Review / Derleme

DOI: 10.4274/tjod.galenos.2024.77489

Turk J Obstet Gynecol 2024;21:104-17

Correlation between the existence of serum autoantibodies and the risk of endometriosis: A systematic review and meta-analysis

Serum otoantikorlarının varlığı ile endometriozis riski arasındaki korelasyon: Sistematik bir derleme ve meta-analiz

Shiva Fekri[1], Reza Hassanzadeh Makoui[2], Negar Ansari[3], Masoud Hassanzadeh Makoui[4]

[1]*Zanjan University Faculty of Medicine, Department of Obstetrics and Gynecology, Zanjan, Iran*
[2]*Zanjan University Faculty of Medicine, Department of Cardiology, Zanjan, Iran*
[3]*Zanjan University Faculty of Medicine, Department of Internal Medicine, Zanjan, Iran*
[4]*Zanjan University of Medical Sciences, Department of Immunology, Zanjan, Iran*

Abstract

Endometriosis is a common condition among women and can cause complications such as abdominal pain, dysmenorrhea, and infertility. One of the potential causes of this disease is autoimmunity. However, evidence regarding the role of autoimmunity is conflicting and inconclusive. The aim of this study was to investigate whether autoantibodies, a sign of autoimmunity, are present in people suffering from endometriosis. Relevant studies up to April 14, 2023 were identified by systematically searching Scopus, PubMed, Web of Science, Embase, and Google Scholar. This meta-analysis includes all qualified case-control studies of human populations that analyzed the association between serum autoantibodies and endometriosis. The odd ratios and 95% confidence intervals were calculated. In addition, heterogeneity and publication bias were examined, and subgroup analyses were performed based on region and target antigens. Forty-one studies were included, comparing 2,825 endometriosis patients with 4,158 healthy controls. The meta-analysis findings indicated a significant association between the presence of autoantibodies in the serum and an increased susceptibility to endometriosis (odds ratio: 4.242, confidence interval 95%: 3.824-4.706, p<0.001). In addition, there was a significant correlation between the presence of endometriosis and serum levels of anti-nuclear antibodies, B2 glycoprotein 1, CA125, carbonic anhydrase 1, cardiolipin, endometrial, laminin-1, smooth muscle, and syntaxin autoantibodies. Upon further analysis, it was found that the serum levels of these autoantibodies were higher in patients with endometriosis from North America than in those from other regions (p=0.001). The study revealed a significant correlation between serum autoantibodies and susceptibility to endometriosis, highlighting autoimmunity as a potential cause.

Keywords: Autoantibody, endometriosis, meta-analysis, serum

Öz

Endometriozis kadınlarda sık görülen bir durumdur ve karın ağrısı, dismenore ve infertilite gibi komplikasyonlara neden olabilir. Bu hastalığın potansiyel nedenlerinden biri otoimmünitedir. Ancak otoimmünitenin rolüne ilişkin kanıtlar çelişkili ve belirsizdir. Bu çalışmanın amacı, endometriozis hastası kişilerde otoimmünite belirtisi olan otoantikorların mevcut olup olmadığını araştırmaktır. 14 Nisan 2023 tarihine kadar olan ilgili çalışmalar Scopus, PubMed, Web of Science, Embase ve Google Scholar'da sistematik olarak arama yapılarak belirlendi. Bu meta-analiz, serum otoantikorları ile endometriozis hastaları arasındaki ilişkiyi analiz eden insan popülasyonlarına ilişkin tüm nitelikli olgu-kontrol çalışmalarını içermektedir. Olasılık oranları ve %95 güven aralıkları hesaplanmıştır. Ayrıca heterojenlik ve yayın yanlılığı incelenmiş, bölge ve hedef antijenlere göre alt grup analizleri yapılmıştır. Bu yazıya 2.825 endometriozis hastasını 4.158 sağlıklı kontrolle karşılaştıran 41 çalışma dahil edilmiştir. Meta-analiz bulguları, serumda otoantikorların varlığı ile endometriozise karşı artan duyarlılık arasında anlamlı bir ilişki olduğunu göstermiştir (risk oranı: 4,242, güven aralığı %95: 3,824-4,706, p<0,001). Ayrıca endometriozis varlığı ile anti-nükleer antikorlar, B2 glikoprotein 1, CA125, karbonik anhidraz 1, kardiyolipin, endometrial, laminin-1, düz kas syntaxin antikorlarının serum seviyeleri arasında anlamlı bir korelasyon olduğu bulunmuştur. Daha ileri analizler sonucunda, Kuzey Amerika'daki endometriozisli hastalarda bu otoantikorların serum seviyelerinin diğer bölgelerdekilere göre daha yüksek olduğu bulunmuştur (p=0,001). Çalışma, serum otoantikorları ile endometriozise yatkınlık arasında anlamlı bir korelasyon olduğunu ortaya çıkarmış ve otoimmünitenin potansiyel bir neden olduğunu vurgulamıştır.

Anahtar Kelimeler: Otoantikor, endometriozis, meta-analiz, serum

Address for Correspondence/Yazışma Adresi: Prof. Masoud Hassanzadeh Makoui MD,
Zanjan University of Medical Sciences, Department of Immunology, Zanjan, Iran
Phone: +989122417196 **E-mail:** dr.m.makoui@zums.ac.ir **ORCID ID:** orcid.org/0000-0002-0821-4420
Received/Geliş Tarihi: 12.03.2024 **Accepted/Kabul Tarihi:** 18.03.2024

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Introduction

Endometriosis is a prevalent medical condition characterized by endometrial tissue in extrauterine locations[1]. This misplaced tissue responds to hormones and can cause internal bleeding, inflammation, and fibrosis[2]. A definitive diagnosis of endometriosis is performed after biopsy by surgery; therefore, its exact prevalence is uncertain[3]. However, it is estimated to affect 10-15% of women of reproductive age[4]. People affected by this disease experience symptoms such as pelvic pain, dysmenorrhea, and infertility[5].

