



The relationship between polycystic ovary syndrome and infertility: a bibliometric analysis

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Background: Polycystic ovary syndrome (PCOS) is common and often causes infertility in women of childbearing age. This study adopted the method of bibliometrics to analyze the current research status of research on PCOS and infertility.

Method: We conducted a literature search based on the Science Citation Index Expanded (SCI-E) database. All records of search results were exported and the records were cited r in plain text format to generate source files for analysis. CiteSpace software was then used to analyze the source files. The content of the analysis included: 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: There were a total of 2,716 documents retrieved, and the frequency of citations was 86,817. Both the number of documents and the number of citations showed an annually increasing trend. In this field of research, the United States was in a leading position, with many important research institutions and researchers. Emphasis was placed on top-level journals in the field of reproduction and top-level comprehensive journals. The use of keywords changed over time: in recent years, popular keywords included meta-analysis, follicular fluid, oxidative stress, and diagnostic criteria.

Conclusions: There are obvious regional differences in PCOS and infertility research. International cooperation, especially cooperation with developing countries, should be strengthened.

Keywords: Polycystic ovary; infertility; bibliometric analysis

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Introduction

Polycystic ovary syndrome (PCOS) is a common hormonal disorder with the main features of hyperandrogenism, anovulation, and polycystic ovaries (1,2). The specific clinical manifestations vary greatly between individuals

(3,4). Patients with PCOS are prone to menstrual disorders, infertility, insulin resistance (IR), and metabolic disorders, and a propensity experience to varying degrees of psychological problems and decreased quality of life (5-8). Infertile patients with polycystic ovary syndrome are often characterized with ovulation disorders (9). Women

with PCOS are at risk of maternal, fetal, and neonatal complications (10). At present, the cause of PCOS is not very clear (11,12). The prevalence of PCOS varies slightly among countries in the world (2). The results of epidemiological surveys in the United States and other countries have shown that according to the 1990 National Institutes of Health (NIH) standard, the prevalence of PCOS in women of childbearing age is 4.0–8%, and according to the 2003 Rotterdam standard, the true prevalence of PCOS might be even higher (13,14). The prevalence of PCOS among women of childbearing age in mainland China has been approximated at 5.61%, although there may be some differences in the results of local epidemiological surveys in various provinces and cities (15,16). There have been relatively few studies on the global prevalence of PCOS in adolescent women (17). According to the 1990 NIH standard, the prevalence of PCOS in adolescence outside of China was 1.14–3.00%; according to the Rotterdam standard, it was 8.3–9.13%. According to the Rotterdam standard, PCOS can be divided into 4 types: type A, oligo – and/or anovulation + hyperandrogenism + polycystic ovary; type B, oligo – and/or anovulation + polycystic ovary; type C, hyperandrogenism + polycystic ovary; type D, oligo – and/or anovulation + hyperandrogenism (18,19). Women's fertility can be adversely affected by PCOS, as follows: infrequent ovulation or anovulation, increasing the risk of spontaneous abortion, reducing the quality of oocytes, insulin resistance leading to hyperinsulinemia and increasing the risk of miscarriage, and prolonged intimal hyperplasia, which is harmful for implantation (20). In their study, Zhao *et al.* found that among 1,208 infertile female patients, the incidence of PCOS was 7.9% (21). Bibliometrics analysis provides an overview on research status of specific topic and help investigators to better understand the current related problems. In order to further understand the current status of research on polycystic ovaries and infertility, this study applied the method of bibliometric (22) analysis to major international medical citation databases, discussed the problems existing in the research in this field, and provided references for future research.

Methods

Literature retrieval

This study referred to the general internationally accepted method of bibliometrics, and retrieved literature based on

the Science Citation Index Expanded (SCI-E) database, since it was the most common database for bibliometrics analysis. The search time was from database inception to 21 September 2021. The retrieval method was subject term searching, with “polycystic ovary syndrome” and “infertility” as the search terms, and the operation method was “AND”.

Analysis method

After obtaining the search results, we exported all the records of the search results and the cited records in plain text format to generate source files for analysis, and then analyzed the source files with CiteSpace software (Chaomei Chen, 2004–2021; <http://cluster.cis.drexel.edu/~cchen/citespace/>). The content of the analysis included: annual changes in the number of publications, distribution of the countries and institutions of the authors of the literature, the distribution of the journals from which the articles were published, the distribution of authors, and the use of keywords.

Statistical analysis

This study was a descriptive study, using quantity and percentage to describe each indicator. Excel 2019 (Microsoft, USA) software was used to conduct data analysis and generate statistical figures.

