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ORIGINAL ARTICLE

The Relationship between Endometriosis and Infertility: A Bibliometric Analysis

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Abstract:

Background: Endometriosis is common in women of childbearing age that has pleiotropic direct and indirect effects on reproduction. This study adopted bibliometric method to analyze the current research on endometriosis and infertility.

Method: We conducted a literature search based on the Science Citation Index Expanded (SCI-E) database. All the search results were exported and cited in plain text format for analysis. CiteSpace and VOSviewer software were used to analyze the source files. The analysis encompasses: annual changes in the number of publications, the distribution of the countries and institutions of the authors of the literature, the distribution of the journals from which the literature was sourced, the distribution of authors, and the use of keywords.

Results: A total of 1377 documents were retrieved. Both the number of documents and the number of citations showed an annually increasing trend. In our research, the USA was in a leading position, with many important research institutions and researchers. Top-level journals in the field of reproduction and top-level comprehensive journals are the key areas of replication. The keywords changed over time: in recent years, popular keywords included "ovarian reserve", "follicular fluid", "in vitro fertilization" and "pathogenesis".

Conclusions: There are significant regional differences in research on endometriosis and infertility. We should strengthen international cooperation, especially with developing countries.

Keywords: Endometriosis; infertility; bibliometric analysis

Introduction

Endometriosis is a chronic, benign, inflammatory disease characterized by the presence of an endometrium-like epithelium and/or stroma outside the endometrium and myometrium, with a large impact not only on a patient's quality of life, but also on social contact and work[1]. Today, nearly 2% to 10% of women of reproductive age suffer from endometriosis[2]. Up to 50% of infertile women suffer from endometriosis[3]. Patients with endometriosis are prone to dysmenorrhea, chronic pelvic pain, dyspareunia, cyclical dyschezia, cyclical bladder pain and voiding difficulty, and infertility[4, 5]. Owing to the almost exclusive reliance on surgical findings, the diagnosis of endometriosis is usually delayed from 4--11 years[6]. The absence of macroscopic lesions or clinical features cannot exclude endometriosis, as infertility might be the only health problem[7, 8]. Early diagnosis is essential in infertile women, because when compounded by the effect of increasing age on the ovarian reserve, the burden of the disease could be even more deleterious.

Despite the wealth of evidence concerning the relationship between endometriosis and infertility, the impact of these conditions on the reproductive trajectory of affected women is not fully understood. The fertility of women can be adversely affected by endometriosis, as follows: dyspareunia leading to avoidance of sexual activity, pelvic adhesions and anatomical distortion, ovarian reserve, impaired ovulation and endometrial receptivity, which is harmful for implantation[9, 10]. Bibliometric analysis

provides an overview of current research on specific topics, which helps researchers better understand the current related problems[11]. To better understand the current research on endometriosis and infertility, this study applied the method of bibliometric analysis to major international medical citation databases, explored the problems existing in this field of research, and provided references for future research.

Method

Literature Retrieval

This study referred to the general internationally accepted bibliometric method, and retrieved literature from the Science Citation Index Expanded (SCI-E) database, which is the most common database used for bibliometrics analysis. The search time ranged from January 2004 to September 2024 and the studies were published in the English language. The retrieval method was subject term searching , with “endometriosis” and “infertility” as the search terms, and the operation method was “AND”. On the other hand, the exclusion criteria were duplicate publications, dissertations, letters, book chapters, conference proceedings, and articles unrelated to the topic or lacking information on fertility outcomes. Articles that could not be adequately assessed for inclusion on the basis of their title or abstract were also excluded.

Analysis Method

Two independent researchers reviewed each article to ensure its relevance to the field. We exported all the records of the search results and the cited records in plain text format to generate source files for analysis, after obtaining the search results were obtained. The information extracted from each article included title, authors, keywords, institutions, countries and regions, year of publication, journal and impact factor. We then analyzed the source files with CiteSpace software (Chaomei Chen, 2004--2021; http://cluster.cis.drexel.edu/~cchen/citespace/)[12] and VOSviewer software (https://www.vosviewer.com/ download) [13]. The content of the analysis included: annual changes in the number of publications, the distribution of the countries and institutions of the authors, the distribution of the journals from which the articles were published, the distribution of authors, and the use of keywords.

Statistical Analysis

Our study was a descriptive study in which quantity and percentage were used to describe each indicator. The Microsoft Office Excel 2019 was used to conduct the data analysis and generate the statistical figures.

Results

Publications Analysis

There were a total of 3503 records in the search results; after all the records were reviewed, 1377 records were included in our study (Figure 1). During these 21 years, research on endometriosis and infertility has remained highly active. The data revealed that the number of publications fluctuated, peaking in 2022.