The exact etiology of this endometriosis remains unknown. However, previous research has shown that both genetic and environmental factors contribute to its development. Epigenetic abnormalities, anomalous estrogen production, retrograde menstruation, autoimmune responses, and allergic reactions are potential etiological factors[6,7].

Several studies have been conducted on the role of autoimmune responses as a potential etiological factor in endometriosis. They have demonstrated that endometriosis is correlated with persistent regional inflammation and autoantibodies. Their results showed that women with endometriosis display immune system abnormalities similar to those seen in autoimmune diseases[8,9]. This includes disrupted immune surveillance, abnormal T and B-cell functions, heightened humoral immune response with increased autoantibodies in the serum, and inflammatory tissue damage[9,10].

Although several studies have explored the connection between the presence of autoantibodies in the serum and the likelihood of developing endometriosis, the results have been inconsistent. The aim of this study was to analyze all relevant research and perform a meta-analysis to investigate this association.

Materials and Methods

Eligibility Criteria, Information Sources, and Search Strategy

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines[11]. Various databases, including Scopus, PubMed, Web of Science, EMBASE, and 30 pages of Google Scholar, were searched to identify relevant studies. The search was not restricted by language and covered the period from April 2023. The references of the included studies were also hand-searched. The search strategies consisted of the terms "endometriosis", "autoantibodies", "serum" and their related synonyms.

Women diagnosed with endometriosis based on standard criteria confirmed by laparoscopic sampling and/or histological examination will participate in this review. This study will compare endometriosis patients with healthy women of the same age group.

Study Selection

This meta-analysis included all available case-control studies that met the following criteria: Analysis of the association between autoantibodies and endometriosis patients provides necessary information for a meta-analysis.

The exclusion criteria were as follows: Letters, editorials, abstracts, conference abstracts, or publications lacking adequate information; studies that used women with diseases other than endometriosis, particularly autoimmune diseases; and studies that explored the presence of autoantibodies in bodily fluids or tissues other than serum.

Data Extraction

Two reviewers independently extracted the pertinent data from the selected studies. If necessary, the investigators resolved the differences through discussion and consultation with a third-party. The information extracted was entered into an Excel form, including the last name of the first author, date and location of the study, number of participants in both the case and control groups, mean age of participants, method of diagnosing endometriosis, subclass of autoantibodies, sample type, method of evaluating autoantibodies, and the number or mean value and standard deviation of autoantibody-positive cases and controls.

Assessment of the Risk of Bias

The articles' quality was evaluated by two reviewers using the Newcastle-Ottawa Quality Assessment scale (NOS)[12], and any discrepancies were resolved by a third reviewer. Articles that achieved a NOS score of 7 or above were classified as high quality, whereas those with scores between 5 and 7 were moderate quality.

Data Synthesis

All data were statistically analyzed using Comprehensive meta-analysis software version 3.0 (Biostat, USA). To determine the odds ratios (ORS) and their corresponding 95% confidence intervals (CIS), the statistical analysis used the groups' sample size, mean serum autoantibody level, and standard deviation for both patients diagnosed with endometriosis and the healthy control group. Some studies presented continuous variables as median and quartile, which were converted to mean and standard deviation using the formula in the Cochrane Handbook[13,14]. The heterogeneity of the studies was assessed using Cochrane Q and I^2 statistics. The random-effects model was used to estimate the outcome data in cases where the Cochrane Q p-value was less than 0.1 and the I^2 value exceeded 50%, indicating the presence of statistical heterogeneity. Conversely, a fixed-effects model was employed in other instances. Subgroup analysis was performed to evaluate the impact of confounding variables on the outcomes of the meta-analysis. A sensitivity analysis was also conducted, in which each study was systematically excluded to assess the stability of the obtained results.

Results

Study Selection

After conducting a comprehensive search of the available resources, 1,053 studies were obtained. We then removed any duplicate sources and examined the titles and abstracts of 663 studies. Of these, 71 studies were selected for full-text review. Finally, after applying the inclusion and exclusion criteria, 41 studies were included in our meta-analysis. The process of literature screening and its outcomes are presented in Figure 1. The studies included in the analysis were assigned ratings ranging from zero to nine based on the Ottawa-Newcastle scale for case-control studies. As shown in Table 1, thirty-three studies were assessed as being of high quality, whereas eight studies were evaluated as being of moderate quality.

Study Characteristics

In line with the research methodology, we included a total of forty-one eligible case-control studies to investigate the correlation between the presence of autoantibodies and the risk of endometriosis. Eighteen studies were conducted in Europe[15-32], eleven in Asia[33-43], nine in North America[29,44-51], and four in South America[52-55]. The basic characteristics of the included studies are listed in Table 1 and Table 2. Table 3 shows the number of studies investigating each autoantibody.

Risk of Bias of the Included Studies

Funnel plots, Begg's rank correlation, and Egger's regression tests were used to examine the existence of publication bias. Figure 2 and Table 3 present the outcomes of publication bias. Based on the results of statistical tests and asymmetry analysis of funnel plots, there is a possible publication bias in the studies that investigated pooled and anti-laminin-1 autoantibodies (as shown in Table 3). However, in other autoantibody studies, although a few exhibits slight visual asymmetry, statistical tests do not indicate any significant publication bias. The funnel plot diagrams, which show the likelihood of publication bias in studies on autoantibodies, were modified using the trim and fill test. The modifications did not result in any significant changes in studies that investigated the total and anti-laminin-1 autoantibodies (data not shown).

