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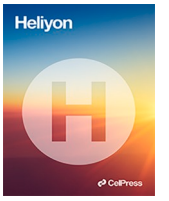

Research article

Hotspots and frontiers in luteal phase defect research: An in-depth global trend bibliometric and visualization analysis over a 52-year period

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ABSTRACT

Luteal phase defect (LPD) is a common female reproductive endocrine defect , which is associated not only with certain diseases but also with the menstrual cycle and fertility in women. With the development of assisted reproductive technology (ART) in recent years, the incidence of luteal phase defect is high among patients using assisted reproductive technology. The aim of this study was to evaluate worldwide research on luteal phase defects using bibliometric analysis. A total of 631 documents related to the study of luteal phase defect were identified over the last 52 years. The current status and trend of globalization can be comprehended by analyzing the annual number of publications, institutions, authors, countries and regions of corresponding authors, journals, influential luteal phase defect publications (which were highly cited), highly cited references in luteal phase defect publications (cocitation analysis) and keywords. The study results provide a comprehensive overview of the development of scientific literature and are of great significance for the future development of the field , especially infertility and early pregnancy loss.

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1. Introduction

Luteal phase defect (LPD) is defined as luteal hypoplasia or premature degeneration. Women with LPD have follicular development and ovulation during the menstrual cycle. However, due to the premature decline of the luteum or insufficient progesterone secretion, these patients' luteal period was shortened, and their secretion of the endometrium was poor. The concept of LPD was first proposed by Jones in 1949. Among the numerous female endocrine dysfunctions, luteal insufficiency is one of the most common causes. LPD is a common female reproductive endocrine defect. In the natural cycle, LPD in women of childbearing age was 3 %–10 %, while the incidence was significantly increased in the ovulation stimulation cycle. With the development of assisted reproductive technology (ART) in recent years, the incidence of LPD is high among patients using ART. Luteal support with progesterone, human chorionic gonadotropin (HCG), oestrogen, and GnRH agonist (GnRH-a) has become an important treatment for ART pregnancy assistance. On the one hand, when a patient develops luteal insufficiency, the progesterone secreted during the luteal period cannot completely transform the endometrium from the hyperplasia period to the secretion period, so the embryo implantation environment cannot be guaranteed. On the other hand, even if the embryo is successfully implanted, the progesterone secreted by the gestational luteum is not enough to maintain embryo development to placental formation. Luteal insufficiency can easily desynchronise the patient's endometrium with embryonic development, resulting in infertility or early pregnancy loss. Clinically, 35 % of early pregnancy loss and 4 % of recurrent pregnancy loss are caused by luteal insufficiency.

The aim of this study was to evaluate worldwide research on luteal phase defects using bibliometric analysis. It is important to deeply study the aetiology of luteal insufficiency and explore the mechanism of luteal support in the prevention and treatment of recurrent pregnancy loss in patients with luteal insufficiency.

Understanding the current status of the field of luteal phase defects, including in-depth analysis of the knowledge base, research hotspots, and changing frontiers, is of great significance for the future development of the field. To analyse and visualise the current status and development trends in luteal phase defect research, the Web of Science Core Collection and VOSviewer software (https://www.vosviewer.com/) were used to search for relevant publications and conduct the bibliometric analysis. Specifically, the annual number of publications, institutions, authors, countries and regions of corresponding authors, journals, influential luteal phase defect publications (which were highly cited), highly cited references in luteal phase defect publications (cocitation analysis), and keywords were analysed. Using the information and method from the above database, we evaluated the current trends in the development of LPD, including the theoretical fundamentals, status, and the applications to experimental data, and illustrated probable future development trends of LPD from the aspects of publications, contributing countries, institutions, and research orientations. This study will provide researchers with insight for a global understanding of LPD and different luteal phase support options.

2. Materials and methods

2.1. Data source and search strategy

The literature was searched using the Web of Science search engine based on the following criteria: (1) The search term was "Luteal phase defect (LPD)" or "luteal insufficiency". (2) Documents published until December 31, 2021 were included. (3) The database was set to "Science Citation Index Expanded". The information of all the literature retrieved was saved in BibTeX and.txt file format.