Results

Search results

There were a total of 2,843 records in the search results, 127 of which were subsequently identified as duplicate records. After removal of the duplicates, the actual related research documents totaled 2,716 (*Figure 1*). Among them, 2,021 were original articles, 568 were reviews, 87 were proceeding papers, 68 were editorial materials, 27 were publications priority, 26 were conference abstracts, 22 were letters, 12 were book chapters, 6 were corrections, 2 were notes, 2 were reprints, 1 was a news item, and 1 was a retraction (note: some documents were classified twice, so the sum of these classified data was consistent with *Figure 1*). The number of these documents roughly showed an increasing annual trend (*Figure 2*, *Table S1*). The citation frequency of these documents totaled 86,817, with an average citation number of 31.97 per article, and an h-index of 126 (*Figure 3*).

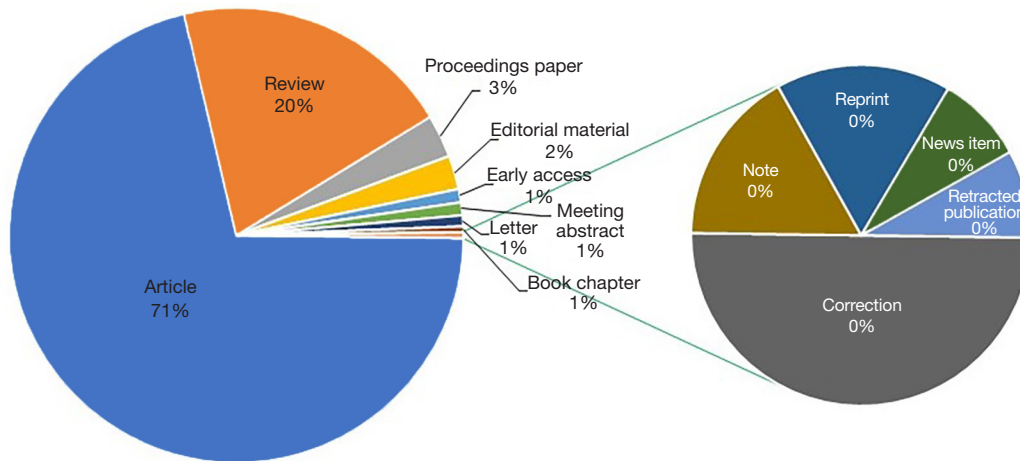


Figure 1 Types of documents. The literature related to this research topic was mainly articles and reviews, which together accounted for more than 90% of the total. Percentage of 2,716.

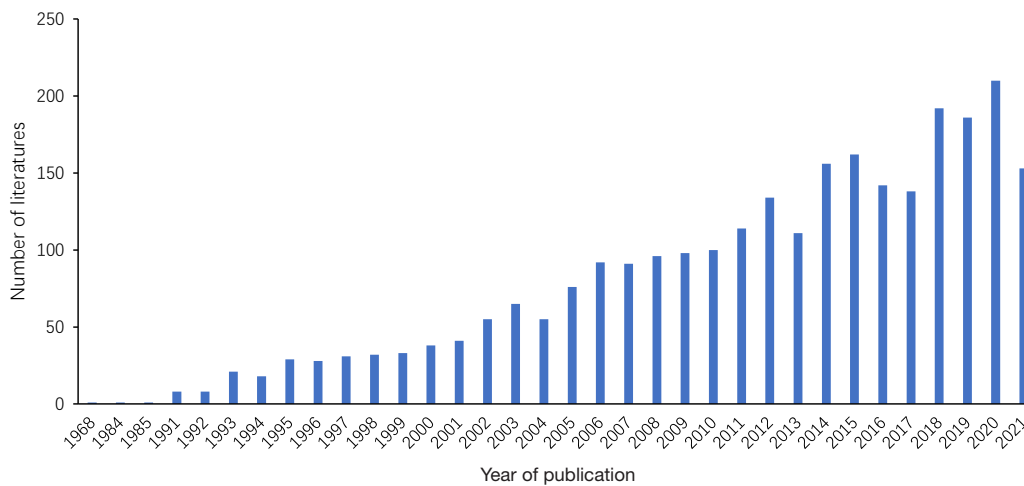


Figure 2 Annual publications.

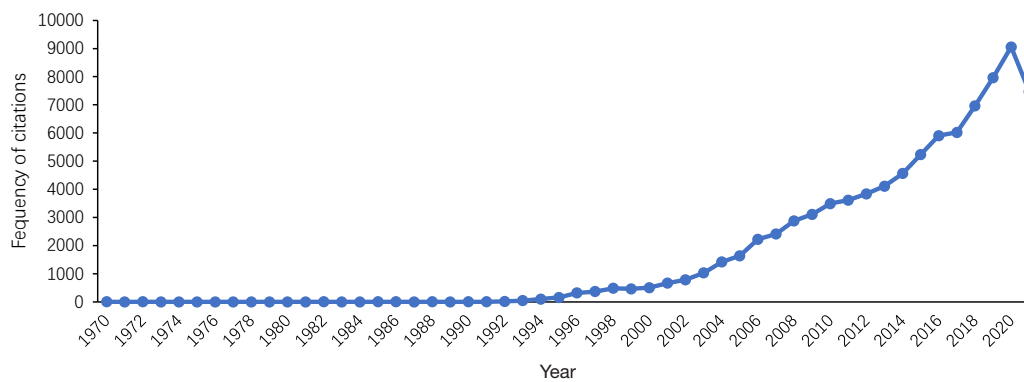


Figure 3 Annual citations.

