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INVITED REVIEW

Omics-based novel strategies in the diagnosis of endometriosis

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ABSTRACT

Endometriosis, an enigmatic and chronic disorder, is considered a debilitating condition despite being benign. Globally, this gynecologic disorder affects up to 10% of females of reproductive age, impacting almost 190 million individuals. A variety of genetic and environmental factors are involved in endometriosis development, hence the pathophysiology and etiology of endometriosis remain unclear. The uncertainty of the etiology of the disease and its complexity along with nonspecific symptoms have led to misdiagnosis or lack of diagnosis of affected people. Biopsy and laparoscopy are referred to as the gold standard for endometriosis diagnosis. However, the invasiveness of the procedure, the unnecessary operation in disease-free women, and the dependence of the reliability of diagnosis on experience in this area are considered the most significant limitations. Therefore, continuous studies have attempted to offer a noninvasive and reliable approach. The recent advances in modern technologies have led to the generation of large-scale biological data sets, known as –omics data, resulting in the proceeding of the –omics century in biomedical sciences. Thereby, the present study critically reviews novel and noninvasive biomarkers that are based on –omics approaches from 2020 onward. The findings reveal that biomarkers identified based on genomics, epigenomics, transcriptomics, proteomics, and metabolomics are potentially able to diagnose endometriosis, predict prognosis, and stage patients, and potentially, in the near future, a multi-panel of these biomarkers will generate clinical benefits.

Abbreviations: ceRNA: competitive endogenous RNA; ESR: estrogen receptor; FSH: follicle-stimulating hormone; GWAS: genome-wide association studies; IL: interleukin; LC-MS/MS: liquid Chromatography with tandem mass spectrometry; LH: luteinizing hormone; miRNA: micro RNA; NGS: next-generation sequencing; RT-PCR: reverse transcriptase polymerase chain reaction; RNAseq: RNA sequencing; SF1: steroidogenic factor 1; SNP: single nucleotide polymorphism; StAR: steroidogenic acute regulatory; WES: whole exome sequencing; WGS: whole genome sequencing

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Introduction

Endometriosis is described as a chronic inflammatory disorder that can create disability in daily life, despite being benign. This gynecologic condition, highlighted by pain and infertility, is considered a socio-economic burden as it affects up to 10% of the females of reproductive age worldwide, which includes a population of about 190 million [1,2]. Nevertheless, the true affected population is hard to estimate due to three main reasons; underreported, undiagnosed, and misdiagnosed cases [3,4]. In affected patients, endometrium-like tissue grows outside the uterus in the peritoneal cavity but progresses into endometriosis lesions when it invades the peritoneum and develops vascularization. Therefore, the overgrowth of a similar structure to the lining of the uterus beyond the innate localization of the endometrium is considered the main cause of endometriosis [5,6].

Severe pain in the pelvis, impaired fecundity, and reduced quality of life are among the most important complications that women of reproductive age with endometriosis experience [7,8]. The involvement of a variety of genetic and environmental factors in the development of endometriosis has turned this disorder into a complex condition. As a result, the pathophysiology and etiology of the disease remain unclear despite a plethora of studies in recent decades [9–11]. Nevertheless, genetic and epigenetic alterations have

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attracted remarkable attention in order to clarify the etiology of endometriosis. In fact, genetic studies have suggested a number of endometriosis-risk loci and epigenetic studies have considered related changes as effectors in disease development [12–14].

Currently, retrograde menstruation and coelomic metaplasia are the most recognized pathogenetic hypotheses. However, recently novel theories such as the embryological theory of pathogenesis have been discussed to describe the etiology of the disease [15–17]. The uncertainty of the etiology of the disease and its complexity along with nonspecific symptoms (severe pelvic pain, dysmenorrhea, dyspareunia, and impaired fertility are considered the main symptoms) have caused misdiagnosis or undiagnosis of affected people. Biopsy and laparoscopy, a surgical visual inspection of the pelvic organs, are referred to as the gold standard for endometriosis diagnosis. Laparoscopic surgery represents some desired strengths as it has acceptable sensitivity and specificity (94% and 79%, respectively) [18], provides samples for subsequent histological analyses [19], and offers treatment opportunities in addition to diagnosis [20]. However, the invasiveness of the procedure (0.001% risk of life-threatening vascular injury, 0.12% risk of urologic injury, and 0.16% risk of bowel injury) [21] and the unnecessary operation in disease-free women (about two-thirds of people underwent operative laparoscopy) [22] are two main limitations of diagnostic laparoscopy. Moreover, emotional consequences [22], and the dependence of the reliability of diagnosis on experience in this area [23] have been reported as other significant limitations of this diagnostic strategy. Therefore, continuous studies have attempted to offer a noninvasive approach that overcomes the limitations of this approach, in addition to providing its strengths. In a recent study, we reviewed novel and noninvasive genetic, immunological, and miscellaneous biomarkers of endometriosis. Setbacks to these biomarkers included being involved in a variety of gynecological and non-gynecological complications, unacceptable specificity and sensitivity, and the need to conduct studies for further investigations [24]. As a result, more efforts and perhaps the application of modern bioinformatics may lead to an early and reliable diagnosis of endometriosis.

Nowadays, stupendous advances in modern technologies have led to providing novel diagnostic strategies such as the generation of large-scale biological data sets, called –omics data, that have led to the proceeding of the –omics century in biomedical sciences. Since the turn of the century, many approaches based on –omics have been reported [25,26] and a remarkable number of studies have used these techniques to diagnose patients with endometriosis and determine the severity of the disease. In 2020, Goulielmos et al. reviewed –omic-based approaches in the diagnosis of endometriosis, and discussed the existing limitations and the necessity for further studies [27]. Considering that during the last three years a large number of studies have addressed related subjects and proposed solutions to improve previous investigations, the present study aimed to critically review novel and noninvasive biomarkers that are based on –omics approaches from 2020 onward. For this purpose, related keywords such as genomics, epigenomics, transcriptomics, proteomics, metabolomics, microbiomics, lipidomics, glycomics, secretomics, interactomics, pharmacogenomics, diagnosis, biomarkers, endometriosis, infertility were searched in Google Scholar, PubMed, and Scopus databases from January 2020 to May 2023 (Figure 1). Studies that were unavailable in English, used duplicate data or had unavailable/irrelevant data were excluded from the analysis. In addition, investigations that were published before 2020 and/or reviewed by Goulielmos et al. (see the review [27]) are occasionally referred to as "previous studies" in the current study.

Genomics in endometriosis

Genomics refers to an interdisciplinary field of biology that studies the structure, function, and evolution of an organism's genomes. In the medical research area, genomics is considered the most mature type of –omics technology. It mainly focuses on the identification of genetic variants associated with the emergence and development of a complex disease, the prognosis, and the response to therapeutic options [28]. In fact, many genetic biomarkers derived from a plethora of valuable research for early detection, monitoring progression, and determination of the prognosis of complex diseases have been obtained, or ongoing research is underway. High throughput techniques such as genome-wide association studies (GWAS), an approach for the identification of genetic variants related to a particular disease, have significantly contributed to the revolution of biological fields. In addition, advanced technologies such as next-generation sequencing (NGS) [29], which could be applied to whole genome sequencing (WGS) and whole exome sequencing (WES), and genotype arrays have made a tremendous contribution in this regard [29,30].

