|   >13 years | 130 (28.9) | 19 (29.7) | 33 (38.4) | 52 (34.7) |
| Chronic hypertension | 3 (0.7) | − | 1 (1.2) | 1 (0.6) |
| Previous low-birth-weight infant (<2,500 gm) | 3 (0.7) | 3 (4.7) | 1 (1.2) | 4 (2.6) |

* Except where indicated otherwise, values are the number (%). There were no statistically significant differences between the overall case group and the control group. BMI = body mass index.

laboratory criteria for the disease). During the postpartum follow-up, 57 (89.1%) of the 64 women classified as having no clinically apparent disease were intermittently or persistently negative for autoantibodies, and 7 (10.9%) were persistently positive for ANA (3 at a titer of 1:80 and 4 at a titer of 1:160).

Factors found to be independently associated with an increased likelihood of persistence of symptoms, as a part of either a definite or a preclinical rheumatic disorder, were ANA positivity at entry (76 of 86 women versus 43 of 64 women; OR 5.1 [95% CI 2–13.4]), IgG aCL positivity at entry (7 of 86 versus 2 of 64; OR 8.6 [95% CI 1.4–52.3]), and arthralgia/swollen joints (35 of 86 versus 14 of 64; OR 2.8 [95% CI 1.3–6.2]). The specificity of these 3 parameters in the prediction of persistence of an autoimmune disorder was 92.1% (95% CI 84.1–96.9).

During the follow-up period after the index pregnancy in the group of women with no clinically apparent disease, there were 4 new pregnancies (1 complicated by severe preeclampsia and preterm birth at 29 weeks' gestation), with reactivation of autoimmunity and ANA results returning to positive after having previously become negative. In the group of women with persistent rheumatic disorders, there were 7 new pregnancies (1 complicated by a spontaneous abortion), all characterized by the persistence of rheumatic symptoms and an increase in ANA titer compared with pre-pregnancy values.

The main demographic and clinical variables in cases and controls are shown in Table 3. The prevalence of smoking during the first trimester of pregnancy and that of a history of a previous low-birth-weight infant were marginally higher among cases than among controls ($P = 0.09$ and $P = 0.07$, respectively), but none of the demographic or variables analyzed differed significantly between cases and controls.

The outcomes of pregnancy according to the presence of rheumatic disease symptoms at follow-up are reported in Table 4. Compared with controls, cases had increased rates of defective placentation as suggested by the higher Doppler pulsatility indices of uterine arteries during the first and second trimesters and of the umbilical artery during the third trimester of pregnancy. As a consequence, cases had increased rates of FGR and SGA and lower infant birth weight and birth weight centile compared with controls. Among the 86 cases with persistence of rheumatic symptoms, the mean ± SD infant birth weight and birth weight centile were 2,892 ± 598 gm and 30.4 ± 32.9, respectively ($P = 0.05$ and $P = 0.02$ versus controls) in the 10 women with a follow-up diagnosis of a rheumatic disease and 3,097 ± 523 gm and 41.4 ± 23.8, respectively ($P = 0.004$ and $P = 0.006$ compared with negative controls) in the 76 women without a definite diagnosis. Mean ± SD umbilical artery Doppler pulsatility indices were higher among women with no apparent disease (0.95 ± 0.2) and in those with persisting symptoms (0.96 ± 0.21) than in controls (0.89 ± 0.12) ($P = 0.01$ and $P < 0.001$, respectively, compared with cases). Mean ± SD umbilical artery pulsatility indices were also higher among symptomatic women, both with and without a definite diagnosis (1.03 ± 0.23 and 0.95 ± 0.21, respectively; $P = 0.004$ and $P = 0.001$ versus controls).

Moderate or severe pregnancy complications (spontaneous abortion, preeclampsia, FGR, delivery before 34 weeks' gestation) were more common among women with rheumatic symptoms than among controls.