Analysis of author country of origin

The analysis showed that the authors of these articles came from 105 countries, and the top 5 countries of origin of the authors were: the United States, China, the United Kingdom, Italy, and Australia (Figure 4). CiteSpace V software was used to analyze the source files and generate a country visualization map (Figure 5). There were 2 countries which appeared in a document 682 times concurrently, that

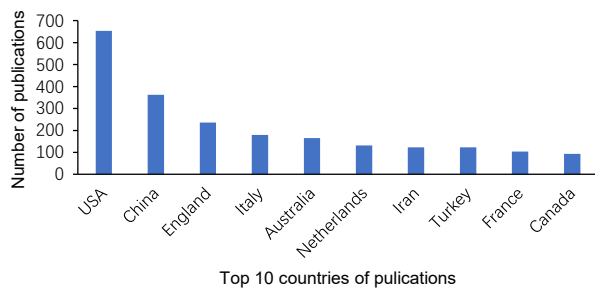


Figure 4 Top 10 countries in the number of publications.

is, both countries cooperated 682 times (Figure 5). The top 5 centrally ranked countries were the United States, the United Kingdom, France, Australia, and Canada (Table 1, Figure 5).

Institutional analysis of literature sources

We used CiteSpace V software to analyze the source files and generate a visualization map of the institutions (Figure 6). The analysis results showed that there were 502 institutions involved in these documents, and any 2 institutions had appeared in a document 1,068 times at the same time, that is, the cooperative relationship between the institutions has reached 1,068 times (Figure 6). The University of Adelaide from Australia had published the most literature on this topic. Ranked by centrality, the institution with the most cooperation was also the University of Adelaide. It can be seen from Tables 2,3 that the institutions with most publications and cooperation were mainly from the United States, Australia, and China.

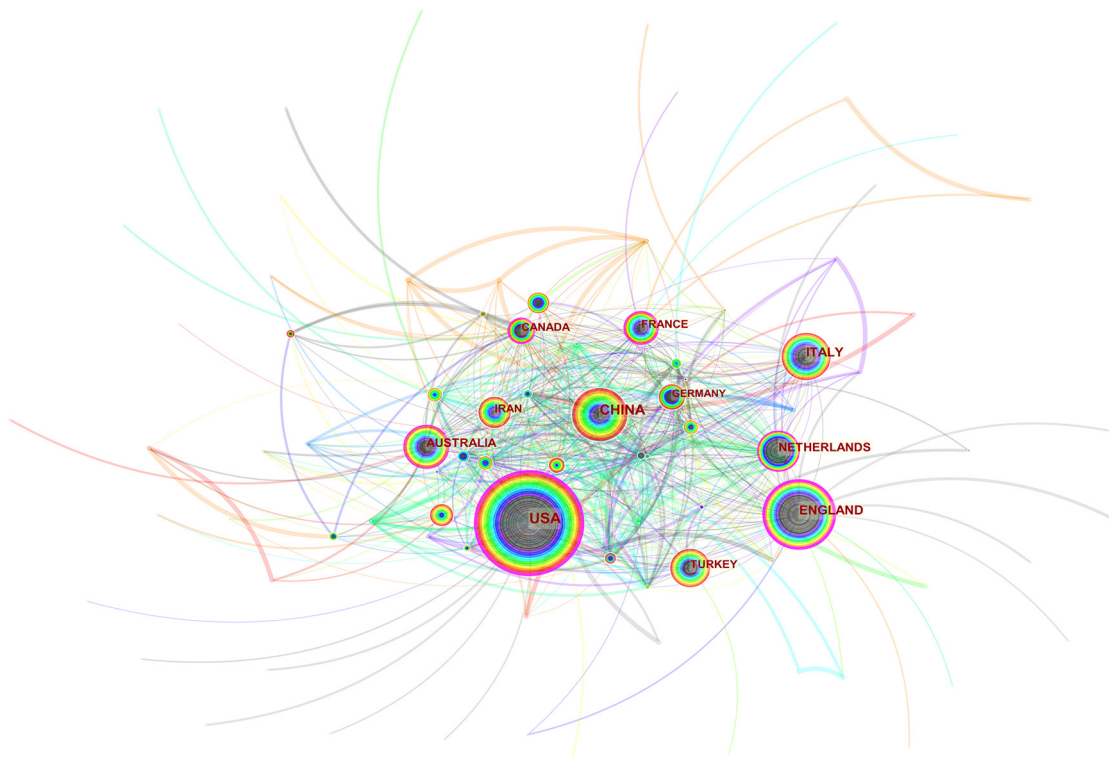


Figure 5 A visualization map of countries. There are 105 nodes (circles) in the figure, representing 105 countries. The larger the circle, the more documents produced by that country. A connection between 2 nodes means that 2 countries appear in a document at the same time, that is, 2 countries have a cooperative relationship in this document.