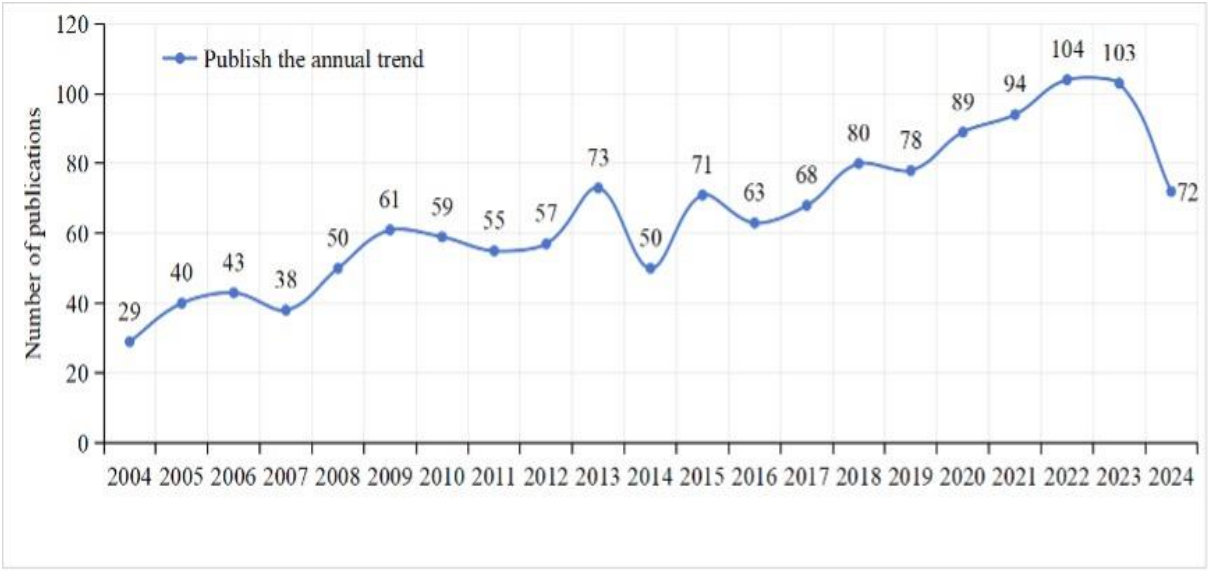

Figure 1.The changing trend of the annual publications.

Country and Institution Analysis

The analysis results revealed that 74 countries/regions participated in this field of research, and the top 5 countries were: China (258,18.74%), the USA (241,17.50%), Italy (155,11.26%), Brazil (114,8.28%) and France (112,8.13%) (Table 1). A country visualization map was generated via CiteSpace software (Figure 2). Nevertheless, Figure 2 indicates a lack of communication between these top 5 countries. There were 433 institutions included in our research, with the top 2 being from France: Assistance Publique Hopitaux Paris (APHP) and Institut National de la Sante et de la Recherche Medicale (Inserm), followed by Universidade de Sao Paulo from Brazil (Table 2). We used CiteSpace software to analyze the institutions and generate a visualization map (Figure 3).

Table 1.Top 10 productive countries/regions

Rank	Country	Article Counts	Proportion
1	China	258	18.74%
2	USA	241	17.50%
3	Italy	155	11.26%
4	Brazil	114	8.28%
5	France	112	8.13%
6	England	66	4.79%
7	Poland	58	4.21%
8	Germany	56	4.07%
9	Japan	55	3.99%
10	Spain	49	3.56%

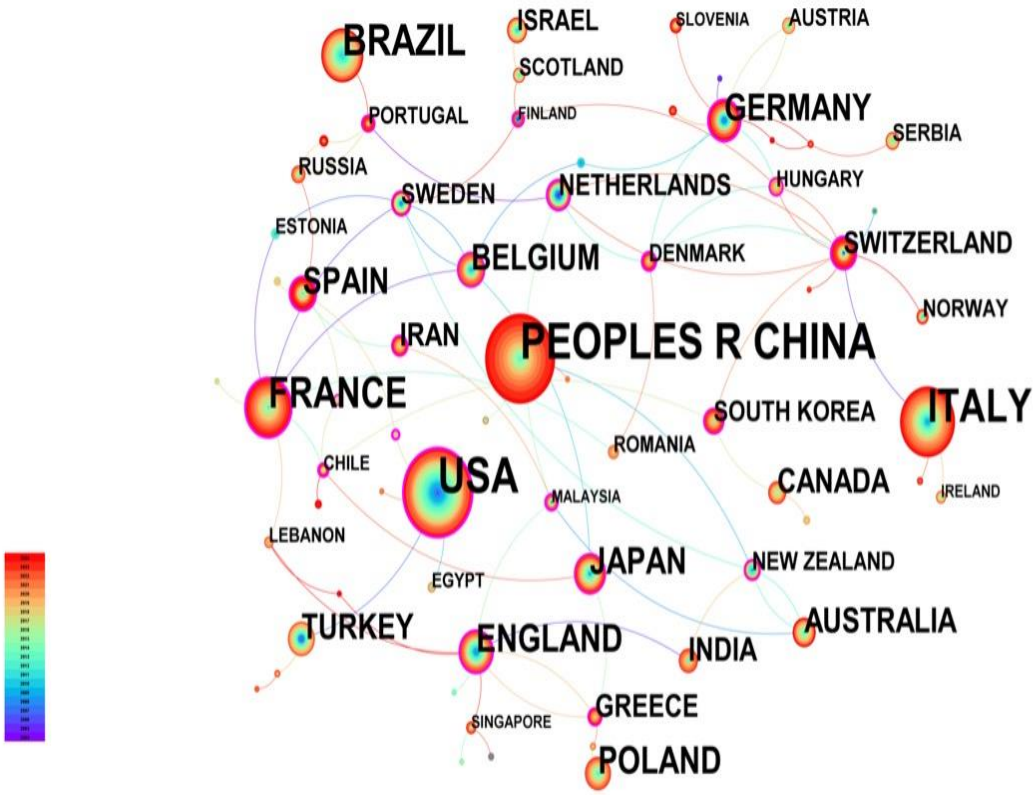

Figure 2.Country visualization map. There are 74 nodes in the figure, representing 75 countries. The larger the node is, the more documents produced by that country. A connection between 2 nodes means that 2 countries appear in a document at the same time and that 2 countries cooperate in this document.