Synthesis of the Results

The findings of the meta-analysis indicate a substantial correlation between the existence of autoantibodies and susceptibility to endometriosis (OR: 4.242, CI 95%: 3.824-4.706, p<0.001) (Figure 3). Furthermore, individuals with endometriosis exhibited significantly higher levels of anti-nuclear antibodies (anti-ANA) (OR: 5.862, CI 95%: 3.454-9.950, p<0.001), B2 glycoprotein 1 (OR: 4.542, CI 95%: 1.360-15.175, p=0.014), CA125 (OR: 3.602, CI 95%: 1.485-8.733, p=0.005), carbonic anhydrase 1 (OR: 6.860, CI 95%: 3.043-15.468, p<0.001), cardiolipin (OR: 6.806, CI 95%: 3.369-13.749, p<0.001), endometrial (OR: 11.793, CI 95%: 2.382-58.383, p=0.002), laminin-1 (OR: 6.340, CI 95%: 3.151-12.757, p<0.001), smooth muscle (OR: 8.041, CI 95%: 4.442-14.557, p<0.001), and syntaxin (OR: 3.815, CI 95%: 1.249-11.649, p=0.019) autoantibodies than healthy controls. Statistical analysis found no significant relationship between autoantibodies against enolase (OR: 2.067, CI 95%: 0.739-5.782, p=0.167) and PDIK1L (PDLIM1 interacting kinase 1 like) (OR: 1.434, CI 95%: 0.241-8.528, p=0.692) and susceptibility to endometriosis.

The relevant forest plots are presented in Figure 4. It is worth mentioning that the conducted studies[52,53,55] failed to detect anti-dsDNA autoantibodies in individuals suffering from endometriosis, indicating the absence of any correlation.

Heterogeneity Test and Subgroup Analysis

The I^2 test and Cochrane Q statistic showed heterogeneity among studies analyzing total, anti-CA125, anti-endometrial, anti-enolase, anti-PDIK1L, and anti-syntaxin autoantibodies. However, studies related to other autoantibodies showed no significant between-study heterogeneity, as shown in Table 3. To investigate the cause of heterogeneity, subgroup analysis was conducted based on the region. The findings revealed that patients with endometriosis from North America had notably higher levels of autoantibody titers than patients from other regions (p=0.001), and the region of living was identified as one of the sources of heterogeneity. In addition, subgroup analysis based on differences in target antigens of autoantibodies demonstrated this factor as a cause of heterogeneity in the study of pooled autoantibodies (p<0.001).

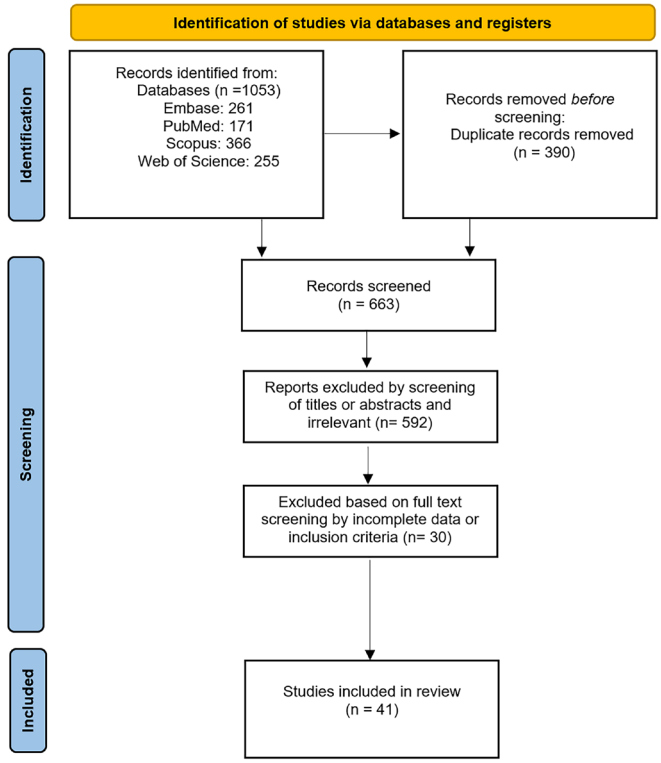

Figure 1. The flow chart of literature search and study selection

Table 1. Basic characteristics of the included studies

First author	Year	Country	Ethnicity	Endometriosis diagnosis protocol	Mean age or age range case	Mean age or age range control	NOS score
Mathur et al.[44]	1982	USA	North American	Laparoscoy and biopsy or laparotomy	26-37	26-37	6
Taylor et al.[15]	1991	UK	European	Laparoscoy and biopsy or laparotomy	33.5	31.6	6
Gorai et al.[33]	1993	Japan	Asian	Laparoscopy or laparotomy	21-46	20-46	7
Fernández-Shaw et al.[16]	1993	UK	European	Laparoscopy	-	-	7
Kiechle et al.[45]	1994	USA	North American	Laparoscoy	34.8	32.6	7
Kim et al.[34]	1995	Korea	Asian	Laparoscopy or laparotomy	30-40	-	6
Aoki et al.[46]	1995	USA	North American	Laparoscopy	33	33	7
Nip et al.[17]	1995	UK	European	Laparoscopy	34	34	8
Odukoya et al.[18]	1995	UK	European	Laparoscopy and histology	33	33	7
Pillai et al.[50]	1996	USA	North American	Laparoscopy	-	25-35	6
Hatayama et al.[35]	1996	Japan	Asian	Laparoscopy or laparotomy	35.3	35.3	6
D'Cruz et al.[47]	1996	USA	North American	Laparoscopy	<45	<45	7
Fernández-Shaw et al.[19]	1996	UK	European	Laparoscopy	-	-	7
Kim et al.[36]	1997	Korea	Asian	Laparoscopy	32	32	7
Kaider et al.[48]	1999	USA	North American	Laparoscopy	-	-	8
Shanti et al.[51]	1999	USA	North American	Histologically	18-45	-	7
Szczepańska et al.[25]	2001	Poland	European	Laparoscopy	29.0	-	7
Reimand et al.[26]	2001	Estonia	European	Laparoscopy and histology	27.5	31.0	8
Ulcová-Gallová et al.[32]	2002	Czech Republic	European	Laparoscopy	35.6	35.6	6
Pasoto et al.[52]	2002	Brazil	South American	Laparoscopy	18-40	18-40	7
Inagaki et al.[43]	2003	Israel	Asian	Laparoscopy and laparotomy	33.7	29.6	7

