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REVIEW

Global Trends and Emerging Frontiers on Ovarian Endometriosis: A Bibliometric and Visualization Analysis

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Purpose: Ovarian endometriosis, a prevalent condition in reproductive-age women, causes dysmenorrhea and infertility, significantly impairing quality of life. To date, there is no systematic description of ovarian endometriosis in the literature. This study aimed to explore the development of ovarian endometriosis via bibliometric analysis and to identify global trends and frontiers.

Methods: We systematically reviewed all pertinent studies up to 2023 from the Web of Science Core Collection (WoSCC) were downloaded. We examined the data via the Bibliometrix program in R (version 4.3.2), CiteSpace software, and the Online Analysis Platform of Literature Metrology (http://biblimetric.com).

Results: A total of 409 eligible records on ovarian endometriosis were identified and included in the analysis. The most productive journal was FERTILITY AND STERILITY. Endometriosis was the most cited reference. The keywords were divided into seven clusters, including atypical endometriosis, laparoscopic cystectomy, angiogenesis, in situ hybridization, estrogen and progesterone receptor, microarray analysis, and treatment. As indicated by the analysis of trending topics, infertility has become a new research hotspot.

Conclusion: In our study, the main directions of ovarian endometriosis include pathogenesis and cancerization. In addition, infertility has received growing attention in recent years. A comprehensive analysis of the publications in this field could help us shape the direction of further research and provide new points of view for solutions to prominent women's health problems.

Keywords: ovarian endometriosis, chocolate cyst of ovary, bibliometric analysis, scientometric analysis, infertility, cancerization

Introduction

Endometriosis is defined as the presence of endometrial-type mucosa outside the uterine cavity. Approximately 10–15% of women of childbearing age are diagnosed as endometriosis.[1,2] When endometriosis involves the ovaries, there may be oxidized blood gathered in the cyst to form a coffee-colored viscous fluid, so ovarian endometriosis is also known as ovarian chocolate cyst. Ovarian endometriosis is the most common type of endometriosis, with a prevalence of 17–44% in patients with endometriosis.[3] Endometriosis is an important cause of dysmenorrhea and infertility. In addition, it is prone to recurrence, which negatively affects the quality of life and physical and mental health of women.[4] Women affected by ovarian endometriosis are at a higher risk of developing ovarian cancer compared to the general female population, and they may also be at increased risk of breast and other cancers as well as autoimmune and atopic disorders.[5] Therefore, effective treatment methods and prevention of disease progression are very important in current research.

In recent years, the study of ovarian endometriosis has made remarkable progress. In terms of diagnosis, with the continuous improvement of imaging technologies such as ultrasound and Magnetic Resonance Imaging (MRI), as well as the discovery of various biomarkers (eg CA-125, CA-199, miR-200 etc.), the accuracy of early diagnosis of diseases has been improved.[6–10] In terms of treatment, surgical techniques have gradually developed from traditional open surgery to

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laparoscopic minimally invasive surgery, and the surgical methods have been continuously optimized. Drug therapy has also developed from traditional progesterone to new drugs such as Gonadotropin-releasing hormone (GnRH) agonists and aromatase inhibitors.[11–13] With the deepening of the research on ovarian endometriosis, the number of related literature presents a rapid increase trend. These studies cover multiple levels from basic to clinical, involving obstetrics and gynecology, reproductive medicine, pathology, molecular biology and other disciplines. However, the current study lacks integration of scattered clinical studies and demonstrates a disconnection between the underlying mechanism and clinical application. Additionally, few attempts have been made to systematically analyze the evolution of scientific findings in ovarian endometriosis research.

Bibliometric analysis maps the knowledge domain of academic literature and can address the aforementioned challenge by identifying current trends, research networks, and related topics.[14,15]

Thus, to systematically analyze the evolution of the scientific results of ovarian endometriosis research, we utilized CiteSpace to extract and visualize information from the Web of Science Core Collection (WoSCC) from diverse perspectives, encompassing various countries, institutions, cocited authors, and cocited references. Additionally, we employed the "bibliometrix" R package and "biblioshiny" tool to generate trending topics and identify research hotspots.[16,17] We aimed to obtain comprehensive information on ovarian endometriosis to help readers better understand research progress and to encourage new researchers to seize the frontier of the field.

Materials and Methods

Data Sources and Search Strategies

To mitigate bias associated with database updates, we conducted a comprehensive search for relevant publications in the WoSCC Science Citation Index Expanded (SCI-Expanded) and Social Sciences Citation Index (SSCI). The search technique employed was as follows: Document type was set to include "Articles" only from inception to the present (last search date on 1 March 2024). After the primary data were searched, two researchers (AX and YL) independently reviewed each manuscript to ensure that it was pertinent to the topic of interest.