Table 2. Top 10 productive institutions

Rank	Institutions	Article Counts	Country	Proportion
1	Assistance Publique Hopitaux Paris (APHP)	59	France	4.28%
2	Institut National de la Sante et de la Recherche Medicale (Inserm)	39	France	2.83%
3	Universidade de Sao Paulo	38	Brazil	2.76%
4	Universite Paris Cite	34	France	2.47%
5	IRCCS Ca Granda Ospedale Maggiore Policlinico	32	Italy	2.32%
6	University of Milan	30	Italy	2.18%
7	Hopital Universitaire Cochin	24	France	1.74%
8	Yale University	23	USA	1.67%
9	Cleveland Clinic Foundation	21	USA	1.53%
10	Hopital Universitaire Tenon	21	France	1.53%

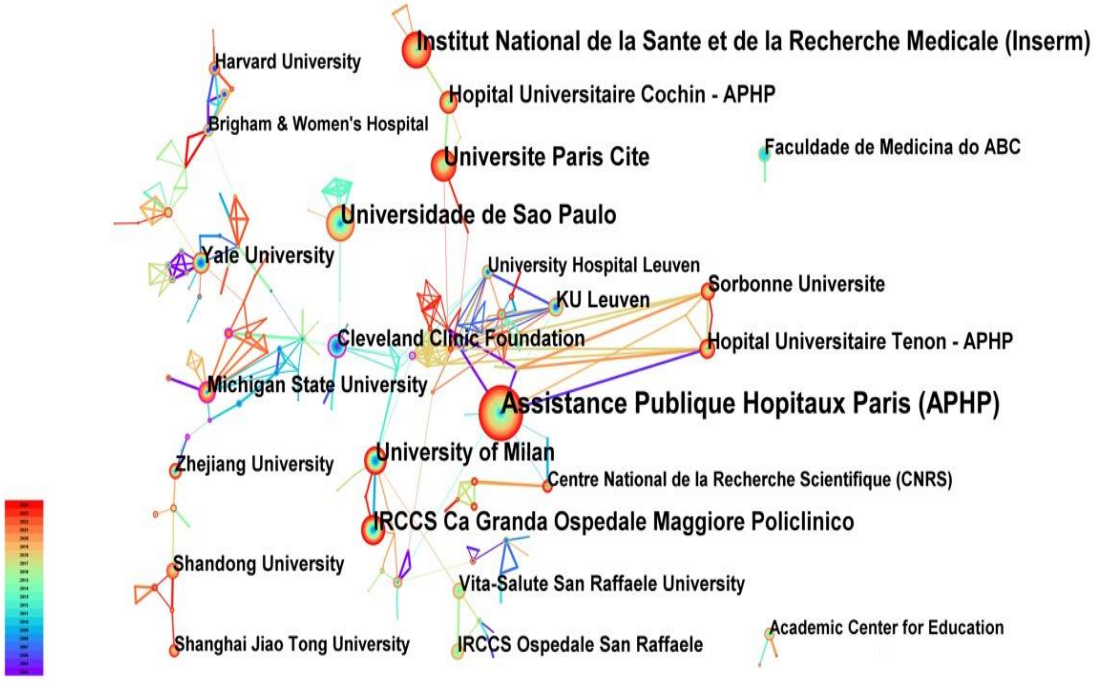

Figure 3. Institutions visualization map. There are 433 nodes in the figure, representing 433 institutions. The larger the node is, the more documents produced by that institution. A connection between 2 nodes means that 2 institutions appear in a document at the same time; that is, 2 institutions cooperate in this document.

Journal Analysis

There were 296 journals included in our research. FERTILITY AND STERILITY was the leading journal, with an impact factors (IFs) of 6.6 and 10827 citations, respectively. It was followed by HUMAN REPODUCTION (6589 citations) and HUMAN REPODUCTION UPDATE (1692 citations) (Table 3, Figure 4). Notably, most of these journals were based in the USA or England. The IF scores of the top 10 journals ranged from 2.1--14.8, with half of them from Quartile 1.These findings indicate that these journals provide an essential foundation for further research on endometriosis and infertility.