**Table 4.** Pregnancy outcomes in the cases and controls*

| | Controls (n = 450) | Cases | | | P, overall case group vs. controls |
| | | No clinically apparent disease (n = 64) | Persistence of symptoms (n = 86) | Overall (n = 150) | |
| --- | --- | --- | --- | --- | --- |
| Gestational age at delivery, mean ± SD weeks | 39.1 ± 1.8 | 39.0 ± 1.81 | 38.88 ± 2.0 | 38.9 ± 1.92 | 0.57 |
| Birth weight, mean ± SD gm | 3,270.35 ± 483.2 | 3,102.31 ± 446.6† | 3,073.87 ± 525.6† | 3,086 ± 492.1 | 0.000 |
| Birth weight, mean ± SD centile | 51.15 ± 28.44 | 40.26 ± 26.38† | 40.26 ± 25.04† | 40.26 ± 25.55 | 0.000 |
| First-trimester uterine artery pulsatility index, mean ± SD | 1.16 ± 0.38 | 1.41 ± 0.36† | 1.35 ± 0.43† | 1.37 ± 0.42 | 0.000 |
| Second-trimester uterine artery pulsatility index, mean ± SD | 0.87 ± 0.37 | 1.05 ± 0.27† | 0.97 ± 0.30† | 1.00 ± 0.29 | 0.000 |
| Third-trimester umbilical artery pulsatility index, mean ± SD | 0.89 ± 0.12 | 0.95 ± 0.20† | 0.96 ± 0.21† | 0.95 ± 0.20 | 0.000 |
| First-trimester bilateral uterine artery notch | 14 (3.1) | 7 (10.9)† | 7 (8.1) | 14 (9.3) | 0.003 |
| Persistent bilateral uterine artery notch | 10 (2.2) | 5 (7.8)† | 4 (4.6) | 9 (6) | 0.03 |
| Umbilical artery pulsatility index >95th percentile | 16 (3.6) | 8 (12.5)† | 16 (18.6)† | 24 (16) | <0.001 |
| Cesarean section | 137 (30.4) | 18 (28.1) | 28 (32.6) | 46 (30.6) | 1 |
| Fetal death | − | − | 1 (1.2) | 1 (0.7) | 0.25 |
| Gestational diabetes | 8 (1.8) | 2 (3.1) | 4 (4.6) | 6 (4.0) | 0.13 |
| Small for gestational age | 42 (9.3) | 12 (18.7) | 16 (18.6)† | 28 (18.7) | 0.002 |
| Fetal growth restriction | 16 (3.6) | 8 (12.5)† | 12 (13.9)† | 20 (13.3) | <0.001 |
| Preeclampsia | 12 (2.7) | 3 (4.7) | 6 (7.0) | 9 (6) | 0.07 |
| Preeclampsia or fetal growth restriction | 23 (5.1) | 8 (12.5)† | 14 (16.3)† | 22 (14.7) | <0.001 |
| Delivery at <34 weeks | 9 (2.0) | 2 (3.1) | 2 (2.3) | 4 (2.6) | 0.75 |
| Moderate or severe adverse outcomes | 22 (4.9) | 6 (9.4) | 12 (13.9)† | 18 (12) | 0.004 |

* Except where indicated otherwise, values are the number (%).
† $P < 0.05$ versus controls, by post hoc testing with Bonferroni correction for multiple comparisons.

In post hoc analysis and after Bonferroni correction for multiple comparisons, there were no significant differences in the uterine and umbilical artery pulsatility index or in birth weight and birth weight centile among cases with no clinically apparent disease compared with those with persistence of rheumatic symptoms. In contrast, in both of these groups of cases the pulsatility index of the uterine and umbilical artery was significantly increased, and birth weight and birth weight centile were significantly reduced, compared with

**Table 5.** Odds ratios in the cases (versus the control group [referent]) for adverse pregnancy outcomes according to rheumatic disease status*

| | No clinically apparent disease (n = 64) | Persistence of symptoms (n = 86) | Overall (n = 150) |
| --- | --- | --- | --- |
| Preeclampsia | 1.9 (0.5−6.7) | 2.9 (0.9−5.7) | 2.4 (0.9−5.7) |
| Fetal growth restriction | 3.8 (1.6−9.5) | 4.6 (2.1−10.0) | 4.2 (2.1−8.3) |
| Preeclampsia or fetal growth restriction | 2.7 (1.1−6.4) | 3.8 (1.9−7.7) | 3.3 (1.8−6.1) |
| Small for gestational age | 2.2 (1.1−4.5) | 2.3 (1.2−4.3) | 2.2 (1.3−3.8) |
| Any adverse pregnancy outcome | 2.0 (0.7−5.1) | 3.2 (1.5−6.7) | 2.6 (1.4−5.0) |