Table 1. continued

First author	Year	Country	Ethnicity	Endometriosis diagnosis protocol	Mean age or age range case	Mean age or age range control	NOS score
Pasoto et al.[53]	2005	Brazil	South American	Laparoscopy or laparotomy and histological	18-40	18-40	7
Haller et al.[27]	2006	Estonia	European	Laparoscopy	33.0±5.5	-	7
Randall et al.[49]	2007	USA	North American	Laparoscopy	31.8±6.5	31.8±6.5	7
Haller et al.[28]	2007	Estonia	European	Laparoscopy	34.0±4.8	44.9±10.7	8
Caccavo et al.[20]	2007	Italy	European	Laparoscopy	34.4±4.2	33.3±3.1	7
Aguiar et al.[54]	2009	Brazil	South American	laparoscopy and histology	29.2±5.6	27.9±4.5	8
Nabeta et al.[37]	2009	Japan	Asian	Laparoscopy	34.7±7.6	35.0±3.7	6
Nabeta et al.[38]	2010	Japan	Asian	laparosccopy or laparotomy	35.2±8.0	34.2±9.3	7
Inagaki et al.[41]	2011	Japan	Asian	Laparoscopy or laparotomy and histology	31.9	29.6	9
Caccavo et al.[21]	2011	Italy	European	laparoscopy and histology	34.8±3.7	-	7
Nabeta et al.[39]	2011	Japan	Asian	Laparoscopy or laparotomy	35.2±8.0	34.2±9.3	7
Gajbhiye et al.[42]	2012	India	Asian	Laparoscopy and histology	31.2±4.9	28.9±5.3	8
Ozhan et al.[22]	2014	Turkey	European	Laparoscopy or laparotomy	32.33±7.01	34.20±6.88	7
Gajbhiye et al.[40]	2017	India	Asian	Laparoscopy and histology	32.6±6.3	32.13±6.03	8
Yu-Rice et al.[29]	2017	USA & Germany	North American and European	-	28-70	18-65	7
Ek et al.[23]	2019	Sweden	European	Laparoscopy	38.0	42.5	7
Toullec et al.[30]	2020	French	European	Histologically	33.00±5.365	-	7
Artymuk et al.[31]	2021	Russia	European	Laparoscopy and histology	31.6±4.8	31.8±6.5	6
Svensson et al.[24]	2022	Sweden	European	Laparoscopy	32.0-43.0	33-53	7
Vilas Boas et al.[55]	2022	Brazil	South American	Laparoscopy and histology	37.2±7.1	37.8±5.6	8

NOS: Newcastle-Ottawa Quality Assessment scale

Table 2. The fundamental details of the selected studies about the evaluation of autoantibodies

First author	Year	Case number	Control number	Ig type	Sample type	Method	The investigated autoantibody
Mathur et al.[44]	1982	13	15	IgG	Serum	Passive haemagglutination	Endometrial Ovary Granulosa Theca
Taylor et al.[15]	1991	71	109	IgG, IgM and IgA	Serum	IF, WB, Counterimmunoelectrophoresis and Double immunodiffusion	Cardiolipin ANA Lupus anti-coagulant Smooth muscle RO (SS-A) La (SS-B)
Gorai et al.[33]	1993	18	27	-	Serum	WB	Endometrial
Fernández-Shaw et al.[16]	1993	13	7	IgG	Serum	IHC	Endometrial Endothelial
Kiechle et al.[45]	1994	23	17	IgG	Serum	WB	Carbonic anhydrase I
Kim et al.[34]	1995	33	20	IgG	Serum	IHC and WB	Endometrial
Aoki et al.[46]	1995	64	97	IgG	Serum	ELISA	Cardiolipin B2 Glycoprotein 1 Antiphospholipid antigens (PA, PG, PE, PI, PS)
Nip et al.[17]	1995	20	20	IgG and IgM	Serum	ELISA and IF	Cardiolipin ANA Smooth muscle
Odukoya et al.[18]	1995	55	43	IgG	Serum	ELISA	Endometrial Ovary Thyroid Skeletal muscle
Pillai et al.[50]	1996	46	18	IgG	Serum	Passive hemagglutination	Endometrial Transferrin Alpha 2-Heremans Schmidt (HS) Glycoprotein
Hatayama et al.[35]	1996	20	20	IgG	Serum	ELISA	Endometrial
D'Cruz et al.[47]	1996	319	100	IgG	Serum	ELISA	Carbonic anhydrase I and II
Fernandéz-Shaw et al.[19]	1996	51	23	IgG	Serum	ELISA	Endometrial
Kim et al.[36]	1997	42	87	IgG	Serum	ELISA	Cardiolipin ANA Lupus anti-coagulant
Kaider et al.[48]	1999	23	105	IgG, IgM and IgA	Serum	ELISA	Antiphospholipid antigens (PL) ANA Thyroid
Shanti et al.[51]	1999	40	16	IgG	Serum	ELISA	Malondialdehyde-modified Oxidized low-density lipoprotein Lipid peroxide-modified
Szczepańska et al.[25]	2001	50	20	IgG	Serum	ELISA	Zona pellucida

