



Endocrine Autoimmunity in Association with Female Infertility

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Article History	Abstract
Received: 06 June 2023 Revised: 15 Sept 2023 Accepted: 30 Oct 2023	<i>Infertility is the inability to conceive after a year of regular unprotected sexual intercourse, affecting 10-15% of couples. Advanced age, obesity, and certain medications can hinder fertility. Endocrine autoimmunity is increasingly recognized as a significant contributor to female infertility, often complicating various gynecological conditions. Autoimmune issues involving the hypothalamus, pituitary gland, thyroid, adrenal glands, and ovaries can impact fertility. A multidisciplinary approach is essential for diagnosing infertility, with a crucial focus on identifying potential endocrine disorders. Here we discuss how to identify endocrine autoimmune patients with ovulatory dysfunction. Women must be advised about limiting factors to be avoided, to protect their fertility. A comprehensive understanding of the underlying mechanisms, coupled with appropriate diagnostic and therapeutic approaches, is crucial for effectively managing this complex condition and helping women achieve their reproductive goals.</i>
CC License CC-BY-NC-SA 4.0	Keywords: Endocrine Autoimmunity, Infertility, Thyroid, PCOS, POI, Endometriosis, Type 1 Diabetic Mellitus, SLE, Multiple Sclerosis.

1. Introduction

Infertility (defined as the failure to conceive after 12 months of regular unprotected sexual intercourse) can be estimated to affect approximately 10% of couples of childbearing ages [1]. Cho & Gregersen suggest that autoimmunity results from the immune system's inability to differentiate between self and nonself, leading to inflammation and processes involving cellular, antibody-mediated, immune-complex-mediated responses in both innate and adaptive immunity [2]. The risk of autoimmune disorder is influenced by gender affecting approximately 78% occurring in females [3]. Interactions between the endocrine, neurological, and immunological systems are frequently characterized by autoimmune disease and chronic inflammation [4].

Most endocrine organs are closely regulated by the hypothalamus; therefore, its disturbance affects the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes [5]. As per Unuane et al., in developed countries, female infertility accounts for 37% of cases, while male infertility contributes to 8%, and a combination of male and female factors is responsible for 35%. Among this group, 5% experience unexplained infertility, and 15% achieve pregnancy during the study. The leading causes of female infertility are ovulatory problems (25%), endometriosis (15%), pelvic adhesions (11%), tubal blockages (11%), other tubal issues (11%), and hyperprolactinemia (7%). These factors collectively contribute to 81% of female infertility cases [6].

In a Swedish study, 10.9% of infertile women had major depression and 14.8% presented some anxiety disorders [7]. In a Chinese prevalence study, 23.2% of infertile women met the criteria for generalized anxiety disorder, and 17% for major depressive disorder [8]. Understanding the intricate relationship between endocrine autoimmunity and the female reproductive system is crucial for diagnosing and managing these conditions effectively. In this study, we mainly focus on the current knowledge, diagnosis, and treatment of endocrine autoimmune disorders, as well as the effects of endocrine autoimmune diseases on female fertility.

2. Materials And Methods

We compiled a dataset of over 50,810 articles and reviews focusing on the relationship between Endocrine Autoimmunity in association with Female Infertility from 1993 to 2023. These sources were obtained from scientific databases like the Science Core Collection, PubMed, and Google Scholar. We narrowed down our selection to approximately 120 articles that met our criteria. Our analysis involved exploring various dimensions, including country, institution, author, journal, keywords, and frequently co-cited references, to provide insights into this research area.

Endocrine Autoimmunity and Female Reproductive System

Endocrine autoimmunity refers to a condition in which the immune system mistakenly targets and attacks the body's own endocrine glands. The endocrine system is responsible for producing hormones that regulate various bodily functions, including those related to the female reproductive system. When autoimmunity affects the endocrine glands involved in female reproductive health, it can lead to a range of hormonal imbalances and reproductive disorders. Deroux et al., estimated that, “on an average, 10% of infertile couples have unexplained infertility, Auto-immune disease accounts for a part of these cases” [9]. Leridon explained that, “generally, infertility can be classified into three main categories based on the prevalence of the causes: female causes (33 to 41 %), male causes (25 to 39 %), and mixed causes (9 to 39 %)” [10].