Data Analysis and Data Visualization

The WoSCC data were downloaded as a tab-delimited text file and transported into Bibliometrics' Online Analysis Platform1, where the "Total volume" option was used for publication trend analysis of various years and the "National total" option was used for publication quantity analysis of countries.

The complete records and cited references for these articles were obtained from the WoSCC database. The TXT files were subsequently imported into the CiteSpace program V6.1R6 (64-bit) Basic (Drexel University, Philadelphia, PA, USA), utilizing the specified parameters. The time span (January 1991–December 2023, years per slice (1), links (strength: cosine, scope: within slices), selection criteria (g-index: k = 25, Top N = 50, Top N% = 10%, maximum number of selected items per slice = 100), pruning (Pathfinder, Pruning sliced networks), and all of the other parameters were left at their default settings. The node type parameter area was set as follows: "Country" was chosen for intercountry analysis, "Institution" was chosen for interinstitutional analysis, "Author" was chosen for author–hip network analysis, and "References" was chosen for document co-citation analysis.

The Bibliometrix package in R (version 4.3.2) and a web interface for bibliometrix, "biblioshiny", were used to obtain the most often cited documents and the most frequent words and trend topics. The TXT format data have already been saved.

Results

Trend Analysis of Publications

After the above parameters were set, 409 articles were included in this study. The Bibliometrics Online Analysis Platform was used to determine the annual number of papers published (Figure 1A). From inception to the present (January 1991 to December 2023), the number of articles published each year was less than 50. There was a significant increase in 2018, which peaked in 2022. Figure 1B shows the contribution of each country. Before 2008, Japan was the largest contributor, and since 2008, China has contributed more and then become the top contributor in this field.

