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Original Paper

Current Research Status on the Etiology of Ovum Maturation Disorders

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Abstract

Ovulation maturation disorders represent one of the underlying causes of recurrent assisted reproductive therapy failures in certain infertile women. With continuous advancements in science and technology, significant progress has been made in the research on ovulation maturation disorders. This review aims to systematically summarize the current state of research on the etiology of ovulation maturation disorders and, by providing an in-depth understanding of the latest advances in this field, to offer patients more effective clinical diagnostic and therapeutic strategies.

Keywords

Ovulation maturation disorder, Etiology, Gene mutation, Endocrine disorder

Main Text

Ovulation disorder refers to a condition where, under normal physiological conditions during the female ovulation period, the follicle fails to mature properly or undergoes ovulation, thereby preventing the patient from achieving pregnancy; alternatively, it encompasses various abnormalities that may occur during the development and maturation of the oocyte, including arrested oocyte development, abnormal oocyte quality, and reduced oocyte count [1]. Oocyte maturation primarily involves both nuclear maturation and cytoplasmic maturation. Only when a series of sequential structural and molecular changes occur in the cumulus cells, zona pellucida, cytoplasm, and nucleus—resulting in complete nuclear and cytoplasmic maturation—does the oocyte acquire the capacity for fertilization and subsequent development [2].

1. Genetic Factors

Genetic factors play a crucial role in the development of oocyte maturation disorders. As genetic research continues to advance, an increasing number of gene variants associated with oocyte maturation disorders

have been identified.

1.1 FMR1 Gene

Mutations in the FMR1 gene represent one of the common genetic causes of impaired oocyte maturation. The protein encoded by this gene, FMRP, plays a critical role in oocyte development and maturation. Premutations in the FMR1 gene may lead to female ovarian insufficiency, resulting in recurrent miscarriages, embryonic arrest, infertility, among other conditions [3]. Approximately 20% of women carrying premutation alleles of the FMR1 gene develop fragile X-associated primary ovarian insufficiency (FXPOI), with the prevalence of this condition varying depending on the length of the CGG repeat expansion; the most common number of CGG repeats ranges from 80 to 100 [4]. Abnormal dynamic mutations in the FMR1 gene can cause neurological abnormalities such as intellectual disability and behavioral disorders, as well as conditions characterized by diminished ovarian reserve, including amenorrhea and reduced fertility [5]. Ovarian insufficiency and diminished ovarian reserve may interfere with the oocyte maturation process, thereby leading to impaired oocyte maturation.

1.2 TUBB8 Gene

In 2016, Wang Lei's team elucidated the relationship between the β-tubulin 8 (TUBB8) gene and female infertility [6]. Studies have shown that mutations in the oocyte TUBB8 gene can impair the proper assembly of microtubules and motor proteins or prevent the formation of the mitotic poles, leading to aberrant spindle assembly and chromosome dynamics, which directly disrupts the meiotic process in oocytes [7] and results in arrested oocyte development [8]. Furthermore, TUBB8 is a core gene regulating spindle formation; oocyte developmental arrest caused by mutations in this gene follows an autosomal dominant inheritance pattern [9]. A single mutation may induce multiple adverse effects, underscoring the critical role of TUBB8 mutations throughout the entire pregnancy process; conversely, mutations at the same locus may yield disparate outcomes, suggesting that besides TUBB8, other genes may also influence oocyte maturation and fertilization processes [10].

1.3 NOBOX Gene

The expression of the human NOBOX gene is restricted to oocytes within the ovaries; however, the NOBOX gene has also been detected in the testes and adult pancreas [11]. The protein encoded by the NOBOX gene plays a crucial role in oocyte development and maturation; consequently, mutations in the NOBOX gene can lead to arrested oocyte development and premature ovarian insufficiency [12].

1.4 MARF1 Gene

Building upon previous studies of mice with MARF1 gene mutations, this study represents the first investigation into the relationship between the MARF1 gene and impaired oocyte maturation in humans. Among patients with oocyte maturation disorders, one novel synonymous mutation in the MARF1 gene, two novel single nucleotide polymorphism (SNP) sites, and five known SNP sites were identified [13]. Although no direct gene mutations causative of oocyte maturation disorders were detected, the functional implications of these newly discovered mutation sites require further investigation. The association between human oocyte maturation disorders and MARF1 gene mutations warrants further elucidation.

1.5 PATL2 Gene

The PATL2 protein is an mRNA-binding protein that is specifically expressed in immature oocytes and inhibits the intracellular post-transcriptional translation process; as oocytes mature, PATL2 expression gradually disappears. PATL2 mutations lead to reduced protein expression, indicating that the level of gene expression plays a crucial role in oocyte maturation [14]. In the absence of PATL2, the expression levels of several highly correlated genes involved in oocyte maturation and early embryonic development are deregulated [15].

1.6 ZP1–ZP3 Genes

The zona pellucida (ZP) is a ubiquitous extracellular matrix surrounding mammalian oocytes, playing a critical role in oogenesis, fertilization, and pre-implantation embryonic development [16]. The ZP1, ZP2, and ZP3 genes encode zona pellucida proteins; mutations in these genes may impair zona pellucida assembly by disrupting the interactions among ZP1, ZP2, ZP3, and ZP4 proteins, leading to zona pellucida deficiency and subsequent antral follicle syndrome [17]. Antral follicle syndrome is a clinically rare reproductive dysfunction syndrome characterized by abnormal oocyte maturation.

