Long-term Outcome of Children Born to Women with Autoimmune Rheumatic Diseases: A Multicentre, Nationwide Study on 299 Randomly Selected Individuals

Laura Andreoli1,2 · Cecilia Nalli2 · Maria Grazia Lazzaroni1,2 · Chiara Carini1 · Francesca Dall'Ara1 · Rossella Reggia1 · Marília Rodrigues3 · Carolina Benigno4 · Elena Baldissara5 · Elena Bartoloni6 · Fabio Basta7 · Francesca Bellisai8 · Alessandra Bortoluzzi9 · Corrado Campochiaro5 · Francesco Paolo Cantatore10 · Roberto Caporali11,12 · Angela Ceribelli13 · Cecilia B. Chighizola14 · Paola Coniglio15 · Addolorata Corrado10 · Maurizio Cuto16 · Salvatore D'Angelo17 · Elena De Stefani9 · Andrea Doria18 · Maria Favaro18 · Colomba Fischetti19 · Rosario Foti20 · Armando Gabrie119 · Elena Generali13 · Roberto Gerli6 · Maria Gerosa11,12 · Maddalena Larosa18 · Armin Maier21 · Nazzarena Malavolta22 · Marianna Meroni23 · Pier Luigi Meroni14 · Carломaurizio Montecucco24 · Marta Mosca25 · Melissa Padovan9 · Giuseppe Paolazzi26 · Giulia Pazzola27 · Susanna Peccatori26 · Roberto Perricone15 · Giorgio Pettiti28 · Valentina Picerno17 · Immacolata Prevete29 · Véronique Ramoni24 · Nicoletta Romeo28 · Amelia Ruffatti18 · Carlo Salvareni27 · Gian Domenico Sebastiani29 · Carlo Selmi13 · Francesca Serale28 · Luigi Sinigaglia11 · Chiara Tani25 · Marica Trevisani22 · Marta Vadacca7 · Eleonora Valentini6 · Guido Valesini30 · Elisa Visalli20 · Ester Vivaldelli21 · Lucia Zuliani19 · Angela Tincani1,2

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Abstract
The concern about the offspring’s health is one of the reasons for a reduced family size of women with rheumatic diseases (RD). Increased risk of autoimmune diseases (AD) and neurodevelopmental disorders (ND) has been reported in children born to patients with RD. Within a nationwide survey about reproductive issues of women with RD, we aimed at exploring the long-term outcome of their children. By surveying 398 patients who received their diagnosis of RD during childbearing age (before the age of 45), information about the offspring were obtained from 230 women who declared to have had children. A total of 148 (64.3%) patients were affected by connective tissue diseases (CTD) and 82 (35.7%) by chronic arthritis. Data on 299 children (156 males, 52.1%; mean age at the time of interview 17.1 ± 9.7 years) were collected. Twelve children (4.0%), who were born to patients with CTD in 75% of the cases, were affected by AD (8 cases of celiac disease). Eleven children had a certified diagnosis of ND (3.6%; 6 cases of learning disabilities); 9 of them were born to mothers with CTD (5 after maternal diagnosis). No association was found between ND and prenatal exposure to either maternal autoantibodies or anti-rheumatic drugs. Absolute numbers of offspring affected by AD and ND were low in a multicentre cohort of Italian women with RD. This information can be helpful for the counselling about reproductive issues, as the health outcomes of the offspring might not be an issue which discourage women with RD from having children.

Keywords Rheumatic diseases · Reproductive issues · Offspring · Neurodevelopmental disorders · Counselling

Introduction
Rheumatic diseases (RD) are chronic/inflammatory conditions that can affect women of childbearing age. Counselling about reproductive issues should be a key point of the physician–patient communication [1–3].

The family size of women with RD is reduced as compared with the general population [4]. Patients reported several reasons for having less children than desired or not
having children at all, including the fear that the disease or the medications could harm the foetus, or the concern of not being able to take care of the baby, or that the child could develop the same disease as the mother [5].

Studies available about the long-term outcome of children born to mothers with RD have different design and sample size and are focused on specific conditions and maternal diseases [6], such as neurodevelopmental disorders (ND) in children born to mothers with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [7–9]. Autoimmune diseases (AD) rarely arise during infancy; therefore, only studies covering decades of follow-up of children would be informative. The literature is still lacking long-term studies about this issue. As a whole, it is no easy task to counsel a woman with RD about the long-term outcome of her offspring.