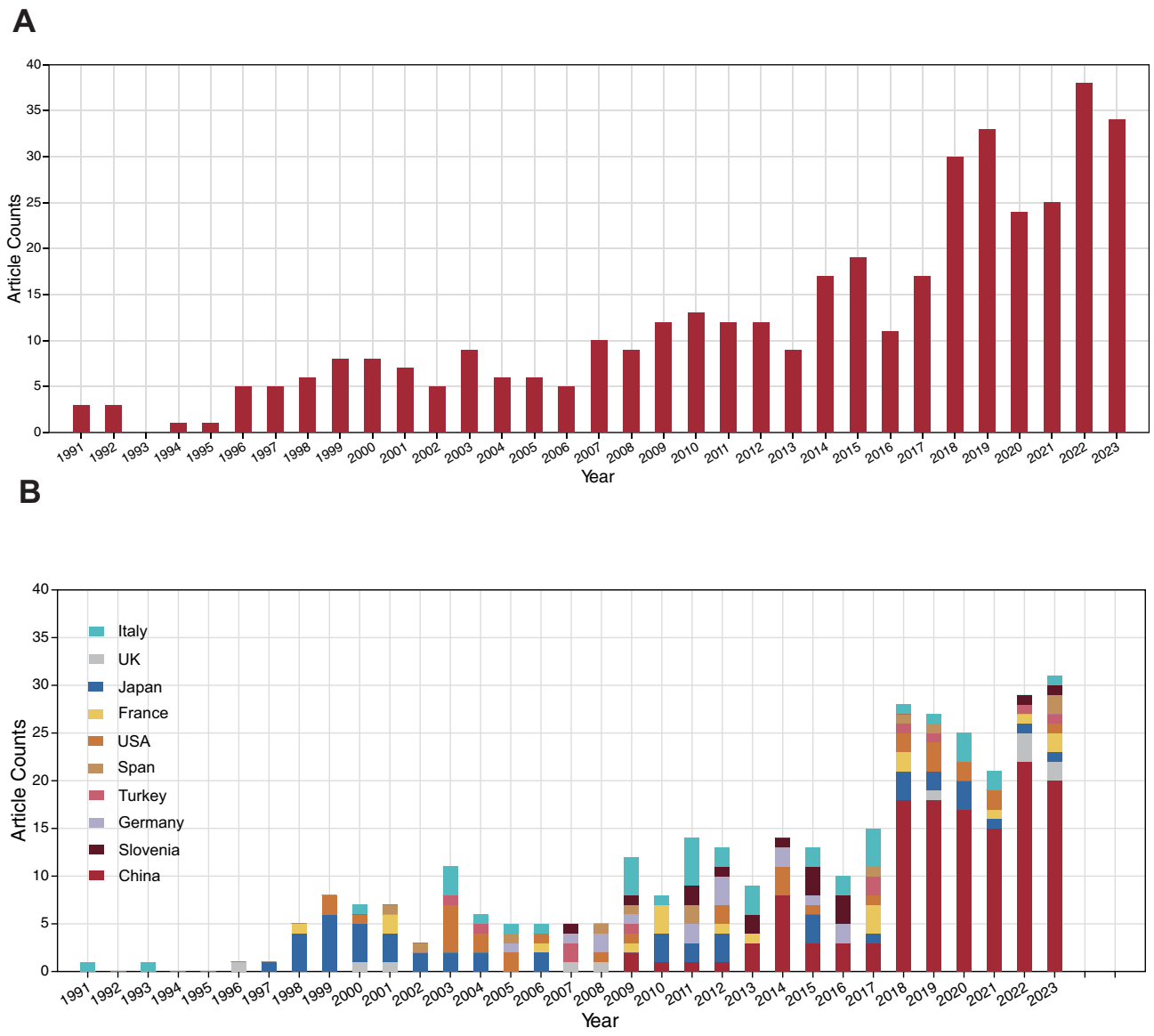

Figure 1 The number of publications on ovarian endometriosis and the growth trend from January 1991 to December 2023. **(A)** Number and growth trends of annual research publications; **(B)** number and growth trends in annual publications in the top 10 countries. Bar chart showing the number of online articles published per year.

Journal Analysis

According to the WoSCC search, the 409 papers included in the current analysis appeared in 153 distinct journals over the course of the last 33 years, starting in 1991. The impact of the journals was examined via online bibliometric analysis. Table 1 lists the 10 most referenced journals. The FERTILITY AND STERILITY methods had the most papers published and the most citations overall (102), with an impact factor of 6.7. The AMERICAN JOURNAL OF ROENTGENOLOGY had an IF of 5 and the greatest average number of citations (6).

Analysis of Countries/Regions, Institutions and Authors

To analyze the research status of ovarian endometriosis, intercountry/regional, interinstitutional and author analyses were performed by using CiteSpace. After removing duplicate entries, 296 published articles were retained for inclusion in the final analysis.

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Table 1 The Top 10 Most Active Journals That Published Articles in the Mechanism of Ovarian Endometriosis (Sorted by Total Citation)

Rank	Journal Title	Frequency	Total Citations	Average Citation Per Paper	Impact Factor-2021	JCR
1	Fertility and Sterility	52	102	1.96	6.7	Q1
2	Human Reproduction	32	20	0.63	6.1	Q1
3	Reproductive Biology and Endocrinology	7	12	1.71	4.4	Q1
4	Journal of Ovarian Research	7	12	1.71	4	Q1
5	Ultrasound in Obstetrics & Gynecology	4	10	2.5	7.1	Q1
6	Journal of Clinical Endocrinology & Metabolism	3	10	3.33	5.8	Q1
7	Gynecologic Oncology	3	10	3.33	4.7	Q1
8	Gynecological Endocrinology	15	9	0.6	2	Q3
9	Modern Pathology	10	8	0.8	7.5	Q1
10	Journal of Steroid Biochemistry and Molecular Biology	2	8	4	4.1	Q2

The results of regional cooperation among countries show that 39 countries have established partnerships and that there are 40 links between them. China (article number = 124) and Japan (article number = 41) have the highest number of publications in this field. However, Slovenia (centrality=0.38) has the most international cooperation with other countries (Figure 2A).

Setting the threshold to 7, the rankings of the 10 most productive institutions are displayed in Figure 2B. The size of the concentric circles represents the number of publications. Thus, the larger concentric circles are, typically, the greater the number of article institutions published. A relationship between two institutions indicates their collaboration in coauthoring publications. The thickness of the lines represents the frequency of their cooperation. In total, 280 nodes and 324 linkages were identified during an investigation into partnerships among different institutions. The majority of these connections involved institutions based in China. The Assistance University of Ljubljana in Slovenia was the most productive (article number = 12). Zhejiang University (article number = 11) was the second institution, followed by Central South University, the Chinese Academy of Medical Sciences – Peking Union Medical College and Hebei Medical University (article number = 9 for each institution).

For author analysis, 625 authors contributed to the study of ovarian endometriosis (Figure 2C). The four top 10 authors were from China; 3 were from Japan; and the other three were from Slovenia, Belgium and Switzerland. These 10 authors contributed 62 papers during the 33 years, accounting for 21% of all ovarian endometriosis -related publications. Many of these authors in the top 10 had collaborative relationships.

Reference Co-Citation and Journal Co-Citation Analysis

Co-citation analysis of references and journals can reveal clusters of relevant literature and journals associated with scientific fields, while the thickness of connecting lines between nodes indicates citation co-occurrence, and the size of circles is positively correlated with citation frequency. To identify crucial insights, we conducted analyses on cited references and cited journals (Figure 3A and B). The most frequently cited article was “Endometriosis”, which was published in New England in 2020 and received 18 citations. Fertility and Sterility emerged as the most cited journals, with a total of 239 citations. Notably, four out of the top ten most cited references were published in the top ten most cited journals. Furthermore, to provide more robust evidence for illustrating research trends, we employed R software along with bibliometrix codes to identify the fifteen locally highly cited documents presented in Table 2.