Table 3. Top 10 most productive journals

Rank	Journal title	Citations	Total link strength	IF(2023)	Quartile in category	Countries/ regions
1	FERTILITY AND	10827	50260	6.6	Q1	USA

	STERILITY		6			
2	HUMAN REPRODUCTION	6589	345497	6	Q1	England
3	HUMAN REPRODUCTION UPDATE	1692	98948	14.8	Q1	England
4	AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY	1494	88397	8.7	Q1	USA
5	JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM	1194	84299	5	Q1	USA
6	JOURNAL OF ASSISTED REPRODUCTION AND GENETICS	969	62330	3.2	Q2	USA
7	EUROPEAN JOURNAL OF OBSTETRICS & GYNECOLOGY AND REPRODUCTIVE BIOLOGY	1016	59071	2.1	Q2	Ireland
8	REPRODUCTIVE SCIENCES	685	57571	2.6	Q2	USA
9	BIOLOGY OF REPRODUCTION	688	48694	3.1	Q2	USA
10	MOLECULAR HUMAN REPRODUCTION	636	44023	3.6	Q2	USA

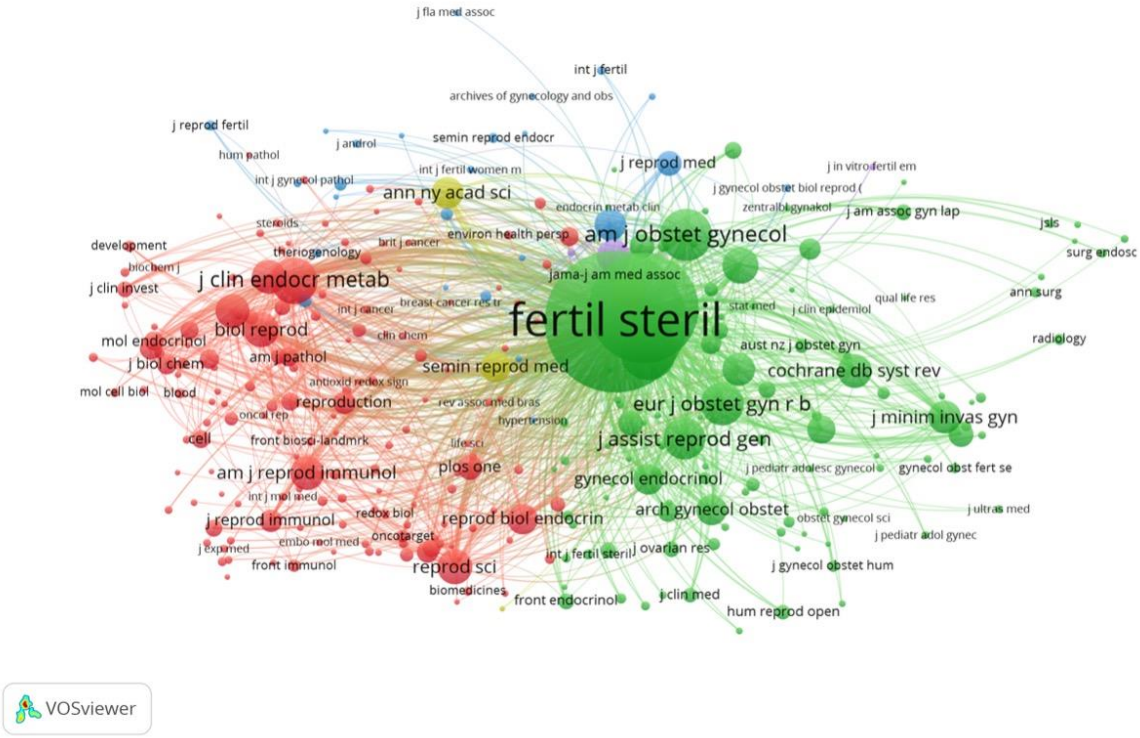

Figure 4. Visualization map of journals. There are 296 nodes in the figure, representing 296 journals. The larger the node is, the more documents produced by that journal. A connection between 2 nodes means that 2 journals are cited in a document at the same time; that is, 2 journals cooperate in this document. Different colored regions represent different research fields.

Author and co-cited author analysis

A total of 657 authors were included in our research, with Table 4 listing the top 10 authors who made significant contributions in this field. Somigliana Edgardo from the University of Milan in Italy, was the most prolific author, publishing 26 articles, followed by Vigano Paola and Vercellini Paolo also from the University of Milan in Italy. Somigliana Edgardo and Vercellini Paolo are also the top 2 co-cited authors at the same time. Figure 5 and Figure 6 reveal connections when 2 or more authors are cited simultaneously, providing a clear understanding of the leading authors and their contributions to this field. Six authors had received more than 1000 citations, whereas Vercellini Paolo was the most co-cited author (655 times). Although the Chinese authors published many documents in this area, they did not have high centrality scores, which means that they had less cooperation with other authors.

Table 4.

Rank	Authors	Article counts	Citations	Country	Institution
1	Somigliana Edgardo	26	1168	Italy	University of Milan
2	Vigano Paola	21	1640	Italy	University of Milan
3	Vercellini Paolo	18	1371	Italy	University of Milan
4	Chapron Charles	17	1274	France	Universite Paris Cite
5	Bianco Bianca	15	372	Brazil	Centro Universitário FMABC
6	Santulli Pietro	14	559	France	Universite Paris Cite
7	Lessey Bruce A	12	1656	USA	Wake Forest University
8	Marcellin Louis	11	390	France	Universite Paris Cite
9	Taylor Hugh S	9	1240	USA	Yale University
10	Benaglia Laura	9	336	Italy	University of Milan

