CHAPTER

1

Overview of Pregnancy in Women with Rheumatic Diseases

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Introduction

Pregnancy in the setting of autoimmune rheumatic diseases (ARDs) presents unique clinical challenges and opportunities. Many ARDs, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and systemic sclerosis (SSc), preferentially affect women in their reproductive years. Though historically associated with poor maternal and fetal outcomes, safe pregnancy in this population has become increasingly possible due to advances in disease understanding, availability of better immunomodulatory therapy, and increasing focus on multidisciplinary care. Yet, the clinical course could remain unpredictable, influenced by immunologic changes during gestation, disease-specific flare of activity, and adverse effects of pharmacologic interventions.[1] This chapter aims at introducing key concepts related to the impact of pregnancy on rheumatic disease and *vice versa*, laying the foundation for disease-specific considerations in the following chapters.

PREVALENCE AND IMPLICATIONS FOR REPRODUCTIVE HEALTH

Most autoimmune rheumatic diseases are more prevalent in women than men, often at a ratio of 3:1 or greater, particularly in the reproductive age group.[2] Epidemiological data reveal that women with SLE and rheumatoid arthritis have lower rates of successful pregnancies and fewer children compared to matched controls.[1] A large Finnish registry study demonstrated increased risks of adverse pregnancy outcomes (APOs), including preeclampsia, preterm birth, small-for-gestational-age neonates, and NICU admission, in women with SLE, primary Sjögren syndrome (pSS), and RA.[3] Other ARDs such as psoriatic arthritis (PsA), systemic vasculitis, and inflammatory myopathies also carry variable but measurable reproductive risk. Multiple mechanisms may contribute to this risk, including disease-related subfertility, exposure to gonadotoxic medication, delayed family planning, and voluntary childlessness driven by fears of adverse outcomes **(Box 1.1)**.

IMMUNOLOGICAL ADAPTATIONS IN PREGNANCY

Pregnancy induces an immunological state of tolerance that facilitates fetal survival despite the fact that fetus is semi-allogeneic. A shift to tolerance does not mean there is a global immune suppression but rather reflects a recalibration of immune responses, which can modulate the course of autoimmune disease.[4]

Box 1.1: Mechanisms through which autoimmune diseases can affect reproductive health

- Active systemic inflammation may impair ovulation and endometrial receptivity
- Cytotoxic medications, especially alkylating agents like cyclophosphamide, may cause irreversible gonadal damage
- Depression, fatigue, and chronic pain reduce libido and contribute to reduced parity
- Patient-driven choices, often influenced by misconceptions or inadequate counseling, also contribute to voluntary childlessness

Key Changes include

Regulatory T Cells (Tregs): Master Regulators of Immune Tolerance

- ***What they are:*** Regulatory T cells (Tregs) are a subset of T lymphocytes that maintain immune tolerance. Their primary job during pregnancy is to suppress potentially harmful immune reactions that could target the fetus.
- ***How they work:*** Pregnancy promotes a significant increase in Tregs, particularly in the decidua (maternal tissue lining the uterus). These cells produce anti-inflammatory cytokines like IL-10 and TGF-β, which dampen immune reactions against fetal antigens.

Clinical Relevance

- Adequate Treg function is critical for preventing pregnancy complications such as recurrent pregnancy loss and preeclampsia.
- In the context of autoimmune diseases, enhanced Treg activity helps suppress autoimmune reactions. For instance, rheumatoid arthritis (RA) often improves during pregnancy because of this immune regulation.
- Conversely, diseases like systemic lupus erythematosus (SLE), which are driven by autoantibodies, may worsen because Tregs do not control antibody production.