Author analysis

We used CiteSpace V software to analyze the source files and generate the author visualization map (Figure 7). The results showed that some authors have published a large

number of papers in this field (Table 4). Many authors have collaborated with researchers from other institutions many times while cooperating with researchers in their own institutions (Figure 7). From Table 4, Figure 7 and Table 5, we can see that Legro not only published the most

Table 1 Top 10 countries with centrality scores

Rank	Countries	Centrality
1	USA	0.36
2	England	0.30
3	France	0.18
4	Australia	0.15
5	Canada	0.12
6	Netherlands	0.11
7	Sweden	0.10
8	Italy	0.08
9	China	0.07
10	Germany	0.07

Table 2 Ranking of institutions by number of contributions (Top 10)

Rank	Institutions	Publications
1	University of Adelaide	62
2	Monash University	52
3	University of Pennsylvania	47
4	Yale University	42
5	Pennsylvania State University	42
6	University of Michigan	32
7	Pennsylvania State College of Medicine	30
8	Shanghai Jiao Tong Univ	30
9	Heilongjiang University of Chinese Medicine	24
10	Virginia Commonwealth University	24

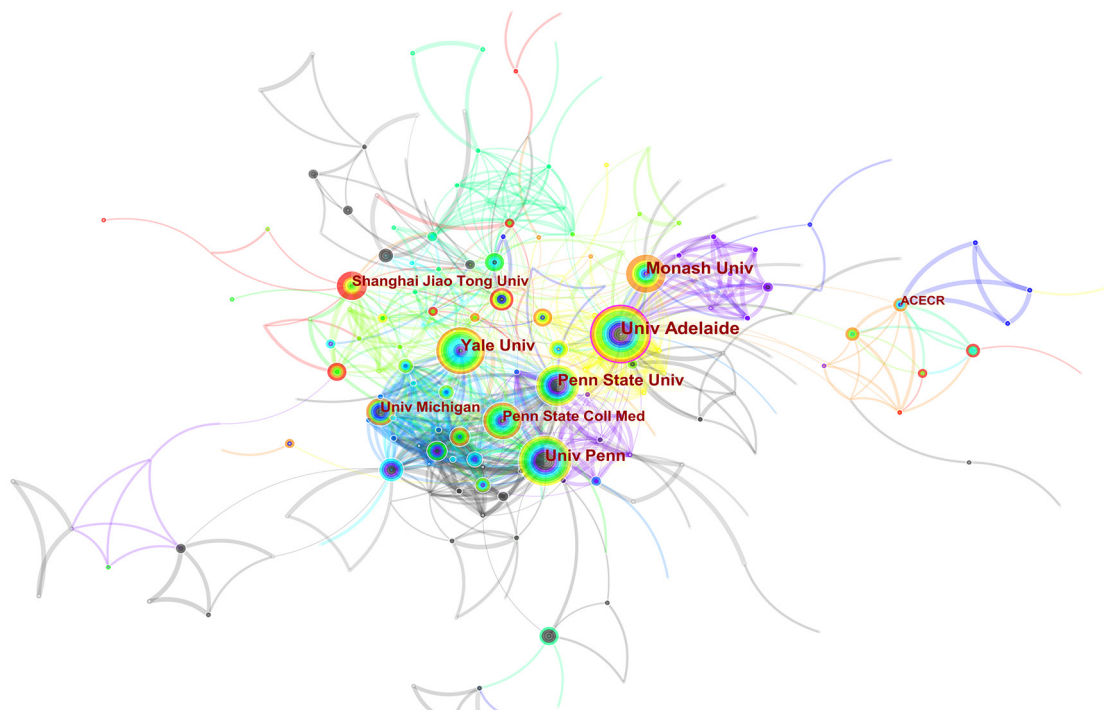


Figure 6 Visualization map of the institution. There are 502 nodes (circles) in the figure, representing 502 institutions. The larger the circle, the more documents produced by that institution. A connection between 2 nodes means that 2 institutions appear in a document at the same time, that is, 2 institutions have a cooperative relationship in this document. There were 1,068 collaboration between these institutions.

documents, but also collaborated with other researchers the most frequently. Although the Chinese author Zhang has published a large number of documents, he did not have high centrality score, suggesting that Zhang had cooperated less with other authors.