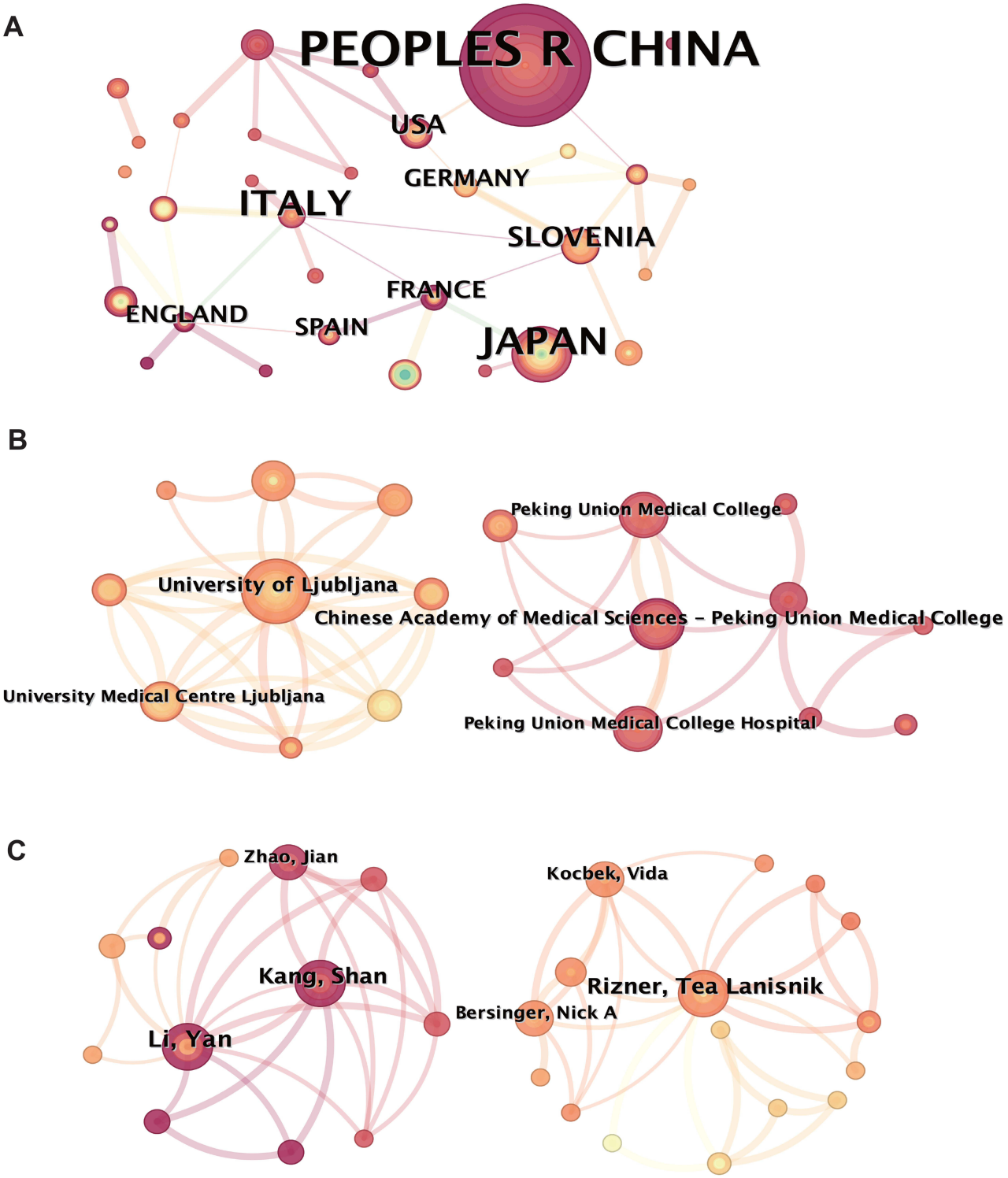

Figure 2 Collaboration to study the mechanism of POP visualized via CiteSpace. **(A)** Intercountry cooperation; **(B)** interinstitutional cooperation; (**C**) interauthor cooperation. Each circle represents a country/institution/author. The size of the circle is positively correlated with the number of articles published by the country/institution, and the link between the two circles indicates the cooperation of the two institutions in the same article. Line thickness is positively correlated with the frequency of collaboration.