The primary reasons for female infertility are ovulation problems, tubal infertility, endometriosis, and/or uterine and cervical causes (cervical stenosis, polyps, tumors, etc). Ovulation disorders include polycystic ovary syndrome, hypothalamus dysfunction, premature ovarian insufficiency, and others [9]. Although the relationship between serum autoantibodies and infertility is still debatable, evidence suggests that it plays a part in idiopathic infertility. An undefined auto-immunity was described as the presence of autoantibodies in a blood sample without meeting any biological or clinical requirements for a specific disease. Both the mother and the fetus implement several tolerance-building strategies throughout implantation and pregnancy. Pre-implantation immunological procedures are in place to ensure that the fetus is optimally prepared for implantation into the mother's endometrium [11]. Even though the presence of a wide range of autoantibodies is correlated with the pathophysiological course of the parturient, there is not always a connection between an antibody and a particular condition that results in infertility.

Endocrine autoimmunity can affect fertility by interfering with the normal functioning of the reproductive system. Hormonal imbalances, such as those seen in conditions like PCOS or autoimmune oophoritis, can lead to difficulties in ovulation, fertilization, and implantation, resulting in reduced fertility or infertility. Even some autoimmune disorders can increase the risk of complications during pregnancy. Carp et al., noted that, “Antithyroid, Antinuclear and Antiphospholipid Autoantibodies have been associated with an increased risk of Miscarriage” [1]. Thyroid hormones can affect the ovaries both directly and through indirect mechanisms. In a study done by Poppe et al., it was found that, “women with infertility seem to have an increased prevalence of thyroid autoimmunity [12]. Prevalence of thyroid autoimmune is especially high in association with PCOS and endometriosis, both conditions have been associated with autoimmunity and inflammation”. Szeliga et al., was of the view that, “POI can occur in isolation, but is often associated with other autoimmune conditions. Concordant thyroid disorders such as hypothyroidism, Hashimoto thyroiditis, and Grave’s disease are most commonly seen” [13].

Endocrine Autoimmune Disorders and Female Infertility

Thyroid disorder

Poppe et al. state that the thyroid gland is frequently targeted by autoimmune diseases, and thyroid autoimmunity (TAI) is the most common autoimmune disorder in women, impacting 5–20% of females of childbearing age [14]. Thyroid autoimmunity is found in approximately 15-20% of normal pregnant women, 20-25% of women with recurrent miscarriages, and 20% of women undergoing IVF [15]. Thyroid autoimmunity can cause subclinical or overt hypothyroidism or it may be associated with them;

it can also be present without thyroid dysfunction and therefore remain latent, asymptomatic or undiagnosed for a long time [16]. Hashimoto's disease and postpartum thyroiditis/painless thyroiditis share a predominately T cell-mediated autoimmunity, while Graves' disease is characterized by a primarily humoral response and the presence of anti-thyroid stimulating hormone receptor antibodies [17]. Numerous research has examined the links between autoimmune thyroid condition (AITD) and female infertility as part of the broad investigation into the relationships between autoimmune disorders and reproductive failure [18].

In a study by Kivity et al., it was demonstrated that the occurrence of vitamin D deficiency was 2.5 times greater in females with thyroid autoimmunity compared to healthy individuals [19]. Additionally, vitamin D deficiency was found to be associated with the presence of thyroid antibodies. Early stages of pregnancy have been linked to mild thyroid dysfunction as a potential explanation for early miscarriages in women with thyroid autoimmunity who are otherwise euthyroid [20]. Rijal et al. stated that subclinical hypothyroidism is a noteworthy thyroid condition associated with infertility [21]. Muller et al. have long suggested that early subclinical thyroid dysfunction in women with thyroid autoimmunity may be a potential underlying cause of infertility and unsuccessful IVF attempts in women seeking pregnancy [22]. As per Krassas et al., Thyrotoxicosis in women is associated with decreased fertility [23]. Krassas et al. found that when considering the collective evidence, most studies indicate a higher occurrence of autoimmune thyroid diseases (AITD) among women seeking treatment at infertility clinics [24].