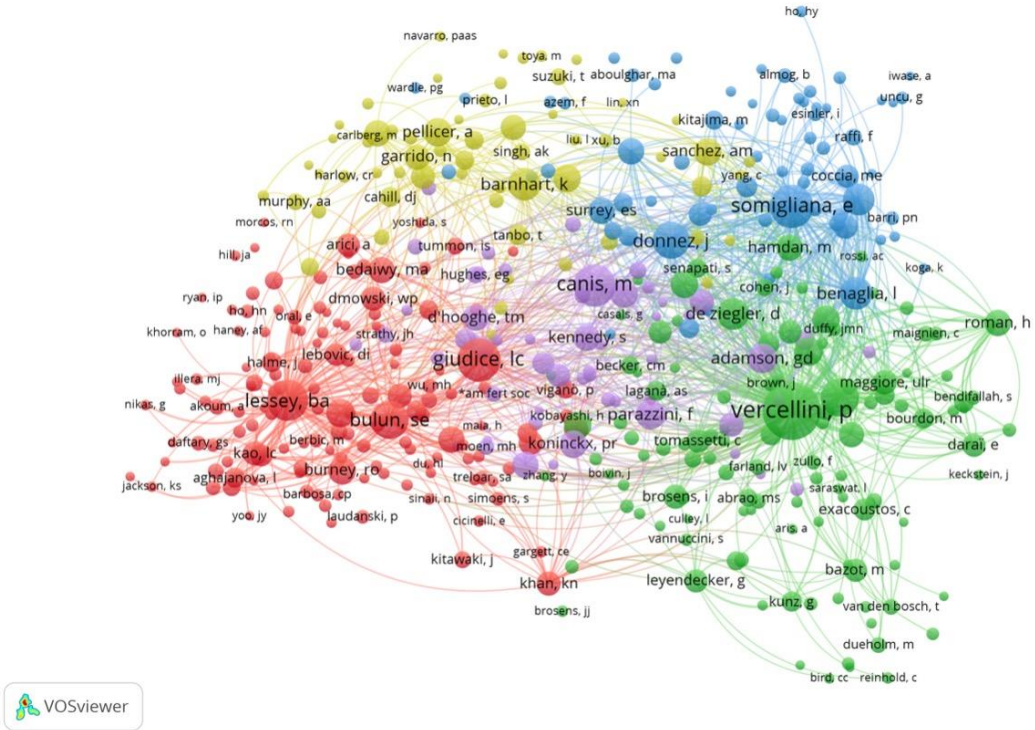

Figure 5. Visualization map of the author. The node size indicates each author's level of involvement, with each line representing a citation and the thickness denoting the citation frequency

Figure 6. Visualization map of co-cited authors. The node size indicates each author's level of involvement, with each line representing these authors cooperating in this field

Hotspot and frontier analysis

Co-word analysis and clustering analysis of keywords

Keywords reflect the themes of articles accurately, with co-word analysis employed to identify research hotspots by the frequency and correlation of keywords. A total of 525 keywords were included in our research totally. After excluding keywords lacking referential significance, the top 10 most frequent keywords were "women", "in vitro fertilization", "infertility", "expression", "peritoneal fluid", "impact", "diagnosis", "assisted reproductive technology", "management" and "follicular fluid" (Figure 7). For the clustering analysis of keywords, similar terms were sorted into the same cluster, and the cluster labels were generated via a minor square filtering algorithm, which extracted prominent noun phrases from the keywords. This process separated the hotspots into different groups and suggested that "ovarian reserve", "follicular fluid", "in vitro fertilization", "pathogenesis", "colorectal endometriosis", "deep infiltrating endometriosis", "anti-Mullerian hormone", "fertility preservation", "oxidative stress" and "embryo quality" were the key points(Figure 8).

According to the CiteSpace software, Figure 9 represents the phased hotspots and their development directions of this are. Our research was conducted with 525 nodes, with different sizes on the timeline representing some keywords with a high citation frequency. From 2004--2014, our research mainly on the therapy and management of endometriosis and infertility, such as assisted reproductive technology, previous surgery and associated ovarian reserve. From 2014--2024, more research was focused on different types of endometriosis and markers.