2. Effects of Endocrine Hormones

Hormones play a pivotal role in regulating ovarian function, follicular development and ovulation, as well as promoting oocyte maturation. The effects of these hormones do not occur in isolation; they are mediated by various feedback regulatory mechanisms. Among the hormones acting on the ovaries, multiple hormones—including androgens, estrogens, progesterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and gonadotropins (Gn)—interact with one another to collectively regulate physiological processes in the human body.

Androgens are one of the steroid hormones secreted by the granulosa cells of the ovary [18]; elevated concentrations of androgens can impair estrogen synthesis and inhibit FSH-induced LH receptor formation. Polycystic ovary syndrome (PCOS) is characterized by inappropriate stimulation by LH, leading to relative deficiency of FSH and excessive androgen levels, wherein the androgens cannot be promptly converted into estrogens [19][20]. FSH promotes germ cell development by acting on the ovarian granulosa cells [21], induces the formation of LH receptors in follicles, and prepares the body for ovulation [22]. LH acts on the granulosa cells of the ovary, regulating local and peripheral steroid hormone concentrations, thereby stimulating follicular development and triggering ovulation [23]. The follicle undergoes further development under the synergistic action of FSH and LH, ultimately initiating ovulation upon exposure to the LH surge [24].

Polycystic ovary syndrome (PCOS) is a common reproductive endocrine metabolic disorder that leads to infertility in female patients. Some PCOS patients exhibit elevated basal LH levels and high serum androgen concentrations, which contribute to abnormal follicular development [25]. Elevated androgen levels over the long term represent one of the pathogenic mechanisms underlying PCOS; consequently, hyperandrogenism constitutes a primary clinical feature of PCOS patients [26][27]. Due to their heightened

sensitivity to gonadotropins and propensity for exaggerated responses, women with PCOS are often misdiagnosed as having an increased risk of ovarian hyperstimulation [28]. Studies have demonstrated that serum prolactin levels in PCOS patients are also significantly lower than those observed in healthy women [29].

3. Autoimmune Factors

3.1 Autoimmune Premature Ovarian Failure

Premature ovarian failure (POF) refers to a syndrome in which women who have experienced normal menarche or delayed puberty, with normal development of secondary sexual characteristics, develop amenorrhea before the age of 40; these patients exhibit elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), where FSH levels are significantly higher than LH levels, while estrogen levels are reduced [30]; furthermore, approximately 45% of POF patients test positive for one or more autoantibodies [31].

The pathogenesis of premature ovarian failure is relatively complex; current evidence suggests that approximately 30% of cases are closely associated with autoimmune dysregulation and metabolic abnormalities, a condition referred to as autoimmune premature ovarian failure (APOF) [32]. In patients with APOF, endometrial thickness, AFC count, uterine volume, and ovarian volume are all significantly lower than those observed in healthy volunteers undergoing routine physical examinations; following the onset of premature ovarian failure, the ovarian reserve function in these patients declines markedly [33]. Study results indicate that elevated MIF levels represent one of the risk factors for APOF development, with MIF playing a role in its pathogenesis. Patients with APOF often present with concomitant autoimmune diseases and various autoantibodies, where high concentrations of these antibodies can induce or exacerbate ovarian dysfunction [34–36].

Since patients with POF often exhibit positivity for multiple autoantibodies compared with healthy controls, it is currently believed that autoimmune dysfunction constitutes one of the primary etiological factors underlying POF.

3.2 Autoimmune Thyroid Diseases

Studies have demonstrated that laparoscopic ovarian drilling can stimulate PCOS patients to produce autoantibodies, indicating altered immune status in PCOS patients [37]. Yao Huajun found that PCOS patients exhibit significant abnormalities in thyroid hormone secretion, with a markedly higher incidence of subclinical hypothyroidism and autoimmune thyroiditis compared to healthy individuals [38]. Thyroid autoimmunity (TAI) is most prevalent among women of reproductive age; among these, thyroid-related diseases such as Hashimoto's thyroiditis are common autoimmune disorders associated with premature ovarian insufficiency (POI), with TAI accounting for 14%–32.7% of women initially diagnosed with POI [39]. Research has shown that thyroid autoantibodies can be detected in all follicular fluid samples from patients with thyroid autoimmunity, but are absent in patients without thyroid autoimmunity [40].

Currently, the main mechanisms by which thyroid dysfunction affects ovarian reserve include: (1) TSH

shares a similar conformation with FSH and possesses a common α subunit; TSH can directly act on the ovaries and oocytes, and elevated TSH levels can impair follicular development and ovarian reserve function [41]; (2) Thyroid hormones directly participate in and influence the metabolism of ovarian estrogen, and can also regulate ovarian function through the secretion of FSH and luteinizing hormone; additionally, thyroid hormones modulate the bioactive levels of sex hormones in the bloodstream by promoting increases in sex hormone-binding globulin levels.

Research on oocyte maturation disorders continues to advance; while the therapeutic approaches currently applied in clinical practice have yielded certain benefits, they primarily target the organs involved in oocyte maturation and have not yet effectively addressed the underlying issue of oocyte maturation disorders. It is hoped that future clinical practice will enable the identification of the etiological factors contributing to oocyte maturation disorders and the development of effective treatment strategies for this condition.

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