Immune Profile Shift: From Th1 to Th2 Dominance

- ***Th1 vs. Th2 responses:*** The maternal immune system can be broadly categorized into two main types of responses:
  - ***Th1 (cell-mediated immunity):*** Dominated by pro-inflammatory cytokines (IFN-γ, TNF-α), which are essential for fighting infections but can cause tissue damage.
  - ***Th2 (humoral immunity):*** Driven by anti-inflammatory cytokines (IL-4, IL-10), which promote antibody production and immune tolerance.[5]
- ***What changes in pregnancy:***
  - Pregnancy naturally shifts the maternal immune response from a Th1 (aggressive) profile to a Th2 (tolerant) profile.
  - This shift is essential to protect the fetus from being attacked by the maternal immune system while maintaining some ability to fight infections.
- ***Clinical implications***
  - ***Th1-driven diseases (RA, multiple sclerosis):*** These diseases tend to improve because the aggressive Th1 response is suppressed.
  - ***Th2-driven diseases (SLE):*** These can worsen because the already overactive Th2 response is further enhanced.
  - ***Balanced approach:*** In clinical practice, understanding this shift can guide the management of pregnant patients with autoimmune diseases.

HLA-G: The Immune Shield at the Maternal-Fetal Interface

- ***What is HLA-G?***
  Human leukocyte antigen-G (HLA-G) is a special molecule expressed on the surface of placental cells (trophoblasts) that directly interacts with maternal immune cells.
- ***How it protects the fetus?***
  - HLA-G binds to inhibitory receptors on maternal immune cells (like natural killer cells), effectively "telling" them not to attack the fetus.
  - It can be found in both membrane-bound and soluble forms, providing local and systemic protection.
- ***Why it matters?***
  - HLA-G is crucial for maintaining immune tolerance at the maternal-fetal interface.
  - Reduced HLA-G expression has been linked to pregnancy complications such as preeclampsia and recurrent pregnancy loss.[6]

Microchimerism: Fetal Cells in the Mother, Maternal Cells in the Fetus

- ***What is microchimerism?***
  During pregnancy, a small number of fetal cells enter the maternal circulation, and maternal cells can enter the fetal circulation. These cells can persist for decades.
- ***How it affects pregnancy and beyond:***
  - Fetal microchimeric cells in the mother may support tissue repair in some cases but can also trigger autoimmune reactions in susceptible individuals (e.g. systemic sclerosis).
  - Maternal microchimeric cells in the child may influence immune development and have been linked to autoimmune diseases like type 1 diabetes.[7]
- ***Clinical perspective:*** Microchimerism is a double-edged sword. It can promote healing or contribute to autoimmune disease, depending on the context.

Decidual Natural Killer (dNK) Cells: Balancing Tolerance and Defense

- ***What are dNK cells?***
  These are a specialized type of natural killer (NK) cells that are found in the uterine lining during pregnancy.
- ***How they function?***
  - Unlike the highly cytotoxic NK cells in circulation, dNK cells are primarily involved in promoting placental development and ensuring proper blood flow to the fetus.
  - They secrete growth factors (e.g. vascular endothelial growth factor, VEGF) that support blood vessel formation.
  - They also help maintain immune tolerance, recognizing the fetus as a protected entity.[8]
- ***Clinical significance:*** Problems with dNK cell function have been associated with conditions like preeclampsia, fetal growth restriction, and recurrent pregnancy loss.

Hormonal Influence on Immunity: The Role of Estrogen, Progesterone, and hCG

- ***Estrogen:*** Promotes a Th2-immune response and supports Treg expansion. This helps suppress Th1-driven autoimmune diseases (like RA). However, it can exacerbate antibody-mediated diseases (like SLE).

- ***Progesterone:*** Further supports Treg activity and has direct anti-inflammatory effects. It is critical for maintaining pregnancy but can promote excessive tolerance, which might allow some infections to persist.
- ***Human chorionic gonadotropin (hCG):*** Stimulates Treg cells and supports immune tolerance, contributing to fetal survival.
- ***Clinical application:*** Hormonal fluctuations can directly influence autoimmune disease activity. Understanding this helps in adjusting therapies for pregnant patients with autoimmune conditions.

These adaptations can result in either attenuation or exacerbation of autoimmune pathophysiological processes, depending on the predominant immune pathways driving the underlying disease.

Effect of Pregnancy on Autoimmune Rheumatic Diseases

The course of autoimmune diseases during pregnancy is heterogeneous. Some conditions may show an improvement in disease activity, while others worsen or remain unchanged.