2.2. Data analysis and visualization

The statistical analyses were performed using R software, version 4.0.2, along with RStudio, version 1.3.959, developed by the R Foundation for Statistical Computing.The Bibliometrix packages were utilized to load the data into R software. Descriptive analyses were conducted using Microsoft Excel version 2016, the Bibliometrix package, and VOSviewer by importing the preprocessed BibTeX and.txt files. An analysis was conducted on various aspects including overall and annual publications, institutions, authors, countries and regions of corresponding authors, journals, influential publications in the domain of LPD that received significant citations, highly cited references within LPD publications through cocitation analysis, and keywords. In addition, the "bibliometrix" R package was used to generate the word tree map, thematic evolution map, and cooccurrence network. A word cloud was created by scaling the font size of each word based on the frequency of keyword usage. A flowchart of the literature search and selection is shown in Fig. 1.

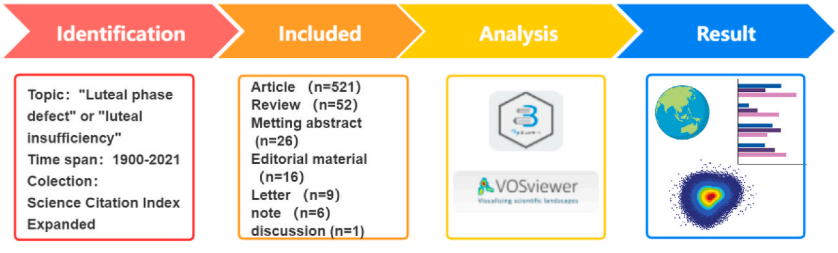

Fig. 1. Flow diagram of the included papers.

3. Results

3.1. Number of documents published and trends

As shown in Table 1, 631 documents from 200 sources published from 1969 to 2021 were included based on the search criteria. These 631 documents were cited 13567 times, with a mean citation rate per article of 21.5 (based on the Web of Science database), and 15556 references were cited by the 631 documents.

The overall trend in the annual number of LPD publications is presented in Fig. 2. The different colours in Fig. 2 represent the annual number of documents in different periods. The number gradually increased from 2 in 1960–1970 to 7.6 in 1986–1990. The number increased sharply to 27.8 per year from 1991 to 1995. Since 1996, the annual number of publications has stabilized at 10–20.

3.2. Distribution by country and region

Based on the countries of the corresponding authors, 41 countries/regions contributed to LPD research publications. Fig. 3A denotes the various countries with different colours based on the number of articles published and shows the distribution of the publications on a world map. The top 15 countries/regions that contributed to the publications are listed in Table 2.

The USA contributed the most publications (178), which accounted for 32.19 % of the total, followed by Japan (37 publications, 6.69 %), the United Kingdom (33 publications, 5.97 %), Germany (30 publications, 5.43 %), Canada (25 publications, 4.52 %), France (24 publications, 4.34 %), Turkey (20 publications, 3.62 %), China (18 publications, 3.26 %), Spain (18 publications, 3.26 %) and India (16 publications, 2.89 %) (Table 2). The top 20 countries with the highest total number of citations and average number of article citations are shown in Fig. 3B and C, respectively. Different colours represent the difference in total citations and average article citations.

The results of the international collaboration analysis are summarized in Fig. 3D and E. The thickness of the line in Fig. 3D reflects the frequency of cooperation. The thicker the line is, the stronger the cooperation. The USA was at the centre of research on LPD and had strong collaborations with Canada, Australia, Italy, China, Spain, Germany, Switzerland, and the United Kingdom. Germany and the United Kingdom made the second greatest contribution and had strong collaborations with the Netherlands and Australia (Fig. 3D). To analyse the 36 countries that met the threshold of more than three publications per country, VOSviewer was used (Fig. 3E). In Fig. 3E, each node represents a country/region, and the size of each country/region's name represents the number of publications. The connecting lines indicate international collaborations, and the thickness of the lines indicates the strength of those collaborations. The different colours in the circles reflect different time periods of publication. Additionally, countries/regions with strong collaborative relationships were represented with similar colours, and those countries/regions formed clusters. There were 8 clusters and 66 links in

Table 1
Main information about data.