Journal distribution

The papers included in this study were from 618 journals. The 2 journals with the most publications were *Fertility and Sterility* (284 papers) and *Human Reproduction* (209 papers),

Table 3 Centrality ranking of institutions (top 8)

Rank	Institutions	Centrality
1	University of Adelaide	0.11
2	Pennsylvania State University	0.05
3	University of Pennsylvania	0.04
4	Virginia Commonwealth University	0.04
5	Yale University	0.03
6	Pennsylvania State College of Medicine	0.03
7	Monash University	0.02
8	Heilongjiang University of Chinese Medicine	0.02

Table 4 Number of articles published by authors (top 10)

Rank	Authors	Literatures
1	Legro RS	69
2	Zhang HP	35
3	Diamond MP	28
4	Fauser B	26
5	Coutifaris C	22
6	Santoro N	21
7	Franks S	20
8	Eisenberg E	16
9	Norman RJ	14
10	Homburg R	14

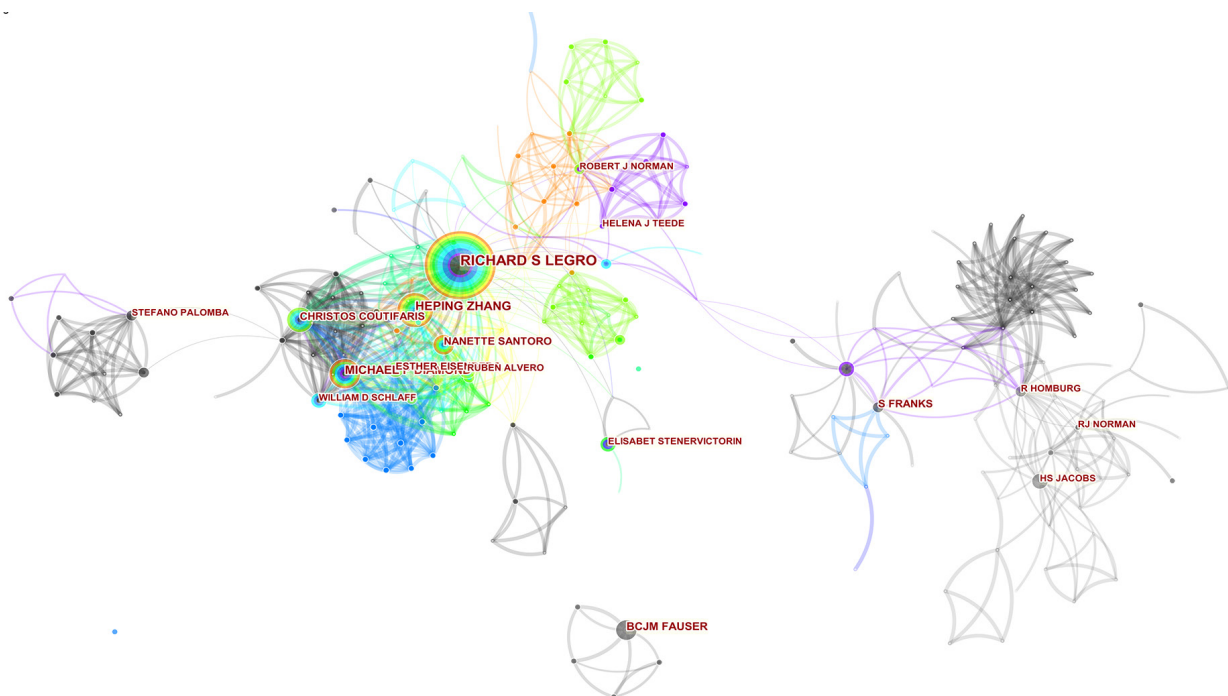


Figure 7 Visualization map of the authors. It can be seen that the collaboration between the authors was distributed in clusters, suggesting that these authors were mainly from the same research institution.

Table 5 Author centrality ranking

Rank	Authors	Centrality
1	Legro RS	0.09
2	Wijeyeratne CN	0.08
3	Franks S	0.04
4	Norman RJ	0.04
5	Fauser BCJM	0.03
6	Balen A	0.03
7	Homburg R	0.02
8	Palomba S	0.02
9	Nestler JE	0.02

Table 6 Top 10 journals in terms of number of publications

Journals	Records	% of 2,716
<i>Fertility and Sterility</i>	284	10.46
<i>Human Reproduction</i>	209	7.70
<i>Gynecological Endocrinology</i>	114	4.20
<i>Journal of Clinical Endocrinology Metabolism</i>	90	3.31
<i>Reproductive Biomedicine Online</i>	62	2.28
<i>Human Reproduction Update</i>	51	1.88
<i>European Journal of Obstetrics Gynecology and Reproductive Biology</i>	42	1.55
<i>Journal Of Assisted Reproduction and Genetics</i>	42	1.55
<i>Archives Of Gynecology and Obstetrics</i>	38	1.40
<i>Journal Of Reproductive Medicine</i>	34	1.25

both of which are top journals in reproductive medicine. The top 10 journals according to the number of publications are shown in *Table 6*. However, the top comprehensive journals, *Journal of the American Medical Association (JAMA)* and *Journal of Endocrinology*, had the highest centrality scores, suggesting that more important related literature has been published in these journals (*Table 7*).

