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## Critical review on infertility due to Systemic Diseases.

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### Abstract:

**Background:** Infertility is a significant concern arising from systemic diseases, impacting reproductive health. Various conditions such as autoimmune disorders, endocrine disturbances, chronic diseases, infections, metabolic disorders, neurological conditions, nutritional deficiencies, and medication side effects can contribute to infertility by disrupting reproductive function.

**Aims/Objective:** This article aims to investigate the relationship between systemic illness and infertility, elucidating underlying mechanisms.

**Methods:** A comprehensive review of relevant literature was conducted, analyzing peer-reviewed articles, clinical studies, and guidelines to gather evidence on the pathophysiology, diagnosis, and management of infertility associated with systemic illness.

**Results:** The discussion section explores the diverse ways systemic illnesses affect fertility, including hormonal imbalances, organ dysfunction, inflammatory processes, and medication-related complications. Challenges in diagnosing and treating infertility in individuals with systemic conditions are discussed, emphasizing interdisciplinary collaboration among healthcare providers.

**Conclusion:** Infertility linked to systemic illness presents a complex clinical challenge requiring a multidimensional approach for effective management. Enhanced awareness and interdisciplinary collaboration among medical specialties are essential in supporting patients facing infertility due to systemic diseases.

**Key Words:** Infertility, Systemic Diseases, Vandhyatva

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**Introduction:**

Infertility is a distressing condition affecting millions of couples worldwide. Infertility, defined as the inability to conceive after a year of regular sexual intercourse without using contraceptives, affects 8–12% of reproductive-aged couples worldwide.<sup>1</sup> While it is commonly associated with reproductive system disorders, systemic diseases can also significantly contribute to infertility. Infertility consists by definition in "failure to achieve a clinical pregnancy after 12 months or more of regular unprotected intercourse" while the term subfertility means a delay to achieve pregnancy. Several factors can contribute to infertility or subfertility in patients with systemic autoimmune diseases. The association of systemic autoimmune conditions with endometriosis, celiac disease and thyroid autoimmunity that are well known causes of infertility and/or subfertility need to be taken in consideration when difficulties in the onset of pregnancy is reported.

Systemic diseases, ranging from metabolic disorders to autoimmune conditions, can disrupt reproductive function through various mechanisms. Understanding the impact of systemic diseases on infertility is crucial for effective diagnosis and management strategies.<sup>2</sup>

**Materials and Methods:**

This critical review utilized a comprehensive search strategy to identify relevant articles from Google Scholar and Scopus databases. Keywords such as "infertility," "systemic diseases," "metabolic disorders," "autoimmune diseases," and "reproductive dysfunction" were used to retrieve peer-

reviewed articles published between 2010 and 2024. The selected articles underwent rigorous screening based on relevance, quality, and applicability to the topic of infertility due to systemic diseases.

**Aims and objective**

1. To explore critical review and comprehensively examine the impact of systemic diseases on infertility.
2. To explore the psychological consequences of infertility related to systemic diseases.
3. To identify the key risk factors, effects, and underlying mechanisms associated with infertility caused by systemic conditions.

**Causes of infertility.**

1. Uterine issues: Polyps, fibroids, or scarring in the uterus cavity, often due to procedures like D&C.
2. Fallopian tube problems: PID, caused by untreated STIs, or endometriosis leading to tube scarring.
3. Ovulation irregularities: Hormonal imbalances, eating disorders, substance abuse, thyroid disorders, stress, or pituitary tumors.
4. Egg count and quality issues: Depletion of egg reserve before menopause, and eggs with chromosomal abnormalities affecting fertilization and fetal development.
5. Systemic diseases: Conditions like autoimmune disorders or diabetes can also impact fertility through various mechanisms.

## **Infertility due to Systemic Diseases**

### **a) Endocrine Disorders:**<sup>3</sup>

**Diabetes Mellitus:** Chronic hyperglycemia in diabetes mellitus can lead to oxidative stress, inflammation, and endothelial dysfunction, compromising blood flow to the reproductive organs. In males, diabetes can impair sperm quality by causing DNA damage and oxidative stress. In females, it can disrupt ovulation through insulin resistance and hyperinsulinemia.

**Polycystic Ovary Syndrome (PCOS):** PCOS is characterized by insulin resistance, hyperandrogenism, and ovarian dysfunction. Insulin resistance leads to hyperinsulinemia, which stimulates ovarian androgen production, disrupting folliculogenesis and ovulation. Hyperandrogenism contributes to menstrual irregularities and anovulation, leading to infertility.