Table 2. continued

First author	Year	Case number	Control number	Ig type	Sample type	Method	The investigated autoantibody
Reimand et al.[26]	2001	38	392	IgG	Serum	IF and ELISA	B2 Glycoprotein 1 Carbonic anhydrase I ANA Smooth muscle Parietal cell Thyroid microsomal Mitochondrial
Ulcová-Gallová et al.[32]	2002	323	101	IgG	Serum	ELISA	Cardiolipin B2 Glycoprotein 1 Antiphospholipid antigens (PA, PG, PE, PI, PS) Zona pellucida
Pasoto et al.[52]	2002	39	18	-	Serum	IF	ANA RO/LA RNP/Sm dsNDA
Inagaki et al.[43]	2003	42	39	IgG	Serum	ELISA	Laminin-1
Pasoto et al.[53]	2005	45	21	IgG and IgM	Serum	IF and ELISA	Cardiolipin Carbonic anhydrase I ANA RO (SS-A) dsDNA Histon Smooth muscle U1RNP
Haller et al.[27]	2006	12	56	IgG	Serum	IF and ELISA	ANA Ovary Smooth muscle Parietal cell Thyroid microsomal Mitochondrial B2 Glycoprotein I Cardiolipin
Randall et al.[49]	2007	278	249	IgG	Serum	IF	Endometrial
Haller et al.[28]	2007	12	85	IgG, IgA and IgM	Serum	ELISA and IF and ImmunoCAP technology	FSH ANA Ovary Smooth muscle Parietal cell Thyroid microsomal Mitochondrial B2 Glycoprotein I Cardiolipin
Caccavo et al.[20]	2007	18	16	IgG and IgM	Serum	ELISA	Cardiolipin
Aguiar et al.[54]	2009	120	1500	IgA	Serum	ELISA and IF	Human tissue transglutaminase Endomysium
Nabeta et al.[37]	2009	65	70	IgG	Serum	ELISA	CA125 Enolase
Nabeta et al.[38]	2010	69	82	IgG	Serum	ELISA	CA125 PDIK1L

Table 2. continued

First author	Year	Case number	Control number	Ig type	Sample type	Method	The investigated autoantibody
Inagaki et al.[41]	2011	45	39	IgG	Serum	ELISA	Laminin-1
Caccavo et al.[21]	2011	35	50	IgG	Serum	ELISA	Laminin-1
Nabeta et al.[39]	2011	69	82	IgG	Serum	ELISA	Syntaxin
Gajbhiye et al.[42]	2012	50	27	IgG	Serum	WB and ELISA	Tropomyosin 3 Stomatin-like protein 2 Tropomodulin 3
Ozhan et al.[22]	2014	60	20	-	Serum	ELISA	Laminin-1 Endometrial CA125 Syntaxin PDIK1L Enolase
Gajbhiye et al.[40]	2017	133	104	-	Serum	ELISA	CA125 CA19-9 Syntaxin PDIK1L Enolase Tropomyosin 3a Tropomyosin 3b Tropomyosin 3c Tropomyosin 3d Stomatin-like protein 2a Stomatin-like protein 2b Stomatin-like protein 2c Tropomodulin 3a Tropomodulin 3b Tropomodulin 3c Tropomodulin 3d
Yu-Rice et al.[29]	2017	18	30	IgG	Serum	ELISA	Selenium binding protein 1
Ek et al.[23]	2019	100	100	IgG	Serum	ELISA	LH LH receptor GnRH1 GnRH1 receptor Matrix metalloproteinase-9 Tenascin-C
Toullec et al.[30]	2020	106	92	IgG	Serum	ELISA	Granulocyte-macrophage colony stimulating factor
Artymuk et al.[31]	2021	100	100	IgG	Serum	ELISA	Estrogen Progesterone
Svensson et al.[24]	2022	53	50	IgG	Serum	ELISA	LH LH receptor FSH FSH receptor TSH TSH receptor HCG
Vilas Boas et al.[55]	2022	94	91	IgG	Serum	IF and ELISA	ANA ENA dsDNA

Ig: Immunoglobulin, IF: Immunofluorescence, WB: Western-Blot, ELISA: Enzyme-Linked Immunosorbent Assay, IHC: Immunohistochemistry, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, PDIK1L: PDLIM1 interacting kinase 1 like, ANA: Anti-nuclear antibodies, TSH: Thyroid-stimulating hormone, HCG: Human chorionic gonadotropin, CA125: Carcinoembryonic antigen 125, CA19-9: Carcinoembryonic antigen 19-9, PA: Antiphospholipid antigen PA, PE: Antiphospholipid antigen PE, PG: Antiphospholipid antigen PG, PI: Antiphospholipid antigen PI, PL: Antiphospholipid antigen PL, PS: Antiphospholipid antigen PS, RO: A kind of extractable nuclear antigens (RO/SSA)

Table 3. The findings related to the analysis of heterogeneity and publication bias of the conducted studies

Variables (autoantibodies)	Number of included studies	I^2 (%)	Q-test's p-value	P-value of Begg's test	P-value of Egger's test
All of the autoantibodies	41	84.47	<0.001	0.130	0.05
Anti-ANA	8	0.00	0.859	0.804	0.406
Anti-B2 glycoprotein 1	3	0.00	0.578	0.601	0.169
Anti-CA125	4	75.25	0.007	0.174	0.415
Anti-carbonic anhydrase I	4	36.39	0.194	1.000	0.663
Anti-cardiolipin	7	1.51	0.413	0.880	0.746
Anti-endometrial	9	93.07	<0.001	0.251	0.788
Anti-enolase	3	73.63	0.023	0.601	0.394
Anti-laminin-1	4	23.43	0.270	0.308	0.036
Anti-PDIK1L	3	92.49	<0.001	0.296	0.125
Anti-smooth muscle	3	0.00	0.620	0.601	0.652
Anti-syntaxin	3	79.70	0.007	0.601	0.940

ANA: Anti-nuclear antibodies, CA125: Carcinoembryonic antigen 125, PDIK1L: PDLIM1 interacting kinase 1 like

Sensitivity Analysis

Sensitivity analyses were conducted to evaluate the potential impact of a single study on the overall effect of autoantibodies in endometriosis. The sensitivity analyses indicated that upon exclusion of each study, the general conclusions remained substantially unchanged. These analyses consistently exhibited the robustness of the meta-analysis outcomes.