Keyword analysis

We used CiteSpace V software to analyze the source files and generate a keyword co-occurrence map (*Figure 8*). The results showed that a total of 511 keywords were used

Table 7 Top 10 journals by centrality

Rank	Journals	Centrality
1	<i>J Am Med Assoc</i>	0.07
2	<i>J Endocrinol</i>	0.06
3	<i>Horm Res</i>	0.06
4	<i>Nature</i>	0.05
5	<i>J Reprod Med</i>	0.05
6	<i>Int J Obesity</i>	0.05
7	<i>Am J Epidemiol</i>	0.05
8	<i>Am J Clin Nutr</i>	0.05
9	<i>Horm Metab Res</i>	0.05
10	<i>Ann Intern Med</i>	0.05

in the documents retrieved in this study. The number of occurrences of any 2 keywords in the same article at the same time was 2,117 times (*Tables 8,9*). In addition to keywords closely related to the subject of this research, keywords such as insulin resistance and metformin were also used more often. Burst detection was performed on keywords that were frequently used. The results revealed that the use of popular keywords has undergone obvious annual changes (*Figure 9*). In recent years, the more popular keywords included meta-analysis, follicular fluid, oxidative stress, and diagnostic criteria.

Discussion

The results of this study showed that in the field where the subject involves both PCOS and infertility, the number of published documents and their citation frequency have shown an annually increasing trend. Researchers in the United States have published the most documents and conducted the most collaborations. However, among institutions, the University of Adelaide in Australia has published the most documents and cooperated most often. Among the authors, Legro from the University of Pennsylvania in the United States has published the most documents and participated most in cooperative efforts. In terms of journals, focused on top journals, comprehensive journals, and endocrinology journals in the field of reproduction. Keyword analysis showed that the focus of research in this field has changed in recent years, and insulin resistance and metformin have also been the focus of research.