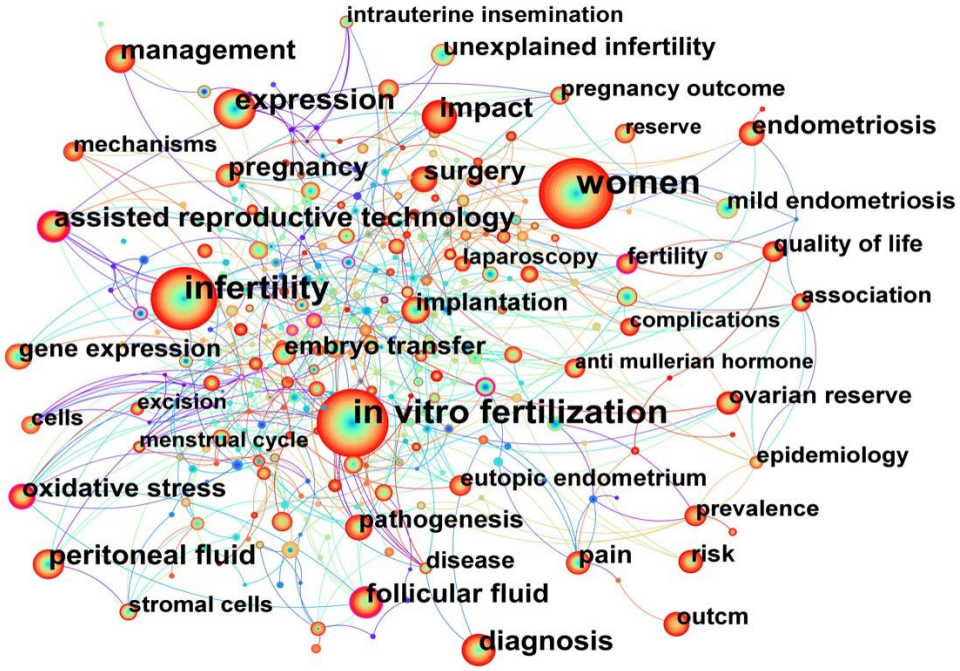

Figure 7. Visualization map of the co-word analysis of keywords

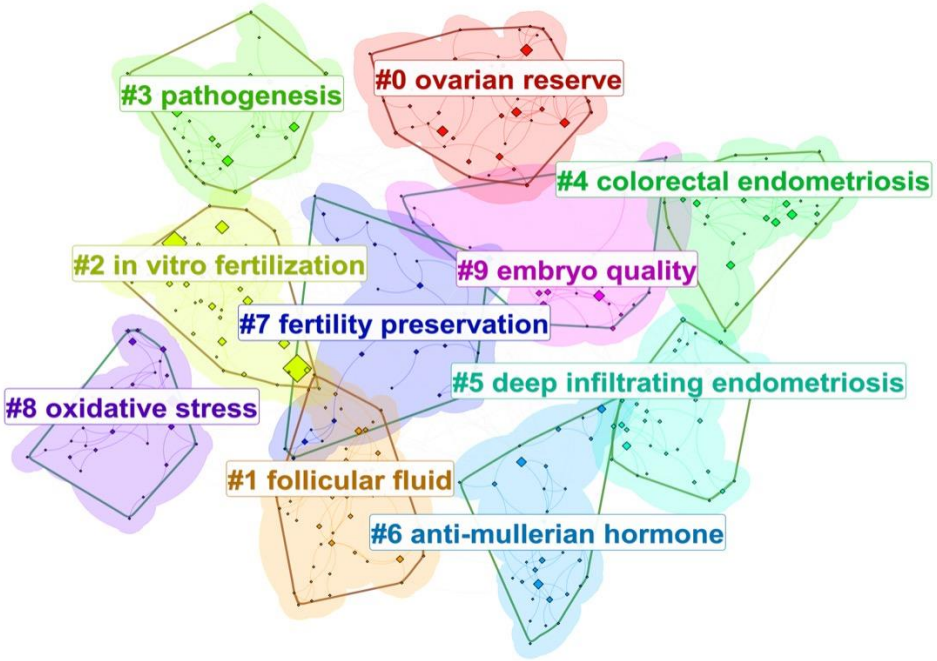

Figure 8. Visualization map of the clustering analysis of keywords

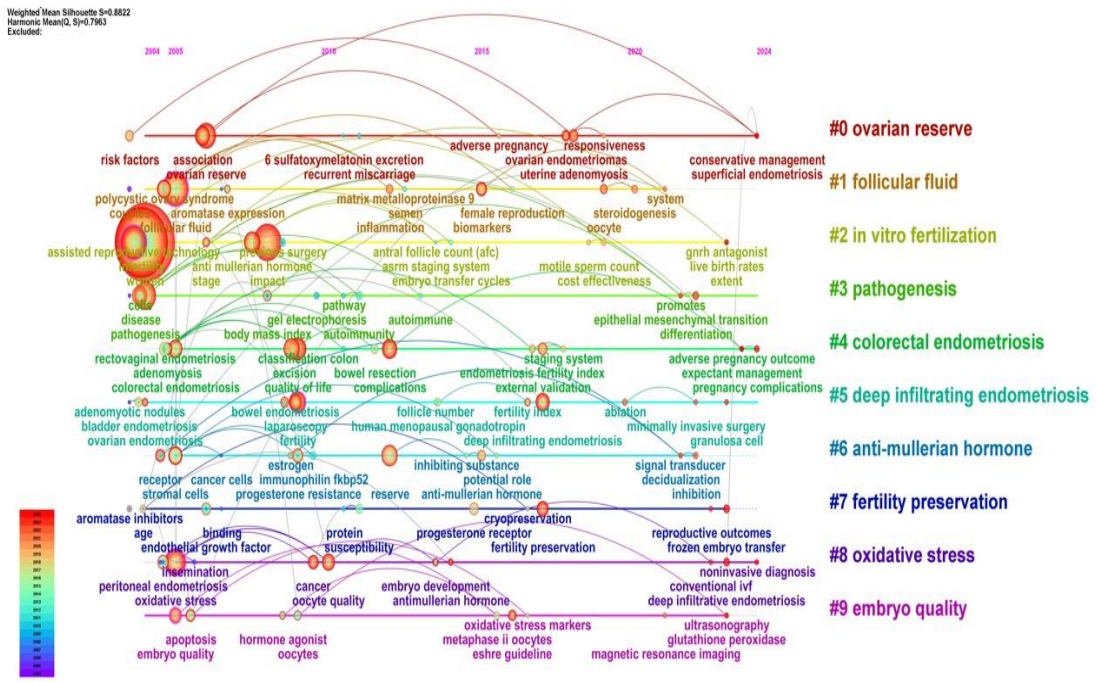

Figure 9. Visualization map of the timeline of keywords

Burstness of keywords

CiteSpace software was used to analyze the source files and generate a burstness keyword map (Figure 10). Twenty-five prominent keywords were identified in our research. The "peritoneal fluid" group presented the highest burst strength, followed by the "embryo transfer" and "unexplained infertility" groups. Over these 21 years, "unexplained infertility" has consistently remained a focus. Nevertheless, "peritoneal fluid" and "stromal cells" demonstrated shorter durations of prominence. Research on keywords such as "impact" (burst strength 7.35) and "fertility preservation" (burst strength 4.45) has been persistent topical in recent years.

