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Original article

An observational multicentre study on the efficacy and safety of assisted reproductive technologies in women with rheumatic diseases

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Abstract

Objectives. The aim was to determine whether assisted reproductive technologies (ARTs) confer additional risk in rheumatic patients (in terms of disease flare and fetal–maternal complications) and whether, if performed, their efficacy is affected by maternal disease.

Methods. Sixty infertile rheumatic women undergoing 111 ART cycles were included. Clinical pregnancy rate, live birth rate, maternal disease flares and maternal–fetal complications were recorded.

Results. One hundred and eleven ART cycles in 60 women were analysed. We reported 46 pregnancies (41.4%), 3 (3.1%) cases of ovarian hyperstimulation syndrome and no cases of thrombosis during stimulation, pregnancy and puerperium. One or more maternal complication was reported in 13 (30.2%) pregnancies, and fetal complications occurred in 11 fetuses (21.1%). The live birth rate was 98%, but we reported three (6%) perinatal deaths in the first days of life. During puerperium, we recorded one (2.5%) post-partum haemorrhage and one (2.5%) articular flare.

Conclusion. The safety and efficacy of the ARTs, demonstrated in the general population, seems to be confirmed also in rheumatic patients. No evidence was found to advise against their application, and the choice of therapy should be made depending on the patient's risk profile, irrespective of whether the pregnancy is natural or artificial induced.

Key words: assisted reproductive technologies, rheumatic disease, prophylaxis, complications, efficacy, safety

CLINICAL SCIENCE

Key messages

- The safety of assisted reproductive technologies seems to be confirmed also in rheumatic patients.
- Fetal–maternal complications are in line with those observed in spontaneous gestation in rheumatic patients.
- Efficacy of assisted reproductive technologies in rheumatic patients does not seem to be adversely affected by maternal disease.

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Introduction

The World Health Organization defines infertility as 'a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse' [1]. It has been estimated that ~12–15% of couples of reproductive age suffer from this condition, and it is therefore not surprising that such a high percentage may also include patients with rheumatic diseases (RDs).

Infertility is likely to be multifactorial in RDs; chronic disease and its treatment can have a negative impact on natural fertility, in addition to all the risk factors identified in the general population (increased maternal age, endometriosis, tobacco use, alteration of the BMI, coeliac disease and dysthyroidisms) [2].

In a Norwegian population-based study, a reduced number of births, longer intervals between pregnancies and shorter reproductive periods were shown in women with RDs when compared with healthy controls [3]. Besides a true reduction in fertility [4], this finding could also be attributable to personal choice of the patients [5] (physical limitations [6], emotional states including anxiety and depression [7], fear of drug side effects on the fetus and/or transmission of the disease to the baby, and fear of not being able to take care of the baby).

The ovarian reserve was investigated in some RDs by means of circulating levels of the anti-Müllerian hormone (AMH). An actual decrease in AMH levels has been demonstrated in SLE [8, 9], APS [10], AS [11], Behçet disease [12], Takayasu arteritis [13] and DM [14], whereas contradictory results have emerged regarding RA [11, 15, 16].

Regarding the influence of autoantibodies, a pathogenic role has been confirmed for anti-sperm [17] and anti-ovarian antibodies [18] only, and their presence represents an indication for medical immunosuppressive treatment and the use of assisted reproductive technologies (ARTs) [19].

Only fragmentary and sometimes contradictory data are available for aPL [20].

Insufficient data are available to draw definitive conclusions about a possible role of ANA and other autoantibodies, although it seems unlikely that they might cause infertility.

DMARDs, such as MTX, MMF, AZA, CSA and tacrolimus, do not seem to affect AMH levels [21]. Conversely, the dose- and age-dependent effects of CYC are well documented both on the decrease of AMH [22] and in the induction of premature ovarian failure [21].

No studies are available on the effects of anti-TNF on female fertility, whereas no influence on sperm quality of exposed men was found [21]. Regarding the use of glucocorticoids, no clear influence has been demonstrated on fertility [21].

An increasing number of women with RDs have been approaching ARTs, posing a problem of counselling on two major issues: the effect of ARTs (and, in particular, of the hormonal stimulation, if required) on the underlying disease; and the effect of the underlying disease (autoantibodies, chronic inflammation, drugs, etc.) on the efficacy of the technology itself, in terms of induction of a pregnancy.

