The outcome of assisted reproductive techniques in women with autoimmune disorders

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The Outcome of Assisted Reproductive Techniques in Women with Autoimmune Disorders

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Abbreviations

1. aCL – Anti-Cardiolipin Antibody
2. ACPA – Anti-Citrullinated Protein Antibody
3. AITD – Autoimmune Thyroid Disease
4. AMH – Anti-Mullerian Hormone
5. ANA – Anti-Nuclear Antibody
6. Anti-β2GPI – Anti-β2-Glycoprotein I Antibody
7. Anti-dsDNA – Anti-Double-Stranded DNA Antibody
8. AOA – Anti-Ovarian Antibody
9. Anti-Sm – Anti-Smith Antibody
10. aPL – Antiphospholipid Antibody
11. APS – Antiphospholipid Syndrome
12. ARTs – Assisted Reproductive Techniques
13. AZA – Azathioprine
14. BD – Behçet's Disease
15. BHPR – British Health Professionals in Rheumatology
16. BSR – British Society for Rheumatology
17. CD – Crohn's Disease
18. COS – Controlled Ovarian Stimulation
19. CP – Cyclophosphamide
20. CSs – Corticosteroids
21. CSA – Cyclosporin A
22. DMARDs – Disease-Modifying Anti-Rheumatic Drugs
23. ECCO – European Crohn's and Colitis Organization
24. ESRF – End-Stage Renal Failure
25. EULAR – European League Against Rheumatism
26. FSH – Follicle Stimulating Hormone
27. GD – Graves' Disease
28. GnRH – Gonadotropin-Releasing Hormone
29. HCQ – Hydroxychloroquine
30. HLA – Human Leukocyte Antigen
31. HPG – Hypothalamic-Pituitary-Gonadal Axis
32. IBD – Inflammatory Bowel Disease
33. ICSI – Intracytoplasmic Sperm Injection
34. IFNγ – Interferon Gamma

35. IL – Interleukin
36. IVF – In Vitro Fertilization
37. LA – Lupus Anticoagulant Antibody
38. LEF – Leflunomide
39. LH – Luteinizing Hormone
40. LMWH – Low Molecular Weight Heparin
41. LT4 – Levothyroxine
42. LUF – Luteinized Unruptured Follicle Syndrome
43. MCP – Metacarpophalangeal (Joint)
44. MTX – Methotrexate
45. NSAIDs – Non-Steroidal Anti-Inflammatory Drugs
46. OHSS – Ovarian Hyperstimulation Syndrome
47. PIP – Proximal Interphalangeal (Joint)
48. POI – Premature Ovarian Insufficiency
49. RA – Rheumatoid Arthritis
50. RANKL – Receptor Activator of Nuclear Factor Kappa B Ligand
51. RF – Rheumatoid Factor
52. SCH – Sub-Clinical Hypothyroidism
53. SHBG – Sex Hormone Binding Globulin
54. SLE – Systemic Lupus Erythematosus
55. STB – Syncytiotrophoblast
56. T3 – Triiodothyronine
57. T4 – Thyroxine
58. TAI – Thyroid Autoimmunity
59. TBG – Thyroid-Binding Globulin
60. T1DM – Type 1 Diabetes Mellitus
61. TgAb – Anti-Thyroglobulin Antibody
62. TNF – Tumor Necrosis Factor
63. TPOAb – Anti-Thyroid Peroxidase Antibody
64. TR-α1 – Thyroid Hormone Receptor α1
65. TR-β1 – Thyroid Hormone Receptor β1
66. TRH – Thyrotropin-Releasing Hormone
67. TSH – Thyroid-Stimulating Hormone
68. TSI – Thyroid-Stimulating Immunoglobulin
69. UC – Ulcerative Colitis
70. WHO – World Health Organization

Content

1. Abstract

Infertility is estimated to affect about 8-12% of reproductive-aged couples across the globe. It is a clinical manifestation of different etiological factors, which may affect males, females, or both. The distribution of the most common causes affecting female fertility varies among different countries; and in developed countries it usually involves disorders of ovulation, endometriosis, pelvic adhesions, fallopian tube blockage, as well as hyperprolactinemia. Autoimmune diseases may also play a role in female infertility, however, in practice it is often overlooked, as it is not considered to be a major cause of female infertility. Nevertheless, we have to be aware of the possible contribution to the diagnosis of infertility, as well as the effect of the treatment of infertility on the course of the disease.

As there is an overall increased prevalence of women with autoimmune disorders seeking infertility treatments, the objectives of this paper were to: a) assess the association between potential fertility impairment and several autoimmune diseases; including systemic lupus erythematosus, antiphospholipid syndrome, autoimmune thyroid disease, rheumatoid arthritis, inflammatory bowel disease, and Behçet's disease; b) learn whether assisted reproductive techniques and the associated hormonal stimulation, may confer additional risk in patients with autoimmune diseases, such as disease flares and other maternal complications; c) learn whether assisted reproductive techniques outcome may be potentially impaired by the underlying disease.

A literature search on PubMed showed 109 related articles. There were 63 relevant articles that were included in this review. When considering all included articles, assisted reproduction generally seems to be safe in patients with the autoimmune diseases mentioned above; however, it is of great importance that the patients are in stable disease remission, and adequately treated. Nevertheless, the available data concerning the relationship between complications associated with the above mentioned diseases and assisted reproduction, seem to be very limited and somewhat controversial, and further research is therefore needed to better understand these issues.

Keywords: assisted reproductive techniques, female infertility, autoimmune diseases and infertility.

2. Sažetak

Neplodnost se dijagnosticira u otprilike 8-12% parova reprodukcijske dobi. To je klinička manifestacija različitih etioloških čimbenika koji mogu utjecati na jednog ili oba partnera. Raspodjela najčešćih uzroka koji utječu na plodnost žena nije ista u svim zemljama.
U razvijenim su zemljama najšeći uzroci poremećaj ovulacije, endometrioza, priraslice u zdjeliic, neprohodni jajovodi i hieprprolaktinemija. Autoimune bolesti također mogu imati važnu ulogu u neplodnosti kod žena, no u praksi ih se često previđa jer se njihova uloga podcjenjuje. Međutim, moramo biti svjesni uloge koju autoimune bolesti mogu imati u neplodnosti te učinak liječenja neplodnosti na tijek osnovne bolesti.

Obzirom da je prevalencija autoimunih bolesti u populaciji žena koje liječe neplodnost u porastu, ciljevi ovog rada su bili: a) procijeniti povezanost izmežu neplodnosti i najčešćih autoimunih bolesti, uključujući sistemski eritemski lupus, antifosfolipidni sindrom, autoimunu bolest štitnjače, reumatoidni artritis, upalnu bolest crijeva i Behçetovu bolest; b) ustanoviti mogu li metode pomognute oplodnje te hormonska stimulacija povezana s njima, utjecati na dodatni rizik pacijentima s autoimunim bolestima; kao što su pogoršanje tijeka bolesti i ostale komplikacije tijekom trudnoće; c) te istražiti može li i osnovna bolest ugroziti ishod liječenja metodama pomognute oplodnje.

Pretraga literature na PubMedu pokazala je 109 povezanih članaka. U ovaj rad uključena su 63 relevantna članka. Medicinski pomognuta oplodnja čini se sigurnom u liječenju bolesnica s navedenim autoimunim bolestima. Međutim, vrlo je važno da pacijenti budu u stabilnoj remisiji bolesti i da su primjereno liječeni. Ipak, dostupni su podaci o vezi između komplikacija osovne bolesti i metoda pomognute oplodnje vrlo ograničeni i dijelom kontroverzni te su stoga neophodna daljnja istraživanja, kako bi bolje razumjeli tu uzročno- posljedična vezu.