The precise etiology of endometriosis remains unknown despite several hypotheses. However, the interaction of environmental and genetic factors is considered the most likely risk factor [6,11] as it is

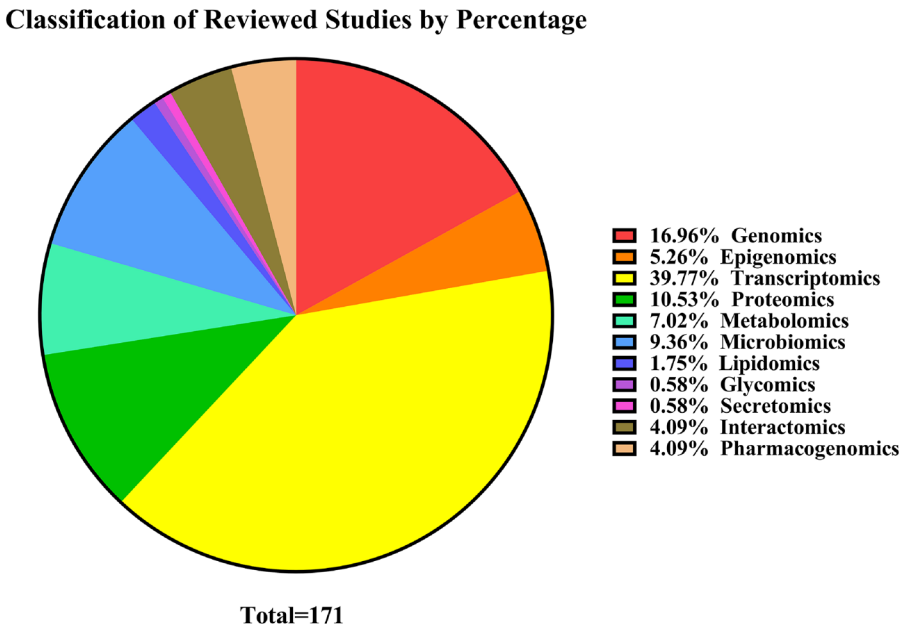

Figure 1. Classification of reviewed studies by percentage. As the figure depicts, the majority of the studies were in the area of transcriptomics (39.77%), genomics (16.96%), proteomics (10.53%), microbiomics (9.36%), metabolomics (7.02%), and epigenomics (5.26%), respectively.

demonstrated that hereditary endometriosis occurs in 50% of cases [31] and the possibility of its occurrence in relatives is significantly more than in unrelated people [32]. Therefore, genomic studies may determine the etiology of the disease and contribute to the identification of diagnostic and prognostic biomarkers. In particular, linkage analysis investigations aimed at determining the genomic regions that harbor polymorphisms associated with the risk of endometriosis, especially hereditary endometriosis, have been directed. Previously, it was suggested that regions on the 10q26, 20p13, and 7p15.2 chromosomes harbor polymorphisms associated with familial endometriosis [27]. In addition, a multiracial study on women with European and Japanese ancestry determined that there are 14 genomic risk loci on chromosome 2q13 within an inflammatory-rich region that coded a variety of transcripts, particularly related to the interleukin (IL)-1 family, which are involved in endometriosis pathogenesis [33]. The analysis of samples from women with different races and ancestry can define a broad perspective of genomic commonality involved in the etiology of the disease. Also, they provide a biomarker of the risk of occurrence and probability of endometriosis development. However, the implication of inflammation in endometriotic lesions is a general topic that may be observed in a wide range of gynecological [34] and non-gynecological [35,36] complications. Therefore, further studies appear to be necessary.

Previously, a wide variety of endometriosis-related loci in samples collected from different racial and ethnic groups have been identified by GWAS studies that were involved in main cellular processes such as the regulation of cell cycle, cell adhesion, inflammation, oxidative stress, metabolism, and intracellular signaling pathways [27]. Gene association studies aim to reveal the association of gene variants with the development of endometriosis by the suggestion of involved gene sequences, single nucleotide polymorphisms (SNPs), and mutations. Identification of polymorphisms in genes encoding inflammatory mediators (e.g. *IL-1* [37], *IL-2* and *IL-6* [38], and *TLR4* [39]), intracellular signaling pathways (*VEGF* [40], *HMOX1* [41], *MALAT1* [42]), as well as microRNA (miRNA) biosynthesis enzymes (*DROSHA* and *DICER1* [43]) have been introduced as markers for diagnosing susceptibility to endometriosis. Additionally, sex hormone polymorphisms, such as *FSH*, *LH*, and *testosterone*, and the *3'UTR* region of *ESR2* and *CYP19A1* can be considered biomarkers of endometriosis risk [44,45]. However, there was no correlation between polymorphism in alleles related to the *FSH receptor* and the *FSH beta chain* with endometriosis [46]. Although these studies have determined the SNPs in European, East Asian, and Middle Eastern women, there are no reports of common polymorphisms between different racial populations. Therefore, the introduction of polymorphism-based markers that can identify endometriosis in women of different ancestries or

determine the risk of susceptibility to the disease requires further research.

In addition to SNPs appearing over-represented in patients with endometriosis, GWAS have determined the association of endometriosis with other gynecological complications such as ovarian cancer, uterine endometrial cancer, uterine cervical cancer [47,48], uterine leiomyomata [49], and common co-morbidities including asthma [50], melanoma [51], and depression [50,52]. The differentially expressed genes involved in immunological, implantation, endocrine, and neurocrine processes before and after surgery are a confirmation of the suitability of genetic biomarkers in diagnosing and monitoring patients with endometriosis [53]. Identification of genetic risk in loci near *ESR1* as well as identification of *MKNK1* and *TOP3A* as ovarian endometriosis risk-associated genes could contribute to the determination of genetic susceptibility to endometriosis [54,55]. The application of NGS has been able to identify genes specifically mutated (including *JAK3*, *KRAS*, and *RB1*) or highly methylated (including *PYCARD*, *RARB*, *RB1*, *IL2*, *CFTR*, *CD44*, and *CDH13*) in samples from women with endometriosis; valuable findings that can be used to differentiate patients with endometriosis from endometrioid carcinoma cases [56]. Similarly, other studies have reported mutation in *KRAS*, which, in addition to diagnosing endometriosis, may be a genetic risk marker of the susceptibility of women with endometriosis to the development of endometrioid carcinoma [57,58]. In addition, mutations in the *ARID1* gene, which is involved in chromatin remodeling, as well as glutathione S-transferase, which mainly plays a role in detoxification, can determine the genetic risk of endometriosis susceptibility [59,60]. However, contradictory findings have been reported [61]. More importantly, the lack of specificity of the reported biomarkers can be considered the most important clinical limitation. Interestingly, the mutation in the dysferlin coding gene has been introduced as one of the potential factors in the pathogenesis of endometriosis [62], which may promise the identification of a specific biomarker in the diagnosis of endometriosis, provided more studies are conducted.

Considering genomic markers as a tool to diagnose endometriosis or monitor patients' response to treatment requires further studies. In addition, since most of the variant-carrying loci associated with endometriosis were located in non-genomic or intergenomic regions, it is necessary to combine genomic findings with transcriptomic, epigenomic, and proteomic findings, as well as functional experiments. It was stated that before 2020, eight GWAS were conducted on women diagnosed with endometriosis, with European and East Asian ancestry [27]. In the last 3 years, dozens of studies have been conducted on women with more genetic diversity, indicating the researchers' focus on this field and promising to propose the etiology of the disease and diagnostic biomarkers. However, most of the introduced markers are obtained by an invasive approach that provides limited clinical utility. In addition to the invasiveness of experiments on endometrial tissue, heterogeneity in endometrial tissue may lead to variation in genetic reports, highlighting the significance of noninvasive samples. Importantly, an 8.7-kb mitochondrial DNA deletion detectable in patients' plasma has been identified as both a diagnostic marker and a useful tool in the clinic for disease management [63]. Thereby, further studies are encouraged, especially on samples that are obtained noninvasively.