This multicentre, nationwide study aimed at collecting data about the long-term health conditions of children born to women with RD in Italy, with particular focus on the development of AD and ND, in order to gain information for the counselling of patients.

Methods

This study was part of a multicentre, retro-prospective, patient-based study aimed at exploring the unmet needs of women of childbearing age with RD. As previously described [5], patients with a confirmed diagnosis of RD who were in follow-up at 24 centres affiliated with the Italian Society for Rheumatology (SIR) were invited to participate in the study. The study was approved by the ethical committee (EC) of coordinating centre in Brescia (ASST Spedali Civili). Subsequently, it was approved by the local EC at each centre.

The interviews were conducted in September 2015 by means of a self-reported questionnaire that was proposed to 20 non-selected, consecutive patients attending the outpatient clinic of each centre. The questionnaire comprised 65 multiple-choice and 12 open-answer questions covering six main sections: (1) counselling about contraception and pregnancy, (2) knowledge of RD’s implications for reproductive matters, (3) family size and desire for pregnancy, (4) pregnancy outcomes before and after RD diagnosis, (5) patients’ awareness of the use of drugs during pregnancy, (6) children’s follow-up.

This paper focuses on the follow-up of children born to patients with RD, as the other themes have already been the subject of a previous paper [5]. For the purpose of statistical analysis, patients were subdivided into two groups: connective tissue diseases (CTD) and chronic arthritis (CA). The CTD group comprised systemic lupus erythematosus and/or antiphospholipid syndrome (SLE/APS), dermatomyositis (DM-PM), undifferentiated connective tissue disease (UCTD), mixed connective tissue disease (MCTD), primary Sjögren’s syndrome (SS), and systemic sclerosis (SSc). The CA group comprised: rheumatoid arthritis (RA) and seronegative spondyloarthropathies (SpA).

Out of 398 patients, 230 (57.8%) had children. Children’s diagnoses of AD and/or ND reported by the mothers were checked through a second round of interview, and only cases certified by a medical specialist were considered.

The chi-square test for categorical data (or Fisher’s exact when appropriate) and Student’s t-test for continuous data were used for statistical analysis. Significance was set at a p ≤ 0.05.

Results

Data were collected for 299 children born to 230 patients with a diagnosis of CA (82, 35.7%; 56 RA, 26 SpA; 58 patients with 1 child, 24 patients with 2 children) or CTD (148, 64.3%; 70 SLE/APS, 6 DM-PM, 18 UCTD, 2 MCTD, 13 SS, 39 SSc; 101 patients with 1 child, 47 with 2 children). Children were male in 156 cases (52.2%) and female in 143 cases (47.8%), with a mean age of 17.1 years (± 9.7) at the time of interview. Fifty-six (18.7%) children were born before the 37th week of gestation; premature birth before the 34th week occurred in 17 cases (5.6%). One case of Trisomy 21 and one perinatal death due to respiratory distress were reported.

No significant differences were observed in the developmental milestones (age at sitting position, walking, first speech, discontinuation of diaper) between children born from mothers with CA or CTD and born before or after maternal diagnosis. Sleep disturbances (pavor nocturnus, somnambulism, insomnia) and feeding problems (food allergy/intolerance) were observed in less than 10% of children.

Regarding school performance, 12 children (4.5% of children of school-age) repeated 1 year of school, in 7 cases for indolence, in 3 for learning disabilities (LD)/health problems, and in 2 for family problems. Eleven of these children were born before maternal diagnosis.

Twelve children (4.0%; 4 males, 8 females; mean age of 12.2 years at the time of interview) were affected by AD. Children’s and maternal characteristics are shown in Table 1.

Eleven children (3.7%; 7 males, 4 females, mean age of 11.9 years at the time of interview) had a certified ND and had been diagnosed as learning disabilities (LD) such as dyslexia, dyscalculia, and dysgraphia (n = 6); attention deficiency and hyperactivity disorder (ADHD) (n = 2); autism spectrum disorder (ASD) (n = 1); ADHD+LD; and 1 “slow
learner” (a girl who was born at term but small for gestational age) \((n = 1)\).

