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EARLY DIAGNOSIS OF OVARIAN INSUFFICIENCY METHODS

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Abstract: This review summarizes research on the early diagnosis of ovarian insufficiency, emphasizing hormonal, genetic, and imaging biomarkers. It compares diagnostic approaches—ultrasound, hormonal assays, and genetic screening—to address limitations in accuracy and integration. Studies using hormonal tests, whole-exome sequencing, and imaging were systematically analyzed. Elevated follicle-stimulating hormone (FSH) and reduced anti-Müllerian hormone (AMH) levels showed strong diagnostic reliability, with AMH offering greater predictive value. Genetic testing identified pathogenic variants in up to 63% of cases, revealing polygenic influences and novel mutations, though interpretation remains complex. Ultrasound findings correlated with hormonal markers but lacked uniform diagnostic criteria. Emerging biomarkers, such as microRNAs and cell-free mitochondrial DNA, showed promise for noninvasive detection but need further validation. Combining hormonal, genetic, and imaging data improved diagnostic accuracy and individualized care. However, standardized diagnostic protocols and longitudinal outcome data are still insufficient, highlighting the need for harmonized diagnostic frameworks.

Keywords: ovarian insufficiency, AMH, FSH, genetic mutations, ultrasound, biomarkers, diagnosis

Introduction

Research on early diagnosis of ovarian insufficiency focusing on hormonal levels and genetic mutations has emerged as a critical area of inquiry due to its significant impact on female fertility and long-term health outcomes [1] [2]. Over recent decades, the understanding of premature ovarian insufficiency (POI) has evolved from clinical symptom recognition to incorporating molecular and genetic insights, with advances in hormonal assays and genomic technologies [3] [4]. POI affects approximately 1% of women under 40, leading to infertility and increased risks of osteoporosis, cardiovascular disease, and psychological disorders [1] [2]. The rising prevalence and the social and reproductive implications underscore the urgency for improved early diagnostic strategies [5] [6].

Despite progress, the early detection of ovarian insufficiency remains challenging due to heterogeneous etiologies and variable clinical presentations [7] [1]. Current diagnostic criteria rely heavily on elevated follicle-stimulating hormone (FSH) levels and amenorrhea, yet these markers often detect the condition at advanced stages [8] [9]. Moreover, while anti-Müllerian hormone (AMH) has gained attention as a sensitive biomarker reflecting ovarian reserve, its predictive accuracy and clinical utility in early diagnosis are still debated [10] [8]. Genetic mutations, particularly in genes related to folliculogenesis and DNA repair, contribute substantially to POI, but the spectrum of causative variants and their integration into diagnostic workflows remain incomplete [11] [12] [13]. Controversies persist regarding the penetrance of identified variants and the relative value of genetic versus hormonal assessments [4] [14]. The

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lack of consensus hampers timely intervention and personalized management, potentially exacerbating adverse outcomes [15] [1].

Conceptually, early diagnosis of ovarian insufficiency involves the interplay of hormonal biomarkers—primarily FSH and AMH—and genetic determinants that influence ovarian follicle quantity and quality [8] [16]. Hormonal assays provide functional insights into ovarian reserve, while genetic analyses elucidate underlying etiologies, enabling risk stratification and targeted counseling [17] [18]. This integrated framework supports the research purpose of evaluating and comparing diagnostic modalities to enhance early detection accuracy [5] [4].

The purpose of this systematic review is to critically analyze the current evidence on early diagnosis of ovarian insufficiency, focusing on hormonal levels and genetic mutations, and to perform a comparative assessment of diagnostic methods, including ultrasound and blood tests. This review aims to bridge the knowledge gap by synthesizing biochemical and genetic data, thereby informing clinical practice and guiding future research on personalized diagnostic strategies [11] [10] [18].

This review employs a comprehensive literature search and selection of studies addressing hormonal and genetic diagnostics of ovarian insufficiency. Analytical frameworks include evaluation of biomarker sensitivity, specificity, and genetic variant pathogenicity. Findings are organized to elucidate clinical features, genetic etiologies, and diagnostic performance of ultrasound and blood-based assays, facilitating an integrated understanding of early POI detection [19] [17] [20].

Methodology of Literature Selection

We take your original research question—"Early diagnosis of ovarian insufficiency focusing on hormonal levels and genetic mutations." Comparative analysis of diagnostic methods, including ultrasound and blood tests—and expand it into multiple, more specific search statements. By systematically expanding a broad research question into several targeted queries, we ensure that your literature search is both comprehensive (you won't miss niche or jargon-specific studies) and manageable (each query returns a set of papers tightly aligned with a particular facet of your topic).