Ključne riječi: metode pomognute oplodnje, neplodnost kod žena, autoimune bolesti i neplodnost.

3. Introduction

Infertility is classified as a disease, which is "*historically defined by the failure to achieve a successful pregnancy after 12 months or more of regular, unprotected sexual intercourse or due to impairment of a person's capacity to reproduce either as an individual or with her/his partner*" [1,2]. Female infertility is further classified into primary and secondary infertility. Primary female infertility is diagnosed in a woman who has never had a clinical pregnancy, and meets the criteria of being classified as having infertility; while secondary female infertility is diagnosed in a woman unable to establish a clinical pregnancy, but who has been diagnosed with a clinical pregnancy previously [3].

Infertility is a common condition, which is estimated to affect 8-12% of reproductive-aged couples across the globe. The prevalence of female infertility differs among different countries, and is estimated to affect one out of seven couples of reproductive age in developed countries, and one out of four couples in developing countries [4,5].

A systematic analysis [6] of 277 health surveys for the time period 1990-2010 was conducted, in order to provide an insight into global trends in infertility, and to estimate the prevalence of primary and secondary infertility among women aged 20-44. The information was obtained from 190 countries and territories, which were grouped into seven regions: High Income, Central/Eastern Europe and Central Asia, South Asia, East Asia/Pacific, North Africa/Middle East, Sub-Saharan Africa and Latin America/Caribbean. According to the results, infertility levels among child-seeking women did not change significantly over the two decades in most regions, with a minor decrease from 2.0% to 1.9% for primary infertility, and an increase from 10.2% to 10.5% for secondary infertility. However, the absolute number of affected couples by primary and secondary infertility increased globally, from 42.0 million in 1990 to 48.5 million in 2010, as a result of a general population growth. Out of the 48.5 million couples affected by infertility, 19.2 million cases were attributed to primary infertility, and 29.3 million to secondary infertility.

The prevalence of primary infertility was found to be higher among women in the age group of 20-24 years (2.7%), in comparison to 25-29 (2.0%) and 30-44 (1.6-1.7%). Contrarily, the prevalence of secondary infertility was significantly higher in the age group 40-44 years (27.1%), in comparison to 20-24 (2.6%) (figure 1).

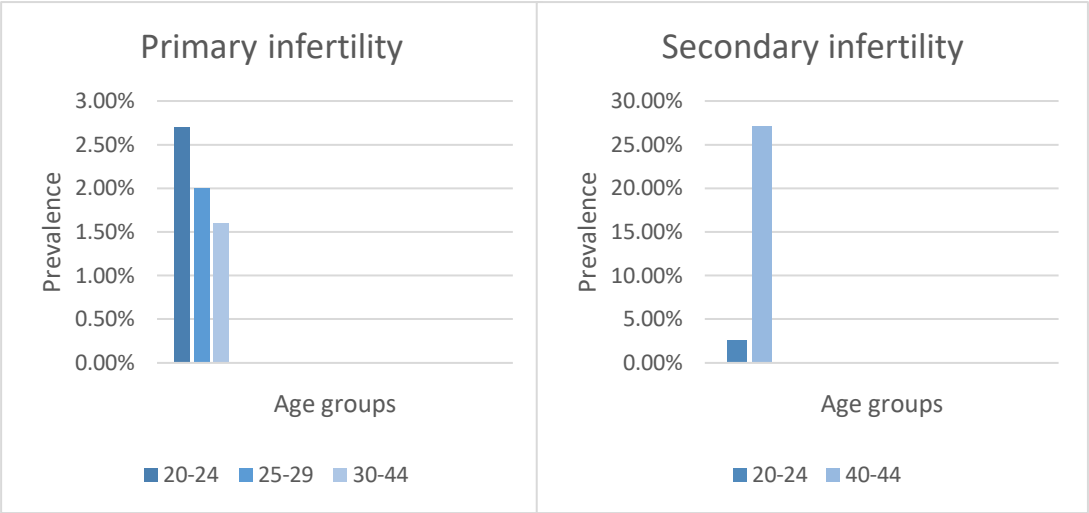

Figure 1: **Global prevalence of primary and secondary infertility in 2010, according to age groups**. The figure above is based on data obtained from the article "National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys" [6].

Despite the general increase in the absolute number of affected couples globally, the number of affected couples has, in fact, decreased in certain regions. These include "High Income" countries, in which infertility was reduced from 4.2 million to 3.6 million over the two decades; and in the Central/Eastern Europe and Central Asia region, in which a reduction from 4.4 million to 3.8 million was noted. According to the authors, this is possibly associated, among other reasons, with changes in fertility preferences and reduced child-seeking behavior in these regions.

Infertility is a clinical manifestation of different etiological factors, which may affect males, females, or both. According to a study conducted by the World Health Organization (WHO) of 8500 couples from 25 countries throughout the world, female causes of infertility were reported in 37% of the couples in developed countries, male causes were reported in 8%, and both female and male causes were reported in 35%. The remaining couples in the study were either able to conceive (15%), or the cause of infertility remained unknown (5%) [7,8].

The distribution of the most common causes of female infertility varies among different countries, and among developed and developing countries. For example, the rates of infection-related bilateral tubal occlusion in developing countries (e.g., Sub-Saharan Africa), are higher than those in developed countries [8]. In developed countries, the most common etiologies of female infertility include disorders of ovulation (25%), endometriosis (15%), pelvic adhesions (12%), fallopian tube blockage (11%), other fallopian tube abnormalities (11%), and hyperprolactinemia (7%) [7,8].

Female infertility may also be associated with uterine-related conditions (e.g., fibroids, anomalies, adhesions), cervical-related conditions (e.g., congenital malformations, trauma), genetic causes, and different factors such as advancing female age. It may also remain unexplained (idiopathic), if a thorough evaluation has not revealed a definite cause.
Lastly, although less common, infertility may be associated with immune factors as well [7].

Autoimmune diseases are the result of abnormal immune reactions against self ("*auto*") antigens, to which normal persons are tolerant. The immune response could be directed against a particular organ or cell type, resulting a localized tissue damage; or multiple organs, causing a systemic disease. There are two recognized mechanisms by which self-reactivity is prevented, the "*central tolerance*", which involves the deletion of self-reactive T and B lymphocytes, as well as receptor editing of self-reactive B cells in central lymphoid organs; and "*peripheral tolerance*", which involves functional inactivation of lymphocytes (*anergy*), suppression by regulatory T cells, deletion by apoptosis, as well as sequestration of certain self-antigens. It is believed that failure of self-tolerance and development of autoimmunity arise from a combination of both genetic and environmental factors, that may influence lymphocyte tolerance and alter the presentation of and response to self-antigens [9].

The prevalence and incidence of autoimmune diseases vary among different diseases, and may differ between geographical regions. However, the overall prevalence of autoimmunity is estimated to be 3-5% in the general population [10,11,12]. The prevalence tends to increase in first-degree relatives and in monozygotic twins (approximately five times higher, and a further five times increase, respectively); and a strong gender bias of most autoimmune diseases is recognized, with many of these diseases being more common in women in comparison to men [9,10,13].

Different factors associated with autoimmune diseases have been reported as contributing to impaired female fertility and pregnancy loss [14]. Nevertheless, autoimmune diseases are not listed among the most common etiologies of female infertility, and consequently may be overlooked; despite the fact that women are more commonly affected by most of the autoimmune diseases, often during their reproductive age.
Moreover, an overall increase in prevalence of women with autoimmune disorders seeking infertility treatments is noted [15], including assisted reproductive techniques (ARTs).