Discussion

Endometriosis is a significant health issue that affects women, but its exact cause remains unknown[56]. Several theories have been proposed to explain its origin, including autoimmunity[57]. However, studies investigating the development of autoantibodies in patients with autoimmune conditions have produced conflicting results. Therefore, the research collected and analyze the current body of information on this topic. The findings of our study indicate that the serum of individuals diagnosed with endometriosis has significantly higher levels of autoantibodies than that of healthy controls.

Studies have shown an increase in both the activity and quantity of B-cells in the serum of individuals with endometriosis[58,59]. The increase in B-cell activity leads to an elevated production of antibodies, which is consistent with the findings of the current study. Research has shown that immune cells, particularly B-cells, demonstrate an increase within lesions associated with endometriosis[60]. In addition, the secretion of cytokines responsible for activating B-cells, such as B lymphocyte-stimulators, also experiences an elevation within these specific regions[59]. These findings validate the results of our study.

Endometriosis relies on estrogen for its development[61] and estrogen has been identified as one of the potential mechanisms that increase the quantity and functionality of B-cells in individuals with endometriosis[62]. Research suggests that estrogen initiates a genetic program that alters the survival and activation of B-cells, leading to a shift in the naive immune system toward autoreactivity[62]. The exact cause of autoantibody formation in endometriosis is not well understood, but it is thought to be related to cellular damage and inflammation that occur in endometriosis-associated lesions. Abnormal exposure of self-antigens from damaged cells to the immune system triggers an autoimmune response, leading to the formation of autoantibodies that target cell-derived antigens[63].

This study suggests that differences in the target antigens of autoantibodies and continent of residence may contribute to the observed heterogeneity. The results of the subgroup analysis show that North American patients with endometriosis have higher levels of autoantibodies. Differences in genetic or environmental factors may explain this disparity. Additionally, according to the literature, autoimmune antibody manifestation varies among North American ethnic groups. Bruner et al.[64] discovered that African Americans with systemic lupus erythematosus exhibit significantly higher levels of anti-ANA autoantibody expression than other North American races. It is important to consider factors beyond ethnicity that can contribute to heterogeneity, such as sampling error, use of varied laboratory tests, body mass index, and age. It is crucial to study these factors in depth in future research efforts.

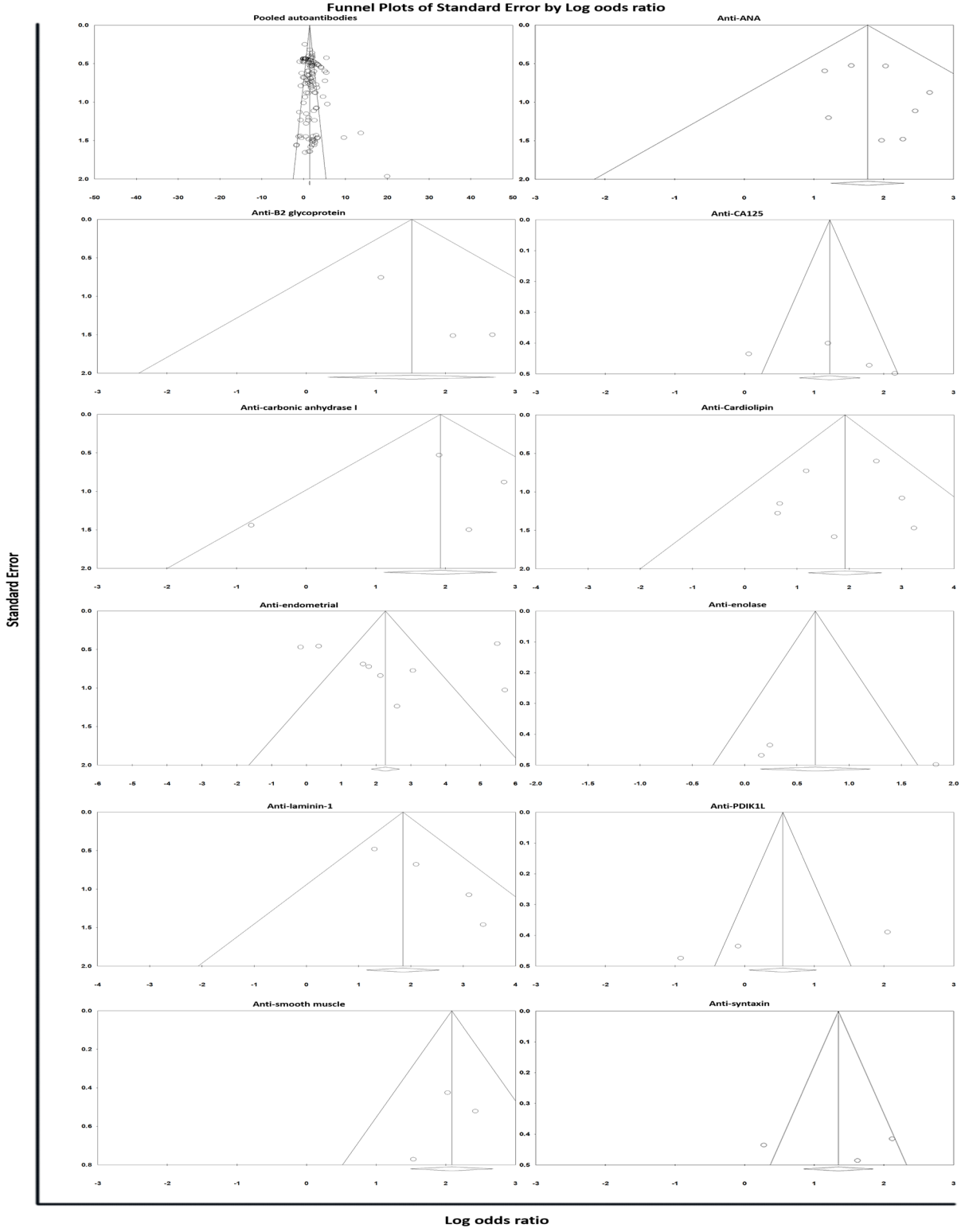

Figure 2. Begg's Funnel Plots of the studies that examined the correlation between serum anti-ANA, anti-B2 glycoprotein 1, anti-CA125, anti-carbonic anhydrase 1, anti-cardiolipin, anti-endometrial, anti-enolase, anti-laminin, anti-PDIK1L, anti-smooth muscle, anti-syntaxin, pooled autoantibodies for the identification of publication bias