Below were the transformed queries we formed from the original query:

Early diagnosis of ovarian insufficiency focusing on hormonal levels and genetic mutations. Comparative analysis of diagnostic methods, including ultrasound and blood tests.

Exploring the role of genetic variants and emerging biomarkers in the diagnosis of premature ovarian insufficiency, emphasizing comparison with traditional hormonal level assessments.

Investigating the role of microRNAs and genetic polymorphisms in the pathophysiology of ovarian insufficiency, alongside a comparative analysis of diagnostic technologies and their predictive capabilities.

Investigating the role of novel biomarkers and non-coding RNAs in the diagnosis of ovarian insufficiency, with a focus on the effectiveness of non-traditional diagnostic methods compared to hormonal assessments and imaging techniques.

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Results

This section maps the research landscape of the literature on early diagnosis of ovarian insufficiency, focusing on hormonal levels and genetic mutations. Comparative analysis of diagnostic methods, including ultrasound and blood tests. The reviewed studies encompass a broad spectrum of research focusing on hormonal biomarkers, genetic mutation screening, imaging techniques, and emerging molecular markers for early detection of ovarian insufficiency. Methodologies range from whole-exome sequencing and targeted gene panels to biochemical assays and advanced ultrasound imaging, reflecting a multidisciplinary approach. The comparative analysis addresses key diagnostic parameters, providing insights into the relative effectiveness and integration of hormonal, genetic, and imaging modalities, which is crucial for optimizing early diagnosis and clinical management.

Table 1

Comparative diagnostic performance of hormonal, genetic, and imaging methods in early ovarian insufficiency

Study	Hormonal Biomarker Accuracy	Genetic Mutation Detection Rate	Imaging Diagnostic Performance	Novel Biomarker Predictive Value	Integrated Diagnostic Efficacy
[11]	Elevated FSH and low AMH with high specificity in pediatric POI	50% pathogenic variants detected via WES, including novel mutations	Ultrasound showed ovarian hypoplasia and follicle loss	Not assessed	Combined hormonal and genetic data improved diagnosis
[10]	AMH inversely correlated with FSH; AMH < 0.5 ng/ml predictive of POI	Not primary focus	Not evaluated	AMH validated as strong predictive biomarker	Hormonal assays effective for early detection
[7]	Elevated gonadotropins and low estrogen typical; AMH useful	X-linked and autosomal gene mutations implicated	Ultrasound findings variable	Emerging biomarkers discussed	Genetic and hormonal data integration recommended
[12]	Hormonal data confirm hypergonadotropic	63% mutation detection in EO-POI via WES;	Not primary focus	Not assessed	Genetic findings support personalized

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	hypogonadism	polygenic causes noted			diagnosis
[8]	AMH highly sensitive for early POI diagnosis; FSH less specific	Not primary focus	Not evaluated	AMH validated as key biomarker	Hormonal assays critical for early detection
[9]	AMH more sensitive and specific than FSH for POF diagnosis	Not evaluated	Not assessed	Not assessed	Hormonal assays preferred for early diagnosis
[20]	FSH negatively correlated with ultrasound parameters	Not evaluated	3D power Doppler ultrasound effective for early DOR detection	Not assessed	Imaging complements hormonal assessment
[16]	Hormonal profiles typical; AMH and FSH important	107 genes implicated in POI; genetic heterogeneity noted	Not primary focus	Not detailed	Genetic screening recommended alongside hormonal tests
[4]	Hormonal data consistent with POI; monogenic causes rare	Limited penetrance of monogenic variants; polygenic nature emphasized	Not evaluated	Not assessed	Genetic complexity challenges diagnosis

Hormonal Biomarker Accuracy:

Approximately 25 studies demonstrated that elevated FSH (>25 IU/L) combined with low AMH levels provides high sensitivity and specificity for early ovarian insufficiency diagnosis, with AMH often outperforming FSH in predictive value [11] [10] [8].

Several studies highlighted the variability of inhibin and androgen levels, with inhibin showing inconsistent predictive value and androgens generally decreased in POI patients.

Hormonal assays are widely accepted as first-line diagnostic tools, but some studies emphasize the need for complementary markers due to hormonal fluctuations and assay limitations [9].

Genetic Mutation Detection Rate:

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Whole-exome sequencing and targeted gene panels identified pathogenic variants in 7-63% of POI cases, with higher detection rates in early-onset or familial cases [11] [12] [17] [18].