According to the WHO, ARTs are defined as: "*all treatments or procedures that include the in vitro handling of both human oocytes and sperm or of embryos for the purpose of establishing a pregnancy. This includes, but is not limited to, in vitro fertilization and embryo transfer, gamete intrafallopian transfer, zygote intrafallopian transfer, tubal embryo transfer, gamete and embryo cryopreservation, oocyte and embryo donation, and gestational surrogacy*" [2].

As there is an increased use of ARTs in women with autoimmune diseases, it is of great importance to take into consideration the effect of ARTs and pregnancy on maternal disease, the impact of disease activity on ARTs outcome and pregnancy, as well as the safety of medications used to control maternal disease during pregnancy.

4. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease in which multiple organs might be involved, mainly through the deposition of immune complexes and binding of a spectrum of autoantibodies to various tissues. Among the different antibodies associated with SLE, commonly reported are the anti-nuclear antibodies (ANAs), anti-double-stranded DNA (Anti-dsDNA), anti-Smith (Anti-Sm) and antiphospholipid (aPL) antibodies. Although any organ may be affected, SLE predominantly affects the skin, joints, kidneys and serosal membranes. Hematologic disorders (e.g., cytopenias), neuropsychiatric disorders (e.g., convulsions, psychosis), as well as cardiovascular manifestations (e.g., valvular "Libman-Sacks" endocarditis) are also observed [9].

The disease predominantly affects women, with a female to male ratio of 9:1 in the age group of 17-55 years. Although SLE may present at any age, it is most often associated with women of reproductive age, especially around their twenties or thirties [9].

The worldwide incidence and prevalence of SLE vary among different countries and ethnic groups. The estimates of incidence and prevalence were reported to be the highest in North America (23.2/100,000 person-year and 241/100,000 persons, respectively), while the lowest incidence was in Africa and Ukraine (0.3/100,000 person-year), and the lowest prevalence in Northern Australia, where no cases of SLE were found in a community study. The incidence and prevalence are reported to be the highest in people of black ethnicity, intermediate in Asian and Hispanic ethnic groups, and the lowest in people of white ethnicity [16-21].

4.1. The association between SLE and impaired female fertility

It appears that menstrual irregularity and anovulation are present in 53% of women with SLE under age of 40. This is possibly associated with high disease activity and high doses of steroid therapy. Corticosteroids (CSs) can impair ovarian function either by influencing the hypothalamic-pituitary-gonadal axis, or directly by binding to CSs receptors on ovarian cells. Other medications used by patients with SLE that may impair fertility include non-steroidal anti-inflammatory drugs (NSAIDs), as well as cyclophosphamide (CP) which might be prescribed in severe cases of organ impairment. The use of NSAIDs may lead to luteinized unruptured follicle syndrome (LUF), whereas CP has been shown to induce premature ovarian insufficiency (POI) [14,15,22-25].

Low levels of anti-mullerian hormone (AMH) were also noted in patients with severe SLE disease and certain prolonged immunosuppressive treatments; and are found to be associated with reduced ovarian reserve [15,26]. Other possible SLE associated factors that were found to impair female fertility include anti-ovarian antibodies (AOAs), nephritis, and aPL antibodies. Anti-ovarian antibodies may result autoimmune oophoritis in SLE patients, which can impair ovarian function, leading to POI [14,15]. Lupus associated nephritis may result in end stage renal failure, causing hyperprolactinemia, hypogonadotropism and amenorrhea [14,27]. Lastly, it is estimated that between 20-60% of women with SLE are positive for serum aPL antibodies, which may be associated with pregnancy loss [14,15,28].

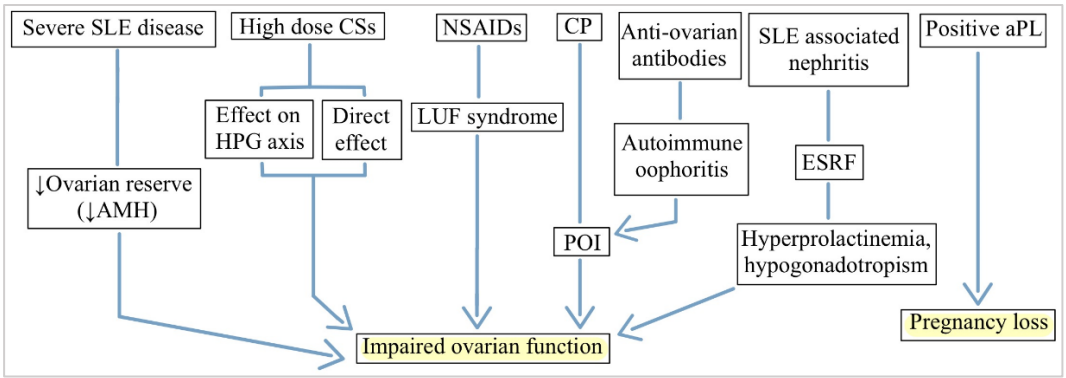

Figure 2: Summarized representation of the different factors associated with SLE, that may impair fertility [14,15,22-28]. **SLE**, systemic lupus erythematosus; **AMH**, anti-mullerian hormone; **CSs**, corticosteroids; **HPG**, hypothalamic-pituitary-gonadal axis; **NSAIDs**, non-steroidal inflammatory drugs; **LUF**, luteinized unruptured follicle syndrome; **CP**, cyclophosphamide; **POI**, premature ovarian insufficiency; **ESRF**, end-stage renal failure; **aPL**, antiphospholipid antibodies.

4.2. Assisted reproductive techniques and SLE

According to a study conducted by Sayaka Tsuda et al [29], the frequency of ARTs appears to be higher in patients with SLE than the general population (11.4% vs 5.1%). The authors also observed an increased risk of disease flare ups during pregnancy (14.7% vs 4.5% prior to conception), as well as increased prevalence of adverse pregnancy outcomes in SLE-complicated pregnancies in comparison to the general population; including preterm delivery (39.4% vs 5.6%), preeclampsia (15.0% vs 5.6%), fetal growth restriction (12.9% vs 4.1%), thromboembolism (2.8% vs 0.1%), and low birth weight (59.6% vs 9.5%). The above adverse pregnancy outcomes were found to be associated with certain risk factors, including active disease during pregnancy, history of lupus nephritis, and increased maternal age.

However, according to another study by Rossella Reggia et al [30], the incidence of disease flares during ART procedures was actually lower than that reported for spontaneous pregnancies, suggesting that it not associated with assisted reproduction. No cases of thrombosis were reported during hormonal stimulation, pregnancy and puerperium. However, 65.1% of the participants were treated with either low-dose aspirin, low molecular weight heparin (LMWH), or combination of the drugs, as a prophylactic therapy during ovarian stimulation procedures; while 76.1% were treated during pregnancy as well. The incidence of both maternal and fetal complications was consistent with that reported in the general populations following assisted reproduction; including ovarian hyperstimulation syndrome (OHSS), thrombocytopenia, preeclampsia, placenta previa, gestational hypertension, intrauterine growth restrictions, oligo/anhydramnios and perinatal death. Finally, the authors concluded that the efficacy of ARTs in these patients does not seem to be adversely affected by maternal disease.