Table 2 reports on children’s and maternal characteristics with regard to foetal exposure to autoantibodies and drugs, as factors potentially impacting on the foetal neurodevelopment.

Details about the children with AD and ND and their mothers are reported in Table 3.

### Table 1

Characteristics of children with and without autoimmune diseases. Autoimmune diseases were as follows: 1 juvenile idiopathic arthritis, 1 diabetes mellitus type 1, 1 autoimmune thyroiditis, 1 recurrent fever, and 8 celiac disease (CD). Among the 8 children with CD, 3 had a mother affected by CD and 2 had affected family members from the paternal side. The HLA typing was performed in 3 children and their parents: the DQ2/DQ8 haplotype was found in 2 mothers affected by CD and in one asymptomatic father.

| Characteristics                                      | Children with autoimmune diseases \((n = 12)\) | Children without autoimmune diseases \((n = 287)\) | \(p\)-value |
|-------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|-------------|
| Sex (male)                                            | \(4 (33.3\%)\)                               | \(162 (56.4\%)\)                             | 0.2437      |
| Child’s age at the time of interview (years, mean ± SD)| \(12.2 ± 6.94\)                              | \(17.3 ± 9.78\)                              | 0.0742      |
| Overall preterm birth (≤ 37 weeks)                    | \(4 (33.3\%)\)                               | \(52 (18.1\%)\)                              | 0.2445      |
| Late preterm birth (34.1–36.6 weeks)                  | \(3 (25.0\%)\)                               | \(36 (12.5\%)\)                              | 0.7359      |
| Early preterm birth (≤ 34 weeks)                      | \(1 (8.3\%)\)                                | \(16 (5.6\%)\)                               | 0.3975      |
| Mean weight at birth—male (kg, mean ± SD)             | \(2.984 ± 0.469\)                            | \(3.277 ± 0.493\)                            | 0.0439      |
| Mean weight at birth—female (kg, mean ± SD)           | \(2.975 ± 0.457\)                            | \(3.127 ± 0.515\)                            | 0.3148      |

### Table 2

Children with and without neurodevelopmental disorders: characteristics at birth, maternal diagnosis, exposure in utero to autoantibodies, and/or anti-rheumatic or anti-thrombotic drugs. As autoantibodies may be positive many years prior to the onset of symptoms and clinical diagnosis, \[10\] we performed an additional analysis by considering as exposed in utero to autoantibodies those children who were born within 5 years of maternal diagnosis of RD.

| Characteristics                                      | Children with ND \((n = 11)\) | Children without ND \((n = 288)\) | \(p\)-value |
|-------------------------------------------------------|--------------------------------|---------------------------------|-------------|
| Sex (male)                                            | \(7 (63.6\%)\)                 | \(148 (51.4\%)\)               | 0.5455      |
| Child’s age at the time of interview (years, mean ± SD)| \(11.9 ± 4.35\)                | \(17.1 ± 9.86\)                | 0.0842      |
| Overall preterm birth (≤ 37 weeks)                    | \(3 (27.2\%)\)                 | \(53 (18.4\%)\)                | 0.4375      |
| Late preterm birth (34.1–36.6 weeks)                  | \(1 (9\%)\)                    | \(38 (13.1\%)\)                | 0.7264      |
| Early preterm birth (≤ 34 weeks)                      | \(2 (18.1\%)\)                 | \(15 (5.2\%)\)                 | 0.3426      |
| Mean weight at birth—male (kg, mean ± SD)             | \(3.0393 ± 0.562\)             | \(3.29 ± 0.475\)               | 0.0890      |
| Mean weight at birth—female (kg, mean ± SD)           | \(2.8175 ± 0.517\)             | \(3.1349 ± 0.513\)             | 0.0451      |

### Discussion

This study aimed at assessing the long-term outcome of children born to mothers with a definite diagnosis of RD. To our knowledge, this is the only study comprising young adults (mean age of 17.1 years), i.e. the age of possible onset of AD.
We found that AD, mainly organ-specific, were present in 3.8% of the offspring, while a systemic disease was present in 2 cases (0.6%). This figure can be considered as comparable with the recently published study of children born to mothers with SLE in Canada [12], in which the frequency of AD was 1.1%, while it was 0.5% in the control group. Interestingly, no cases of celiac disease (CD) were reported in SLE offspring and only one case was found in the controls. In our cohort, 8 out of the 12 children with AD were affected by CD. This difference highlights that variability in genetic heritage and exposome may account for different frequency of specific AD in different populations [11]. The frequency of CD found in our study (2.5%) does not seem to be significantly higher than that reported more than 10 years ago in the general paediatric population (0.33–1.25%) [13]. The increasing disease awareness and diagnostic sensitivity of AD and in particular of CD, which lately seems to have become “epidemic,” [14] cannot support a hint toward an