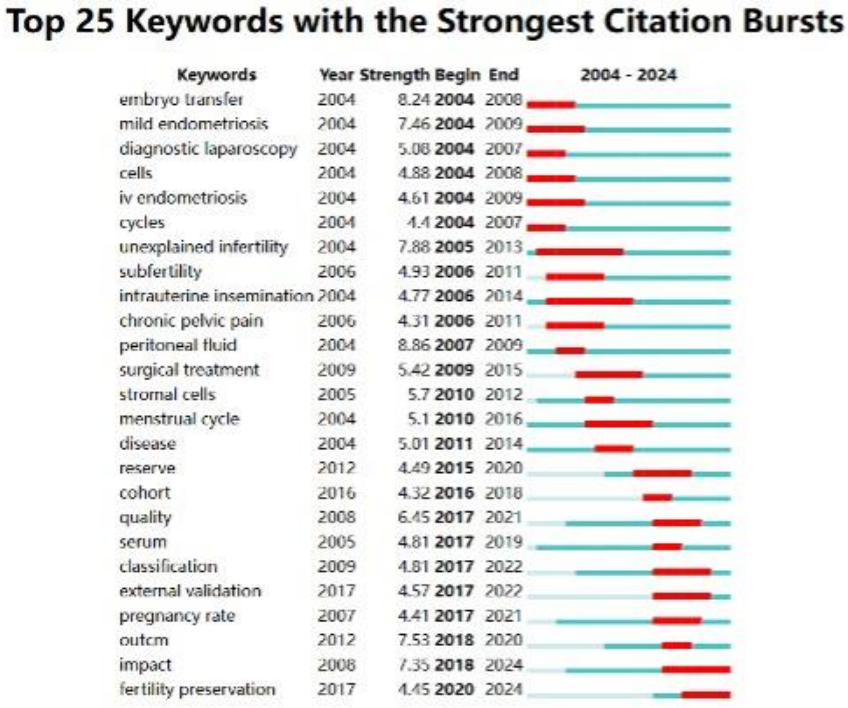

Figure 10. Visualization map of the top 25 keywords with the strongest citation bursts

Discussion

The relationship between endometriosis and infertility was first suggested in the Corpus Hippocraticum[14]. Although the relationship between endometriosis and infertility is known clinically, the exact mechanisms implicated in endometriosis-associated infertility are still uncertain and this situation is currently considered multifactorial[15]. There has been a substantial volume of research on endometriosis and infertility, with numerous findings being broadly disseminated. There is a marked interest in examining the current trends and landscape of this topic. Our study conducted an in-depth bibliometric analysis to delineate the current state and key areas of the relationship between endometriosis and infertility.

The results of our research revealed that in the field where the subject is involved in endometriosis and infertility, the number of publications and their citation frequency have shown an annually increasing trend. A rapid increase in the volume of publications was observed in China, accounting for an essential proportion in recent years. Researchers from China had published the most documents, however, researchers from the USA conducted the most collaborations. Further international cooperation could lead to more significant advancements in this field of research. Assistance Publique Hopitaux Paris (APHP) in France published the most documents among all the institutions. Among all the authors, Somiglianan Edgardo from the University of Milan in Italy had published the most documents and participated the most in cooperation. She focused on the assisted reproductive technology as a therapy for endometriosis-associated infertility[16]. She proposed that the threshold to be used to distinguish between endometriomas and ovarian response might be 4 cm in diameter[17]. Vercellini Paolo also had a significant impact in this field; he proposed that the number and amount of menstrual cycles together with genetic and environmental factors determine the degree of phenotypic expression of endometriosis[18]. Journal analysis revealed that journals focused on fertility and reproduction had a comprehensive influence in this field. Among all the documents, a review article from NEW ENGLAND JOURNAL OF MEDICINE about endometriosis and infertility had the most citations[19]. This suggests that more documents will be published in these journals. However, most journals did not have high IF scores, which means that there is a need for more high-quality research. Furthermore, we believe that there will be more international cooperation, especially multicenter clinical studies and epidemiological research involving developing countries in the future.

The complex influences of endometriosis subtype, inflammation, pain, pelvic anatomy, pelvic adhesions, ovarian preservation and compromised endometrial receptivity define endometriosis-associated infertility[20]. Our study highlights the main hotspots of this field, namely, embryo transfer, fertility preservation and peritoneal fluid, which can be further divided into three stages on the basis of timeline and burst analysis. Endometriosis is a multifactorial and systemic disease that has direct and indirect effects on fertility.