ANA: Anti-nuclear antibodies, CA125: Carcinoembryonic antigen 125, PDIK1L: PDLIM1 interacting kinase 1 like

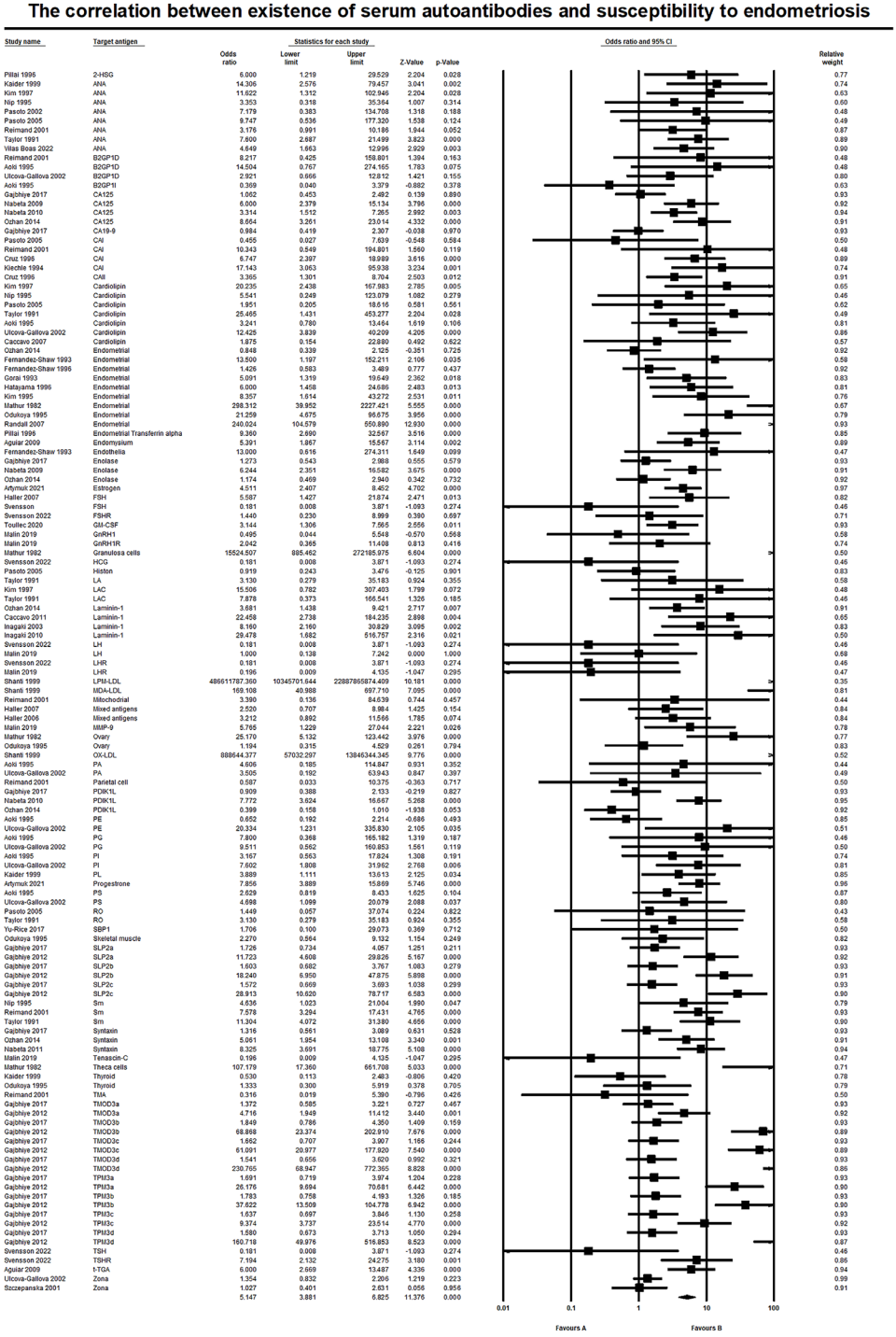

Figure 3. Forest plot investigating the link between serum autoantibodies and endometriosis risk

2-HSG: 2-Heremans Schmidt Glycoprotein, ANA: Anti-nuclear antibodies, B2GP1D: B2 glycoprotein 1 dependent, B2GP1I: B2 glycoprotein 1 independent, CA125: Carcinoembryonic antigen 125, CA19-9: Carcinoembryonic antigen 19-9, CAI, Carbonic anhydrase 1, CAII: Carbonic anhydrase II, FSH: Follicle-stimulating hormone, GM-CSF: Granulocyte-macrophage colony-stimulating factor, GnRH1: Gonadotropin releasing hormone 1, GnRH1R: Gonadotropin releasing hormone 1 receptor, HCG: Human chorionic gonadotropin, LA: One kind of neutrophile antigens (LA/SSB), LAC: Lupus anti-coagulant, LH: Luteinizing hormone, LHR: Luteinizing hormone receptor, LPM-LDL: Lipid peroxide-modified LDL, DMA-LDL: Malondialdehyde-modified LDL, MMP-9: Matrix metallopeptidase-9, OX-LDL: Oxidized low-density lipoprotein, PA: Antiphospholipid antigen PA, PDIK1L: PDLIM1 interacting kinase 1 like, PE: Antiphospholipid antigen PE, PG: Antiphospholipid antigen PG, PI: Antiphospholipid antigen PI, PL: Antiphospholipid antigen PL, PS: Antiphospholipid antigen PS, RO: A kind of extractable nuclear antigens (RO/SSA), SBP1: Selenium binding protein 1, SLP2a,b,c: Stomatin-like protein 2a,b,c ,Sm: Smooth muscle, TMA:, TMOD3a,b,c,d: Tropomodulin 3a,b,c,d, TPM3a,b,c,d: Tropomyosin 3a,b,c,d, TSH: Thyroid-stimulating hormone, TSHR: Thyroid-stimulating hormone receptor, t-TGA: Thyroglobulin