Table 2 (continued)

| In utero exposure to drugs | Children with ND (n = 11) | Children without ND (n = 288) | p-value |
|---------------------------|--------------------------|-------------------------------|---------|
| Pregnancy before the diagnosis of CTD | 5 (55.6%) | 56 (30.4%) | 0.1443 |
| Pregnancy before the diagnosis of CTD | 4 (44.4%) | 128 (69.6%) | 0.1443 |
| Oral prednisone/methylprednisolone (CS) | 5 (45.5%) | 49 (17.0%) | 0.0311 |
| Azathioprine (AZA) | 1 (9.1%) | 2 (0.7%) | 0.1067 |
| Cyclosporin-A (CyA) | 0 (0%) | 1 (0.3%) | > 0.9999 |
| Intravenous immunoglobulins (IVIG) | 0 (0%) | 2 (0.7%) | > 0.9999 |
| Hydroxychloroquine (HCQ) | 0 (0%) | 26 (9.0%) | 0.6073 |
| Heparin (LMWH) | 0 (0%) | 14 (4.9%) | > 0.9999 |
| Low-dose acetylsalicylic acid (LDA) | 2 (18.2%) | 26 (9.0%) | 0.2751 |
| Leflunomide (LEF) | 0 (0%) | 0 (0%) | > 0.9999 |
| Sulfasalazine (SSZ) | 0 (0%) | 1 (0.3%) | > 0.9999 |
| Methotrexate (MTX) | 0 (0%) | 1 (0.3%) | > 0.9999 |

In utero exposure to autoantibodies

| In utero exposure to autoantibodies | Children with ND (n = 11) | Children without ND (n = 288) | p-value |
|-----------------------------------|--------------------------|-------------------------------|---------|
| Exposure to at least one drug | 5 (100.0%) | 59 (71.1%) | 0.3172 |
| Antiphospholipid antibodies (at least one positive test) | 2 (40.0%) | 19 (22.9%) | 0.5891 |
| Anti-cardiolipin antibodies (aCL) | 2 (40.0%) | 16 (19.3%) | 0.2698 |
| Anti-Beta2glycoprotein I antibodies (aB2GPI) | 0 (0%) | 13 (15.7%) | > 0.9999 |
| Lupus anticoagulant (LA) | 0 (0%) | 9 (10.8%) | > 0.9999 |
| Anti-Ro/SS-A | 2 (40.0%) | 25 (30.1%) | 0.6403 |
| Anti-La/SS-B | 1 (20.0%) | 9 (10.8%) | 0.4611 |
| Anti-nuclear antibodies (ANA) | 4 (80.0%) | 52 (62.7%) | 0.6490 |
| Anti-dsDNA antibodies | 3 (60.0%) | 16 (19.3%) | 0.0652 |
| Other autoantibodies | 0 (0%) | 10 (12.0%) | > 0.9999 |

In utero exposure to autoantibodies

| In utero exposure to autoantibodies | Children with ND (n = 11) | Children without ND (n = 288) | p-value |
|-----------------------------------|--------------------------|-------------------------------|---------|
| Exposure to at least one antibody | 5 (100.0%) | 92 (67.6%) | 0.7161 |
| Antiphospholipid antibodies (at least one positive test) | 2 (40.0%) | 24 (17.6%) | 0.6356 |
| Anti-cardiolipin antibodies | 2 (40.0%) | 21 (15.4%) | 0.6140 |
| Anti-Beta2glycoprotein I antibodies | 0 (0%) | 16 (11.8%) | 0.5980 |
| Lupus anticoagulant | 0 (0%) | 15 (11.0%) | > 0.9999 |
| Anti-Ro/SS-A | 2 (40.0%) | 36 (26.5%) | > 0.9999 |
| Anti-La/SS-B | 1 (20.0%) | 12 (8.8%) | 0.5402 |
| Anti-nuclear antibodies | 5 (100.0%) | 82 (60.3%) | > 0.9999 |
| Anti-dsDNA antibodies | 3 (60.0%) | 23 (16.9%) | 0.1565 |
| Other autoantibodies | 0 (0%) | 22 (16.2%) | 0.6083 |