Epigenomics in endometriosis

Epigenomic studies assess hereditary changes in the function of genes that do not include any changes in the sequence of DNA bases. Moreover, the study of reversible changes in DNA proteins, including DNA methylation and histone acetylation (Figure 2), which lead to alteration in gene expression, is included in epigenomic studies. Continuous studies have made it clear that epigenetic changes are involved in biological processes, whether physiological or pathological, from which the occurrence and development of endometriosis are not excluded [10,64]. There is cumulative evidence that epigenomic changes have contributed to the development of endometriosis and the most attention of epigenomic-wide studies in recent years has been focused on DNA methylation, although few have reported changes in histone acetylation. The lack of attention to histone acetylation changes was previously critically reviewed [27], and despite a few studies, it has not been appropriately determined in the last three years. Therefore, conducting further studies to clarify the possibility of participation of the acetylation process in the etiology of endometriosis and also to identify promising biomarkers is encouraged.

It was previously suggested that higher methylation throughout the promoter and coding regions of *GATA* is one of the characteristics of endometriotic stromal cells that can be used to distinguish them from endometrial stromal cells. In addition, heavy methylation of the steroidogenic factor 1 (*SF1*) gene, an orphan receptor that is absent in normal cells, causes its expression 12,000-fold in endometriotic stromal cells. Therefore it could be considered another suitable option for diagnosing endometriosis [27]. Furthermore, hypermethylation in genes coding *ERβ*, *E-cadherin*, *cycloxygenase-2*,

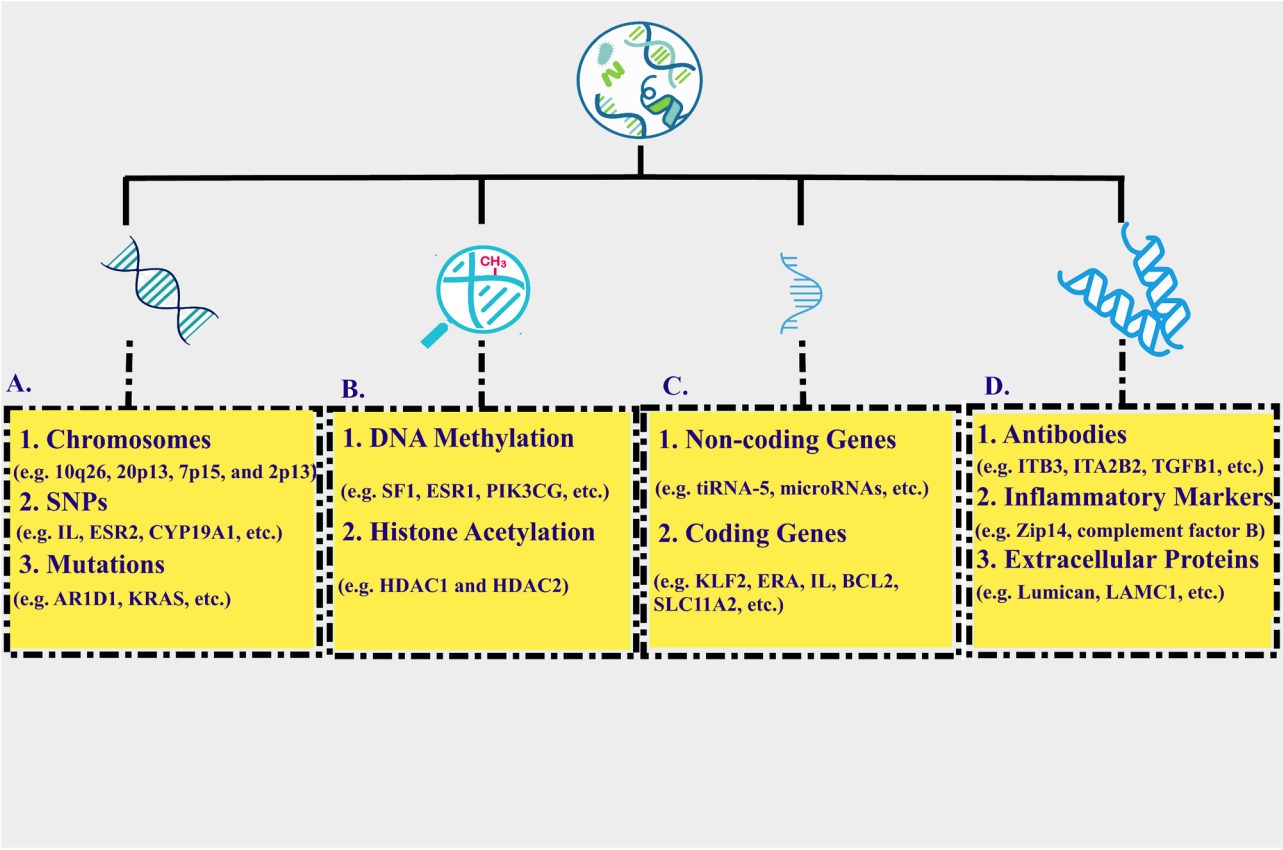

Figure 2. Four main omics-based techniques in the diagnosis of endometriosis. Genomics (a), epigenomics (B), transcriptomics (C), and proteomics (D) are known as the 4 main sets of omics, each of which has proposed potential biomarkers for noninvasive diagnosis of endometriosis.

homeobox A10, *IL-12*, and *PR*β were previously reported in endometriosis patients, which may have diagnostic merits [27]. The integrated analysis of differentially methylated genes by GWAS strategy suggested *ESR1*, *TMEM184A*, *HPGD*, *SFN*, *KIR3DX1*, *BST2*, *GREM2*, *PIK3CG*, and *RNASE1* as promising candidate genes to diagnose patients with ovarian endometriosis [65].

Further studies have determined that overexpression of *ERβ* is caused by trimethylation of the *H3K4me3* in the promoter and exon1, which may be influenced by environmental exposure mediated by WDR5/TET2 [66]. Provingly, steroid hormones, especially estrogen, through epigenetic interactions including both methylation and acetylation cause changes in gene expression in endometrial stromal fibroblasts, which has both therapeutic and diagnostic merits [67]. Determining the effect of exposure to endocrine disruptors on the level of DNA methylation, especially in immunologic, oncologic, endocrine, and cell regulatory processes is further evidence of the diagnostic value of epigenomic biomarkers in distinguishing women with and without endometriosis. Moreover, signalings involved in the embryologic reproductive tract development and function such as *FoxO*, *Wnt*, and *Hedgehog* signaling represent the diagnostic merits of epigenomic biomarkers [68]. Differences in DNA methylation age of ectopic lesions, which is an indicator of distinct developmental origin for a subset of lesions, could be considered a promising biomarker in the clinical classification of disease and possibly help to determine the prognosis and select treatment options [69]. The aberrant DNA hypermethylation in the *intron VII* of the *HLA-C*07* gene appears to be positively correlated with the occurrence of endometriosis [70]. However, it is important to consider that not all aberrant DNA methylations are of diagnostic value. For instance, the DNA methylation and H3K27me3 levels in the promoter region of the *TET1* gene are not able to distinguish between infertile patients with endometriosis, infertile patients, and fertile patients without endometriosis [71].