Given the paucity of the literature on this topic [23–31], the aim of the present study was to investigate a cohort of patients with different RDs undergoing ARTs, in an attempt to answer these questions.

Methods

This is a multicentre, observational, non-interventional, retrospective study. We included consecutive patients with RDs (diagnosis according to internationally validated criteria) prospectively followed up during one or more cycles of ARTs at the pregnancy clinics of Brescia, Padua, Pavia, Rome and Milan, Italy.

Infertility has been defined as primary if diagnosed in a patient who had never spontaneously conceived and as secondary if the problem arose after one or more spontaneous pregnancies.

Pregnancy trimesters were defined as follows: first trimester: up to 13^{+6} weeks of gestation; second: from 14th to 26^{+6} weeks; third: after 27th week.

Disease activity was assessed according to medical judgement and, when available, using specific indexes. For SLE, we used the SLEDAI at conception and the SLEDAI-P (modified for pregnancy) during gestation [32]; a cut-off value of six was arbitrarily chosen to define the disease as active. For chronic arthritis or CTDs with articular involvement, the DAS-28 (remission for values <2.6, low disease activity for values between 2.6 and 3.2, medium between 3.2 and 5.1 and high disease activity for values >5.1) was used. A flare was defined according to disease indexes, when available, or to medical judgement.

ART procedures have been classified as unstimulated (applied during a natural menstrual cycle without ovarian stimulation) or stimulated (when ovarian stimulation was performed before the sperm or the embryo transfer).

In particular, we included the following protocols: the gonadotrophin-only protocol (with human menopausal gonadotrophins, follicle-stimulating hormone or luteinizing hormone); the agonist protocol [with the administration of a gonadotrophin-releasing hormone (GnRH) agonist: triptorelin, leuprorelin or buserelin]; the antagonist protocol (with the administration of a GnRH antagonist: ganirelix or cetrorelix); the clomiphene protocol ('mild ovarian stimulation' with clomiphene citrate, without gonadotrophins); the homologous protocol when the sperm was obtained from the partner [intrauterine insemination (IUI)]; and the heterologous protocol when the semen or the oocyte was obtained from a donor [*in vitro* fertilization (IVF) with embryo transfer or intracytoplasmic sperm injection (ICSI) or embryo donation].

The previous obstetrical history and the observed pregnancy outcome were defined as follows: at term delivery: vaginal or caesarean delivery occurred beyond the 36th week of gestation; preterm delivery: occurred before the 36th week of gestation; miscarriage: fetal death occurred within the 10th week of gestation;

intrauterine death: fetal death occurred after the 10th week of gestation; and perinatal death: occurred by day 28 after the birth of a live fetus, premature or at term.

The main maternal–fetal complications assessed were defined as follows: pre-eclampsia: resting blood pressure of ≥140/90 mmHg on two occasions ≥4 h apart in previously normotensive women and the development of *de novo* proteinuria (≥300mg/24 h) or a twofold worsening in women without and with pre-existing proteinuria, respectively, after 20 weeks of pregnancy [33]; thrombosis: one or more arterial or venous thrombotic event, confirmed by appropriate diagnostic images; intrauterine growth restriction: rate of fetal growth that is less than normal for the growth potential; oligohydramnios: decrease in the amniotic fluid to <500 ml until its almost complete absence (anhydramnios); and pre-labour rupture of membranes.

Our main efficacy outcome was the induction of a pregnancy, and our main safety outcome was the onset of maternal disease flares and of fetal–maternal complications.

The study was performed according to the Declaration of Helsinki. Approval from the ASST Spedali Civili of Brescia ethical committee was obtained (protocol n'2170, 20 October 2015). All patients gave their informed consent before their inclusion in the study.

Statistical analysis

Categorical variables were reported as a proportion and/or percentage. Continuous variables were reported as the median [interquartile range (IQR)] value. Fisher's exact or χ^2 test for categorical variables and Student's *t* test or the Wilcoxon–Mann–Whitney test for continuous variables were used as appropriate. Multivariate analysis was performed. Associations between variables were examined by Pearson correlation test. Values of $P < 0.05$ were considered significant.

Results

We analysed 111 ART procedures performed in 60 women from 1997 to 2016. The main features of the cohort are available in Table 1.