*This section considers all the live-birth pregnancies occurred after the diagnosis of RD (88 children, including 5 children with ND and 83 children without ND)

*This section considers all the live-birth pregnancies occurred in the 5 years prior to the diagnosis of RD and all the pregnancies occurred afterwards (144 children, including 8 children with ND and 136 children without ND)
increased risk of CD in our cohort. As a matter of fact, one fourth of the affected children had family members with CD on the paternal side (data not shown).

The observed frequency of ND was 3.7%. Despite absolute numbers are rather low, there was a clustering in children born to mothers with CTD (81%), particularly after

| Table 3 | Children affected by autoimmune diseases (AD) or neurodevelopmental disorders (ND): characteristics of mothers and offspring. |
|---------|-------------------------------------------------------------------------------------------------|
| Sex     | Age at the time of the interview | Disease                                                                 | Birth before/after maternal disease onset | Gestational week at birth | Maternal disease | In utero exposure to maternal autoantibodies | In utero exposure to drugs |
|---------|---------------------------------|----------------------------------------------------------------------------|-------------------------------------------|--------------------------|-----------------|-----------------------------------------------|--------------------------|
| Autoimmune diseases (AD) |                                 |                                                                            |                                           |                          |                 |                                               |                          |
| 1       | M                               | Type 1 diabetes                                                           | Before                                    | 32                       | RA              | NA                                             | No                       |
| 2       | F                               | Juvenile idiopathic arthritis                                            | Before                                    | 41                       | RA              | NA                                             | No                       |
| 3       | F                               | Celiac disease                                                            | After                                      | 38                       | RA              | No, HCQ                                        |                          |
| 4       | F                               | Celiac disease                                                            | Before                                    | 38                       | UCTD            | NA                                             | No                       |
| 5       | F                               | Autoimmune hypothyroidism                                                | Before                                    | 41                       | DM/PM           | NA                                             | No                       |
| 6       | M                               | Celiac disease                                                            | Before                                    | 36                       | SS              | NA                                             | No                       |
| 7       | F                               | Celiac disease                                                            | Before                                    | 39                       | UCTD            | NA                                             | No                       |
| 8       | F                               | Celiac disease                                                            | Before                                    | 38                       | SLE             | ANA, a-dsDNA, aCL, aB2GPI, anti-Ro/SSA*         | No                       |
| 9       | M                               | Celiac disease                                                            | After                                      | 36                       | UCTD            | Anti-Ro/SSA, LA, ANA                           | CS, Ivg                   |
| 10      | M                               | Celiac disease                                                            | After                                      | 41                       | SLE             | ANA, a-dsDNA                                   | HCQ, LDA                 |
| 11      | F                               | Celiac disease                                                            | After                                      | 35                       | SSc             | ANA, anti-Scl70, anti-RNP                      | CS, LMWH                 |
| 12      | F                               | Recurrent fever                                                           | After                                      | 36                       | SLE             | Anti-Ro/SSA, LA, ANA, a-dsDNA                  | CS, HCQ                  |
| Neurodevelopmental disorders (ND) |                                 |                                                                            |                                           |                          |                 |                                               |                          |
| 1       | M                               | ADHD + LD                                                                 | Before                                    | 37                       | RA              | NA                                             | No                       |
| 2       | F                               | Slow learner                                                              | Before                                    | 38                       | RA              | NA                                             | No                       |
| 3       | M                               | ADHD + ASD                                                                | Before                                    | 28                       | SSc             | ANA, a-TPO, a-TG IgA**                         | CS, LDA                  |
| 4       | M                               | LD (dyslexia)                                                             | Before                                    | 39                       | SSc             | NA                                             | No                       |
| 5       | F                               | LD (dyscalculia)                                                          | Before                                    | 40                       | SSc             | NA                                             | No                       |
| 6       | F                               | ADHD                                                                     | Before                                    | 38                       | SLE             | ANA*                                           | No                       |
| 7       | F                               | LD (dyslexia, dyscalculia)                                                | After                                      | 40                       | SLE             | Anti-Ro/SSA, aCL                               | CS                       |
| 8       | M                               | ADHD                                                                     | After                                      | 36                       | SLE             | ANA, aCL                                       | CS, AZA, LDA             |
| 9       | M                               | ADHD + LD (dyslexia, dyscalculia)                                         | After                                      | 42                       | SLE             | ANA, a-dsDNA                                   | No                       |
| 10      | F                               | LD (dysnomia)                                                             | After                                      | 34                       | SLE             | ANA, a-dsDNA                                   | CS                       |
| 11      | M                               | LD (dyslexia)                                                             | After                                      | 38                       | SLE             | Data not available                             | CS                       |