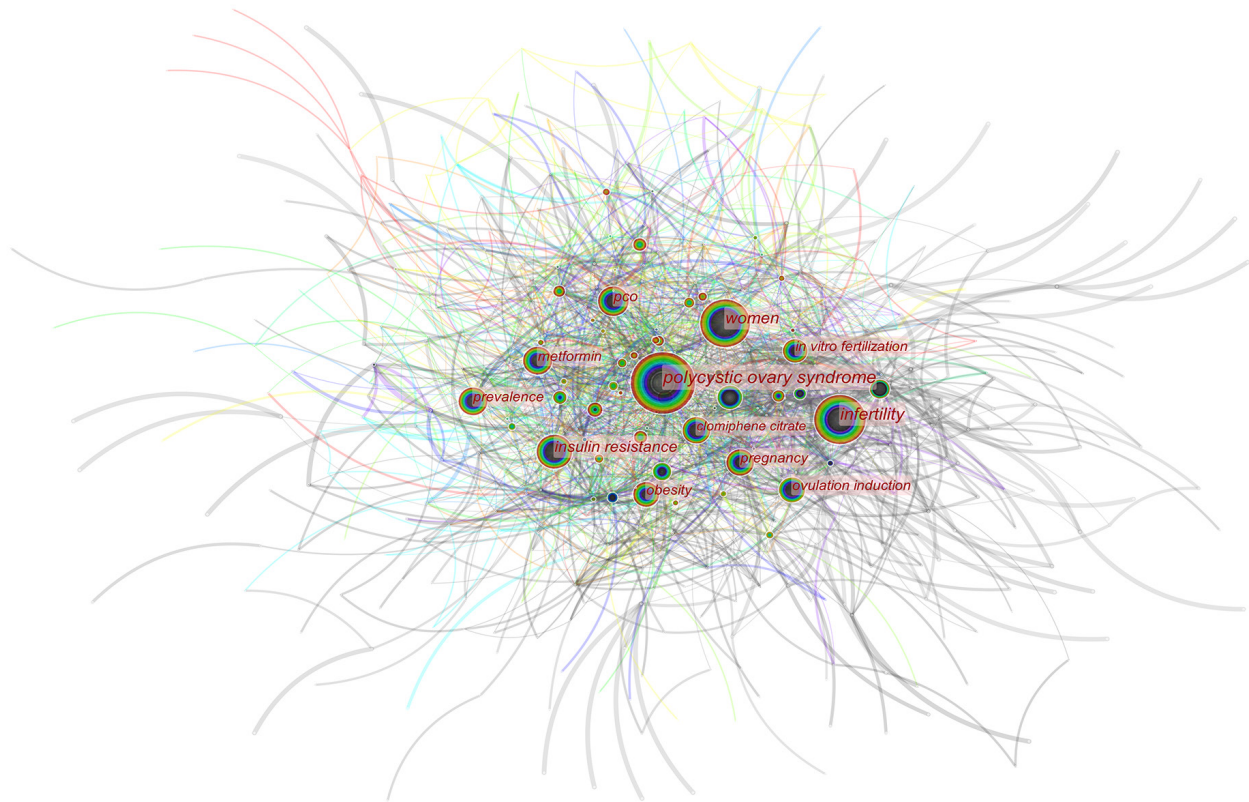


Figure 8 Keyword co-occurrence visualization map.

Table 8 Ranking of keyword usage frequency

Rank	Keywords	Frequency
1	Polycystic ovary syndrome	1503
2	Infertility	932
3	Women	890
4	Insulin resistance	563
5	PCO	472
6	Prevalence	316
7	Obesity	312
8	Metformin	296
9	Ovulation induction	288
10	In vitro fertilization	286

Table 9 Keyword centrality ranking

Rank	Keywords	Centrality
1	Follicle stimulating hormone	0.11
2	Gonadotropin	0.10
3	Hirsutism	0.09
4	Insulin resistance	0.08
5	Ovulation induction	0.08
6	Double blind	0.08
7	In vitro fertilization	0.07
8	Ovulation	0.07
9	Granulosa cell	0.07
10	Obese women	0.07

The main clinical problem of PCOS is the imbalance of hormone levels, which leads to irregular menstrual cycle and anovulation, which affects fertility. It is the most common cause of anovulation in infertility. Progression

of PCOS can be complicated by diabetes, obesity, and increased cholesterol, which will eventually lead to multi-system and multi-organ involvement. Some countries have issued relevant diagnosis and treatment guidelines regarding

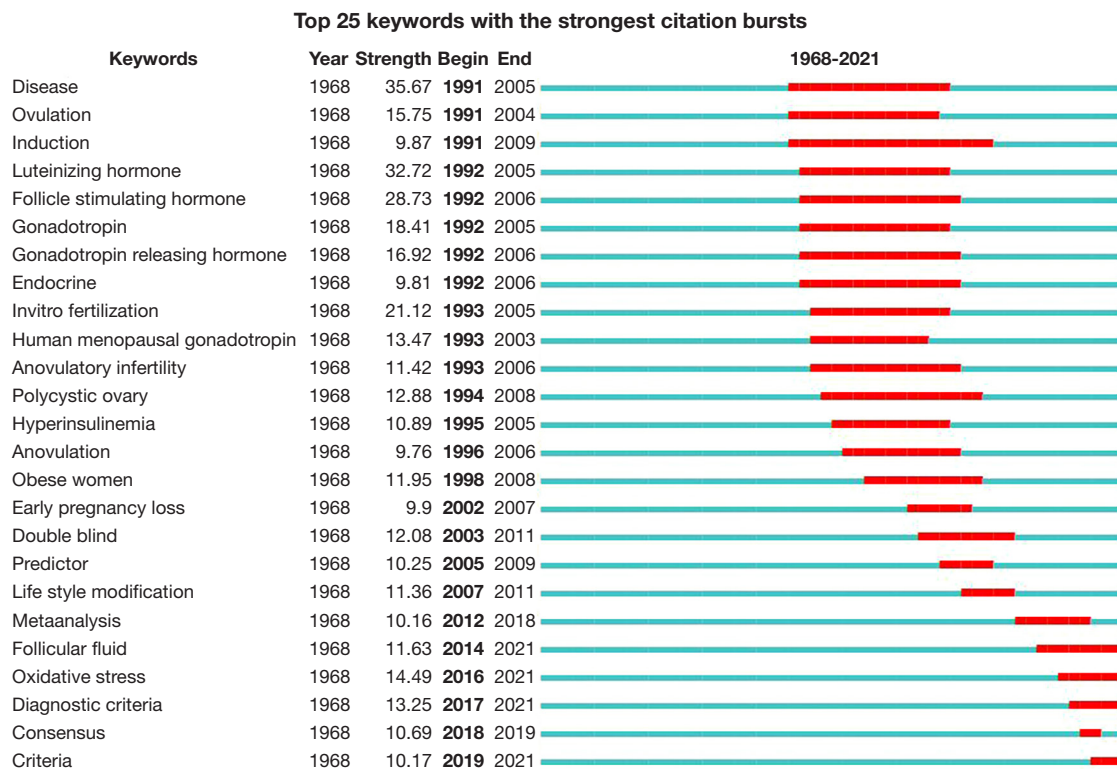


Figure 9 Top 25 keywords with the strongest citation bursts.