In another study, conducted by Pauline Orquevaux et al [31], the authors observed eight in vitro fertilization (IVF) cycles (about 8%) that were complicated by SLE flares (four cases), and thromboembolic events (another four cases), in patients with lupus, as well as in those with lupus and anti-phospholipid antibody syndrome. However, four of the complicated cases (two SLE flares and two thromboembolic events) occurred in patients with poor treatment adherence, while almost all other women were in clinical remission during ovarian stimulation. No cases of OHSS were reported. The pregnancy and live-birth rates were close to that reported in the general population (28% and 85%, respectively). Therefore, given the low complications rate, the authors concluded that IVF can be safely and successfully performed in women with SLE who are in clinical remission and with good treatment adherence.

Contrarily, Ragab A. et al [32] observed four cases (8.9%) of lupus flare, and another four cases (8.9%) that were complicated by OHSS, following ovulation induction. The authors suggested that this could be associated with certain ovulation induction protocols, as gonadotropins are associated with an increased risk of lupus flares and OHSS, in comparison to other treatment protocols such as those involving clomiphene. Nevertheless, the authors concluded that ovarian stimulation seems to be safe and successful when the disease is in clinical remission, and when appropriate co-adjuvant therapy is administered, including prophylactic anticoagulants and immunosuppressants.

Other studies reported an association between AOA and ARTs failure [33]; however, no association was found between AOA and poor response to controlled ovarian stimulation (COS) [34], nor any significant impact of COS on the level of autoantibodies, including ANAs and AOA [35,36].

As can be observed from the above studies, active disease may be associated with adverse pregnancy outcomes. Therefore, it seems rational to delay conception, both natural and by ARTs, until clinically stable disease is achieved. In certain cases, as in patients with severe SLE disease, immediate therapy with CP may be required. As CP may cause POI [37], several studies proposed the treatment with gonadotropin-releasing hormone (GnRH) agonists, as a mean of preventing POI [38-41], and possibly with GnRH antagonists as well [42]. According to the European League Against Rheumatism recommendations (EULAR) [43], fertility preservation with GnRH agonists should indeed be considered prior to the use of alkylating agents. In regards to medications administered during ART procedures, antiplatelets and/or anticoagulants should be used in women with lupus and anti-phospholipid antibody syndrome. Hydroxychloroquine (HCQ), oral CSs, azathioprine (AZA), cyclosporin A (CSA) and tacrolimus can all be used to prevent or manage SLE flares during pregnancy. Moderate-severe flares can be additionally managed with CS intravenous pulse therapy, intravenous immunoglobulin and plasmapheresis. However, mycophenolic acid, leflunomide (LEF) and methotrexate (MTX) should be avoided due to teratogenic effects.

Taken together, it appears that the information regarding the outcome of ARTs in women with SLE is very limited. Most of the articles included have certain important limitations, including a retrospective study design and small sample size. Therefore, further research is warranted in order to confirm the results, and to have a better understanding of the effect of ARTs on the underlying disease, and vice versa.

5. Anti-phospholipid antibody syndrome

Anti-phospholipid antibody syndrome (APS) is an autoimmune disease, associated with circulating antibodies that bind different phospholipids and proteins, including plasma protein β2-glycoprotein I, that is found on the surface of endothelial cells and trophoblasts, and prothrombin. Commonly tested antibodies are lupus anticoagulant (LA), anti-cardiolipin (aCL), and anti-β2-glycoprotein I (anti-β2GPI) antibodies. It is hypothesized that these antibodies induce hypercoagulable state, through uncertain mechanism. The clinical picture of APS is variable. Depending on the vascular bed involved, patients may develop venous or arterial thrombosis, that may lead to pulmonary embolism and pulmonary hypertension, cerebral and ocular ischemia, bowel infarction, as well as renovascular hypertension. Other clinical manifestations include cardiac valve vegetations and thrombocytopenia [9,15,44].

Anti-phospholipid antibody syndrome has a primary and secondary forms. In primary APS, patients only present with manifestations of a hypercoagulable state, with no associated autoimmune disorders; and it may appear following exposure to certain medications or infections. In secondary APS, the patients have an associated autoimmune disorder, such as SLE [9].

The disease predominantly affects women, with a female to male ratio of 5:1; and is more common in young to middle-aged adults. However, it may also manifest in children and elderly [45,46]. The incidence of APS is estimated to be 5/100,000 persons per year, and the prevalence in approximately 40-50/100,000 persons [47]. According to a critical review conducted by Laura Andreoli et al [48], the frequency of aPL is estimated to be 13.5% in patients with stroke, 11% in myocardial infarction, and 9.5% in deep vein thrombosis. However, due to certain limitations of the reviewed literature (e.g., old literature, heterogeneous cutoffs), further research should be performed with appropriately designed studies, in order to confirm these estimations.

5.1. The association between APS and impaired female fertility

The frequency of aPL in patients with pregnancy morbidity is estimated to be 6% [48]. Female patients with positive aPL antibodies may develop venous or arterial thrombosis, which may be associated with recurrent spontaneous miscarriages. Fetal loss is also believed to stem from an antibody-mediated interference with the growth and differentiation of trophoblasts, leading to placentation failure [9].

The association between aPL antibodies and infertility per se, however, is still debated. Nevertheless, infertile women are commonly screened for aPL, and an increased rate of positive aPL antibodies tests has been reported [15]. In a study conducted by Mario Vega et al [49], a total of 351 infertile female patients were investigated for positive immune tests, including aPL antibodies, to inspect whether there is an association with low AMH levels. According to the results, 50 women (14.2% of the participants in the study) who had abnormally elevated levels of one or more aPL antibodies, were also reported to have significantly low levels of AMH. However, according to Jamilya Khizroeva et al [15], it was not clear whether the women participated in the study were healthy carriers or affected by an autoimmune disease, and what was their disease activity, if present, at time of sampling; which altogether were a major limiting factor in the study.

Another systematic review aimed to identify whether there is an association between aPL and infertility, was conducted by Cecilia B. Chighizola et al [50]. In the selected studies, aCL antibodies were most commonly assayed (93.5%, 29/31 of the studies), while the other two criteria aPL antibodies, LA and anti-β2GPI, were only tested in 41.9% (13/31) and 12.9% (4/31) of the studies, respectively. Also, 48.4% (15/31) of the studies assessed non-criteria aPL antibodies. According to their results, almost half (45%) of the studies confirmed an association between aCL antibodies and infertility; while 31% confirmed an association with LA antibodies, and 75% with anti-β2GPI antibodies. A positive association with infertility was also found among studies assessing non-criteria aPL, with a rate of association ranging from 44.4 to 83.3%.

That being said, several limitations in the selected studies were observed; including wide heterogeneity in study populations, and aPL cutoffs which do not follow the international guidelines. Also, the association between aPL and ARTs outcome was not supported by most selected studies, and treating aPL-positive women did not seem to improve ARTs outcome. Therefore, it is still not clear whether testing the positivity to aPL antibodies is clinically significant, and it is generally not recommended in international guidelines. The authors concluded that further, well-designed studies are warranted in order to investigate the relationship between aPL antibodies and infertility, and to achieve a more conclusive, evidence-based recommendations about aPL testing in infertile women [15,50].

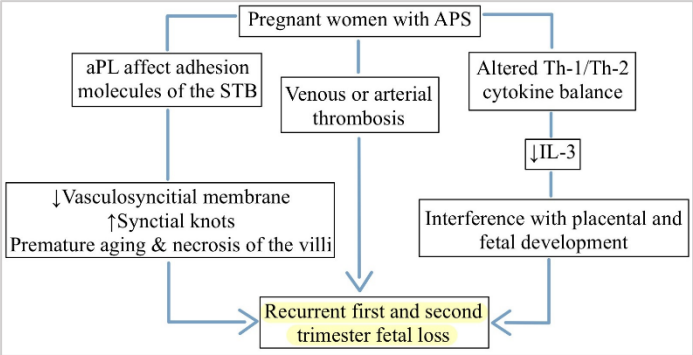

Figure 3: Possible pathophysiological mechanisms associated with fetal loss in women with APS [9,14,51-54]. **aPL**, antiphospholipid antibodies; **STB**, syncytiotrophoblast; **IL-3**, interleukin 3.