Previously, several studies applied microarray-based DNA methylation analysis to investigate aberrant epigenetic patterns in eutopic endometria of endometriosis patients and suggested several related genes (for a review see [27]). Recently, similar investigations have

suggested altered DNA methylation in *RNPC3*, *SLC18A2*, *PGLYRP2*, *ANXA3*, *HIST1H4F*, *PGK2*, *AHR*, *CCDC146*, *HOX*, *PLEKHF2*, and *HLA-C* as diagnostic tools valuable in the identification of the subset of women with endometriosis-associated infertility [70,72,73]. The excessive influence of epigenetic changes on menstrual cycle phases [74], the extreme necessity to determine the level of functional products, and the lack of diagnostic cutoff in the level of changes [24] are some main drawbacks of the performed studies. In addition, the limited sample size and the invasiveness of the examined samples are other disadvantages of the conducted studies, all of which clarifies the necessity of further studies.

Unfortunately, histone acetylation studies, in addition to the insufficient number, have not been successful in identifying functional biomarkers due to some contradictions. A case report found that the difference between eutopic and ectopic endometrium regarding *H3K9ac* and *H3K27ac* levels was not significant [75]. Conversely, histone acetylation and aberrant levels of histone deacetylases are associated with endometriosis. A significantly elevated level of *HDAC 1* expression along with decreased levels of *HDAC 2* expression levels are reported during endometriosis compared to normal endometrium correlating with lower acetylation levels of *H3* and *H4* [76–78]. There is also a report of histone *H3K27ac* modifications in response to estrogen which suggests the possibility of aberrant histone acetylation as a diagnostic tool for endometriosis [67]. Therefore, the diagnostic availability of these markers is unclear, making it necessary to encourage further studies.

Transcriptomics in endometriosis

The study of gene patterns or the transcriptome is described as transcriptomics, which is also known as functional genomics. A transcriptome is a set of gene transcripts or mRNA that is present within the cell at a specific time and under certain conditions. Therefore, the quantitative and qualitative measurement of the RNA level of the whole genome is in the transcriptomic domain. It has been shown that although about 3% of the cell genome encodes proteins, 80% of it is transcribed [79,80]. The application of transcriptomics can appropriately determine whether the changes identified in the genome by genomics and epigenomics have led to a change in gene expression and to what extent it has changed transcription [79,80].

The microarray-based genome-wide studies lead to the capability of researchers to analyze the expression levels of thousands of genes simultaneously [81]. In relation to endometriosis, various studies have investigated the differential expression of genes in ectopic endometrium compared to corresponding eutopic counterparts as well as healthy endometrium using this methodology. These investigations led to the identification of genes involved in *MAPK*, *PI3K*, and *RAS* signaling pathways as well as genes associated with immunological, endocrinal, and neurological functions (e.g. *ERBB* family, *CHEK1*, *laminin gamma*, and *Ki-67*) [27]. In addition, it is suggested that Y chromosome microchimerism leads to the differential transcript expression of seven coding and non-coding genes that contribute to endometriosis development and infertility [82]. Also, several recent studies have identified the differential expression of genes involved in immunological function using this methodology [83–85], and the diagnostic value of *HOXB6* and *KLF2* has been validated [83]. In addition to immunological function, genes involved in other cell processes such as cell proliferation, cell adhesion, the response to mechanical stimulus, the inflammatory response, and extracellular matrix organization were differentially expressed [86]. Furthermore, during the last three years, more than 15 microRNAs have been suggested as biomarkers for the diagnosis of endometriosis [87,88]. Although all introduced biomarkers were obtained invasively, the identification of salivary microRNA signature [89] promises to propose noninvasive and reliable biomarkers for the diagnosis of endometriosis.

Analysis of gene expression using quantified reverse transcriptase polymerase chain reaction (qRT-PCR), despite some limitations, is the most available and perhaps the simplest approach to measure the level of transcripts, which is currently used in medical laboratories [90,91]. A wide variety of recent studies have used qRT-PCR to measure the difference in the level of transcripts between endometriotic and healthy patients in ectopic endometrium compared to corresponding eutopic endometrium. These studies identified the differential expression of non-coding genes (*tiRNA-5*) [92], and coding genes involved in immune function (*C3*, *VCAM1*, *MMP3*, *MMP10*, and *TIMP2*) [93,94], endocrine function (*ERA*, *ZEB1*) [95–97], endometrial development and endometriosis progression (*HOX*, *ITGA7*, *IGHM*, *ITGBL1*, and *SORBS1*) [98,99], coagulation (central complement factors including *C1S*, *C1QA*, *C1R*, and *C3*) [100], inflammatory response (*IL1β*, *IL6*, *IL8*, *TNFA*, and *TGFB*) [97,101], angiogenesis (*VEGF*) [97], apoptosis (*BAX*, *BCL2*), and cuproptosis (*PDHA1*) [102]. Interestingly, transcripts of *ITGA7*, *ITGBL1*, *IGHM*, *LGMNP1*, and *SORBS1* are suitable for distinguishing between endometriosis and ovarian cancer, describing the invasive nature of endometriosis, and serve as novel promising predictive

biomarkers for disease recurrence [99,103]. More importantly, the identification of some of these markers in menstrual blood-derived stromal cells can strengthen the potential of noninvasive biomarkers [97].

In addition to microarray-based genome-wide studies, qRT-PCR has been successful in identifying microRNAs capable of diagnosing patients with endometriosis. It is revealed that for endometriosis (*miR-99b* and *miR-125a*), endometrioid carcinoma of the ovary (*miR-143*), and endometrioid endometrial cancer (*miR-16*, *miR-99b*, and *miR-145*) represent the highest levels, therefore, *miR-125a* can be suggested as a specific biomarker for endometriosis diagnosis [104]. Several competitive endogenous RNA (ceRNA) network studies have identified non-coding RNAs and target transcripts such as *CHL1*, *NFASC*, *ACLY*, *ADH1B*, *PTGFR*, and *MYOM1* as biomarkers of endometriosis development, response to therapy, and recurrence [105–108]. Similarly, exosomal RNA-based biomarkers detected by ceRNA network analysis can contribute to the diagnosis of endometriosis [109,110]. In addition, in noninvasive derived samples such as serum and plasma, *miR-199b-3p*, *miR-224-5p*, *let-7b*, *miR-92a-3p*, *miR-22-3p*, *miR-320a*, and *miR-93-5p* levels are considered potential endometriosis biomarkers [111–113]. The identification of noninvasive biomarkers is one of the advantages of miRNAs in the diagnosis of endometriosis. Nonetheless, the heterogeneity of the presented results and the lack of reporting consistent miRNAs for the diagnosis of the disease is a tremendous challenge that limits the current findings. Therefore, an in-depth analysis of miRNome in endometriosis patients and its comparison with disorders with similar symptoms as well as healthy subjects may provide the pathoetiology of the disease as well as the suggestion of reliable biomarkers.