PCOS (23). There is also some expert consensus on the treatment of PCOS-related infertility. First of all, lifestyle adjustment has become a consensus in the treatment of PCOS and has been recommended by various guidelines. Studies have found that if overweight and obese PCOS patients lose 5–10% of their weight, their fertility would significantly improve, along with metabolic indicators and psychological status (24,25). In a recent meta-analysis, the author concluded that lifestyle intervention can improve free androgen index (FAI), weight, and body mass index (BMI) in women with PCOS, but the effect of lifestyle intervention on glucose tolerance remained unclear. We did not locate any high-quality in-depth studies on the impact of lifestyle interventions on live birth, miscarriage, or menstrual patterns (25). After active lifestyle adjustment, patients who have not resumed ovulation can be treated with ovulation-stimulating drugs. Commonly used drugs are letrozole (26), clomiphene (27), and metformin (28). Studies have shown that letrozole monotherapy may be better than clomiphene monotherapy (26); however, the combination of these drugs may be better than single-agent therapy (27). Gonadotropin (29) and laparoscopic

ovarian drilling (LOD) are second-line treatments for PCOS (30,31) and used for patients with poor treatment effect of letrozole and clomiphene and other treatment difficulties. A recent meta-analysis found that compared with drugs alone to induce ovulation, laparoscopic ovarian drilling might reduce the rate of live births in women with anovulatory PCOS and clomiphene citrate (CC) resistance, regardless of whether they were combined with drugs to promote ovulation (31). Traditional Chinese medicine and acupuncture may also have certain therapeutic effects on PCOS, but more randomized controlled trials (RCTs) are needed for validation (32-35). When none of the above treatments can achieve satisfactory results, or the patient has other problems, assisted reproduction can be considered (36). There are 2 main types of assisted reproductive technology, intrauterine insemination (IUI) (37) and *in vitro* fertilization-embryo transfer (IVF-ET) (38,39). The clinical pregnancy rate and live birth rate of PCOS patients receiving IVF are similar to those of non-PCOS patients (40). However, metformin may not improve the clinical pregnancy rate and live birth rate after IVF-ET (41).

From our research results, we can deduce that the annual changes in commonly used keywords reflect changes in the focus of research in this field. Among them, medical treatment and IVF have received more attention. At the same time, rigorously designed double-blind clinical studies have also been the focus in recent years. In-depth analysis of the included literature shows that current clinical studies mainly focus on the comparison of the efficacy of first-line drugs, evaluation of the effects and safety of multi-drug combination therapy, and the application of artificial assisted reproductive technology in PCOS patients. When we analyzed the literature, we also noticed that the role of some auxiliary drugs has gradually come into focus, including drugs such as statins and resveratrol, which can improve patients' metabolic indicators and improve hormone levels (42).

Our analysis showed that in the research on PCOS-related infertility, the majority of key results come from the United States, United Kingdom, Australia, and other countries, and most of the institutions with more research results were from the United States. This suggested that the research has not been balanced between districts and countries, especially for developing countries and regions. In fact, PCOS is as common in developing countries, causing a series of psychological and social problems for affected patients (43,44). Therefore, we believe that in future there will be more international cooperation, especially multi-center clinical research and epidemiological research involving developing countries.

The limitations of this study were as follows: due to the diversity of keywords and subject terms used in the literature, it was difficult to accurately retrieve all the literature in this field. Part of the literature did not specify whether RCT is in the keywords or subject terms, which makes it impossible for us to accurately analyze the development of RCTs. To address this problem, future research should adopt the methods of systematic review and meta-analysis to conduct a comprehensive analysis of RCT research in this field.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-714/coif>).

The authors have no conflicts of interest to declare.

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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Table S1 Annual publications of literatures

Year of publication	Records	% of 2,716
2021	153	5.63
2020	210	7.73
2019	186	6.85
2018	192	7.07
2017	138	5.08
2016	142	5.23
2015	162	5.96
2014	156	5.74
2013	111	4.09
2012	134	4.93
2011	114	4.20
2010	100	3.68
2009	98	3.61
2008	96	3.53
2007	91	3.35
2006	92	3.39
2005	76	2.80
2004	55	2.03
2003	65	2.39
2002	55	2.03
2001	41	1.51
2000	38	1.40
1999	33	1.22
1998	32	1.18
1997	31	1.14
1996	28	1.03
1995	29	1.07
1994	18	0.66
1993	21	0.77
1992	8	0.29
1991	8	0.29
1985	1	0.04
1984	1	0.04
1968	1	0.04