Description	Results
Main Information About Data	
Timespan	1969:2021
Sources (Journals, Books, etc)	200
Documents	631
Average years from publication	21.5
Average citations per documents	27.8
Average citations per year per doc	1.546
References	15556
Document Types	
Article	521
review	52
meeting abstract	26
editorial material	16
letter	9
note	6
discussion	1
Document Contents	
Keywords Plus (ID)	1659
Author's Keywords (DE)	1070
AUTHORS	
Authors	2155
Author Appearances	2672
Authors of single-authored documents	66
Authors of multi-authored documents	2089
Authors Collaboration	
Single-authored documents	77
Documents per Author	0.293
Authors per Document	3.42
Co-Authors per Documents	4.23
Collaboration Index	3.77

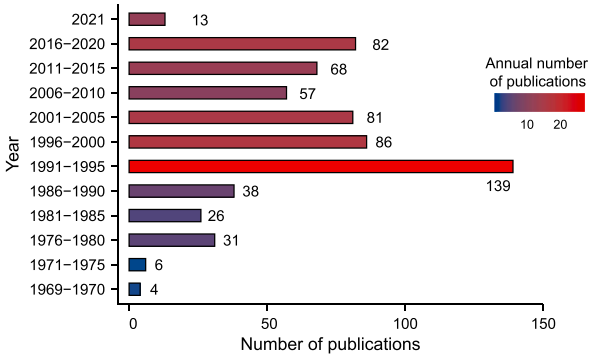

Fig. 2. The overall trend in the annual number of LPD publications.