A wide variety of other transcriptomic studies have also been conducted with the aim of determining whether the expression of genes in the endometria of endometriotic patients is different from that of healthy individuals. In this regard, transcriptomic studies have identified potential biomarkers that are mainly related to immune responses. Compared to non-endometriosis subjects, *AEBP1*, *HOXB6*, *HOXC8*, *ARNTL*, *MMP11*, *PIWIL2*, *TGFB*, *KLF2*, *IL10*, *IL23A*, *FLT1*, *IL6*, *CD74*, *CD83*, *CXCL16*, *CCL3*, *GNLY*, and *RORB* genes were expressed differently. These genes are involved in inflammatory responses, the function of T lymphocytes, NK cells, and macrophages, tissue remodeling, infertility, cell survival, and migration, respectively [83,114–117]. More importantly, transcriptomic analysis of cumulus cells in patients with minimal and mild endometriosis reveals evidence of differential expression of genes involved in immune responses [118]. In addition, the differential expression of genes related to endocrine function (StAR) and ferroptosis-based regulated cell death program (*ACSL5*, *SLC11A2*, *SLC7A11*, *HMOX1*, *CP*, *GCLM*, *PRNP*, *LPCAT3*, *FTL*, and *CYBB*) are considered potential biomarkers of endometriosis that provide different expression in eutopic compared to ectopic endometrium of patients with endometriosis [117,119]. However, the transcriptomic analysis of eutopic endometrium from women with endometriosis and chlamydial endometritis indicates the almost differential expression of genes involved in the immune cells' function and DNA repair [120]. The different transcriptome content between eutopic endometrium from stage I-II and III-IV endometriosis [121], as well as after pharmacotherapy and surgery [122–124], highlights the potential of transcriptomic analysis for disease staging and post-treatment follow-up. Interestingly, the identification of genes whose expression is different independent of hormonal milieu, stage, and cycle phase in eutopic endometrium, as well as the regulation of guidelines for the discovery of biomarkers independent from the menstrual cycle demonstrate the promising findings in this area [121,125].

With the advance of transcriptomic studies in combination with NGS, RNA sequencing (RNAseq), and bioinformatic tools, the identification of potential biomarkers and finding the etiology of endometriosis have become promising. In fact, RNAseq is able to simultaneously sequence and quantify millions of RNA fragments and when combined with bioinformatic tools it will represent a perfect approach to reading transcriptome completely [126]. Although previously few studies have been done in this field, several genes with different expressions were identified [27]. Fortunately, over the past three years, there have been dozens of RNAseq studies that have succeeded in identifying the differentially expressed genes involved in immune responses [101,127–130], basic cellular processes [131–133], and reproductive-related endocrine function [101,134–136]. Remarkably, several noninvasive biomarkers obtained from salivary (*miRNAs*), plasma (*lncRNAs*), seminal plasma (*IL11*), menstrual-blood derived mesenchymal stem cells (*PI3K*, *AKT*, *MTOR*, *TGFB*, *NFKB*, *TNFA*, *IL6*, and *STAT3*), and peritoneal fluid (*CD1C*, *THBD*, *CLEC9A XCR1*, *IRF4,* and *IRF8*) samples have been identified that may be able to distinguish between patients with endometriosis and non-endometriotic patients/healthy individuals [89,101,137–141]. Furthermore, an In silico analysis revealed that upregulated genes (*FOS*, *EGR1*, *ZFP36*, *JUNB*, *APOD*, *CST1*, *GPX3*, and *PER1*) and downregulated ones (*DIO2*, *CPM*, *OLFM4*, *PALLD*, *BAG5*, *TOP2A*, *PKP4*, *CDC20B*, and *SNTN*) could potentially be considered as

novel biomarkers [142]. Further bioinformatic studies have been able to identify and validate biomarkers among which *CXCL12*, *PDGFRL*, *AGTR1*, *PTGER3*, and *S1PR1* have been functionally proposed [143,144]. According to what was discussed, transcriptomic studies have been almost more successful in finding biomarkers for the diagnosis of endometriosis, especially noninvasive ones. Moreover, identifying biomarkers that are independent of the menstrual cycle and steroid hormones, as well as the presence of guidance regarding how to find independent biomarkers could be considered the merits. The heterogeneity of the reported transcripts and lack of validation of most of them, especially by clinical studies with large sample sizes and from different racial populations, are current limitations that need to be resolved in the future.

Proteomics in endometriosis

The study of all proteins translated from a single genome, whether within the cell or secreted into body fluids, is classified in the proteomic studies area. Because the protein content of each cell or organism varies from cell to cell and depends on the interaction of many different factors, it has been assumed that proteomics is substantially more complicated than genomics. The detection of proteins or peptides expressed differently in samples or special conditions, for example in a pathological state, has been defined as the basis of proteomics [145,146]. The different expression of proteins may be a precursor to endometriosis or could be a consequence of the disease, which in both cases may be applicable to determine the risk of the disease, early diagnosis, and follow-up of the patient [27]. Previous studies have identified several biomarkers by comparing the differently expressed protein content in patients with endometriosis and controls, including in noninvasive samples such as urine and blood, as well as comparing eutopic with ectopic endometrium. However, few of them were validated to determine the etiology of the disease [27].

Previous research has clarified that the levels of proteins involved in apoptosis, immunity, transcriptional regulation, and cell structure have the potential to detect endometriosis [27]. Recently, extensive studies have been conducted to suggest desired biomarkers using a wide range of protein level determination techniques, from ELISA and western blot to bioinformatics and other methodologies. For example, a multi-omic study has shown that proteins involved in the interaction of the complement system with the coagulation cascade are involved in the development of endometriosis [100]. The plasma level of ITB3, ITA2B2, and ACVL-1 analyzed by the antibody array platform was able to detect peritoneal endometriosis [147]. In addition, in a case-control study consisting of 32 patients with peritoneal endometriosis and 26 patients with unexplained infertility, the antibody microarrays suggested TGFBI as a novel biomarker in the peritoneal fluid, with a sensitivity of 0.81 and specificity of 1.00 [148]. In addition, a study based on ELISA revealed that in 68 women with stage III/IV endometriosis, the dysregulation of osteopontin (detected in serum) and urinary plasminogen activator, which are involved in the migration of endometrial stromal cells, can be a therapeutic and possibly diagnostic target [149]. However, validating this assumption and determining the sensitivity and specificity requires further studies. The report on the non-significant different prevalence of autoantibodies in endometriosis patients compared to controls by the proteome microarrays using plasma and peritoneal fluids may reveal the need for further extensive studies [150].

Proteomic analyses of eutopic endometrium of infertile patients with endometriosis have demonstrated that inflammatory markers along with alpha-1-acid glycoprotein 2, complement factor B, and zinc transporter Zip14 could be considered potential biomarkers for the detection of endometriosis-related infertility [151,152]. In line with the growing evidence depicting the necessity of an early and noninvasive diagnostic strategy, extended studies of the proteomic content of the endometrial fluid from endometriosis patients have been directed. A shotgun quantitative proteomics method has deciphered 27 promising serological biomarkers, involved in immunity, inflammation, cell adhesion, cell migration, and blood coagulation, in women with endometriosis [153]. Although the small sample size could be considered a major limitation threatening the validity of the mentioned study [153], the examination of the samples obtained from 142 women with endometriosis suggested circulating proteins involved in immune cell migration/activation and inflammation as diagnostic biomarkers [154]. Furthermore, the characterization of peritoneal fluid exosomes has proposed five exclusively expressed proteins, including ANXA2, PRDX1, ITIH4, H2A type 2-C, and the tubulin a-chain, in samples from 28 women with endometriosis [155].

In recent years, the combination of liquid chromatography with tandem mass spectrometry (LC-MS/MS)-based methodology with other techniques (e.g. RNAseq, RT-PCR, and metabolomics), have identified differentially expressed proteins. The mentioned methods have investigated the protein content of eutopic endometrium and epithelial cell lines derived

from endometriotic lesions compared to matched control samples. Lumican, mimecan, LAMC1, LAMB2, integrin beta-4, annexin A5, serotransferrin, and inflammatory-related metabolites capable of detecting the disease are examples of differentially expressed proteins with potential diagnostic merits [151,156,157]. Moreover, UHPLC-MS/MS combined with RNAseq in menstrual blood-derived mesenchymal stem cells has suggested that MT2A, TYMP, COL1A1, COL6A2, and NID2 proteins are able to noninvasively diagnose endometriosis [158]. A multi-omics study along with bioinformatics approaches investigated the differentially expressed proteins in different phases of the menstrual cycle. This study led to the identification of differences in the estrogen signaling pathway, extracellular matrix organization, and endothelial cell chemotaxis as the molecular patterns underlying the pathogenesis of endometriosis [159]. In addition, a number of reviewed studies that used the western blot technique succeeded in validating the concentration of differentially expressed proteins [94,100,103,155]. Interestingly, distinct plasma proteomic profiles have been exhibited by endometriosis-associated pain subtypes [160].