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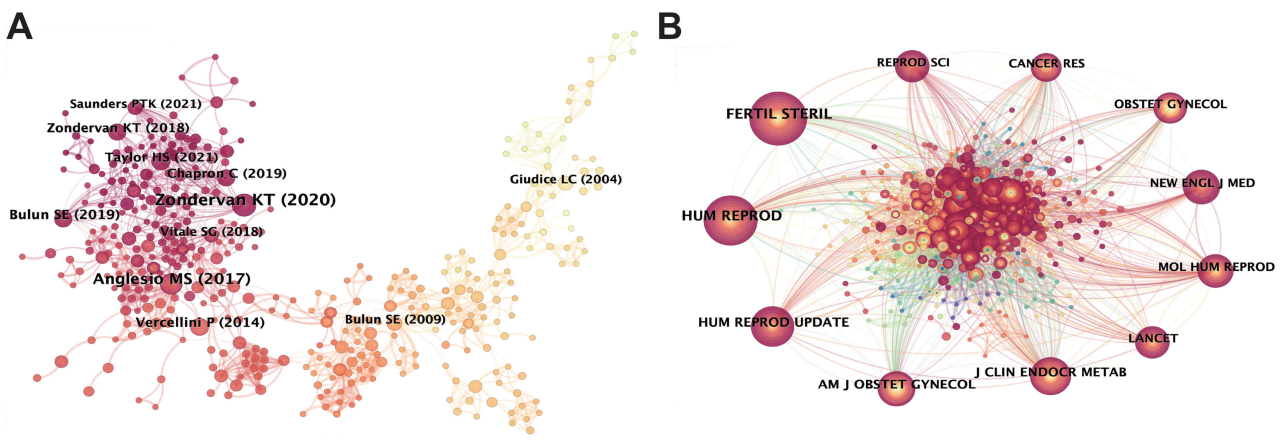

Figure 3 Reference co-citation and journal co-citation analysis. **(A)** Co-cited reference in the field of research on ovarian endometriosis. Each circle represents an author. The size of the circle is positively correlated with the number of citations by the author, and the link between the two circles represents the collaboration of two authors on the same article. Line thickness is positively correlated with the frequency of collaboration. **(B)** Co-citation of journals on ovarian endometriosis. Each circle represents a reference. The size of the circle is positively correlated with the frequency of citations, and the link between the two circles represents two references cited in the same article.

Analysis of Keywords

Keywords provide a succinct overview of the most pertinent terms and trending topics, offering valuable insights for academic research. There were 492 keywords extracted from the retrieved records. Setting the minimum number to 15, the network map of the 12 keywords is shown in Figure 4A. The top 25 keywords were screened according to outbreak intensity (Figure 4B). The green line represents the 20-year period, and the red line indicates the timeline from the beginning to the end of the outbreak.

Table 2 The Top 15 Most Local Cited Documents in in the Mechanism of Pelvic Organ Prolapse During 1997 to 2022

Rank	Document	Title	Year	Local Citations	Global Citations	LC/GC Ratio (%)	Normalized Local Citations	Normalized Global Citations
1	Nisolle M, 1997, Fertil Steril-a	Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities	1997	28	904	3.10	3.59	4.05
2	Nisolle M, 1997, Fertil Steril	Immunohistochemical analysis of proliferative activity and steroid receptor expression in peritoneal and ovarian endometriosis	1997	8	125	6.40	1.03	0.56
3	Miyakoshi K, 1998, AM J Roentgenol	Decidualized ovarian endometriosis mimicking malignancy	1998	6	51	11.76	7.00	1.45
4	Redwine DB, 1999, Fertil Steril	Ovarian endometriosis: a marker for more extensive pelvic and intestinal disease	1999	6	293	2.05	5.33	5.92

(*Continued*)

Table 2 (Continued).

Rank	Document	Title	Year	Local Citations	Global Citations	LC/GC Ratio (%)	Normalized Local Citations	Normalized Global Citations
5	Reis FM, 2001, Fertil Steril	Evidence for local production of inhibin A and activin A in patients with ovarian endometriosis	2001	6	44	13.64	2.63	1.17
6	Li XY, 2019, J Ovarian Res	Risk factors for postoperative recurrence of ovarian endometriosis: long-term follow-up of 358 women	2019	6	36	16.67	11.00	2.45
7	Ogawa S, 2000, Gynecoloncel	Ovarian endometriosis associated with ovarian carcinoma: a clinicopathological and immunohistochemical study	2000	5	201	2.49	4.44	3.12
8	Matsuzaki S, 2001, Fertil Steril	Expression of estrogen receptor alpha and beta in peritoneal and ovarian endometriosis	2001	5	100	5.00	2.19	2.66
9	Vouk K, 2012, Hum Reprod	Discovery of phosphatidylcholines and sphingomyelins as biomarkers for ovarian endometriosis	2012	5	88	5.68	5.42	3.26
10	Candiani GB, 1991, Fertil Steril	Reproductive and menstrual factors and risk of peritoneal and ovarian endometriosis	1991	4	60	6.67	1.71	1.61
11	Anaf V, 2002, Hum Reprod	Hyperalgesia, nerve infiltration and nerve growth factor expression in deep adenomyotic nodules, peritoneal and ovarian endometriosis	2002	4	230	1.74	2.86	3.41
12	Arimoto T, 2003, Int J Oncol	Genome-wide cDNA microarray analysis of gene-expression profiles involved in ovarian endometriosis	2003	4	104	3.85	6.67	4.62
13	Zheng WX, 2005, Int J Gynecol Pathol	Initial endometriosis showing direct morphologic evidence of metaplasia in the pathogenesis of ovarian endometriosis	2005	4	29	13.79	6.00	1.74

(*Continued*)

Table 2 (Continued).