Procedures analysis

One hundred and eleven ARTs cycles were analysed: 13 IUI, 44 IVF (3 heterologous), 53 ICSI (14 heterologous) and 1 embryo donation. Procedures were unstimulated (during a natural cycle) in 15 (13.5%) cases and

Table 1 Main clinical and serological features of the 60 women included in the study

60 women undergoing 111 ART attempts	
Diagnosis	22 SLE (2+APS), 12 UCTD, 6 PAPS, 8 RA, 4 AS, 2 SS, 1 DM, 1 PA, 1 Takayasu arteritis, 1 EGPA, 1 Behçet disease, 1 SSc
Maternal age at the time of ART, median (range), years	37 (19–45)
Disease duration at the time of ART, median (range), years	6 (1–22)
Disease activity at the time of procedure	*n* = 3 (active arthritis, in 1 RA patient, 1 UCTD patient and 1 SLE patient), all with low disease activity
Additional risk factors: abdominal pelvic surgery, uterine myomas, endometriosis, POCS, obesity, hormonal and anatomical alterations	*n* = 26 (43.3%): • Single: 21 (80.8%) • Multiple: 5 (19.2%)
Type of diagnosed infertility	• Primary: 40 (68%): 5 (12.5%) male, 6 (15%) female, 1 (2.5%) mixed male+female, 28 (70%) idiopathic • Secondary: 20 (32%): 3 (15%) female, 17 (85%) idiopathic
Thyroid alterations, available in 54 (90%) patients	*n* = 27 (50%): • isolated autoantibody positivity with euthyroidism: 7 (25.9%) • hypothyroidism on replacement therapy: 20 (74.1%)
Autoantibodies	ANA: *n* = 44 (73.3%); anti-ENA: *n* = 23 (38.3%). In detail: 11 anti-Ro-SSA, 6 anti-Ro-SSA+anti-La-SSB, 3 anti-U1RNP, 1 anti-centromere, 1 anti-Ro-SSA+anti-Sm+anti-U1RNP, 1 anti-Ro-SSA+anti-centromere aPL: *n* = 23 (38.3%); single positivity in 14 (23.3%), double in 6 (10%), triple in 3 (5%)
Inherited thrombophilia, available in 28 (46.7%) patients	*n* = 16 (58.5%): single: 94.4%; multiple: 5.6%. In detail: • MTHFR mutation: *n* = 12, 10 heterozygous and 2 homozygous; • Factor V Leiden: *n* = 5, all heterozygous; • Factor II mutation: *n* = 1; • PAI mutation: *n* = 1

Abbreviations: ART: assisted reproductive technology; EGPA: eosinophilic granulomatosis with polyangiitis; MTHFR: methylene tetrahydrofolate reductase; PA: psoriasic arthritis; PAI: plasminogen activator inhibitor; PAPS: primary APS; POCS: polycystic ovary syndrome.

performed after ovarian stimulation in 96 (86.5%): with the GnRH agonist protocol in 59 (61.4%), with the GnRH antagonist protocol in 26 (26.8%), with gonadotrophins only in 7 (7.3%) and with clomiphene in 4 (4.1%) cases. The median number of cycles per patient was 1.85, with a range of 1–7. Fifty-eight per cent of patients undergone only one procedure; the other 42% had made between two and seven attempts, but in all cases the type of procedure performed was the same.

Prophylaxis during ovarian stimulation procedures and complications

Data regarding the prophylactic therapy of the ovarian stimulation were available for 109 cycles (98.2%). Seventy-one (65.1%) cycles were treated: 23 (32.4%) with low-dose aspirin (LDA) only, 25 (35.2%) with a prophylactic dose of low-molecular-weight heparin (LMWH) and 23 (32.4%) with LDA plus prophylactic LMWH.

aPL were positive in 45 (40.5%) cycles: single positivity in 27, double in 13 and triple in 5. Of those cycles, 5 (2 single and 2 double positivity) were not subjected to prophylaxis, and no thrombotic events were reported.

We registered three (3.1%) cases of ovarian hyperstimulation syndrome (OHSS), all after IVF procedures performed with the agonist protocol. These patients were affected by SLE, UCTD and Churg–Strauss vasculitis, respectively. One of the patients (33.3%) presented major risk factors for OHSS development (young age, low body weight and polycystic ovary syndrome).

Outcome of procedures

Overall, 111 cycles yielded 46 pregnancies (41.4%), with a pregnancy rate of 38.7% for homologous procedures and 55.5% for heterologous procedures.