Despite the extended efforts so far, the heterogeneity of the identified biomarkers, low sample size, lack of extraordinary specificity, and lack of measuring the diagnostic sensitivity and specificity of the identified biomarkers can be enumerated as the current main limitations. CA-125, for example, has been reported as a perfect single glycoprotein marker in discriminating endometriosis from healthy women [27]. However, a plethora of evidence has recommended it as a biomarker of prevalent female carcinomas such as breast, cervical, endometrial, and ovarian cancer [161–164]. Therefore, it is encouraged that future studies focus on more specific biomarkers that can distinguish endometriosis from pathological conditions with similar symptoms, and in addition to identification, validate and measure diagnostic sensitivity and specificity.

Metabolomics in endometriosis

Quantitative measurement of perturbations in the metabolite complement of a single cell or a specific cell type caused by pharmaceuticals, disease, and physical conditions was the initial definition of metabolomics [165,166]. The expansion and improvement of methods that analyze low-weight molecules (e.g. carbohydrates, fatty acids, and amino acids) as well as other products of cell metabolic functions in a variety of biological systems are in the field of metabolomic studies [167,168]. Representing the final downstream products of gene transcription, which could be closely associated with organism phenotype, is a beneficial characteristic of the cellular metabolome. It is widely proposed that the metabolome could be of high importance in attempting to identify any biomarkers or design therapeutic strategies as it represents a valuable set of information regarding the impact of the environment and genetics on disease. Hence, it is thought that the development of novel biomarkers distinguishing active from dysregulated pathways is a main subject in metabolomics [169]. However, previous studies have found that any single biomarker in the majority of cases demonstrates insufficient specificity for diagnostic approaches [27].

Previous studies have reported a variety of metabolites, including amino acids, vitamin E, and superoxide dismutase, in a wide range of samples, especially noninvasive samples such as plasma, serum, and urine, which can be used to identify endometriosis and determine the stage of the disease [27]. Recently, several metabolomic studies have been carried out on serum, plasma, fecal, peritoneal fluid, and follicular fluid samples to develop noninvasive or minimally invasive biomarkers for the diagnosis of endometriosis, detection of disease progression, and risk of infertility. In this regard, a variety of amino acids, fatty acids, monosaccharides, and other metabolites such as ketone bodies have been proposed. It is suggested that upregulated sera levels of glutamine and β-hydroxybutyric acid along with downregulated tryptophan levels could be used as biomarkers of severe stage III/IV endometriosis [170]. Moreover, the increased circulatory proline/glutamine ratio is considered a noninvasive diagnostic and prognostic screening biomarker to distinguish patients with endometriosis from healthy subjects [171]. A study conducted LC-MS/MS metabolomics analysis revealed that phenylalanyl-isoleucine increased levels in the serum could reliably detect peritoneal endometriosis [172]. Similarly, other metabolomics studies have suggested that increased levels of threonic acid, 3-hydroxybutyric acid, proline, and phenylalanine along with decreased levels of alanine and valine could be used as diagnostic biomarkers of endometriosis and related infertility [173–176].

Measuring the level of metabolites such as 7,8-dihydrobiopterin, 7,8-dihydro neopterin, normetanephrine, epinephrine, phosphoethanolamine, acylcarnitine, and kynurenine may serve as a biomarker of neuropathic pain and disease progression [151,177]. Additionally, an increase in the level of fatty acids, ketone bodies, and metabolites involved in the synthesis of ceramides, along with a decrease in glucose, citrate, and creatine levels, have been reported in patients with endometriosis compared to healthy people [174,176,178]. The significant enrichment of

Table 1. An overview of the advantages and disadvantages of major studies in the novel -omics area of endometriosis.

-Omics	Limitations	Strengths	Suggestions
Genomics	• Fails to study all races • Contradictions and insufficiency of the data • Lack of specificity of the reported biomarkers • Overwhelming invasiveness of the identified biomarkers	• Analysis of samples from females with European, East Asian, and Middle Eastern ancestry • Finds evidence of disease etiology • Introduces some possibly specific genetic biomarkers	• Study all races to define genomic commonality • Combine genomic findings with transcriptomic, epigenomic, and proteomic findings • Validate potentially sensitive and specific biomarkers
Epigenomics	• Unsatisfactory data on histone acetylation changes • Excessive influence of epigenetic changes on menstrual cycle phases • Limited sample size • Invasiveness of the examined samples	• Finds evidence of disease etiology • Proposes some possibly specific differential biomarkers	• Combine findings with analysis of functional products • Look for functional products in noninvasive samples such as serum, plasma, saliva, urine, etc.
Transcriptomics	• Heterogeneity of the reported transcripts • Lack of validation of most of the suggested biomarkers • Small sample size of most studies • Fails to examine the possible impact of racial differences	• Validates some suggested biomarkers • Identifies salivary, plasma, and serum miRNAs signature • Biomarkers distinguish endometriosis from ovarian cancer, endometrioid carcinoma of the ovary, and endometrioid endometrial cancer • Ability to distinguish mild forms of the disease from severe ones • Independence of the menstrual cycle and steroid hormones	• Complete in-depth analysis of miRNome in endometriosis patients and its comparison with symptomatic disorders • Validate proposed biomarkers by human studies with high sample sizes and participation of people from different races
Proteomics	• Heterogeneity of the identified biomarkers • Small sample size in most studies • Lack of extraordinary specificity • Possible intersection of some proposed biomarkers with symptomatic conditions	• Relatively acceptable sensitivity and specificity of some biomarkers • Large number of biomarkers from noninvasive samples • Provides potentially exclusive biomarkers • Distinguishes stage I/II from stage III/IV	• Emphasize more specific biomarkers able to distinguish endometriosis from conditions with similar symptoms • Validate and measure diagnostic sensitivity and specificity
Metabolomics	• Small sample size • Failure of validation of most of the proposed biomarkers	• Proposes biomarkers extracted from mostly noninvasive samples • Determines the stage of the disease • Identifies some exclusive biomarkers	• Validate the diagnostic potential of diagnostic metabolites • Determine the sensitivity and specificity • Complete the assessment of a probable diagnostic panel based on multi-metabolites.
Microbiomics	• The possibility of misdiagnosis with similar conditions • Lack of establishing acceptable specificity	• Contributes to early diagnosis and staging of patients • Distinguishes endometriosis from other benign gynecological conditions • High sensitivity of microbiota for early detection of disease	• Measure the sensitivity and specificity of potential biomarkers • Combine microbiome differences with other biomarkers.