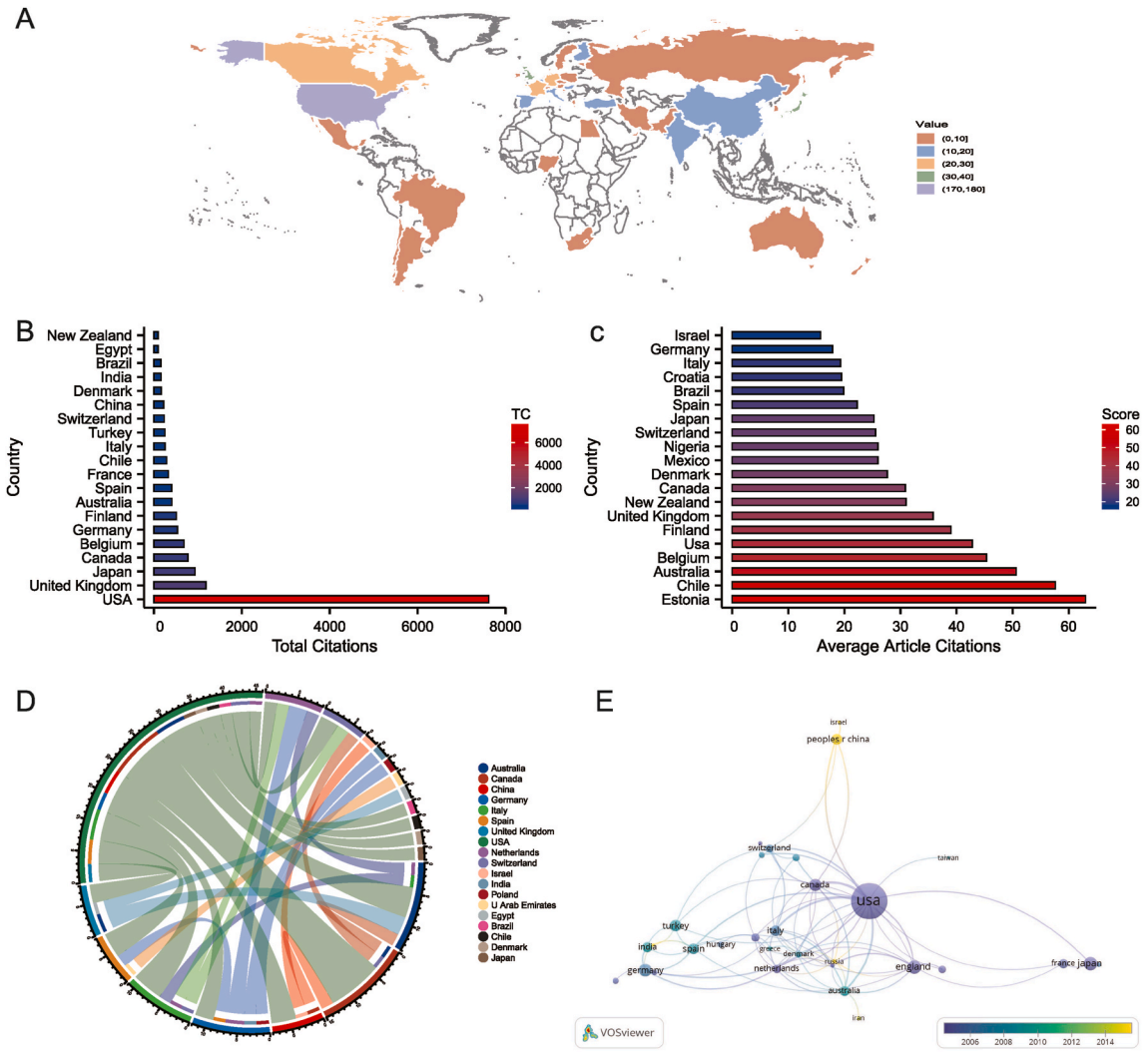

Fig. 3. Countries contributing to LPD. **(A)** World map displaying the global distribution of LPD research. Different corresponding authors'countries were denoted with different colours based on the number of articles published. **(B, C)** Total citations and annual citations of related articles from top 20 countries. **(D)** Distribution and international cooperation of countries that are involved in LPD research. The thickness of the line reflects the frequency of the cooperation. The thicker the line, the stronger the cooperation. **(E)** Network map of co-authorship between countries with more than three publications generated by the VOS viewer.Each node represents a country, and node size indicates the number of publications. The connection between the nodes represents a citation relationship,and the thickness of the lines indicates citation strength (weights on the TLS).

Table 2
The top 15 countries or regions contributing to publications in LPD.

Rank	Country	Articles	Freq	SCP	MCP	MCP_Ratio
1	USA	178	32.19 %	162	16	8.99 %
2	Japan	37	6.69 %	35	2	5.41 %
3	United Kingdom	33	5.97 %	29	4	12.12 %
4	Germany	30	5.43 %	22	8	26.67 %
5	Canada	25	4.52 %	17	8	32.00 %
6	France	24	4.34 %	22	2	8.33 %
7	Turkey	20	3.62 %	18	2	10.00 %
8	China	18	3.26 %	15	3	16.67 %
9	Spain	18	3.26 %	15	3	16.67 %
10	India	16	2.89 %	15	1	6.25 %
11	Belgium	15	2.71 %	14	1	6.67 %
12	Finland	13	2.35 %	13	0	0.00 %
13	Italy	13	2.35 %	12	1	7.69 %
14	Hungary	12	2.17 %	10	2	16.67 %
15	Egypt	10	1.81 %	8	2	20.00 %

the network. The total link strength (TLS) was 131. The USA had the highest TLS (51), indicating that it participated in the most collaborations with other countries, mainly Canada, India, Mexico, Norway, Portugal, and Russia. Canada and Italy had the second (22) and third (20) highest TLS.

3.3. Distribution by institution

The results of the search and the statistical analysis showed that 679 institutions contributed to the LPD publications. Table 3 shows the top 20 institutions, contributing 54.39 % of all publications (343 articles). The University Of Medicine And Dentistry Of New Jersey School was the largest contributor (25 articles), followed by the Pennsylvania State University (24 articles), University of Michigan (24 articles), Baylor College of Medicine (21 articles), Harvard University (20 articles), University of California—Davis (20 articles), University of Pennsylvania (17 articles), University of Barcelona (16 articles), University of Connecticut (15 articles), and University of North Carolina at Chapel Hill (15 articles). It is worth noting that all of the top 10 research institutions were located in the USA. The institutions ranked 11–20 included some hospitals and university research institutions from Canada, China, Finland, Germany, Japan, and the United Kingdom. VOSviewer was used to construct an institutional collaboration network of the 140 institutions that met the threshold of more than two publications per institution (Fig. 4). Each node represents an institution. The size of the node represents the number of publications, and the thickness of the 187 links between nodes represents the strength of collaborations. The three institutions with the highest TLS were the University of Pennsylvania (24), the National Institute of Child Health and Human Development (22), and Duke University (137).

Table 3
The top 20 productive institutions in LPD research.