The global pregnancy rate was not influenced by mean maternal age at the time of the procedure (35.7 years in women with successful procedures *vs* 36.9 years in women with unsuccessful procedures, $P=0.20$). An adjusted analysis with pregnancy as the outcome (adjusting by fertility treatment, time under fertility treatment, number of times with fertility treatment, age, disease duration, thyroid alterations, etc.) was performed and did not show any statistical significance.

Homologous procedures

IUI was effective in 8 (61.5%) cases, homologous IVF in 19 (46.3%) and homologous ICSI in 9 (23.1%). Procedures performed during a natural cycle had a pregnancy rate of 87.5% ($n = 7/8$), those with the agonist protocol of 28.6% ($n=2/7$), with the antagonist protocol of 48% ($n=12/25$), with the gonadotrophin-only protocol of 40% ($n=2/5$) and with the clomiphene protocol of 0%.

The pregnancy rate was higher in younger women (mean age of 34.8 years in women with successful procedures *vs* 36.7 years in women with unsuccessful procedures, $P=0.05$).

Heterologous procedures

Heterologous IVF were effective in 3/3 (100%) and heterologous ICSI in 7/14 (50%) cases. The single case of embryo adoption was not effective.

The procedures performed during a natural cycle showed a pregnancy rate of 71.4% ($n=5/7$), those performed with the agonist protocol of 16.7% ($n=1/6$), with the antagonist protocol of 0% (0/1), with the gonadotrophin-only protocol of 100% ($n=2/2$) and with the clomiphene protocol of 100% (n: 2/2).

Mean maternal age at the time of the procedure did not influence the pregnancy rate (39 years in women with successful procedures *vs* 38.5 years in women with unsuccessful procedures, $P=0.83$).

We registered a mean number of transferred embryos of 1.6 (median: 2; range: 1–4). A single embryo transfer strategy was performed in 32 (31.2%) cases, with a pregnancy rate of 50%, whereas a multiple embryo transfer was applied in 48 (68.8%) cycles, with a pregnancy rate of 39.6% ($P=0.37$). The main variables (maternal age, autoantibodies, inherited thrombophilia, thyroid alterations, maternal disease, use of frozen or fresh embyos, and hormonal stimulation) that could have influenced the efficacy of the procedures were analysed, and we did not find any statistical significance.

Pregnancy prophylaxis and outcome

A prophylactic therapy was administered in 35 (76.1%) pregnancies: LDA in 9 (25.7%), prophylactic dosage of LMWH in 4 (11.4%), therapeutic dosage of Unfrationated Heparin in 1 (2.9%), LDA plus a prophylactic dosage of LMWH in 20 (57.1%), and LDA plus a therapeutic dosage of LMWH in 1 (2.9%).

Disease flares occurred in five (11.2%) pregnancies: four articular (two in RA patients, two in SLE patients) and one haematological (haemolytic anaemia in one SLE patient, after spontaneous discontinuation of therapy). None of the variables that could have influenced a flare onset (maternal age, autoantibodies, inherited thrombophilia, thyroid alterations, maternal disease, use of frozen or fresh embyos, and hormonal stimulation) showed statistical significance. No cases of thrombosis were reported.

Maternal complications other than flares and fetal–neonatal complications are reported in Table 2.

Both fetal ($P= 0.002$) and neonatal ($P=0.01$) complications were significantly higher in babies born from twin pregnancies.

We recorded 4 (7.6%) fetal malformations; specifically, one case of severe multiple malformations, 2 cases of partial corpus callosum agenesis and 1 case of major cardiac malformations. All malformations developed in twin pregnancies, carried by women affected by UCTD. The procedures performed to induce the pregnancies burdened with malformations were one IUI, one IVF and one ICSI. In two of the three gestations, women received stimulation with the agonist protocol, and in the other with the gonadotrophin-only protocol.