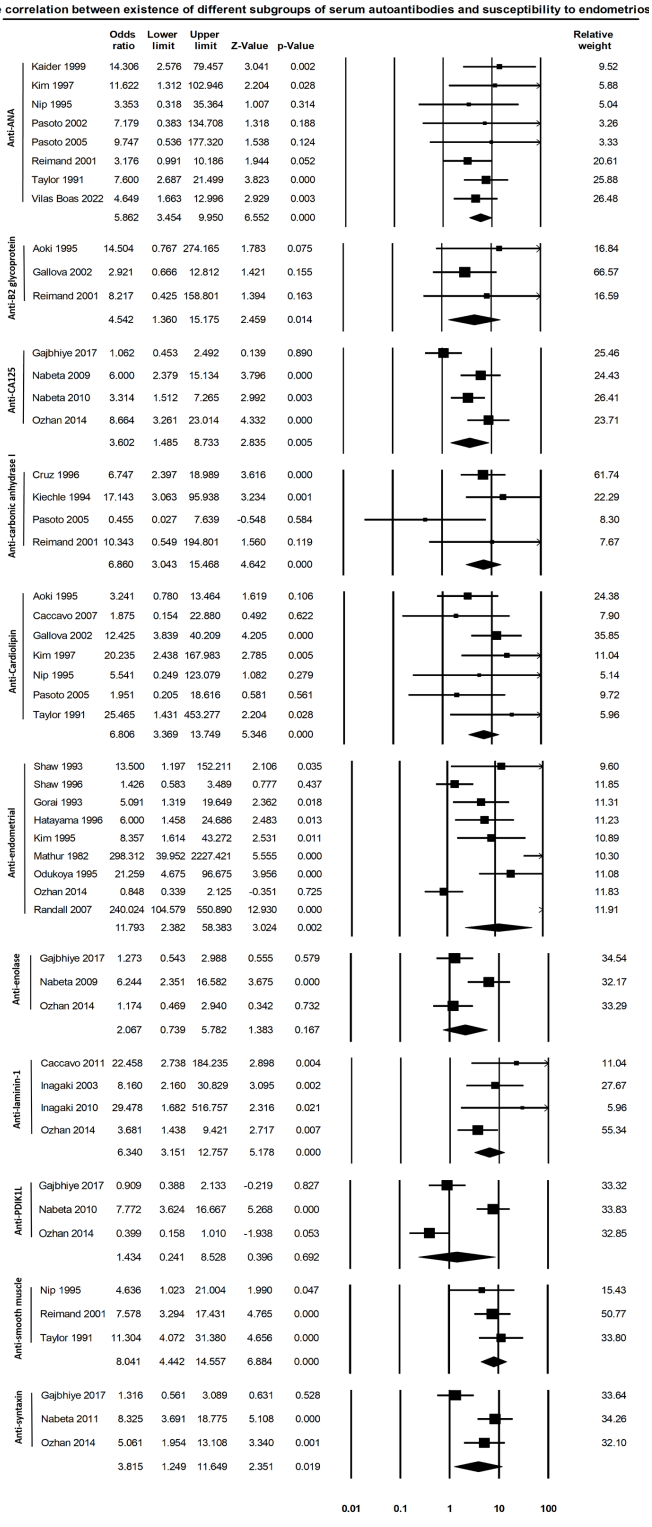

Figure 4. Forest plots exploring the link between serum anti-ANA, anti-B2 glycoprotein 1, anti-CA125, anti-carbonic anhydrase 1, anti-cardiolipin, anti-endometrial, anti-enolase, anti-laminin, anti-PDIK1L, anti-smooth muscle and anti-syntaxin autoantibodies and risk of endometriosis

ANA: Anti-nuclear antibodies, CA125: Carcinoembryonic antigen 125, PDIK1L: PDLIM1 interacting kinase 1 like

This meta-analysis is the most comprehensive study that systematically reviews and analyzes the relationship between autoantibodies and endometriosis, synthesizing over three decades of research. In addition, this study included a large sample size of 2,731 patients diagnosed with endometriosis and 4,067 healthy controls, potentially providing a definitive outcome with high accuracy and minimal bias for the general population.

It is important to note that there are limitations to this study. The laboratory data were measured in different centers using various methods and detection kits, which may have resulted in inconsistencies. Furthermore, the use of varying cutoff points across investigations could lead to inconsistencies in the outcome. In addition, the limited and insufficient data regarding the participants in the selected studies hindered our ability to examine other factors that may have an impact on heterogeneity, such as age and BMI. Therefore, future research should focus on exploring this aspect in more detail.

Conclusion

In conclusion, our meta-analysis revealed that patients diagnosed with endometriosis exhibit a greater prevalence of autoantibodies than healthy individuals. Based on the findings of this study, it is likely that autoimmune reactions are associated with the progression of endometriosis. However, further studies are required to determine the mechanism underlying autoantibody production in endometriosis. Future research should also investigate autoantibody levels during different phases of endometriosis.

Ethics

Authorship Contributions

Design: S.F., M.H.M., Data Collection or Processing: R.H.M., N.A., Analysis or Interpretation: S.F., R.H.M., N.A., M.H.M., Literature Search: M.H.M., Writing: S.F., R.H.M., N.A., M.H.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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