Rheumatoid arthritis (RA): Disease activity improves in 50–70% of women with RA during pregnancy due to the anti-inflammatory immune environment and HLA class II mismatch between mother and fetus.[4] Disease activity often shows a rising trend in the postpartum period, with flares noted in up to 46% of patients.[9]

Systemic lupus erythematosus (SLE): Approximately 25–60% of women with SLE are observed to have a flare during pregnancy, particularly when conception has occurred during active disease.[10,11] Presence of lupus nephritis, low complement levels, and hydroxychloroquine (HCQ) withdrawal are factors associated with increased risk.[12–14]

Primary Sjögren's syndrome (pSS): Most patients with pSS remain clinically stable during pregnancy.[15] However, maternal anti-Ro/SSA and anti-La/SSB antibodies are associated with neonatal lupus and congenital heart block (CHB). CHB occurs in 1–2% of cases with recurrence rates up to 20% and hence close fetal monitoring is warranted.[16]

Antiphospholipid syndrome (APS): APS is a leading cause of recurrent miscarriage and late fetal loss. Use of low-dose aspirin and low-molecular-weight heparin has shown significant improvement in outcomes.[17]

Systemic sclerosis (SSc): Disease activity typically remains stable. Women with diffuse cutaneous disease and pulmonary hypertension are at higher risk of complications which include scleroderma renal crisis and poor fetal growth.[18]

Spondyloarthritides (SpA): Axial SpA and PsA may remain unchanged or mildly worsen. They are usually not typically associated with high disease activity during pregnancy. However, active disease can increase the rate of cesarean section and preterm birth.[19]

Mixed connective tissue disease (MCTD): MCTD may show fluctuations in disease activity like SLE during pregnancy, especially when anti-RNP antibodies are present. Risk of CHB and preeclampsia is higher, requiring fetal surveillance.[20]

Idiopathic inflammatory myopathies (IIM): Active disease in polymyositis and dermatomyositis during pregnancy is associated with an increased risk of fetal loss, IUGR, and preeclampsia. Quiescent disease typically has favorable outcomes.[21, 22]

Primary systemic vasculitides: Pregnancy in GPA, EGPA, and Takayasu arteritis is associated with high-risk of adverse outcomes if disease is active. Takayasu arteritis,

a large vessel vasculitis common among young Indian women, may worsen due to hemodynamic strain, necessitating close cardiovascular monitoring.[23,24]

Behçet syndrome: Typically improves during pregnancy, though flares are observed in the postpartum period. Thrombotic risk must be considered, particularly in patients with vascular Behçets.[25]

Effect of Autoimmune Diseases on Pregnancy Outcomes

The immunological and vascular dysfunction associated with many ARDs increases the risk of obstetric complications. Common adverse pregnancy outcomes observed in women with ARDs include:

- Preeclampsia and gestational hypertension
- Preterm birth and premature rupture of membranes
- Intrauterine growth restriction (IUGR)
- Stillbirth and recurrent miscarriage
- CHB and neonatal lupus
- NICU admission and neonatal mortality

Autoimmune diseases significantly increase the risk of adverse pregnancy outcomes. For instance, women with Sjögren's syndrome and systemic lupus erythematosus (SLE) face markedly higher risks of miscarriage (relative risk 8.85 and odds ratio 4.90, respectively). Preeclampsia is more frequent in those with type 1 diabetes mellitus (T1DM) (OR 4.19) and SLE (OR 3.20). Data from large cohorts indicate that women with SLE have a 2–4 fold increased risk of preeclampsia and fetal loss compared to healthy counterparts.[26] Similarly, women with RA are more likely to undergo cesarean sections and have preterm deliveries.[27]

Women with SLE are more likely to deliver low birth weight (OR 5.95) or small-for-gestational-age infants (OR 2.49), and face elevated neonatal mortality (OR 8.32). Systemic sclerosis raises the likelihood of intrauterine growth restriction (OR 3.20) and low birth weight (OR 3.80). Inflammatory bowel disease increases the odds of gestational diabetes (OR 2.96), ectopic pregnancy (OR ~1.5), and stillbirth (OR 1.57). Autoimmune thyroid disease, particularly in the presence of thyroid peroxidase antibodies, is associated with higher rates of miscarriage (OR ~2.7), recurrent pregnancy loss (OR ~1.9), and preterm birth (OR ~1.3).[27] Rheumatoid arthritis and psoriatic diseases show modest but consistent associations with miscarriage, preterm birth, and hypertensive disorders of pregnancy.[28] These patterns highlight the shared inflammatory and vascular pathways that may underlie pregnancy complications in autoimmune disorders. Multidisciplinary care, involving rheumatologists, obstetricians, and neonatologists, is crucial for optimal outcomes.[29–31] **Table 1.1** summarizes the frequency of disease flares and adverse pregnancy outcomes in autoimmune diseases.