* Values are the odds ratio (95% confidence interval), obtained by penalized logistic regression including pregnancy outcome as the dependent variable and rheumatic disease status (controls/no clinically apparent disease/persistence of symptoms), previous low-birth-weight infant (yes/no), and first-trimester smoking (yes/no) as explanatory variables.

controls. Compared with controls and after correction for multiple comparisons, moderate/severe complications of pregnancy were significantly more common only in the group of cases with persistence of rheumatic symptoms.

Table 5 presents the results of penalized logistic regression analysis. Compared with controls and after correction for potential confounders, measures of fetal growth, such as the prevalence of SGA as obtained with customized growth charts and FGR with abnormal Doppler findings, were significantly higher both in the group of women with no clinically apparent disease and in those with persisting rheumatic symptoms. Logistic analysis confirmed that only the subgroup of cases with persisting rheumatic symptoms had increased rates of moderate/severe pregnancy complications compared with controls.

## DISCUSSION

Data from multiple previous studies suggest that systemic autoimmune diseases, such as SLE, RA, SSc, SS, and APS, are often preceded (for a long period of time, often lasting several years) by the presence of detectable autoantibodies and few signs or symptoms, not fulfilling diagnostic criteria for a definite rheumatic disease (2,3). The clinical phases that antedate the development of an overt autoimmune disorder have often been referred to as early, incomplete, undifferentiated, or preclinical autoimmune rheumatic disease (4,5,22,23). Earlier phases of autoimmune diseases or incomplete disorders are not entirely benign and have been associated with increased rates of cardiovascular and lung disorders, accelerated atherosclerosis, and, at least for non-criteria APS, increased rates of adverse obstetric events (24,25).

Our results showed that in pregnant women with mild preclinical or incomplete rheumatic diseases detected during the first trimester of pregnancy, the rates of fetal growth disorders and of adverse obstetric events were significantly higher than those in negative controls. The increased Doppler pulsatility index of the uterine artery during the first and second trimesters and of the umbilical artery during the third trimester of pregnancy suggest that the increased risk of fetal growth failure among pregnant women with rheumatic symptoms and antibodies was a direct consequence of defective placentation. Although we were able to demonstrate increased rates of adverse pregnancy outcomes only among subjects with persistence of rheumatologic symptoms after delivery, women with transient rheumatologic symptoms and autoantibody positivity during pregnancy had increased rates of either preeclampsia/FGR or SGA, relative to negative controls.

The prospective design with recruitment during the first trimester of pregnancy and subsequent evaluation of both rheumatologic and obstetric outcomes are the main strengths of the present study. Previous epidemiologic investigations into the relationship between obstetric antecedents of subsequent rheumatic disease were based mainly on retrospective evaluations of obstetric history before the development of a definite rheumatic disease (26,27). Van Wyk et al have shown that, compared with healthy controls, the reproductive history of women who later developed SSc was characterized by increased rates of FGR and preeclampsia (28). Other retrospective studies of obstetric history before and after a diagnosis of SLE (29) suggested that preclinical SLE was associated with increased rates of FGR and pregnancy complications. In a recent study, Arkema and colleagues (30), using population-based Swedish registries, found that compared with the general population, women with pre-SLE had increased rates of preeclampsia, premature delivery, and adverse neonatal outcomes such as infection and mortality.

A large, epidemiologic, population-based retrospective study in Denmark showed that children exposed to preclinical maternal RA were more often born preterm and with a placental and neonatal weight lower than that recorded among unexposed controls (31). Finally, the so-called non-criteria APS, that is, the presence of incomplete clinical and/or laboratory manifestations of APS, is associated with an increased risk of pregnancy complications, such as recurrent fetal loss and adverse pregnancy outcomes mediated by placental insufficiency (25). Our results are consistent with all of these data suggesting that early, preclinical, or incomplete autoimmune rheumatic diseases diagnosed during the first trimester of pregnancy are associated with increased rates of preeclampsia and/or fetal growth failure.