Regarding disease flares, none of the variables that could have influenced the onset of maternal and fetal

Table 2 Complications and neonatal features in the whole cohort and in the SLE/APS subgroup

Complication	Whole cohort (46 pregnancies)	SLE/APS patients (18 pregnancies)
Maternal complications	13 (30.2)	6 (33.3)
Gestational diabetes, *n* (%)	4 (8.7)	0
Thrombocytopenia, *n* (%)	2 (4.3)	2 (11.1)
Pre-eclampsia, *n* (%)	2 (4.3)	1 (5.5)
Placenta praevia, *n* (%)	2 (4.3)	2 (11.1)
Gestational hypothyroidism, *n* (%)	1 (2.1)	0
Gestational hypertension, *n* (%)	1 (2.1)	1 (5.5)
Cholestasis of pregnancy, *n* (%)	1 (2.1)	0
	Whole cohort (52 neonates)	**SLE/APS patients (20 neonates)**
Fetal complications	11 (21.1)	5 (25)
IUGR, *n* (%)	3 (5.8)	2 (10)
Oligo/anhydramnios, *n* (%)	3 (5.8)	3 (15)
SGA neonate, *n* (%)	1 (1.9)	0
Fetal malformations[a], *n* (%)	4 (7.7)	0
Neonatal complications	5 (1)	0
Neonatal hypoglycaemia, *n* (%)	1 (20)	0
Respiratory distress syndrome, *n* (%)	2 (40)	0
Intestinal resection due to ischaemia, *n* (%)	1 (20)	0
Neonatal jaundice, *n* (%)	1 (20)	0
Gestational week at delivery, median (IQR)	38 (37–39)	37 (36–38)
At term deliveries, *n* (%)	38 (84.4)[b]	14 (77.8)
Birth weight, median (IQR), g	3005 (2501–3270)	2860 (2342–3148)
Birth length, median (IQR), cm	49 (46–51)	48.5 (45–50)

[a]Details in the text.
[b]One woman lost to follow-up.
Abbreviations: IQR: interquartile range; IUGR: intrauterine growth restriction; SGA: small for gestational age.

complications showed statistical significance. We found a significantly higher incidence of fetal complications only in twin pregnancies, as previously reported.

Pregnancies yielded 38 singleton and 7 twin live births (for a total of 52 babies); 1 was lost to follow-up.

We report no miscarriages and 1 stillbirth for severe multiple malformations. The live birth rate was 98%, but we recorded 3 (6%) perinatal deaths in the first days of life owing to complications of very severe prematurity (24th, 25th and 29th weeks, respectively).

Puerperium

During the puerperium we recorded 1 (2.5%) post-partum haemorrhage (uterine atony after a pre-term caesarean section on the patient affected by EGPA, not treated with anticoagulant therapy during pregnancy) and 1 (2.5%) articular flare 3 weeks after delivery in a patient affected by RA who also experienced a disease reactivation during pregnancy (etanercept administered from the second trimester to 32 weeks of gestation).

Subanalysis of SLE and APS patients

We included in the study 58 cycles performed in 28 women affected by SLE and/or primary APS (20 SLE, 2 SLE+APS and 6 primary APS). Infertility was primary in 19 (68%) women and secondary in 9 (32%). Underlying causes of infertility were of female origin in 2 cases (7.1%), of male origin in 3 (10.8%), mixed in 1 (3.5%) and unknown in 22 (78.6%). Four patients had been exposed to CYC, and 1 (25%) of them had a premature ovarian failure. A subanalysis, adjusted by age and CYC treatment, did not show any statistical significance.

The median number of cycles performed per patient was 2.1, with a range of 1–5.

Ten procedures (17.2%) were performed during natural cycles, 48 (82.8%) after ovarian stimulation (30 with GnRH agonist, 12 with GnRH antagonist, 2 with clomiphene, and 4 with the gonadotrophin-only protocol). Overall, the 58 cycles yielded 18 pregnancies (16 singleton, 2 twin), with a global pregnancy rate of 31% (25.6% in homologous and 46.7% in heterologous procedures). No thrombotic events were reported. An OHSS onset was observed in 1 (2%) cycle (SLE patient after IVF with the agonist protocol), and a disease flare was recorded in 3 (5.1%) cases (all SLE patients: 2 mild articular flare, and 1 haematological flare after spontaneous discontinuation of therapy).

Maternal, fetal and neonatal complications are reported in Table 2.

We report no miscarriages. The live birth rate was 100%, but we recorded two (10%) perinatal deaths in the first days of life, owing to complications of very severe prematurity (24th and 29th weeks, respectively).

An adjusted analysis of flares by fertility treatment, age and disease duration in this sub-population could not be performed, owing to the small sample size.

Discussion

ARTs performed in rheumatic patients raise two important questions: whether they could confer risks additional to those reported for the general population (because they often require hormonal stimulation with gonadotrophins, which determine an oestrogenic peak) and whether, if performed, their effectiveness is affected by maternal disease.