5.2. Assisted reproductive techniques and APS

In the study conducted by Rossella Reggia et al [30], no cases of thrombosis were reported in patients with APS; however, as was stressed previously, a great percentage of the participants were treated prophylactically. No cases of OHSS were reported, and in a sub-analysis of SLE and/or APS patients, the incidence of other maternal complications was consistent with that reported in the general populations following assisted reproduction. However, fetal complications were significantly more frequent in aPL-positive women (44% vs 10%). Nevertheless, the authors concluded that positivity for aPL does not seem to be a negative prognostic factor for the efficacy of the ART procedures. However, other studies suggest that aPL antibodies, among others, can significantly reduce the success of assisted reproduction, and cause obstetrical complications as well [33,55,56].

According to Pauline Orquevaux et al [31], out of eight IVF complicated cycles (8%), there were four cases of SLE flares (in three women), of which two patients were diagnosed with SLE+APS, and one patient with SLE only. Another four cases of thromboembolic events were reported in two patients with SLE+APS, and two patients with primary APS. However, no cases of disease flares nor thromboembolic events were reported in patients with SLE which are aPL positive, suggesting that it is not enough to result in these complications.
As mentioned previously, half of the complicated cases occurred in patients with poor treatment adherence. The authors concluded that IVF can be safely and successfully performed in women with SLE and/or APS who are in remission, and adequately treated.

According to EULAR recommendations [43], antiplatelets and/or anticoagulants should be used in women with primary APS or SLE+APS, in order to prevent complications.
As the data are very limited, further research is needed in order to better understand the effects of assisted reproduction on women with APS, and whether APS can impair ARTs outcome.

6. Autoimmune thyroid disease

The term "autoimmune thyroid disease" (AITD) encompasses a variety of thyroid conditions, in which their underlying pathophysiology involves antibody-mediated disturbances in the thyroid function. Hashimoto thyroiditis and Graves' diseases (GD) are among the most common causes of thyroid dysfunction.

Hashimoto thyroiditis is the most common cause of hypothyroidism, where iodine levels are sufficient. It is caused by multiple immunologic mechanisms, including production of autoantibodies anti-thyroglobulin antibody (TgAb), and anti-thyroid peroxidase antibody (TPOAb) to thyroid antigens, which leads to cell-mediated cytotoxicity, and gradual depletion of functional thyroid tissue with formation of fibrosis. Hashimoto is usually characterized by painless enlargement of the thyroid and hypothyroidism, with low triiodothyronine and thyroxine (T3 and T4, respectively), and high thyroid-stimulating hormone (TSH) levels. However, different clinical presentations are possible, including the disruption of thyroid follicles, that may lead to the release of thyroid hormones, causing a transient thyrotoxicosis. Patients with Hashimoto thyroiditis often have other autoimmune disorders [9].

It is the most common autoimmune disease, with a prevalence estimated between 10-12% in the general population. The prevalence is higher in females, with a female to male ratio ranging from 10:1 to 20:1; and increases with age, most commonly presented at ages 45-65. The worldwide incidence is estimated to be 30-150/100,000 persons per year [9,57,58].

Graves' disease is the most common cause of endogenous hyperthyroidism. There are multiple auto-antibodies involved in the pathophysiological processes underlying the disease, including thyroid-stimulating immunoglobulin (TSI), which is detected in almost all patients. The above antibody binds to TSH receptors, stimulating adenylyl cyclase to increase serum levels of thyroid hormones. T-cell mediated immune response is also involved, and contributes to some of the clinical manifestations associated with the disease. The disease may be characterized by thyrotoxicosis, ophthalmopathy with exophthalmos (40% of the patients), and pretibial myxedema (in minority of cases); as well as elevated serum T3 and T4, and depressed serum TSH levels. However, it might show no associated thyroid dysfunction, and therefore, can remain undiagnosed [9,15].

As with Hashimoto thyroiditis, there is an increased frequency of other autoimmune diseases occurring concomitantly, including SLE, pernicious anemia, type 1 diabetes mellitus (T1DM) and Addison disease [9].

Graves' disease more commonly affects women, with a female to male ratio of up to 7:1, and a peak incidence between 20-40 years of age. The incidence is estimated to be 20-50/100,000 persons per year. Genetic factors are also involved in GD, and the incidence was shown to be increased among relatives of affected patients and in monozygotic twins [9,59,60].

6.1. The association between AITD and impaired female fertility

AITDs are prevalent in women of reproductive age, and have been found to be associated with adverse pregnancy outcome and impaired fertility. The relative risk of female infertility was reported to be increased in patients with TPOAb (RR=2.25; 95% CI 1.02-5.12, p=0.045); while significant number of women with recurrent pregnancy loss were found to have both TgAb and TPOAb [15,61,62].

Multiple reproductive organs and tissues were found to have receptors for TSH and/ or thyroid hormones, such as thyroid hormone receptor α1 (TR-α1) and thyroid hormone receptor β1 (TR-β1). These include ovarian surface epithelium, oocytes, granulosa cells, ovarian stromal cells, and endometrium. Therefore, TSH and thyroid hormones seem to have a role in the regulation of ovarian function, and perhaps of other reproductive organs as well. Furthermore, T3 hormone was found to modulate the action of luteinizing hormone (LH) and FSH; while TSH was found to stimulate granulosa cells, thereby further demonstrating the interaction between the hypothalamic-pituitary-thyroid axis and the reproductive system. According to the above findings, it seems that an adequate level of thyroid hormones is important for the normal functioning of the reproductive system, and therefore, thyroid dysfunction has been proposed as a possible factor contributing to adverse fertility and pregnancy outcomes [15,61,63,64].

Hypothyroidism has been shown to affect ovarian function via several mechanisms, including reduction in sex hormone binding globulin (SHBG), and hyperprolactinemia, which is present in 46% of women with hypothyroidism. The elevated prolactin levels are caused by increased thyrotropin-releasing hormone (TRH) secretion. The resultant hyperprolactinemia interferes with the pulsatile secretion of GnRH, causing ovulatory dysfunction. Moreover, thyroid hormones were shown to be involved in the production of estrogen and progesterone, and therefore, inadequate thyroid hormones levels may cause infertility [15].

Other hormonal changes associated with hypothyroidism include increased serum androstenedione and estrone, as a result of a decrease in metabolic clearance; as well as increased peripheral aromatization. Together with the decrease in SHBG, the unbound form of these sex hormones is increased, causing hormonal disturbances. The clinical presentation may encompass changes in menstrual cycle length and volume of bleeding, including oligomenorrhea and amenorrhea, as well as polycystic ovaries. Menstrual abnormalities are estimated to affect 25-60% of women with hypothyroidism, in comparison to 10% in women with normal thyroid function [15,61].

Due to limited data in literature, the extent to which hyperthyroidism is associated with infertility is not well established. However, menstrual disturbances are commonly reported in women with hyperthyroidism (up to 65%, in comparison to 17% in healthy women), and may include hypomenorrhea, hypermenorrhea, oligomenorrhea, and polymenorrhea. Hyperthyroidism is associated with early pregnancy loss if not treated properly [61].