Polycystic ovary syndrome (PCOS)

As per Ndefo, U. A et al., Polycystic ovary syndrome (PCOS) is an endocrine and reproductive condition that impacts 7 to 15% of women during their reproductive years [25]. Cuhaci mentioned that PCOS, a cluster of symptoms that affect women in their reproductive years, is on the rise and becoming more common [26]. Wild et al. mentioned that women with PCOS can exhibit symptoms like hirsutism, acne, and fertility challenges [27]. According to Fauser et al., individuals with PCOS face an elevated risk of metabolic syndrome and insulin resistance, which can ultimately lead to cardiovascular disease and type 2 diabetes [28]. Obesity, insulin resistance and low vitamin D levels are present in more than 50% of patients with PCOS, these factors along with hyperandrogenism could have adverse effects on long term health [29].

Tsutsumi & Webster noted that irregular pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus plays a role in contributing to PCOS [30]. Klein et al. explained that GnRH (Gonadotropin-Releasing Hormone) triggers the pituitary gland to release FSH (Follicle-Stimulating Hormone) and LH (Luteinizing Hormone), essential for regulating the menstrual cycle. In cases of PCOS, inadequate levels of these hormones can disrupt egg development and release from the follicle [31]. In PCOS low level of progesterone over-stimulates the immune system which leads to the production of autoantibodies and therefore it can be labeled as an autoimmune disorder [32]. Anti-mullerian hormone (AMH) is a useful test in the evaluation of infertility [33]. PCOS-afflicted women exhibit AMH levels that are 2 to 3 times higher than those without PCOS, primarily due to an elevated count of preantral and small antral follicles. This increased AMH level appears to be linked to the severity of PCOS [34].

Premature ovarian insufficiency (POI)

According to Domniz et al., Premature Ovarian Insufficiency (POI) is a clinical syndrome marked by the loss of ovarian function before the age of 40. It is characterized by menstrual irregularities (amenorrhea or infrequent periods), elevated gonadotropin levels, and decreased estradiol [35]. About 1–2% of women are affected by POI, a phenotypically and etiologically heterogeneous condition characterized by primary or secondary amenorrhea, infertility, decreased estrogen production, elevated gonadotropins and increased risk for osteoporosis and cardiovascular disease [36]. When patients with idiopathic POI are screened for the presence of autoimmune illnesses, thyroid abnormalities, which are the most prevalent and can be discovered in 12–40% of patients, are shown to be related with clinical autoimmune disease between 10 and 55% of the time [37]. Autoantibodies against ovarian antigens, observed in various studies, the occurrence of lymphocytic oophoritis, associations with other autoimmune conditions, collectively provide strong evidence for an autoimmune origin in POI [38].

Autoimmunity is responsible for approximately 4–30% of POI cases [39]. According to Kirshenbaum, the most common autoimmune condition associated with Primary Ovarian Insufficiency (POI) is thyroid autoimmunity. Although diabetes mellitus is less frequent, being reported in only 2.5% of cases, low DHEAS (dehydroepiandrosterone sulfate) levels were observed in 65% of patients, hinting at a

potential connection with POI [40]. According to Novosad et al., about 10-20% of Addison's disease patients can also experience Primary Ovarian Insufficiency (POI), while women with POI may display signs of adrenal autoimmunity ranging from 2.5% to 20% [41]. The link between POI and Addison's disease may be attributed to the existence of cross-reacting autoantibodies, specifically those targeting the side-chain cleavage enzyme, which react against auto-antigens shared by steroid-producing cells from diverse sources [42]. The second most prevalent condition linked to Primary Ovarian Insufficiency (POI) is an autoimmune ailment impacting the adrenal glands. About 2.5% of women with diabetes mellitus might experience the onset of POI [43].