Rank	Document	Title	Year	Local Citations	Global Citations	LC/GC Ratio (%)	Normalized Local Citations	Normalized Global Citations
14	Mori M, 2015, Redox Biol	Ovarian endometriosis-associated stromal cells reveal persistently high affinity for iron	2015	4	34	11.76	9.50	1.71
15	Vercellini P, 1991, Fertil Steril	Reliability of the visual diagnosis of ovarian endometriosis	1991	3	52	5.77	1.29	1.39

To delve deeper into the keywords, we performed a cluster network analysis. According to the logic of homogeneity, if two (or more) articles have many similar keywords, they tend to be homogeneous, and we can divide these keywords into several clusters. By setting the smallest size (K = 20) of a cluster to show, 7 clusters finally appeared (Figure 4C), including #0 atypical endometriosis, #1 laparoscopic cystectomy, #2 angiogenesis, #3 in situ hybridization, #4 expression, #5 estrogen and progesterone receptor, #6 microarray analysis, and #7 treatment.

According to the analysis of trend topics (setting the field as the author's keywords), infertility has become the trend topic of the study of ovarian endometriosis since 2020, and it is still the top topic (Figure 4C).

Discussion

In the present study, we conducted the first visual citation analysis of research articles on ovarian endometriosis from 1991–2023. By utilizing three analytical tools, a comprehensive overview was obtained from various perspectives. Since 2006, the number of published articles on this topic has rapidly increased, with approximately 30 articles per year by 2021. Additionally, we performed intercountry, interinstitutional, and journal co-citation analyses as well as keyword analyses to provide a systematic understanding of the field over the past 33 years. To enhance the comprehension of highly cited papers, we discuss the content of the top 15 locally cited articles that have significantly contributed to advancements in this area. The research content was categorized into two main areas: pathogenesis and cancerization. Notably, infertility emerged as an important theme on the basis of the authors' keywords; therefore, we also explored the relationship between ovarian endometriosis and infertility.

Pathogenesis

Migration of the retrograde menstruation is the most classic theory of ovarian endometriosis.[18] In our study, a review of top 15 locally cited articles indicated that 8 specifically focused on the mechanism of ovarian endometriosis.[19–26] Notably, the earliest article among the 15 articles was published in 2000, and we analyzed these articles in chronological order of publication. Nisille M et al reported that mesothelial invagination on a continuum with endometriotic tissue suggests that metaplastic histogenesis of ovarian endometriotic lesions occurs.[23] In addition, this team also discovered that the high proliferative activity and the persistence of estrogen receptors (ERs) and progesterone receptors (PRs) in the stroma of red lesions and ovarian endometriomas emphasize the primordial role of the stroma in the development of endometriosis and suggest different mechanisms of proliferation control from those observed in the eutopic endometrium.[19] Their research emphasized the importance of the stroma in the development of endometriosis and provided a new perspective for understanding the heterotopic occurrence process of ovarian endometriosis. G B Candiani et al reported that parity and irregular/long menses lower the risk of endometriosis. These findings were similar across different disease locations and indications for surgery, providing strong evidence of the consistency of the general results and offering new insights for prevention.[27] Research conducted by S Matsuzaki et al revealed that the predominant expression of ER-alpha in both glandular epithelial and stromal cells may be essential for the development and growth of peritoneal and ovarian endometriosis.[28] These findings point to new directions for the treatment of this disease. In 2001,