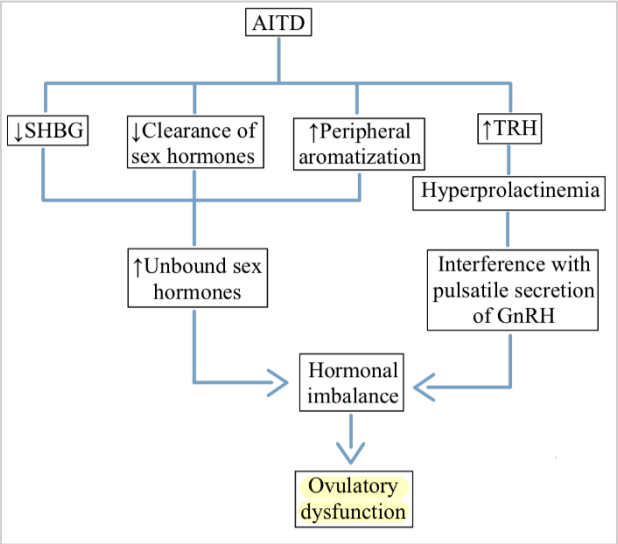

Figure 4: Summarized representation of the pathophysiological mechanisms associated with infertility in women with autoimmune hypothyroidism [15,61]. **AITD**, autoimmune thyroid disease; **SHBG**, sex hormone binding globulin; **TRH**, thyrotropin-releasing hormone; **GnRH**, gonadotropin-releasing hormone.

6.2. Assisted reproductive techniques and AITD

An increased prevalence of thyroid autoimmunity (TAI) is observed in women attending fertility treatments [65]. Interestingly, the outcome of ARTs in these patients is the most extensively researched; however, the impact of TAI on assisted reproduction is somewhat still controversial, especially among euthyroid women, and those with sub-clinical hypothyroidism (SCH). Several studies observed an increased risk of impaired COS outcome [66,67], impaired embryo quality [68,69] as well as increased prevalence of adverse pregnancy outcomes; including lower clinical pregnancy rate [70-76], increased miscarriage rate [65,70,77], and a lower live birth rate [65,71,78].

However, other studies observed no compromising effect of TAI positivity on pregnancy outcomes such as clinical pregnancy rate, miscarriage rate [79-83], and live birth rate [79,80,83-85]. A possible explanation for the discrepancy in outcomes among different studies, is that different studies used different assisted reproductive techniques. The use of intracytoplasmic sperm injection (ICSI) may overcome the possible effect of thyroid antibodies in the follicular fluid; and it is therefore not associated with an increased risk of adverse pregnancy outcomes [86-90]. Furthermore, there are different factors that may affect the results, including effect modifiers such as age and TSH level, types of GnRH protocols, types of thyroid autoantibodies tested, the presence of other autoantibodies and other causes of infertility; as well as study design of low power and small sample size. Therefore, further well-designed studies are warranted in order to have a better understanding of the outcome of ARTs in patients with TAI.

When considering the effect of ARTs on AITD, it is possible that women with AITD may be more prone to severely impaired thyroid function. Patients who undergo ART procedures may have excessive estrogen concentrations as a result of COS, that stimulate the liver to increase the production of thyroid-binding globulin (TBG). Thyroid-binding globulin, in turn, binds thyroid hormones, decreasing their availability and impairing thyroid function; thereby affecting the patient, as well as the ARTs outcome [15,91]. Salvatore Gizzo et al [92] also suggested that certain types of GnRH protocols used during COS, may interfere with the physiological function of thyroid axis, as was observed by the significant increase in TSH levels following the administration of GnRH antagonists.

As several studies suggested that both overt hypothyroidism and SCH are associated with increased risk of adverse pregnancy outcomes; the effect of levothyroxine (LT4) supplementation in patients undergoing ARTs has been researched, in order to determine whether LT4 treatment may improve pregnancy outcomes. Several studies proposed that LT4 supplementation may decrease miscarriage rate [93-95], while the effect on clinical pregnancy rate and live birth rate was controversial; with some studies reporting an improvement in clinical pregnancy rate [96,97] and live birth rate [95,97], while other show no significant effect [93,94]. It has also been suggested that AMH levels may increase after supplementation with LT4 in patients with Hashimoto's disease, thereby relieving possible adverse effects on ovaries caused by TAI [98]. Finally, due to changes in thyroid axis functioning, it is important to keep in mind that hypothyroid-treated women who achieve pregnancy by ARTs may need an increase in the LT4 dose during gestation [99].

Katarzyna Litwicka et al [100] also observed an improvement in clinical pregnancy and miscarriage rates following therapy with prednisolone, in women with TAI undergoing IVF treatments. However, further research is necessary to confirm these findings.

7. Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease, associated with a chronic inflammatory state mediated by the production of antibodies against self-antigens such as anti-citrullinated protein antibody (ACPA), and rheumatoid factor (RF); as well as cytokines that are predominantly secreted by CD4+ T helper cells (e.g., IFNγ, IL-17, RANKL, TNF, IL-1). Both genetic (e.g., HLA class II) and environmental factors (e.g., infections, tobacco smoking) are postulated to be involved in the pathogenesis of RA [9].

Rheumatoid arthritis primarily affects the joints, but may also involve the skin, heart, blood vessels and lungs. The joints of the hands, wrists, elbows, feet, ankles and knees are most commonly affected, usually in a symmetrical pattern; and the metacarpophalangeal (MCP) and proximal inter-phalangeal (PIP) joints are often involved. The affected joints are clinically presented as swollen, warm and painful; and are usually stiff following a period of inactivity. The patients may experience a decreased range of motion in the involved joints, as well as deformities (e.g., swan-neck, boutonnière deformity). Other symptoms such as malaise, fatigue and generalized musculoskeletal pain may also occur [9].

The disease primarily affects women, with a female to male ratio of 3:1; and most commonly presented in women in their third through fifth decades of life. The worldwide prevalence rate is estimated to be 0.24%; however, the prevalence estimates are higher in the United States and Northern European countries (0.5-1%), and the incidence in these regions of the world is estimated to be 40/100,000 persons per year [9,101-105].

7.1. The association between RA and impaired female fertility

It seems that women with RA tend to have less children and higher incidence of nulliparity. However, the mechanism by which it occurs is not completely understood, and multiple factors have been postulated as possible explanations [15,106]. Firstly, decreased fertility and difficulties in conceiving (indicated by longer time to pregnancy) were reported in women with RA. According to a study conducted by Jenny Brouwer et al, 42% of the patients with RA experienced a time to pregnancy of more than 12 months.

Interestingly, according to the authors, 67% of women with an active disease were shown to have a time to pregnancy of more than 12 months, in comparison to 30% of women who were in disease remission; suggesting that disease activity may play a role in the development of subfertility in patients with RA. The use of medications such as NSAIDs and prednisone (>7.5 mg daily), has also shown to result a prolonged time to pregnancy, due to effect on ovulation and ovarian function [107,108]. Moreover, a reduction in ovarian reserve, indicated by lower levels of AMH, was noted in women with an established RA disease; suggesting a correlation between RA disease-related processes and subfertility [107,109].

Finally, other factors that may contribute to decreased family size include age-related fertility decline, personal choice (often associated with disease-related concerns), as well as decreased sexual desire and lower intercourse frequency for multiple reasons, including fatigue and mental distress [15,106,107,110,111].