Whereas the association of preclinical autoimmune disorders with persisting postpartum symptoms and adverse pregnancy outcome seems convincing, the association of increasing rates of preeclampsia or FGR among subjects with transient clinical and laboratory rheumatic abnormalities during pregnancy with subsequent classification as having no clinically apparent rheumatic disease is less obvious. However, previously reported data suggest that the detection of antiphospholipid antibodies is associated with increased rates of pregnancy failure and subsequent pregnancy complications, irrespective of the simultaneous presence of rheumatologic symptoms (32). In addition, ANAs have been associated with recurrent pregnancy loss and with increased rates of preeclampsia, even among previously asymptomatic pregnant women (25). All of these data suggest that autoantibodies can interfere with early placentation, leading to increased pregnancy

complications irrespective of the simultaneous presence or persistence of rheumatologic symptoms. The higher first- and second-trimester uterine artery Doppler pulsatility indices among pregnant women with transient rheumatologic abnormalities in our study support these findings.

Although the association between preclinical rheumatic diseases and pregnancy complications seems very plausible, our study was not population based, and therefore the results cannot be generalized to other populations. In addition, little is known about the prevalence of preclinical rheumatic diseases in the general population, a variable that could heavily influence the burden of subsequent complications (33). The major systemic autoimmune rheumatic diseases, including RA, SLE, SS, and other CTDs, are relatively common, with a 5% prevalence in the general population and a lifetime risk of 8.4% among women (34). However, the natural history of these disorders follows a pattern of progression lasting several years from a preclinical, nondiagnostic phase to overt disease (2,3). Thus, the 2.9% prevalence of preclinical or transient autoimmune disorders among young women recruited into our study (150 of 5,232) was not surprising.

The biologic basis of the association between preclinical autoimmune disorders and pregnancy complications involves both the role of proinflammatory cytokines and that of endothelial dysfunction associated with inflammation (1). In particular, among subjects with early UCTD, plasma concentrations of markers of endothelial cell activation and damage are higher than those in controls, suggesting an increased risk of atherosclerosis (35). In addition, in these subjects there is an imbalance between proinflammatory cytokines (interleukin-6 [IL-6], IL-7, IL-12, IL-23) and regulatory cytokines (IL-10) that favors vessel damage (7). Endothelial dysfunction and cytokine imbalance during pregnancy can cause inadequate trophoblast invasion of the spiral arteries with a subsequent defective establishment of maternal–fetal vascularization and oxygen and nutrient exchange, leading to FGR and preeclampsia (1,36). An early first-trimester increase in uterine artery Doppler pulsatility indices, a hallmark of probable defective placentation (18) among pregnant women with preclinical rheumatic disease, is consistent with these data.

In conclusion, the evidence from this study suggests that early, incomplete, or preclinical rheumatic disorders diagnosed during the first trimester of pregnancy are associated with an increased risk of preeclampsia/ FGR, SGA, or other adverse pregnancy outcomes. Even positive autoantibody status during the first trimester with no clinically apparent rheumatic disease at postpartum follow-up is associated with an increased risk of fetal growth failure. The current findings add to a growing body of literature indicating that preclinical phases of rheumatic disorders, although characterized by few or absent symptoms, could have significant adverse effects on reproductive outcomes. Since most previously published data on this topic are based on retrospective analyses, additional population cohort studies are needed to confirm the association between preclinical rheumatic diseases and adverse obstetric outcomes and to establish the potential role of screening measures for rheumatic disorders in the counseling for, prevention of, and diagnostic evaluation of fetal growth failure or preeclampsia.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Spinillo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
**Study conception and design.** Spinillo, Ramoni, Montecucco.
**Acquisition of data.** Beneventi, Locatelli, Ramoni, Caporali, Alpini, Albonico, Cavagnoli.
**Analysis and interpretation of data.** Spinillo, Ramoni, Caporali.

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