The table briefly discusses the merits and demerits of the areas of –omics of endometriosis that have included the majority of studies. In addition, considerations for further studies are suggested in each area. Characteristics related to less studied areas are not reviewed.

biosynthesis of second bile acid and alpha-linolenic acid metabolism leads to an elevated abundance of chenodeoxycholic and ursodeoxycholic acids as well as the decreased abundance of alpha-linolenic acid and 12,13s-epoxy-9z,11,15zoctadecatrienoic acid in the feces of endometriotic animals [179]. In addition, the relationship between metabolism, gut microbiota, and endometriosis may also play a role in understanding the etiology of endometriosis and identifying biomarkers [179]. The application of metabolomics in the identification and possible function of diagnostic biomarkers may be partially dependent on the methodology used. The use of symptomatology and serum nuclear magnetic resonance metabolomics, a method able to provide highly reproducible and throughout quantitation of measurable metabolites in an unbiased fashion, could not descry any distinguishable different serum metabolome between endometriotic patients and controls [180]. Nevertheless, the commonality of reports on metabolomic alterations, particularly on amino acids and lipid-related metabolites, reveals the potential ability to serve as a biomarker for identifying endometriosis. Validating the diagnostic potential of these metabolites requires conducting further studies with a larger sample size, determining the sensitivity and specificity of every single metabolite or diagnostic panel based on multi-metabolites, and designing a prompt and affordable diagnostic tool (Table 1).

Microbiomics in endometriosis

Microbiomics focuses on the study of microbiota consisting of all microorganisms including bacteria, viruses, and fungi that colonize human mucosal surfaces, skin, and gut, while the genes of this microbiota constitute the microbiome [181,182]. It is documented that microbiota contributes to disease development, however,

the human microbiome is extremely complex and there is a high degree of microbial diversity among people [181,182]. Therefore it is complicated to identify the microbial constituents leading to diseases. In this regard, several studies have been conducted to determine the microbiota involved in the pathophysiology of endometriosis and to identify possible biomarkers [27]. Previous studies have determined that the difference in the gut and reproductive tract microbiota may be involved in the pathophysiology of endometriosis (Figure 3) by affecting steroid hormones, vaginal pH, metabolites, and inflammatory mediators, and could also improve the early diagnosis and staging of patients [27].

The analysis of animal models of endometriosis has determined that the gut microbiota is involved in the survival of endometriotic epithelial cells and disease progression by modulating the population of immune cells and changing metabolites such as alpha-linolenic acid and quinic acid [179,183]. In addition, the higher ratio of *Firmicutes* to *Bacteroidetes* and the difference in microbiota can contribute to disrupting the level of estradiol and IL-8 and potentially cause the disease progression to stages III/IV [184,185]. In addition, *Ruminococcus* and *Pseudomonas* in the feces and peritoneal fluid have been proposed as early diagnostic biomarkers, and more importantly, gut microbiota exceeds cervical in diagnosing endometriosis [186]. Finally, the difference in microbiota belonging to *Actinobacteria*, *Bacilli*, *Bacteroidia*, *Blautia*, *Clostridia*, *Coriobacteriia*, *Dorea*, *Tenericutes*, and *Streptococcus* between endometriotic patients and healthy subjects shows the possible potential of gut microbiota in disease diagnosis [185,187].

On the other hand, the microbial content of the reproductive tract, including the cervix, endometrium, and vagina, has been associated with endometriosis progression [184,188,189]. It is widely accepted that *Lactobacillus* dominates the lower reproductive tract and the decrement of *Lactobacillus* (*jensenii*, *reuteri*, and *iners*) in vaginal flora accompanied by the predominance of *Clostridium* (*butyricum* and *disporicum*) *Alloscardovia* (*omnicolens*), and *Veillonella* (*montpellierensis*) is associated with endometriosis [190–193]. More importantly, the analysis of vaginal microbiota along with sera CA-125 measurement represent an acceptable sensitivity (89.19%) in the diagnosis of endometriosis patients, while the specificity, with or without CA-125 remains relatively unacceptable [191]. The complete absence of *Atopobium* in the vaginal microbiota along with the analysis of the presence of *Anaerococcus*

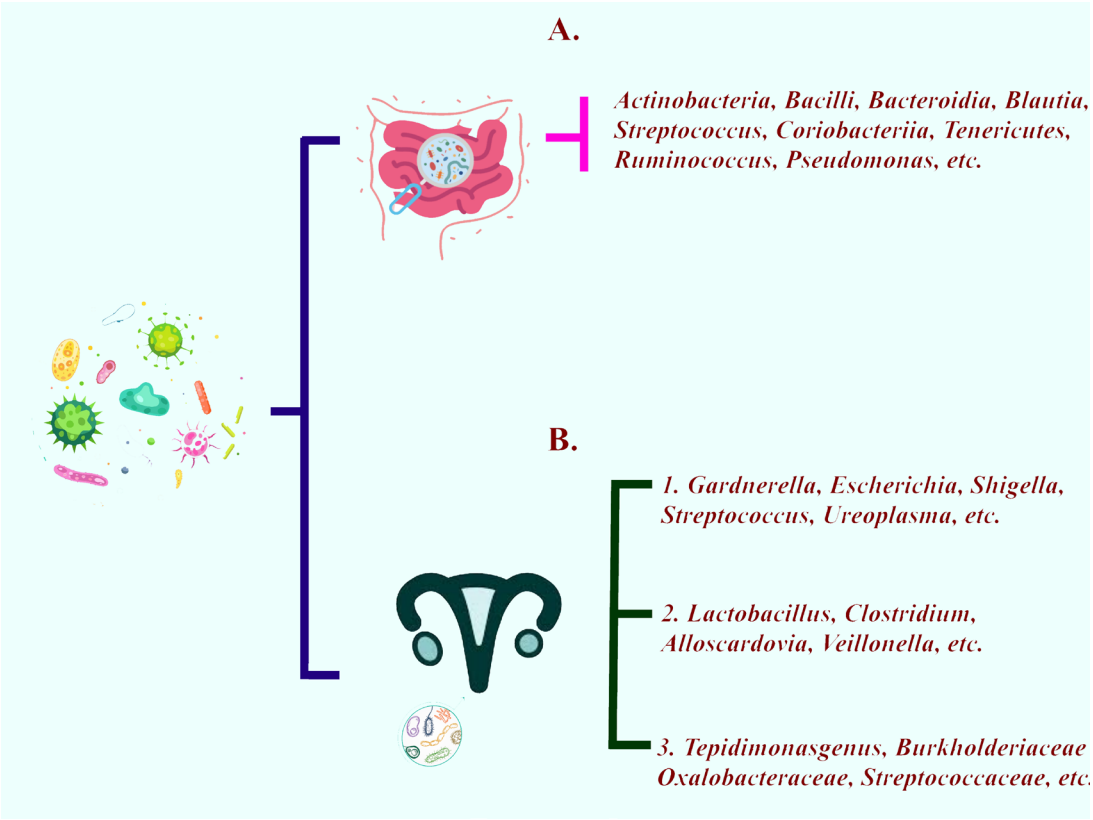

Figure 3. Microbiomics in endometriosis. Gut (A) and reproductive tract (B) microbiota can be used in the diagnosis of endometriosis. Reproductive tract microbiota includes bacteria present in the cervix (1), vagina (2), and endometrium (3).

can be assumed as biomarkers for distinguishing mild from severe endometriosis [184,194]. Although the presence of *Atopobium* in cervical microbiota may be a marker of adenomyosis-endometriosis [193]. In addition, *Gardnerella*, *Escherichia*, *Shigella*, *Streptococcus*, and *Ureoplasma* in the cervical microbiota could be considered a marker of severe endometriosis [184,195]. The endometrial microbiota analysis could diagnose patients with true endometriosis, from symptomatic controls with pelvic pain but other benign gynecological diagnoses. Bacteria belonging to *Actinobacteria phylum*, *Oxalobacteraceae* and *Streptococcaceae* families, and *Tepidimonasgenus* genus have been associated with a diagnosis of endometriosis, while *Burkholderiaceae* and *Ralstonia* bacterium are associated with other gynecological diagnoses [196].