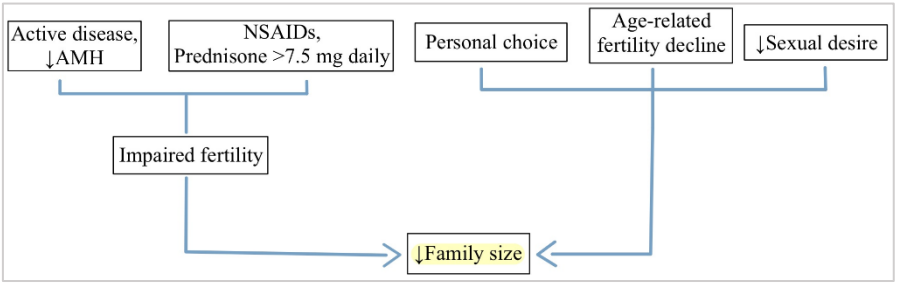

Figure 5: Women with RA tend to have less children. The mechanism by which it occurs is not completely understood; nevertheless, multiple factors have been suggested, and are summarized in the figure above [15,106-111]. **AMH**, anti-mullerian hormone; **NSAIDs**, non-steroidal inflammatory drugs.

7.2. Assisted reproductive techniques and RA

According to the study conducted by Rossella Reggia et al [30], out of sixty women participated in the study, eight were diagnosed with RA. Disease flares occurred in five pregnancies (11.2%), two of them were patients with RA. However, the authors concluded that the rates are similar to those reported for natural pregnancies. Also, three cases of OHSS were reported (3.1%), but none of them was affected by RA. Other maternal complications (e.g., gestational diabetes and hypertension), occurred in approximately one-third of the pregnancies, a rate which is consistent with that reported in the general population following ARTs. Therefore, the authors concluded that ARTs seem to be safe in these patients.

Another study conducted by Sayaka Tsuda et al [29], did not find an increased frequency of active RA disease during pregnancy than prior to conception; however, the authors reported increased risk of obstetric adverse outcomes in comparison to the general population, including increased prevalence of preterm delivery (27.5% vs 5.6%), and low birth weight (51.6% vs 9.6%). Decreased chance of having a live birth per embryo transfer in women with RA was also reported [112].

The database search yielded no other studies concerning the outcome of ARTs in patients with RA. As the data are very limited, further research is warranted in order to have a better understanding on the outcome of ARTs in female patients with RA.

Kieran E. Murray et al [113] reviewed different publications concerning pharmacological management of patients with RA during pregnancy; including the guidelines published by The British Society for Rheumatology (BSR), British Health Professionals in Rheumatology (BHPR) and EULAR. The aim was to create a standardized approach to management of these patients, as there is a concern about the teratogenic effects of different disease-modifying anti-rheumatic drugs (DMARDs) and the limited data of new therapeutic options in pregnancy. According to the authors, MTX and LEF are contraindicated at conception and in pregnancy due to increased risk of teratogenicity; and HCQ and Sulfasalazine should be considered instead. Steroids (preferably prednisolone or hydrocortisone), although considered generally safe, should be administered only if required, with the lowest effective dose as possible, due to several risks associated both with the fetus and mother (e.g., preterm delivery, oral cleft, infection). NSAIDs are not recommended before pregnancy, due to adverse effect on fertility; and should be avoided during pregnancy due to possible increased risk of miscarriage, and premature closure of ductus arteriosus. Finally, TNF inhibitors, may be used before pregnancy, while certolizumab can be administered throughout pregnancy, and other types of TNF inhibitors must be stopped at different points of time during pregnancy, often during the second trimester. Other biologic agents should be stopped before conception, due to limited data.

8. Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic condition, which encompasses two entities, Crohn disease (CD) and ulcerative colitis (UC). It is caused by an inappropriate mucosal immune activation in the intestine. The precise pathophysiology is not completely understood; however, it is believed to stem from the combination of altered composition of the gut microbiome, alterations in its interactions with the host, intestinal epithelial dysfunction, as well as aberrant mucosal immune response [9].

Crohn disease usually results transmural inflammatory lesions, that may involve any area of the gastro-intestinal tract, with frequent ileal involvement. The clinical presentation is variable, and may include intermittent attacks of diarrhea with or without blood, fever and abdominal pain. As a result of malabsorption, patients with CD may develop iron deficiency anemia, as well as generalized deficiency of nutrients, including vitamin B12, and bile salts. Other complications include formation of strictures and fistulas, often connecting bowel loops to the urinary bladder, vagina, and abdominal/perianal skin; perforation and peritoneal abscesses; as well as higher risk of developing colonic adenocarcinoma. Extra-intestinal manifestations are also possible, and may include uveitis, migratory polyarthritis, sacroiliitis, ankylosing spondylitis and erythema nodosum. Ulcerative colitis, on the other hand, results inflammatory lesions that extend to the mucosa and submucosa only, and are limited to the colon and rectum. Patients with UC often present with relapsing attacks of bloody diarrhea and abdominal pain. As with CD, there is a higher risk of developing colonic neoplasia [9].

Small differences in IBD incidence between females to males have been reported.
A slight female predominance was noted in adult-onset CD, possibly associated with hormonal factors; while a male predominance was noted in UC [114,115]. Both CD and UC frequently present in adolescents and young adults; however, a small peak in incidence was noted after the fifth decade of life [9]. The geographic distribution of IBD is highly variable. The incidence of IBD was found to be the highest in Canada (up to 19.2 for UC and 20.2 for CD per 100,000 person-year), Northern Europe (up to 24.3 for UC and 12.7 for CD per 100,000 person-year) and Australia (17.4 for UC and 29.3 for CD per 100,000 person-year). Similarly, the prevalence is also the highest in Europe (up to 505 for UC and 322 for CD per 100,000 persons) and Canada (up to 248.6 for UC and 318.5 for CD per 100,000 persons). Contrarily, Asia and Middle East seem to have a lower incidence and prevalence rates of IBD, with an incidence of up to 6.3 for UC and 5 for CD per 100,000 person-year; and prevalence of up to 168.3 for UC and 67.9 for CD per 100,000 persons [9,116,117]. The risk for

developing IBD is increased among people of white ethnicity, Ashkenazi Jews and those with an affected family member. However, the concordance rate for monozygotic twins is higher in CD (approximately 50%), in comparison to UC (16%), suggesting that genetic factors are less dominant in the pathogenesis of UC [9].

8.1. The association between IBD and impaired female fertility

According to a consensus paper published by the European Crohn's and Colitis Organization (ECCO), there is no evidence that UC or inactive CD impair fertility [118]. However, active CD may reduce fertility by inducing inflammation in the fallopian tubes and ovaries, as well as by causing dyspareunia due to involvement of the perianal area.

Furthermore, surgical interventions may lead to the formation of fallopian tube adhesions, which might also contribute the reduced fertility [118,119]. Several studies have also noted a reduction in ovarian reserve in CD (indicated by lower serum levels of AMH), in patients with an active disease, colonic location of the disease, and those over 30 years of age [118,120,121]. However, it seems that the number of women with IBD who choose not to have children voluntarily, often due to personal reasons and incorrect beliefs about the impact of IBD on fertility and pregnancy outcome, exceeds the number of patients with IBD experiencing fertility issues [118,122,123].

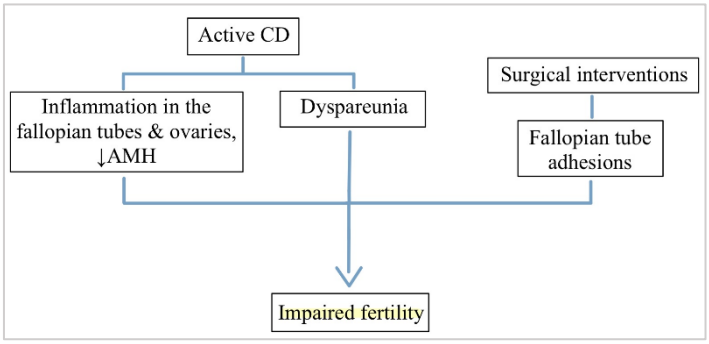

Figure 6: Possible etiologies by which female patients with IBD may experience reduced fertility [118-123].
CD, Crohn's disease; **AMH**, anti-mullerian hormone.