In order to answer to both these questions, we analysed a case series of 111 ART procedures performed in a multicentre cohort of 60 rheumatic women.

The safety of the procedures seems to be assured by the fact that no case of thrombosis has been registered during hormonal stimulation or throughout pregnancy and the puerperium. This finding is even more reassuring considering that ∼40% of the procedures have been performed in aPL-positive women. We registered 3 (3.1%) cases of OHSS; this incidence is in line with that reported in the general population (3–8% of cycles, with peaks of 20% in high-risk categories [34]) and with data published in SLE and APS patients (0–6.2% [23–27] *vs* 2% in this subpopulation in our cohort). Disease flares were registered in 12.5% of pregnancies, with a higher frequency (albeit not significant) in women with CTDs and vasculitis than in those with arthritis, as reported for natural pregnancies [35]. No correlation with any of the potential precipitating factors, such as disease phenotype, autoantibody positivity and prophylactic therapy administered, has been found.

To compare our data with those previously published, we extracted the SLE and APS subpopulation from our cohort, and we noticed that during the 58 cycles performed in these patients only 3 (5.2%) disease flares were recorded, in line with what has been reported in the two most recently published cohorts [23, 27] (6.1%) and significantly lower than in the 3 older studies [24–26] (16–37.5%) [35].

Maternal complications other than disease flare developed in about one-third of the pregnancies. The incidence is not negligible, but it is consistent with that reported in the general population after ARTs; in particular: gestational diabetes in 8.7% of the pregnancies (*vs* 6–7% in the general population) [36] and gestational hypertension in 2.2% (*vs* 6–13%) [37]. A higher rate of maternal complications has been found after the transfer of frozen embryos (57 *vs* 21%), as reported in healthy women [38] and in patients affected by CTDs (10 *vs* 5% in those with arthritis).

Fetal complications were experienced in 22% of pregnancies and, not surprisingly, they were significantly more frequent in aPL-positive women (44 *vs* 10%) and during multiple pregnancies (57 *vs* 15.4%).

Regarding the efficacy of the procedures in rheumatic patients, the data seem to be satisfactory, with a cumulative pregnancy rate of 41.4%.

Analysing the possible influence of autoimmunity on the efficacy of the procedures, we cannot confirm the apparent negative role played by ANA and ENA antibodies previously reported in the literature [39].

The positivity for aPL does not seem to be a negative prognostic factor for the efficacy of procedures, and the administration of LDA and/or LMWH does not seem to improve the pregnancy rate. The prophylaxis is, however, indicated to protect the woman from thrombotic complications [20, 40].

The pregnancy rate registered in SLE and APS women was 37.5%, slightly higher than those previous reported (16–31%) [23–27], and the live birth rate was 100%, far above those recorded so far (50–87%) [23–27]. The cumulative live birth rate for the study was 98%, demonstrating that a tight control strategy, based on a multi-specialist follow-up of the pregnancy and the administration of correct prophylaxis, provides significant success rate.

Although the present study has clear limitations, mainly attributable to the small sample size, the lack of a control group and the inclusion of different protocols, some important points seem to emerge: the safety and the efficacy of the ARTs seems to be confirmed in rheumatic patients, regardless of their autoimmune profile; thromboprophylaxis during ovarian stimulation and, if appropriate, during pregnancy, seems to protect patients against the increased risk connected to the oestrogenic peak, although it did not improve pregnancy rate: the choice of therapy should therefore be made depending on the patient risk profile, irrespective of whether the pregnancy is natural or artificially induced; the rate of fetal–maternal complications is in line with that observed in the general population after ARTs and in spontaneous gestation in rheumatic patients, indicating that the disease itself, rather than the procedure applied, is probably the cause of their onset; maternal disease flares were mild or moderate in severity, without any influence on gestational outcome; in lupus patients, the incidence of flares was lower than that reported in spontaneous gestations, suggesting that the flare onset is probably determined by the pregnancy itself rather than by ARTs; a single embryo transfer strategy should be recommended in order to avoid twin pregnancies and improve gestational outcomes.

The main achievement of this multicentre study is that no evidence was found to advise against the application of ARTs in rheumatic patients. Pre-conception counselling is essential to determine the best time for pregnancy, to adjust the prophylactic treatment and to ensure the best gestational outcome [41]. No additional or closer monitoring than that applied in natural pregnancies seems to be needed in women with RDs.

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