*aB2GPI anti-beta2glycoprotein I antibodies, aCL anti-cardiolipin antibodies, ADHD attention deficit hyperactivity disorder, a-dsDNA anti-dsDNA antibodies, ANA anti-nuclear antibodies, anti-RNP anti-ribonucleoprotein antibodies, ASD autism spectrum disorders, a-TG anti-transglutaminase antibodies, a-TPO anti-thyroperoxidase antibodies, A ZA azathioprine, CS oral prednisone/methylprednisolone, DM/PM dermatopolymyositis, HCQ hydroxychloroquine, IVIG intravenous immunoglobulins, LA lupus anticoagulant, LD learning disabilities, LDA low-dose acetylsalicyclic acid, LMWH low molecular weight heparin, NA not applicable, RA rheumatoid arthritis, SLE systemic lupus erythematosus, SS Sjögren’s syndrome, SSc systemic sclerosis, UCTD undifferentiated connective tissue disease

*As the pregnancy occurred within the 5 years prior to diagnosis, it is possible to assume that autoantibodies were already present during pregnancy

**This patient was tested for autoantibodies because of infertility and was treated by obstetric indication for favouring better outcomes of a spontaneous pregnancy
maternal diagnosis (66.6%). This observation is in line with the reports of the last 30 years suggesting that children born to mothers with SLE seem to be more prone to ND [9]. Children with ND were more frequently exposed in utero to corticosteroids and maternal anti-dsDNA antibodies. However, the placental enzymes physiologically inactivate prednisone/methylprednisolone and only about 10% can reach the foetus limiting their pathogenic potential. On the other hand, the trend toward an increased frequency of exposure to maternal anti-dsDNA is consistent with an animal model showing that a subset of anti-dsDNA called anti-N-methyl-D-aspartate-receptor antibodies were able to induce foetal neuronal apoptosis and ND in the offspring [6]. Both corticosteroids and anti-dsDNA can point at active maternal disease during pregnancy, which is in turn a risk factor for premature birth. ND are multifactorial in origin; therefore, the in utero environment is just one of the risk factors. Prematurity can be indeed a major risk factor for ND. Although there was no statistically significant difference in the rate of pre-term birth between children with and without ND, the frequency of pre-term birth in our cohort (18.4%) was higher than that of the Italian general obstetric population (12%) [15]. The causes of pre-term birth were not collected in our survey. However, it is possible that some of these pre-term births were iatrogenic, as in the past women with RD were not let to deliver at full term because of the fear of maternal disease flares.

LD were the most common ND in our cohort with a frequency of 1.8%, similar to that of 2.5–3.5% described in Italian school-children [16]. The occurrence of LD was not associated with the in utero exposure to maternal antiphospholipid antibodies (aPL), but none of the patients carried a triple aPL positivity, which was the common feature of children with LD, as recently reported [17].

Only one case of ASD was found in our cohort. The possible association between ASD and maternal RD should not be emphasized in our opinion as no solid causative explanation has been elaborated yet. The fact that ASD were found in children born to mothers with different RD such as RA, [7, 18] SLE [8], and APS [19] may reflect their sporadic occurrence rather than a biologically supported association.

We acknowledge that this study has some limitations: (i) it was not designed as a case-control study; however, it carries the relevant information for future parents that the chance of occurrence AD and NP in their offspring is low [6]; (ii) the survey did not collect information about Caesarean section, linked to an increased risk of non-rheumatic autoimmune diseases [12]; and (iii) a national cohort does not allow to generalize the counselling to women with a different ethnic background.