8.2. Assisted reproductive techniques and IBD

According to recent studies, the frequency of active IBD does not seem to change significantly during pregnancy [29], and the rates of flare-ups in women with IBD undergoing ARTs are comparable to women with IBD who conceive spontaneously, suggesting that ARTs are generally safe in these patients. However, an increased risk of gestational diabetes among patients with UC was noted.

Also, a lower rate of vaginal delivery (34.7% vs 57.1%), as well as increased rate of elective cesarean section (32.7% vs 14.3%) was reported in patients with IBD undergoing ARTs, in comparison to healthy women with spontaneous pregnancies [124]. Nevertheless, women with IBD who underwent ARTs did not show a significant increase in preterm delivery, or significant differences in other adverse pregnancy outcomes [124], including implantation rate, clinical pregnancy rate, miscarriage rate [125] and live birth rate [126]. Contrarily, other studies have noted lower odds of a live birth in women with UC [127], higher frequencies of fetal growth restriction and low birth weight in patients with CD, as well as higher frequencies of preterm delivery and low birth weight in patients with UC [29].

The odds of having a live birth with IVF do not seem to be adversely affected by prior surgeries in women with UC [128-130]. It is worth to mention, however, that low birth rate was shown to be significantly reduced in women with UC who underwent restorative proctocolectomy that has failed, in comparison to women with a successful surgery [131]. Moreover, prior surgeries may be associated with increased IVF procedures, time to pregnancy, and rate of cesarean section, as well as low birth weight [132]. The impact of prior surgery on live births in patients with CD is somewhat controversial; Sonia Friedman et al [133] suggested that live birth may be reduced, possibly because CD is not curable, and therefore inflammation may persist despite surgical interventions; while Sveta S. Oza et al reported no association of prior surgeries with live birth outcome in patients with CD [159].

Taken together, it seems that ARTs are generally safe in patients with IBD; however, further research is warranted in order to confirm the above findings on pregnancy outcomes, as different limitations such as study design, small sample size, and limited data (e.g., disease activity/severity) may bias the results.

According to the British Society of Gastroenterology consensus guidelines on the management of IBD, active IBD prior to conception is associated with poor pregnancy outcomes. Medications used both for maintenance and flares include 5-Aminosalicylic Acid, thiopurines, TNF inhibitors and CSs. Patients with active disease or at high risk of relapse, receiving TNF inhibitors, are suggested to continue the drug throughout pregnancy; while for those with inactive disease who wish to discontinue therapy, it may be reasonable to stop at the start of the third trimester. MTX is not recommended to women of childbearing age, and should be prescribed only with concomitant contraception. Prior to conception, however, it should be discontinued for 6 months.

There are very limited data about outcomes of pregnancies and safety of other biological agents such as vedolizumab, ustekinumab and tofacitinib. Until further data are available, the authors recommend that the same practice that is used for TNF inhibitors is applied to the above-mentioned biological agents [134].

9. Behçet's disease

Behçet's disease (BD) is an inflammatory disease, in which most of the clinical manifestations are believed to stem from vasculitis of blood vessels of all sizes. The etiology of the disease is not known. However, it is hypothesized to be caused by an aberrant immune activity, triggered by exposure to different agents such as viral or bacterial antigens, and other environmental sources; possibly in people with a genetic predisposition. Clinically, BD is commonly characterized by recurrent, usually painful, mucocutaneous ulcers in the oral cavity and the genital area. Other clinical manifestations may include cutaneous lesions, as well as spectrum of ocular, neurologic, vascular, articular, and gastrointestinal diseases. The severity of the clinical manifestations is generally greater in men [135,136,137].

Behçet's disease is more common along the ancient silk road, which extends from Eastern Asia to the Mediterranean. The disease usually presents in people of 20-40 years of age, and tends to be more common in men in the Eastern Mediterranean area; while in Northern European countries it is more common in women. The disease is most common in Turkey, with a prevalence rate of 80-370/100,000 persons. In Japan, Korea, China, Iran and Saudi Arabia, the prevalence rate ranges from 13.5 to 20/100,000 persons; while in the United States and Europe the prevalence ranges from 0.12 to 7.5/100,000 persons [135,138].

9.1. Behçet's disease and female fertility

The association between BD and reduced female fertility is somewhat controversial. Several studies have shown that infertility is not increased among female patients with BD, besides those with major organ involvement who use cyclophosphamide as a treatment [139]; and that there was no statistically significant difference in the levels of AMH in patients with BD, in comparison to healthy subjects [140]. However, other studies have noted a significant reduction in AMH levels in patients with BD, suggesting that BD patients may have diminished ovarian reserve [109,141]. Therefore, it seems that further research is required, as the data are scarce and inconclusive.

Nonetheless, BD may have an adverse effect on pregnancy, including increased risk of miscarriages. According to a study conducted by Jim Jadaon et al [142], the rate of miscarriages was found to be increased in those with BD (18%), in comparison to the control group (7%).

9.2. Assisted reproductive techniques and BD

According to the literature previously covered [142], the rate of miscarriages was found to be increased in patients with BD, as well as the rate of other pregnancy complications, such as thromboembolic events; suggesting that BD may have an adverse effect on pregnancy outcome [142]. However, the database search yielded no other studies concerning the outcome of ARTs in patients with BD. As the data are very limited, further research is warranted in order to have a better understanding on the outcome of ARTs in patients with BD.

In regards to the management of BD during pregnancy, colchicine is the drug most commonly prescribed in patients with BD, and may be continued during pregnancy in case of flares. Other possible medications are CSs, AZA, CSA and TNF inhibitors (Infliximab). LMWH may also be considered, together with low-dose CSs and salicylates, in order to reduce inflammation and prevent thromboembolic events [143].

10. Conclusion

Although autoimmune diseases are not considered to be a major cause of female infertility, infertility is often multifactorial, and different autoimmune diseases may also play a role in its development, through different pathophysiological mechanisms.

As there is an overall increased prevalence of women with autoimmune disorders seeking infertility treatments, it is of great importance to assess the effect of fertility treatments on different autoimmune diseases, the ARTs outcome, and the safety of medications used to control active disease and prevent flares.

ART procedures generally seem to be safe in patients with autoimmune diseases as discussed previously; however, it is of great importance that the patients are in stable disease remission, and adequately treated. Nevertheless, the data concerning disease-related complications and ARTs outcomes seem to be very limited and somewhat controversial. Therefore, further research is warranted with well-organized studies, in order to confirm the current existing findings; and to establish the relationship between different autoimmune diseases and female infertility, as well as its clinical significance in terms of ARTs outcome and the effect on the underlying disease.

Moreover, when couples present with infertility issues and difficulties in conceiving, it is important to keep in mind that male factors may also play an important role; and therefore, both male and female partners should be thoroughly evaluated.

Finally, patients with autoimmune disease may experience diminished ovarian reserve and POI for different reasons; either as a direct consequence of disease-related processes, or as a result of the circumstances surrounding the disease, such as the choice of certain medications that are known to affect ovarian reserve. As women with autoimmune diseases may choose to delay pregnancy, either due to personal choice or because of disease status; these patients should be managed by a multidisciplinary team, including fertility specialists, in order to discuss the option of fertility preservation treatments, and increase the chances to conceive later in life, when they are ready.

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