The use of noninvasive samples such as urine, feces, and vaginal secretions, and the communal documentation of changes in the microbiome after endometriosis as well as during the progression of the disease, can be counted among the major merits of biomarkers identified by microbiomics. Despite a few reports of the high sensitivity of microbiota for early detection of disease, acceptable specificity has not been established, even with the multi-analysis of several biomarkers. As a result, further studies investigating the sensitivity and specificity of potential biomarkers are encouraged, and the possibility of mixing microbiome differences with other biomarkers is reemphasized.

Lipidomics and glycomics in endometriosis

Lipidomics and glycomics along with metabolomics are integral parts of biological systems that represent multidisciplinary fields [197,198]. This area of investigation focuses on the assessment of complicated interactions in biological systems and proposes beneficial tools to understand the underlying mechanisms of a specific disease related to lipids, carbohydrates, and metabolites [197,198]. Lipidomics is referred to as the study of time-dependent or stimuli-dependent alterations in the whole quantity of lipids within a single cell or a specific cell type. Lipidomics is considered a beneficial tool for the description of cellular phenotype in the disease and in response to pharmacological treatments [27,197].

Dysregulation of the mechanisms of biosynthesis of ceramides/sphingolipids is considered one of the factors involved in the occurrence of endometriosis. The decreased expression of genes such as *SPHK1*, *ASAH1*, and *SGPP1*, which are involved in the biosynthesis of ceramides, along with the increased expression of *CERS1* and *UGCG*, contribute to the pathogenesis of the disease [178]. The damaged ceramide signaling pathway is also considered one of the characteristics of ectopic and eutopic stromal endometriotic cells [199]. In addition, the presence of fibrotic structure inside/around the lesions, which contributes to the classic endometriosis-related symptoms is related to the action of bioactive sphingolipid sphingosine 1-phosphate [200]. Previous studies have revealed that reduced levels of sphingolipids and ceramides as well as elevated levels of glycerolipids, glycerophospholipids, and acylcarnitines in the endometrial fluid could distinguish women with endometriosis from non-endometriotic controls [27]. It has been recently suggested that sphingomyelin, phosphatidylcholine, and phosphatidylserine in peripheral blood and endometrial, peritoneal, and follicular fluid, as well as lipid metabolites in eutopic endometrium tissue, are beneficial diagnostic tools able to detect early endometriosis, predict endometriosis-related infertility, and classify disease [201,202]. These lipid compounds represent auxiliary functions such as participation in the active proliferation of endometriosis, facilitating the migration and invasion of endometriotic cells, programmed cell death, inflammatory responses, etc. These functions along with changes in their levels during endometriosis development suggest the contribution of lipid compounds in the pathogenesis and consequently the diagnosis of endometriosis [203]. Remarkable increases in sphingolipids and decreases in glycerolipids and most phospholipids are reported in human ectopic endometrial stromal cells derived from women with endometriosis [204]. The whole metabolome analysis of endometrial tissue in patients with endometriosis and recurrent implantation failure revealed lower levels of PUFAs compared to women with unexplained infertility [205]. The review of glycomic studies can be considered one of the forgotten or less important parts of previous studies [27]. Previous analysis of the human plasma N-glycome in patients with endometriosis has suggested noninvasive biomarkers for the diagnosis of the disease and determination of the stage of endometriosis [206]. Lipidomics and glycomics of endometriosis can be assumed as the most preliminary studies in the –omics area of endometriosis. The insignificant number of studies is a sign of the lack of attention to determining the lipid- and glyco-related characteristics in endometriosis conditions and also the crucial necessity to conduct further studies.

Secretomics in endometriosis

The study of proteins regulating a variety of biological and physiological processes secreted by a cell, tissue,

or organism under specific conditions is the subject of secretomics studies. Previous studies mainly emphasized the participation of secretome in uterine tissue development, receptivity, implantation, and fertility/infertility function, and unfortunately, ignored the dysregulation of secretions caused by endometriosis or their role in the progression of the disease [27]. A recent analysis of the endometrial secretions of patients with and without endometriosis has revealed that levels of IL-1α and IL-6 increased in patients with severe endometriosis. Moreover, multi-analysis of IL-1α, IL-1β, and IL-6 in endometrial secretions can detect stage III/IV endometriosis with a sensitivity of 75% and specificity of 70% [207]. Additionally, other studies have focused on immunophenotyping and immune secretory profile analysis to diagnose patients with endometriosis [208,209].

The insufficient number of studies and the lack of deep understanding of the role of secretions in endometriosis demonstrate the need for further research. Many proteins are secreted into the blood, sweat, vaginal fluid, and saliva that most of them participate in the processes involved in the development or suppression of endometriosis. This fact clarifies the significant clinical importance of these proteins for noninvasive diagnosis and therapeutic benefits, and thereby, the necessity of extensive studies to be directed.

Interactomics in endometriosis

The global interaction between genes, proteins, metabolites, and ligands is referred to as interactomics. Interactomics is described as the intersection discipline of biology and bioinformatics. Although this area of -omics studies is able to depict cellular networks underlying genotype-phenotype in pathophysiological conditions, unfortunately, no related studies had been done until 2020 [27]. Recent studies have suggested that the interaction between microRNAs, particularly *miR-155-5p*, with transcriptional factors related to cellular signaling pathways represents great promise for diagnostic and therapeutic approaches [210]. The protein interactome study described endometriosis as an inflammatory systemic disease in which neutrophil degranulation could be considered a therapeutic target, and perhaps a diagnostic tool [211]. The interaction between epigenetic modifications and inflammatory responses strengthens the possible function of this hypothesis [212]. The interaction between gene-gene [213], gene-ubiquitination [214], gene-steroid hormones [67], gene-uterine homeostasis [215], and epigenetics-steroid hormones [67] have been documented as underlying mechanisms of endometriosis and possibly diagnostic strategies. The mentioned studies can be considered an introduction to the clinical importance of the interactome in understanding the underlying etiology of endometriosis and its diagnosis, therefore future studies should aim to supplement existing research.

Pharmacogenomics in endometriosis

The global study of how the genome of a patient affects the response to therapy is referred to as pharmacogenomic or pharmacogenetics. Pharmacogenomics can mainly be used to determine the probability of response to treatment, disease-free index, and therefore the prognosis of the disease. During the last three years, several pharmacogenomic studies have determined the association of Peiminine with the *MAPK* pathway [216], luteolin, coumarin, and quercetin with *STAT3*, *PIK3R1*, and *MAPK1* [217], and herbal compounds with serotonergic synapse, the neurotrophin signaling pathway, dopaminergic synapse, *IL6*, apoptosis, *TLR*, *VEGF*, and *MAPK* signaling pathways, and *ESR1* [218–222].

Conclusion

The current review revealed that biomarkers identified by genomics, epigenomics, transcriptomics, proteomics, and metabolomics studies are the most potent tools to diagnose endometriosis, determine disease stage, and predict prognosis. The identification of noninvasive diagnostic biomarkers, which had relatively acceptable sensitivity, is of high clinical importance. There is potential that, in the near future, multi-biomarkers identified by –omics studies could be used in clinical laboratories. However, as discussed, the present limitations are required to be addressed by further studies and complementary validation.

Authors' contributions

MSN and NJ contributed to the conception, data extraction, literature search, revision, and drafting of the manuscript. SAR and AS contributed to the revision of the manuscript.

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