The most common endocrine autoimmune disorder linked with POI patients without adrenal autoimmunity is thyroid autoimmunity (25–60%) [44]. Thyroid autoimmune disease, most commonly Hashimoto's thyroiditis, is present in 14-27% of women at the initial diagnosis of POI [45]. A case report has even described how hypothyroidism caused intermittent secondary amenorrhea and eventually POI at the age of 35 years in an otherwise healthy patient [46]. In idiopathic POI attention should be paid to indirect autoimmune signs, such as association with possible autoimmune diseases (clinical aspects, hormone levels, and antibodies) ovarian function may return after regression of the autoimmune status and control of coexistent endocrine disease [47, 48]. Autoimmune polyglandular syndrome (APS), a disorder in which autoimmune activity results in particular endocrine organ dysfunction, might also include autoimmune-related POI [49]. Ebrahimi & Asbagh explained that, “an alteration in the AIRE gene, which controls immunological tolerance, results in APS-1. About 40–70% of women in APS-1 will develop POI” [50].

Table 1: Autoimmune Endocrine Disorders in relation to female infertility

Autoimmune Endocrine Disorder	Prevalence	Hormonal abnormalities	Comments on Fertility	References
Hashimoto's Thyroiditis	5% to 15% among reproductive- aged women	Elevated thyroid peroxidase (TPO) antibodies, decreased free thyroxine (FT4)	Disturbed folliculogenesis, decreased implantation rates	[51, 52]
Systemic lupus erythematosus (SLE)	Less prevalent	Autoantibodies, immune dysregulation	Potential impact on hormonal regulation and reproductive organs	[53]
Polycystic Ovary Syndrome (PCOS)	Affects 7 to 15% of women in reproductive age	Hyperandrogenism, increased LH/FSH ratio, insulin resistance	Anovulation, impaired oocyte maturation	[54]
Multiple Sclerosis	Ranges from 5 to 20 per 100,000 inhabitants, including women of childbearing age.	Autoimmune-mediated demyelination of the central nervous system	Potential impact on neuroendocrine control of reproduction	[55]
Premature Ovarian Insufficiency (POI)	Affects ~1% of women prior to age 40, and ~0.1% prior to age 30	Decreased anti-Müllerian hormone (AMH), elevated follicle-stimulating hormone (FSH)	Diminished ovarian reserve, reduced fertility potential	[56, 57]
Type 1 diabetes mellitus (T1DM)	Affects 40% of women	Autoimmune destruction of pancreatic beta cells	Potential impact on insulin production and glucose regulation	[58]

Endometriosis

According to Greenbaum et al., endometriosis is described as a persistent inflammatory condition marked by the existence of endometrial-like tissue located outside the uterus [59]. Eisenberg's findings in epidemiological studies indicate that approximately 1% of women are affected by endometriosis [60, 61] as well as in 10% of women during their reproductive years [62]. The prevalence is highest among infertile women (20-30%) [63] and women undergoing surgery [64]. Infertility is the other major symptom of endometriosis, even though a diagnosis of endometriosis does not always imply infertility endometriosis is identified in approximately 30% of women in infertile couples [65]. The disease adversely affects fertility by different mechanisms acting at the level of the pelvic cavity, ovary and uterus [66].

Various reproductive factors have consistently demonstrated a connection to the risk of developing endometriosis, as highlighted in Table 2, indicating that hormonal fluctuations may play a significant role. For example, factors such as a younger age of menarche [68] and menstrual cycles of shorter duration [71] have been linked to an elevated risk.

Table 2: Risk for the development of endometriosis

	Factors associated with Endometriosis	Reference
1.	Alcohol Consumption	[67]
2	Early onset of menarche	[68]
3	Greater stature	[69]
4	Caffeine intake	[70]
5	Menstrual cycles of shorter duration	[71]

Isenberg et al. proposed that endometriosis fulfills various classification criteria resembling autoimmune diseases. These include polyclonal B cell activation, disruptions in T and B cell functions, tissue damage, and the engagement of multiple organs [72]. Another important similarity between endometriosis and autoimmune diseases is the deregulation of the apoptotic process [73]. There is also a familial occurrence with a possible genetic preference, a female preponderance, and an increased likelihood of other autoimmune diseases [74]. The two primary clinical manifestations that emerge from an imbalance in tolerance against thyroid-specific antigens are Grave's disease and Hashimoto's thyroiditis [75]. Chronic lymphocytic thyroiditis called Hashimoto's thyroiditis causes hypothyroidism by gradually destroying the thyroid gland [76]. Anti-thyroid-stimulating hormone (TSH) receptor Abs that result in hyperthyroidism are a hallmark of Grave's disease [77]. Numerous investigations have revealed a link between endometriosis and the existence of thyroid Abs with AITD leading either to hypothyroidism or hyperthyroidism.