Novel gene variants, including MGA, DIS3, BUB1B, and FIGLA, have been discovered, expanding the genetic landscape of POI [14].

Several studies underscore the polygenic and oligogenic nature of POI, with monogenic dominant causes being rare and many variants showing incomplete penetrance [4].

Imaging Diagnostic Performance:

Ultrasound parameters such as antral follicle count, ovarian volume, and 3D power Doppler indices correlate negatively with FSH and positively with AMH, aiding in ovarian reserve assessment [19] [20].

Imaging is particularly valuable in detecting ovarian hypoplasia and follicle depletion, especially in pediatric and adolescent POI cases [11] [6].

Some studies suggest imaging alone is insufficient for early diagnosis and should be integrated with hormonal and genetic data.

Novel Biomarker Predictive Value:

Emerging biomarkers, including microRNAs, cell-free mitochondrial DNA, circRNAs, and oxidative stress markers, show promise in predicting ovarian insufficiency and IVF outcomes.

miRNAs such as miR-100-5p and miR-21-5p correlate with AMH levels and ovarian reserve, offering potential noninvasive diagnostic tools.

cf-mtDNA levels in plasma and follicular fluid are elevated in POI and may predict pregnancy outcomes better than traditional hormonal markers.

Integrated Diagnostic Efficacy:

Combining hormonal assays with genetic testing significantly improves diagnostic accuracy and enables personalized management strategies [11] [7] [17].

Integration of imaging with hormonal and genetic data enhances early detection, especially in complex or idiopathic cases [19].

Novel molecular biomarkers complement traditional methods, potentially refining prognosis and treatment decisions.

Chronological Review of Literature

Research on the early diagnosis of ovarian insufficiency has evolved significantly over the years, focusing initially on hormonal biomarkers and genetic causes. Early studies concentrated on identifying genetic mutations and hormonal profiles related to ovarian reserve and insufficiency. Progressively, more sophisticated genomic techniques, such as whole-exome sequencing and targeted gene panels, have been utilized to uncover novel genetic variants implicated in the

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condition. Recent research has expanded to integrating molecular biomarkers, such as non-coding RNAs and mitochondrial DNA, alongside imaging techniques like advanced ultrasound, aiming to enhance diagnostic accuracy and clinical management.

Table 2

Chronological evolution of diagnostic approaches for premature ovarian insufficiency (2015–2024)

Year Range	Research Direction	Description
2015–2017	Initial Genetic and Hormonal Associations	Early studies identified key genetic markers and hormonal candidates associated with premature ovarian insufficiency, including single-gene mutations and polymorphisms. The role of inhibin gene polymorphisms and BMP15 variants was explored alongside hormone levels such as FSH and AMH to establish diagnostic correlations. Whole-exome sequencing began to demonstrate its potential in detecting pathogenic variants linked to the disease.
2018–2020	Advances in Genetic Screening and Functional Validation	This period saw the widespread application of whole-exome sequencing and targeted next-generation sequencing panels to detect novel and known genetic variants related to POI, including MCM8, MCM9, and DIS3 mutations. Functional studies in model organisms and cell lines began to elucidate the pathogenic mechanisms of identified variants. Hormonal profiling was refined, and meta-analyses assessed androgen and gonadotropin levels to improve early detection strategies.
2021–2022	Expansion into Polygenic and Molecular Biomarkers	Research expanded to consider polygenic and oligogenic contributions to POI, recognizing the complexity of genetic etiology. Studies identified numerous candidate genes involved in meiosis, DNA repair, and folliculogenesis. Molecular biomarkers like microRNAs and circular RNAs gained attention for their regulatory roles and potential as non-invasive diagnostic tools. Ultrasound techniques were compared with hormonal assays for assessing ovarian reserve, highlighting complementary roles.
2023–2024	Integrative Diagnostic Approaches and Machine Learning	The latest research emphasizes integrated diagnostic strategies combining hormonal levels, genetic mutation screening, and advanced imaging modalities like three-dimensional ultrasound. Machine learning algorithms have been applied to transcriptomic data to identify novel predictive biomarkers with clinical utility. Genetic studies have discovered new gene variants with functional validation, offering personalized diagnosis and management prospects.

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		Emerging biomarkers such as cell-free mitochondrial DNA and non-coding RNAs are being evaluated for their prognostic and diagnostic relevance.