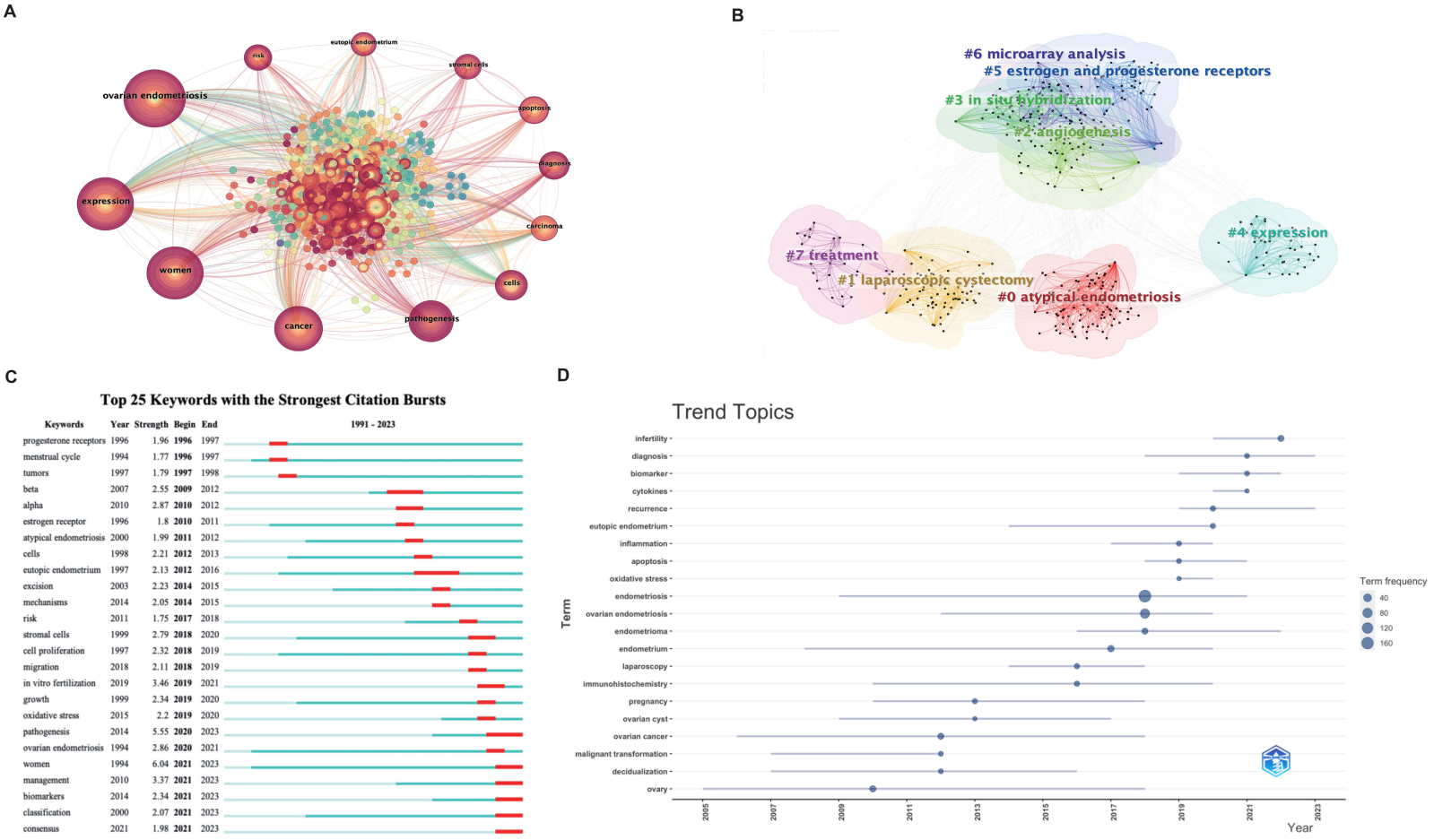

Figure 4 Analysis of author keywords. **(A)** The most relevant words; **(B)** Top 25 keywords with the strongest citation bursts; **(C)** A cluster network of keywords via CiteSpace; **(D)** Trend topics are shown.

F. M. Reis et al reported that ovarian endometriosis can produce and secrete inhibin A and activin A such that this family of regulatory proteins may play a role in the local modulation of endometriosis cell growth and differentiation.[20] This study of regulatory proteins produced by ovarian endometriosis has provided important clues for our understanding of the growth and differentiation of endometriosis cells. Takahide A et al researched the genome-wide cDNA microarray analysis of gene expression profiles involved in ovarian endometriosis and concluded that the candidate genes could serve as molecular targets for the diagnosis or treatment of endometriosis,[26] undoubtedly offering new possibilities for the search for diagnostic and therapeutic strategies. A study by WX Zheng indicated that the morphologic transitions from ovarian surface epithelium or OEI (ovarian epithelial inclusions) to IE lesions provide direct metaplastic evidence for the pathogenesis of ovarian endometriosis,[25] deepening our understanding of the pathogenesis of ovarian endometriosis. These studies described the pathogenesis of ovarian endometriosis at different levels and provided plans for diagnosis and treatment.