Indian Context

In India, pregnancy in ARDs is underreported and understudied. Challenges include late diagnosis, limited access to biologics, and underutilization of preconception counseling. Takayasu arteritis and tuberculosis pose additional management complexities in the Indian setting. Establishing national pregnancy registries and integrating rheumatology-obstetrics services is imperative to improve outcomes.

Table 1.1: Frequency of flares and adverse pregnancy outcomes in autoimmune diseases

Disease	Flares in pregnancy	Postpartum flare	Key adverse pregnancy outcomes
RA	↓ (50–70%)	↑ (~46%)	IUGR, preterm birth, GHTN
SLE	↑ (25–60%)	Moderate	Fetal loss, preeclampsia, CHB, IUGR
APS	N/A	N/A	Recurrent miscarriage, PE, thrombosis
pSS	Rare	Low	CHB, neonatal lupus
SSc	Rare	Possible	IUGR, preterm birth, renal crisis
SpA	Mild ↑	Yes	C-section, preterm labor
MCTD	Variable	Moderate	CHB, fetal loss, PE
IIM	If active	Yes	IUGR, stillbirth
Vasculitis	Risk if active	High	Fetal loss, PE, vasculopathy
Behçet's	↓	↑	Vascular flares, thrombosis

(RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; APS: Antiphospholipid syndrome; pSS: Primary Sjögren's syndrome; SSc: Systemic sclerosis; SpA: Spondyloarthritis; MCTD: Mixed connective tissue disease; IIM: Idiopathic inflammatory myopathies; PE: Preeclampsia; CHB: Congenital heart block; GHTN: Gestational hypertension; IUGR: Intrauterine growth restriction; N/A: Not applicable)

Conclusion

Pregnancy is becoming increasingly achievable and safe for women with autoimmune rheumatic diseases, provided there is comprehensive planning, disease control, and coordinated multi-disciplinary care. Immunologic changes during gestation offer both opportunities and challenges, modulating disease activity in ways that can be beneficial or harmful depending on the underlying rheumatic condition. Understanding these dynamics and applying individualized, evidence-based treatment is key to ensuring successful maternal and fetal outcomes.

Key Points

- Pregnancy in women with autoimmune rheumatic diseases (ARDs) presents unique challenges due to the potential for disease flares, adverse pregnancy outcomes (APOs), and the impact of immunological changes on maternal health.
- ARDs are more common in women, especially during reproductive years, and are associated with lower pregnancy success rates and higher risks of APOs, including preeclampsia, preterm birth, and neonatal complications.
- Factors such as active systemic inflammation, cytotoxic medications, depression, fatigue, and patient-driven decisions contribute to subfertility and lower parity in affected women.
- Pregnancy triggers immune tolerance through mechanisms like regulatory T cells (Tregs), a shift from Th1 to Th2 immune response, HLA-G expression, microchimerism, and decidual NK cells, which collectively influence disease activity.
- The course of ARDs during pregnancy is variable, with some conditions improving (like rheumatoid arthritis), while others worsen (like systemic lupus erythematosus), and some remaining stable (like systemic sclerosis).
- Women with ARDs have higher risks of APOs, including preeclampsia, preterm birth, intrauterine growth restriction (IUGR), fetal loss, and neonatal complications, due to underlying inflammation and vascular dysfunction.
- Successful pregnancy management in ARDs requires coordinated care between rheumatologists, obstetricians, and neonatologists, with emphasis on preconception counseling, disease control, and individualized treatment plans.
- In India, pregnancy in ARDs is underreported, with additional complexities from delayed diagnosis, limited access to biologics, and challenges posed by endemic conditions like tuberculosis.

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