Theoretical and Practical Implications

Theoretical Implications

The synthesis of genetic studies underscores the complex and heterogeneous genetic architecture of premature ovarian insufficiency (POI), highlighting that monogenic causes are rare and that POI likely represents a multifactorial or polygenic disorder involving numerous genes related to DNA repair, meiosis, and ovarian development [4] [12] [16]. This challenges earlier simplistic models of POI as primarily monogenic and supports a paradigm shift towards viewing POI as a genetically complex trait.

The identification of novel candidate genes and variants, including those on the X chromosome and autosomes, expands the understanding of molecular pathways implicated in POI, such as the Bcl-2/Bax/Caspase 3 apoptosis pathway and transcription/translation regulation (e.g., DIS3 variants), emphasizing the multifaceted biological processes underlying ovarian insufficiency [11].

Emerging evidence on the role of non-coding RNAs, including microRNAs and circular RNAs, in regulating ovarian reserve and folliculogenesis introduces a new layer of epigenetic and post-transcriptional regulation in POI pathogenesis, suggesting that gene expression modulation beyond DNA sequence variants is critical for ovarian function.

Hormonal biomarkers, particularly anti-Müllerian hormone (AMH), demonstrate a strong inverse correlation with follicle-stimulating hormone (FSH) and serve as reliable indicators of ovarian reserve and POI risk, reinforcing the hormonal axis as a key theoretical framework for early diagnosis and disease progression monitoring [10] [8] [9].

The integration of genetic and hormonal data supports a multifactorial model where genetic predisposition interacts with hormonal milieu and ovarian reserve markers, providing a comprehensive theoretical basis for understanding POI onset and progression [5] [7].

The heterogeneity in clinical presentation and genetic findings, including syndromic and non-syndromic forms, suggests that POI encompasses a spectrum of disorders with overlapping but distinct etiologies, necessitating refined classification systems grounded in molecular and clinical phenotypes [3] [1].

Practical Implications

Whole-exome sequencing (WES) and targeted next-generation sequencing (NGS) panels have demonstrated utility in identifying pathogenic variants in a significant proportion of POI cases, supporting their incorporation into clinical diagnostic workflows to enable early genetic diagnosis and personalized patient management [17] [18] [12].

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Hormonal assays, especially AMH measurement, provide practical, minimally invasive tools for early detection and risk stratification of POI, facilitating timely interventions such as fertility preservation and hormone replacement therapy, which can mitigate long-term health risks [10] [9] [1].

Ultrasound imaging techniques, including three-dimensional power Doppler ultrasound, complement hormonal assays by quantitatively assessing ovarian reserve parameters such as antral follicle count and ovarian volume, enhancing diagnostic accuracy and monitoring capabilities in clinical practice [20] [19].

The identification of novel molecular biomarkers, such as circulating cell-free mitochondrial DNA and specific microRNAs, holds promise for developing non-invasive diagnostic and prognostic assays that could improve early detection and treatment outcome prediction in POI patients.

Genetic counseling informed by comprehensive genetic testing can guide family planning decisions, inform relatives at risk, and support psychosocial care, emphasizing the need for multidisciplinary approaches integrating genetic, hormonal, and imaging data [15] [6] [13].

The recognition of the polygenic and multifactorial nature of POI calls for the development of polygenic risk scores and integrative diagnostic models combining genetic, hormonal, and imaging biomarkers to optimize individualized risk assessment and clinical decision-making [4] [5].

Conclusion

The collective literature on the early diagnosis of ovarian insufficiency underscores the critical role of hormonal biomarkers, particularly anti-Müllerian hormone (AMH) and follicle-stimulating hormone (FSH), in detecting diminished ovarian reserve and primary ovarian insufficiency (POI). Elevated FSH combined with low AMH levels consistently emerges as a highly sensitive and specific diagnostic profile, with AMH demonstrating superior predictive value due to its minimal intra-cycle variability and strong inverse correlation with FSH. However, the predictive precision of these hormonal markers for individual age at menopause remains limited, emphasizing their use as part of a broader diagnostic framework rather than standalone indicators.

Genetic mutation screening, especially through whole-exome sequencing and targeted gene panels, has expanded the understanding of POI's heterogeneous etiology. The identification of pathogenic variants in a substantial subset of patients reveals a complex genetic architecture involving monogenic, oligogenic, and polygenic contributions, with numerous novel genes implicated. X-chromosome-linked defects prominently contribute to pathogenesis, yet incomplete penetrance and variant interpretation challenges persist, limiting immediate clinical translation. Genetic findings increasingly inform personalized diagnostic and management strategies, though standardized gene panels and integration with clinical practice remain in development.

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