A new focus on progesterone resistance has been reported in the endometrium of women with endometriosis providing a logical explanation for both the fertility problems associated with endometriosis and its pathophysiology [78]. Progesterone has anti-inflammatory properties in uterine cells, but endometriosis is an inflammatory disease [79]. Estrogens have a major role in endometriotic tissue attachment to the peritoneum, lesion survival, production of inflammatory substances (metalloproteinases, cytokines, or prostaglandins, and growth factors) and angiogenesis [80]. Women with endometriosis and severe endometriosis-related pain (dysmenorrhea, pelvic pain, dyspareunia) usually present with very high scores of perceived stresses [81]. According to Kuznetsov, the contemporary approach to endometriosis involves a lifelong management strategy that focuses on maximizing the use of medically safe treatments without the need for histological confirmation of the disease, thereby reducing the need for repeated surgical procedures [82].

Type 1 diabetes mellitus

Type 1 diabetes mellitus (DM) is an autoimmune condition characterized by the destruction of β cells, necessitating lifelong insulin replacement therapy [83]. Many women with diabetes experience reproductive issues, with up to 40% facing significant menstrual or reproductive disorders in their lifetime [84].

Reproductive issues can emerge early in the reproductive years for those with childhood and adolescent-onset diabetes, leading to conditions like delayed puberty and primary amenorrhea [85]. Diabetic women experience significant reproductive issues throughout their lives, including delayed onset of menstruation, irregular menstrual cycles, problems with ovulation, heightened occurrence of polycystic

ovary syndrome, reduced fertility, complications during pregnancy, and the potential for early menopause [86]. Although assisted reproductive technology use is very common in polycystic ovary syndrome, it is unclear whether its use is also increased in women with DM [87, 88]. Regular monitoring of blood glucose and thyroid function in infertile women can facilitate the early detection of diabetes and related thyroid conditions [89].

Table 3: Impact of Type 1 Diabetes Mellitus on Reproductive Function

	Aspect of Type 1 Diabetes and Reproductive Function	Description	Reference
1.	Type 1 Diabetes Mellitus (DM)	Destruction of β cells, necessitating lifelong insulin therapy for management.	[83]
2	Reproductive Dysfunction in Women with DM	Reproductive issues are 40% encountering significant menstrual and reproductive problems throughout their lives.	[84]

Systemic lupus erythematosus (SLE)

Fava et al. described Systemic lupus erythematosus (SLE) as a chronic autoimmune disease that impacts multiple organs and systems. It exhibits variability in clinical presentation and severity, which can differ among individuals and change over time [90]. Similar to many autoimmune conditions, SLE is more common in women than in men, with female-to-male ratios surpassing 9:1 [91]. SLE affects, particularly, women of childbearing age [92]. Fertility may be affected in women with SLE due to amenorrhea accompanying severe flares, renal insufficiency-related hypo fertility and ovarian failure secondary to SLE therapy such as cyclophosphamide [93]. The onset of SLE is typically associated with the peak of estrogen levels in a female, which led investigators to investigate how endogenous estrogen may contribute to SLE pathogenesis and course [94].

Ovarian reserve testing could be valuable for women with SLE to assess fertility, potentially at an earlier stage than typically recommended, considering the various fertility risk factors they face [95]. When diagnosing female infertility, assessing ovarian reserve involves examining reproductive potential based on the quantity and quality of remaining oocytes [96]. Henderson et al., [97] noted “the adoption of cyclophosphamide as a treatment for severe lupus nephritis contributed to a reduction in mortality in lupus nephritis from 70% in 1950 to 1960 to approximately 10% in recent years”. Cyclophosphamide, an alkylating drug, can have significant gonadotoxic effects, especially concerning the fertility of SLE patients in their reproductive years [94]. Cyclophosphamide can lead to temporary amenorrhea and, less commonly, result in infertility or premature ovarian failure in women due to ovarian follicle depletion [98]. Most women who complete treatment with cyclophosphamide continue to be able to conceive spontaneously and have successful pregnancies thanks to the commonly lower cumulative dosages of the drug that are now used in practice [99].