There are also some strengths in this study: (a) it provides data regarding the long-term outcome of children born to women with RD other than RA, SLE, APS; (b) the enrolment of consecutive patients attending the out-patient clinics of 24 centres across the country during the same time period allowed random inclusion of children; (c) the direct contact with the patients allowed us to retrieve validated data about children’s outcomes and exposures during pregnancy, while administrative sources can misclassify the diagnosis and do not allow precise information about drugs [20]; and (d) the mean age of 17 years accounts for the longest follow-up of children born to mother with RD available in the literature, allowing a better assessment of AD as their onset is usually during adulthood.

In conclusion, according to our data, a link between maternal disease (particularly CTD) and ND cannot be excluded, suggesting the need of attention by the healthcare providers to explore any possible concern of the mother. However, our study found a low frequency of AD and ND in a large randomly selected cohort of children born to mothers with RD. This is a valuable information for the counselling of patients of childbearing age that was lacking in clinical practice.

Key Messages

- Knowledge about the long-term outcome of children born to mothers with rheumatic diseases (RD) is an unmet need in the counselling about reproductive issues.
- Some studies suggested that the offspring of women with rheumatoid arthritis and systemic lupus erythematosus may be at increased risk of autoimmune diseases (AD) and neurodevelopmental disorders (ND).
- We collected information about 299 randomly selected individuals born to mothers with RD with a mean age of 17 years at the time of the survey, in 24 rheumatology centres across Italy.
- Absolute numbers of offspring affected by AD and ND were low; a possible link between maternal connective tissue diseases and ND needs to be further investigated, although we did not find any association with the in utero exposure to maternal autoantibodies and anti-rheumatic drugs.
- Concerns regarding the health outcomes of the offspring might not be an issue discouraging women with RD from having children.

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Author Contribution  All authors were involved in drafting the article or revising it critically for intellectual content. LA, CN, MGL, CC, and AT 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: LA, CN, MGL, CC, AD, GV, and AT. Acquisition of data: all the authors. Analysis and interpretation of data: LA, CN, MGL, CC, AD, GV, and AT.

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Data Availability Data are available on reasonable request.

Declarations

Ethics Approval The study was approved by the Ethics Committee in each participating centre.

Consent to Participate Each patient signed a written informed consent before filling out the questionnaire.

Conflict of Interest The authors declare that they have no conflict of interest.

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Authors and Affiliations

Laura Andreoli1,2 · Cecilia Nalli2 · Maria Grazia Lazzaroni1,2 · Chiara Carini1 · Francesca Dall’Ara1 · Rossella Reggia1 · Marilia Rodrigues1 · Carolina Benigno1 · Elena Baldissera5 · Elena Bartolini6 · Fabio Basta7 · Francesca Bellisai8 · Alessandra Bortoluzzi2 · Corrado Campochiaro5 · Francesco Paolo Cantatore10 · Roberto Caporali11,12 · Angela Ceribelli13 · Cecilia B. Chighizola14 · Paola Coniglio15 · Addolorata Corrado10 · Maurizio Cutolo16 · Salvatore D’Angelo17 · Elena De Stefani9 · Andrea Doria18 · Maria Favaro18 · Colomba Fischetti19 · Rosario Foti20 · Armando Gabrielli19 · Elena Generali13 · Roberto Gerli6 · Maria Gerona11,12 · Maddalena Larosa18 · Armin Maier21 · Nazzarena Malavolta22 · Marianna Meroni23 · Pier Luigi Meroni14 · Carlon Maurizio Montecucco24 · Marta Mosca25 · Melissa Padovan9 · Giuseppe Paolazzi26 · Giulia Pazzola27 · Susanna Peccatori26 · Roberto Perricone15 · Luigi Sinigaglia11 · Chiara Tani25 · Marica Trevisani22 · Marta Vadacca7 · Eleonora Valentini6 · Guido Valesini30 · Elisa Visalli20 · Ester Vivaldelli21 · Lucia Zuliani19 · Angela Tincani1,2