### **b) Autoimmune Conditions:**

**Systemic Lupus Erythematosus (SLE):**<sup>4</sup> SLE can affect fertility through multiple mechanisms, including immune-mediated damage to reproductive organs, hormonal disturbances, and adverse effects of immunosuppressive medications. Antiphospholipid antibodies in SLE patients are associated with recurrent pregnancy loss and implantation failure.

**Rheumatoid Arthritis (RA):**<sup>5</sup> In RA, chronic inflammation and immune dysregulation can impair fertility. Inflammatory cytokines may disrupt endometrial receptivity and embryo implantation. Additionally, medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) can have

adverse effects on reproductive function. Nonsteroidal anti-inflammatory drugs can cause temporary infertility and corticosteroids are associated to a prolonged time to pregnancy in some rheumatic diseases.

### **c) Metabolic Disorders:**<sup>6</sup>

**Obesity:** Obesity is associated with insulin resistance, hyperinsulinemia, dyslipidemia, and chronic low-grade inflammation, collectively termed as metabolic syndrome. These metabolic disturbances can disrupt ovarian function, lead to menstrual irregularities, and impair embryo implantation, contributing to infertility.

**Metabolic Syndrome:** Metabolic disorders are caused by a malfunction in body metabolism. Metabolic syndrome components, including central obesity, hypertension, dyslipidemia, and insulin resistance, are independently associated with male and female infertility. Insulin resistance and hyperinsulinemia disrupt ovarian and testicular function, impairing folliculogenesis, spermatogenesis, and steroidogenesis.

### **d) Cardiovascular Health:**<sup>7</sup>

Cardiovascular diseases (CVDs) such as hypertension, atherosclerosis, and coronary artery disease can impair fertility by compromising blood flow to the reproductive organs. Endothelial dysfunction, oxidative stress, and vascular inflammation in CVDs can disrupt ovarian and testicular function, impairing gametogenesis and embryo implantation.

### **e) Gastrointestinal Disorders:**<sup>8</sup>



**Inflammatory Bowel Disease (IBD):** Chronic inflammation in IBD can lead to malabsorption of nutrients essential for reproductive function, including vitamins and minerals. Intestinal inflammation may disrupt the gut microbiota, influencing systemic inflammation and hormonal balance, thereby affecting fertility.

**Celiac Disease:** Celiac disease, characterized by gluten intolerance, can lead to nutrient malabsorption and nutritional deficiencies, such as iron, folate, and vitamin D, which are essential for reproductive health. Malabsorption of nutrients may impair ovarian function and menstrual regularity, leading to infertility.

**f) Neurological Conditions:**<sup>9</sup>

**Epilepsy:** Antiepileptic drugs (AEDs) used to manage epilepsy can have adverse effects on reproductive function. Some AEDs may alter sex hormone levels, leading to menstrual irregularities and anovulation in females and impaired spermatogenesis in males.

**Multiple Sclerosis (MS):** MS can disrupt the hypothalamic-pituitary-gonadal axis through demyelination and neuroinflammation, leading to hormonal imbalances and impaired fertility. Additionally, MS-related disability and fatigue may affect sexual function and reproductive outcomes.

**Discussion:**

Systemic diseases such as diabetes mellitus, polycystic ovary syndrome (PCOS), thyroid disorders, and autoimmune diseases have been implicated in infertility. Diabetes mellitus, characterized by hyperglycemia, can lead to impaired sperm function and ovulatory dysfunction in women. PCOS, a common endocrine disorder, is associated

with menstrual irregularities, anovulation, and hyperandrogenism, contributing to infertility. Thyroid disorders, including hypothyroidism and hyperthyroidism, can disrupt the hypothalamic-pituitary-gonadal axis, affecting reproductive hormone levels and menstrual cycles. Autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) may cause inflammation and immune-mediated damage to reproductive organs, resulting in infertility. Several mechanisms underlie the association between systemic diseases and infertility. Metabolic imbalances, hormonal disturbances, inflammation, oxidative stress, and immune dysfunction play key roles in disrupting reproductive function. Additionally, the adverse effects of medications used to manage systemic diseases can further exacerbate infertility.

**Conclusion:**

Infertility associated with systemic diseases presents a complex clinical challenge that requires a multidisciplinary approach. Healthcare providers must recognize the potential impact of systemic diseases on reproductive health and implement appropriate screening, diagnostic, and treatment strategies. Lifestyle modifications, pharmacological interventions, and assisted reproductive technologies may be necessary to optimize fertility outcomes in individuals with systemic diseases. Future research should focus on elucidating the underlying pathophysiological mechanisms and evaluating novel therapeutic approaches to mitigate infertility in this population.

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