Multiple sclerosis

According to McGrogan et al., Multiple sclerosis (MS) is the most common autoimmune disorder that affects the hypothalamus [100]. Greer et al. mentioned that, “the disease is more frequent in women than men, and this sex difference intensifies with increasing age” [101]. Before a diagnosis, fertility seems to be declining, and it keeps declining in disorders that have already been diagnosed [102]. Thone et al., show that anti-mullerian hormone (AMH) levels were lower in young women with relapsing–remitting MS compared with controls, it provides evidence that women with MS may have reduced ovarian reserve and hence reduced fertility [103]. MS were to lead to a biological cause of impaired fertility in women, it might be anticipated that a similar effect would be observed in men [104].

Magyari et al., found that men with MS had a significantly higher risk of having concurrent autoimmune disorders compared to controls, indicating a gender difference. In women with MS, the development of POI may be attributed to a genetic predisposition for autoimmune diseases, as the genes that make individuals susceptible to MS also increase susceptibility to other autoimmune conditions [105]. Premature ovarian failure (POF), also known as POI and amenorrhea, is a result of MS treatment with the synthetic cytotoxic medication mitoxantrone or with -interferon, the most popular disease-modifying therapy [106].

Autoimmune polyglandular syndrome

As per Michels & Gottlieb, Autoimmune polyglandular syndromes (APS), alternatively known as polyglandular autoimmune syndromes (PAG), are a collection of conditions marked by the coexistence

of various autoimmune disorders and, in certain instances, immunodeficiency [107]. Cutulo added that, “the two major autoimmune polyendocrine syndromes, (autoimmune polyendocrine syndromes type1–type2/APS-1 and APS-2), both have Addison’s disease as a prominent component, but also exist APS-3 and APS-4” [108]. Patients with APS-1 or APS-2 develop multiple diseases over time, and around one in seven of their relatives may have an undiagnosed autoimmune condition [109]. The diseases associated with autoimmunity can be found in around 40% of women with premature ovarian failure and are associated with poorer infertility treatment outcomes [110]. Reato et al. reported that within APS-1, a higher risk of primary ovarian failure (POF) at 40% is linked to chronic candidiasis and/or chronic hypoparathyroidism. In APS-4, POF is slightly less common at 30%, and in APS-2, it is the least prevalent at 16%, associated with autoimmune thyroid disease and/or type 1 diabetes mellitus [111]. Michalakis & Coppack estimated that, “POI is frequently associated with autoimmune disorders (10–30%), particularly hypothyroidism (25%), Addison’s disease (3%) and diabetes mellitus (2.5%)” [112].

Table 4: Genetic Links in Autoimmune Polyglandular Syndrome (APS)

	Conditions/Diseases	Key Findings and Associations	Reference
1.	Autoimmune Premature Ovarian Failure (POF), Autoimmune Addison's Disease	Strong association between autoimmune POF and autoimmune Addison's disease in patients with APS	[111]
2.	Autoimmune Disorders, Autoimmune-Mediated POF	AIRE gene's involvement in autoimmune disorders and its potential contribution to autoimmune-mediated POF	[112]
3	Premature Ovarian Failure (POF)	- Transplantation studies have established a connection between diminished AIRE gene expression in the thymus and Premature Ovarian Failure (POF). - Several genes are associated with POF, such as FMR1, FMR2, BMP15, FSHR, FOXO3, and FOXL2. - Among these genes, it's noteworthy that only the AIRE gene is specifically linked to autoimmune-mediated POF.	[114]

According to Reato et al., “autoimmune POF is strongly associated with autoimmune Addison's disease in patients with APS” [111]. Jasti et al. have provided longstanding evidence indicating the involvement of the AIRE gene in autoimmune disorders, suggesting its potential role in autoimmune-mediated POF [113]. The transplantation study by Cordts et al., unequivocally showed that “POF is caused by decreased AIRE expression in the thymus. Only the AIRE gene has been connected to autoimmune-mediated POF, despite the fact that numerous other genes (such as FMR1, FMR2, BMP15, FSHR, FOXO3, and FOXL2) have been demonstrated to be involved with POF” [114].