Building upon these historical findings, recent research literature has further elucidated several key mechanisms in the pathogenesis of ovarian endometriotic. The inflammatory microenvironment plays a pivotal role in the development and progression of ovarian endometriotic. A study from J Zhang etc. confirmed iron overload-induced GSDME-mediated pyroptosis as a key trigger for IL-16 activation and release, and active IL-16 has a driver function in endometriosis-associated inflammation. Based on this result, their research led to the development of Z30702029, a compound inhibiting GSDME-NTD-mediated pyroptosis, which shows promise as a therapeutic intervention for endometriosis.[29] Another Single-cell analysis from J Yan team demonstrate that ectopic endometrial epithelial cells mediate T cell activation through HLA class II complex and chemokine secretion, establishing an IFN-γ-dependent inflammatory feedback loop that perpetuates chronic inflammation and T cell exhaustion.[30] Excessive fibrosis in endometriosis, driven by recurrent tissue injury-repair cycles, manifests as a key pathological mechanism that induces scarring, pelvic pain symptoms, and reproductive dysfunction through impaired tubal function and diminished follicular reserve.[31,32] In the newly research from G Yang et al, Gal-3 could promotes fibrosis in ovarian endometriotic, which could be a prospective therapeutic target for mitigating fibrosis in endometriosis.[33] These mechanisms interact and form cause-effect relationships, collectively constituting a complex network in the pathogenesis of ovarian endometriosis.

Cancerization

Based on clinicopathological and epidemiological findings, the precursor of ovarian clear cell carcinoma (OCCC) and ovarian endometrioid carcinoma is endometriosis.[34–36] Among these 15 articles, 2 reported the relationship between cancer and ovarian endometriosis.[21,37] The team of K Miyakoshi shared a case of a pregnant woman with a history of endometriosis whose ovarian tumor was found during pregnancy. They reported that the massive decidualization of ovarian endometriosis could have been part of a widespread decidual transformation that occurs during pregnancy, simulating the features of a malignant ovarian tumor. They suggested that an ectopic endometrial stroma can be transformed during pregnancy, and although the mechanism of ectopic decidualization is not clear, it seems to be related to the presence of progesterone. Therefore, in patients with a history of ovarian endometriosis, structural changes inside the tumor during pregnancy may be the result of pregnancy itself rather than malignancy.[37] S Ogawa et al researched this association by describing the clinicopathological, immunohistochemical and molecular characteristics of extrauterine mesonephric-like carcinoma (ExUMLC) compared with other common upper gynecologic Mullerian carcinomas and concluded that ovarian carcinomas, especially OCCC and endometrioid adenocarcinomas, are highly associated with endometriosis. Atypical endometriosis shows proliferation activity intermediate to that of typical endometriosis and ovarian carcinoma, suggesting that it is a precancerous state.[21] These studies have deepened our understanding of the relationship between endometriosis and ovarian tumors, thereby contributing to a more accurate diagnosis and treatment. However, newly research conducted by Y He shows that co-existing endometriosis was not a prognostic factor for survival in patients with OCCC.[38] Thus, the intrinsic link between ovarian endometriosis and OCCC requires further research.

Infertility

According to the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO), infertility is defined as a condition where the reproductive system is incapable to secure

a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.[39] Ovarian endometriosis is closely associated with infertility, manifesting from its pathogenesis to treatment modalities. In 2014, S Kang et al reported that among patients with ovarian endometriosis, having the CC genotype of rs8049282 in the E-cadherin gene may increase the risk of primary infertility, which is more significant than that in control women or endometriosis patients who have successfully given birth. These findings suggest that genetic variants in the E-cadherin gene may be involved in endometriosis-related infertility.[40] In 2021, H Zhang et al studied the role of genetic variation in glutathione S-transferase M1 (GSTM1) in the development of ovarian endometriosis and endometriosis-related primary infertility risk. Compared with individuals with the positive genotype, those with the null genotype face a greater risk of developing ovarian endometriosis, and they also have a significantly increased risk of primary infertility. Additionally, while GSTM1 mRNA is expressed in the endometrial tissue of all patients, the expression level is nearly ten times greater in patients with the positive genotype.[41] These studies proposed a new approach to address this problem from a genetic perspective. In recent years, an increasing number of scholars have recognized and emphasized the need to protect fertility in patients with ovarian endometriosis.[42] However, medical and surgical treatments for endometriosis have different effects on a woman's chances of conception.[43] Therefore, it is very important to find a solution, and this hotspot also provides us with a more direct direction to further our study.

The limitations of the current analysis must be considered. A single database served as the source for the data. Bibliometric analysis, which is a quantitative evaluation of academic works, can be applied only to works that have been cited and indexed in other works; it cannot be applied to works that have not yet been published or that have appeared in unindexed journals, papers, books, or government reports. To gain a more in-depth and comprehensive understanding of this research subject, future studies could consider adopting an integrated analysis approach by utilizing multiple databases and employing multimethod strategies in subsequent investigations.

Conclusion

In our study, we fill the gap in bibliometric analysis of ovarian endometriosis. We also find that the primary research directions in ovarian endometriosis encompass pathogenesis and cancerization. Furthermore, infertility has emerged as a novel research hotspot. A comprehensive analysis of publications within this field can not only guide the direction of future research but also provide new insights into addressing significant women's health issues.

Ethics Committee Approval Statement

The study did not involve humans or animals, so ethical approval was not needed.

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Disclosure

The authors report no conflicts of interest in this work.

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