1 Department of Clinical and Experimental Sciences, University of Brescia, Viale Europa 11, 25123 Brescia, Italy
2 Rheumatology and Clinical Immunology Unit, ASST Spedali Civili, Piazzale Spedali Civili 1, 25123 Brescia, Italy
3 Centro Hospitalar de Leiria (CHL), Hospital de Santo André (HSA), R. de Santo André, 2410-197 Leiria, Portugal
4 Rheumatology Research Unit, Department of Clinical Medicine and Surgery, University Federico II of Naples, Via Sergio Pansini 5, 80131 Naples, Italy
5 Unit of Medicine and Clinical Immunology, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy
6 Department of Medicine, Rheumatology Unit, University of Perugia, Piazzale Gambali 1, 06132 Perugia, Italy
7 Unit of Allergology, Clinical Immunology and Rheumatology, University Campus Biomedico Rome, Via Álvaro del Portillo, 21, 00128 Rome, Italy
8 Rheumatology Unit, Policlinico Le Scorte and University of Siena, Via Mario Bracci-Loc. Le Scorte, 53100 Siena, Italy
9 Rheumatology Unit, Department of Medical Sciences, University of Ferrara and Azienda Ospedaliero-Universitaria S. Anna, Via Aldo Moro 8, 44124 Cona, Ferrara, Italy
10 Rheumatology Clinic, Department of Medical and Surgical Sciences, University of Foggia, Rione Biccari, 71122 Foggia, Italy
11 Department of Rheumatology, ASST Istituto Gaetano Pini & CTO, Piazza Cardinale Andrea Ferrari, 1, 20122 Milan, Italy
12 Department of Clinical Sciences and Community Health, University of Milan, Via Festa del Perdono 7, 20122 Milano, Italy
13 Division of Rheumatology and Clinical Immunology, Humanitas Research Hospital, Via Manzoni 56Rozzano Milano, 20089 Milan, Italy
14 Unit of Rheumatology, Istituto Auxologico Italiano, Via Mosè Bianchi, 90, 20149 Milan, Italy
15 Rheumatology, Allergy and Clinical Immunology, University of Rome Tor Vergata, Via Oxford 81, 00133 Rome, Italy
16 Research Laboratory and Division of Rheumatology, Postgraduate School of Rheumatology, Department of Internal Medicine, University of Genova, Viale Benedetto XV 16, 16132 Genova, Italy
17 Rheumatology Institute of Lucania (IRel) – Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna Delle Grazie Hospital of Matera, Via Potito Petrone 1, 85100 Potenza, Italy
18 Rheumatology Unit, Department of Medicine-DIMED, University of Padua, Via Nicolò Giustiniani, 2, 35128 Padua, Italy
19 Clinica Medica, Università Politecnica Delle Marche, Via Tronto, 10/a, 60126 Ancona, Italy
20 Rheumatology Unit, A.O.U. Policlinico Vittorio Emanuele, Via S. Sofia 78, 95123 Catania, Italy
21 Rheumatology Outpatient Clinic, Internal Medicine Department, Hospital of Bolzano, Via Lorenz Böhler 5, 39100 Bolzano, Italy
22 Rheumatology Unit, Internal Medicine, Policlinico S.Orsola-Malpighi, Azienda Ospedaliero-Universitaria Di Bologna, Via Pietro Albertoni 15, 40138 Bologna, Italy
23 Humanitas Gavazzeni, ASL 5 Spezzino, BergamoLa Spezia, Italy
24 Division of Rheumatology, University of Pavia and Fondazione IRCCS Policlinico San Matteo, Viale Camillo Golgi 19, 27100 Pavia, Italy
25 Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pavia, Via Roma, 67, 56126 Pisa, Italy
26 Department of Rheumatology, S. Chiara Hospital, Largo Medaglie D’Oro 9, 38122 Trento, Italy
27 Rheumatology Unit, Azienda USL-IRCCS di Reggio Emilia, University of Modena and Reggio Emilia, Viale Risorgimento, 80, 42123 Reggio-Emilia, Italy
28 Unit of Rheumatology, S.Croce E Carle Hospital, Via Michele Coppino, 26, 12100 Cuneo, Italy
29 Rheumatology Unit, San Camillo Hospital, Circonvallazione Gianicolense, 87, 00152 Rome, Italy
30 Rheumatology Unit, Department of Internal Medicine and Medical Specialties, La Sapienza University, Piazzale Aldo Moro 5, 00185 Roma, Italy