GWAS on Endocrine Autoimmune Disorders

In recent years, rapid advances in human genetics have enabled researchers to identify previously unknown risk alleles associated with common diseases, such as type 1 diabetes, SLE and thyroiditis. As a result of studies conducted by Dosiou [115], infertility and low ovarian reserve are associated with thyroid-stimulating hormone (TSH) elevation and/or thyroid autoimmunity in subsets of women. These findings have contributed to a better understanding of thyroid autoimmunity and infertility pathogenesis. Krassas et al., denoted that, “when autoimmune thyroid disease is present, the impact of controlled ovarian hyperstimulation may become more severe, depending on pre-existing thyroid abnormalities” [116]. GWAS have revealed multiple loci potentially associated with POI in Chinese, Korean, and Dutch women [117].

Table: 5 Genetic Associations with Common Diseases and Conditions

Study and Year	Conditions/Diseases Studied	Key Findings and Associations	Reference
Kim et al. (2022)	Autoimmune Thyroid Disease (AITD), PCOS	- PCOS patients, particularly those with hypothyroidism, show a heightened prevalence of AITD.	[120]

		- The TGF- β signaling pathway is associated with both PCOS and Hashimoto's thyroiditis.	
Dosiou (2020)	Infertility, low ovarian reserve	Associated with TSH elevation and thyroid autoimmunity in subsets of women	[115]
Laven (2016)	Premature Ovarian Insufficiency (POI)	Multiple loci potentially associated with POI in Chinese, Korean, and Dutch women	[117]
Krassas et al. (2010)	Autoimmune thyroid disease, ovarian hyperstimulation Type 1 Diabetes (T1D)	Pre-existing thyroid issues can exacerbate the impact of controlled ovarian hyperstimulation.	[116]
Lette & Rioux (2008)	Type 1 Diabetes (T1D)	Genetic loci unlinked to the MHC region account for 8% of disease risk in T1D	[118]
WTCCC (2007)	Type 1 Diabetes (T1D)	Confirmed genetic associations in MHC class II locus, CTLA4, PTPN22, and IL2RA genes with T1D	[119]

As per Lettre & Rioux., it is suggested that a substantial portion, approximately 8%, of the disease risk in Type 1 Diabetes (T1D) can be attributed to genetic loci outside of the MHC region [118]. The Wellcome Trust Case Control Consortium study confirmed the MHC class II locus, as well as the CTLA4, PTPN22, and IL2RA genes, were established to be related with T1D prior to the development of GWAS [119]. In a report by Kim et al., they estimate that there is an increased prevalence of AITD among patients with PCOS, and particularly hypothyroidism [120]. The TGF- β signaling pathway is a well-documented genetic association between PCOS and Hashimoto's thyroiditis (HT). As these genes play crucial roles in the immune system, hormone regulation, inflammation, cell proliferation, tissue differentiation, apoptosis, and metabolic consequences such as insulin resistance (IR), they are strong candidate susceptibility genes for both syndromes. These studies provide insights into the genetic basis of these conditions and contribute to our understanding of their underlying mechanisms.

4. Conclusion

Many autoimmune endocrine disorders can lead to female infertility by interacting and impairing normal reproductive function. It is particularly relevant considering that autoimmune diseases affect women preferentially, often during their reproductive age. Our main focus of the study is to treat the cause of disease and to identify individuals early to restore homeostasis before autoimmune diseases occur. Various medications which are in use for autoimmune conditions are currently being used on an empirical basis to enhance fertility with conflicting supporting evidence. The new era of treatment and control of endocrine autoimmunity is already here and we predict an upcoming storm in the clinical trials and treatment of autoimmune research.

Conflict Of Interest

The authors confirm that they do not have any conflicts of interest.

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