In the early stage (2004--2010), researchers focused on the pathogenesis of endometriosis-associated infertility. Most patients with endometriosis have pelvic adhesions[21]. Pelvic adhesions may disrupt the pelvic anatomy, interfere with oocyte release, or obstruct the fallopian tubes and impede oocyte uptake [22-24]. In the affected ovaries, focal inflammation might increase follicular recruitment and maintain the follicular niche[25]. During the luteal phase, a lower level of progesterone reflects luteal dysfunction in women with endometriosis, including dysfunction of small (follicular membrane) and large (granular) luteal cells, leading to reduced secretion of progesterone[26, 27]. Even in women with mild endometriosis, the implantation rate is clearly decreases during both natural cycles and ART, which might be due to a reduced endometrial receptivity or decidualization capacity[28, 29]. Compared with those of healthy women, the eutopic endometria of women with endometriosis present several functional and molecular abnormalities [30, 31]. In terms of treatment, operative laparoscopy for endometriosis represents a treatment option for endometriosis-related pain and visceral obstruction[32]. Assisted reproductive technology became an option for women with endometriosis-associated infertility during this period[33].

In the middle stage (2011-2016), research on the

mechanism of endometriosis-associated infertility is increasing, and new intervention methods are also being attempted for treatment. The epigenetic theory has a key role in the pathogenesis of endometriosis[34]. DNA methylation is active in the endometrium and influences the implantation process in the eutopic endometria of women with endometriosis[35]. Homebox protein-A10 (HOXA10) plays an essential role in endometrial receptivity, and reducing HOXA10 gene expression in the endometria of women with endometriosis might impair endometrial receptivity[36-38]. Accumulating evidence indicates that NK cells are involved in the etiology of endometriosis-associated infertility[39, 40]. Endometriosis is related to the ability of NK cell cytotoxicity to eliminate endometrial cells, which can contribute to the development and progression of endometriosis-associated infertility[41-43]. Estrogen signaling involves multiple signal transduction pathways, and the MAPK (mitogen activated protein kinase) pathway plays important roles in stimulating the proliferation of endometriotic stromal cells, the production of inflammatory factors and the neovascularization, which are related to the pathogenesis of endometriosis[44, 45]. Taken together, these findings suggest that endometriosis-associated infertility might be caused by affecting follicular development and reducing ovarian function. The focus of clinical treatment research has gradually shifted to nonhormone therapies, such as vascular endothelial growth factor inhibitors[46, 47], immune modulators[48, 49], and stem cells[50, 51].

In the later stage (2017-2024), researchers summarized the preliminary research and paid more attention to not only to diagnosis and treatment, but also to patients' psychological state and quality of life[52]. Many studies have aimed to investigate the mental health of women with endometriosis-associated infertility, revealing a relevant connection with anxiety and depressive disorders[53, 54]. A large amount of scientific data indicate that women with endometriosis have a significantly greater risk of mental disorders than healthy women do[55, 56]. Many studies have shown that the incapacity to procreate is extremely distressing for the couple [57-59], which might result in a loss of self-esteem, low mood, anxiety, depression, impaired of sexual function and guilt [60, 61]. In addition, psychological factors can affect the success rate of fertility treatments and create a vicious cycle[62]. Given the significant psychological effect of endometriosis-associated infertility, multidisciplinary management is important to improve patients' quality of life and mental health[63-65]. In terms of treatment, several studies have explored how group behavioral therapy, cognitive behavioral therapy and mindfulness can reduce depression in women with endometriosis[66, 67]. Early psychological support should be provided to couples with endometriosis-associated infertility including counseling by psychologists and sexologists, to reduce the potential negative impact of the disease.

Our research revealed that the annual changes in keywords represent changes in the key points of research in this field. Among all the keywords, ovarian reserve and IVF have received more attention. More rigorously designed, double-blind clinical trials have also been the focus of interest in recent years. Current clinical studies have focused mainly on comparing the efficacy of first-line drugs and evaluating the effects and safety of multidrug combination therapy, psychological therapy and assisted reproductive technology in patients with endometriosis-associated infertility. We also noted that some second-line drugs, such as resveratrol and statins, can improve patients' hormone levels, and metabolic indicators have gradually attracted interest in this era. At present, many studies and guidelines suggest that early diagnosis and management of patients with endometriosis-associated infertility are needed[68-70]. Clinical physicians should conduct infertility-related examinations and fertility assessments for patients, and focus on their quality of life, and provide personalized diagnosis and treatment. Further chronic disease management for endometriosis-associated infertility is urgently needed in the future.

Limitations

This study presents the most up-to-date research characteristics of the relationship between endometriosis and infertility, introducing new opinions. However, this study has several limitations. First, to ensure the comprehension and

accessibility among academics from different countries, only English-language publications were included in our study, which might have neglected relevant research in other languages. Second, owing to the diversity of keywords, it was difficult to retrieve all the publications in this field accurately. Third, relying on a single database might limit the breadth of our results. Fourth, in the process of data analysis, keywords with the same meaning are merged, but there is a lack of reference standards and subjectivity, which might affect the accuracy of the results. To address these problems, we aimed to conduct a more comprehensive search encompassing a wider range of studies on the relationship between endometriosis and infertility, and adopted methods of systematic review or meta-analysis in this field.

Conclusions

This study elaborates on the research characteristics and trends of endometriosis and infertility through bibliometric analysis. The main research areas are ovarian reserve, follicular fluid, in vitro fertilization and pathogenesis. These findings are valuable for research directions and assist in identifying potential challenges.

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Declarations

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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