Rank	Affiliations	Country	Articles	Percentage
1	University Of Medicine And Dentistry Of New Jersey School	USA	25	3.96 %
2	Pennsylvania State University	USA	24	3.80 %
3	University of Michigan	USA	24	3.80 %
4	Baylor College of Medicine	USA	21	3.33 %
5	Harvard University	USA	20	3.17 %
6	University of California—Davis	USA	20	3.17 %
7	University of Pennsylvania	USA	17	2.69 %
8	University of Barcelona	USA	16	2.54 %
9	University of Connecticut	USA	15	2.38 %
10	University of North Carolina at Chapel Hill	USA	15	2.38 %
11	University of Texas at Austin	USA	13	2.06 %
12	University of Toronto	Canada	12	1.90 %
13	Yale University	USA	12	1.90 %
14	Nanjing University of Chinese Medicine	China	11	1.74 %
15	University of Helsinki	Finland	11	1.74 %
16	University of Wisconsin	USA	11	1.74 %
17	Yamaguchi University	Japan	11	1.74 %
18	Duke University	USA	10	1.58 %
19	Free University of Berlin	Germany	10	1.58 %
20	Jessop Hospital for Women	United Kingdom	9	1.43 %

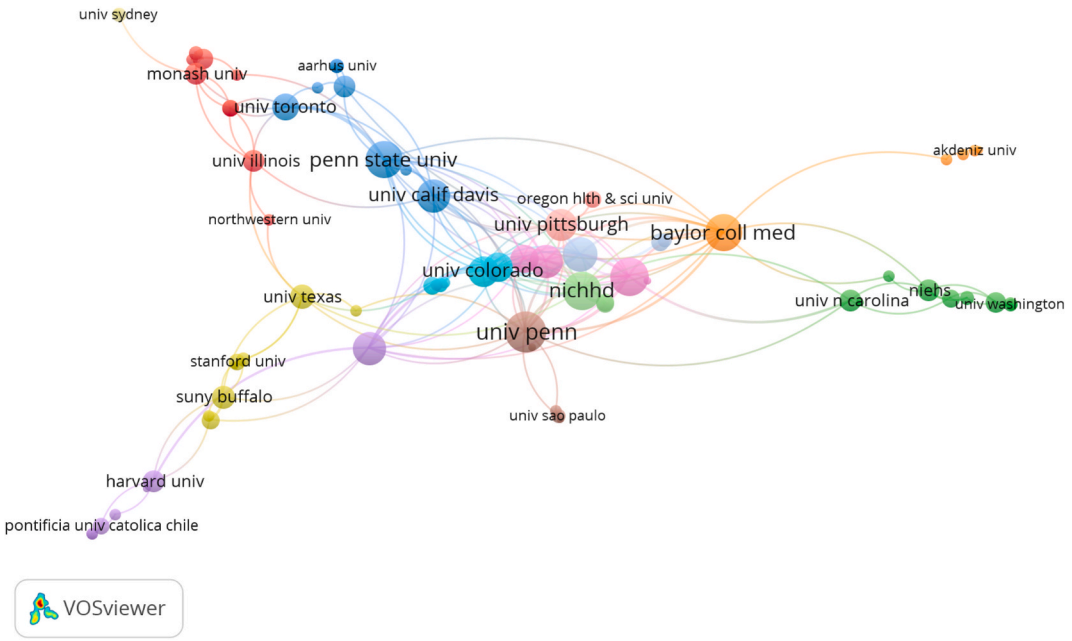

Fig. 4. Institutional collaboration network.Each node represents an institution, the size of the node represents the number of publications, and the thickness of the links between nodes represents the strength of collaborations.

3.4. Distribution by journal

The 631 articles were published in 200 journals and books, 10 of which published more than ten articles. The top 20 most productive journals in the field of LPD are listed in Table 4 and Fig. 5B. *Fertility And Sterility* published the highest number of articles (99), followed by *Human Reproduction* (51), *American Journal Of Obstetrics And Gynaecology* (20), *Journal Of Clinical Endocrinology Metabolism* (19), and *Gynaecological Endocrinology* (15). Fig. 5A shows the cumulative number of articles published by the top 10 journals from 1969 to 2021.

Table 5 shows the top journals by the total number of times their LPD publications were cited and their h-indices. Based on the former parameter (Table 5a and Fig. 5C), *Fertility And Sterility* (3860), *Journal of Ethnopharmacology* (2170), *Human Reproduction* (2099), *Journal of Clinical Endocrinology Metabolism* (1444), *Human Reproduction Update* (839), and *American Journal of Obstetrics and Gynaecology* (678) were the top five journals. Based on the h-index (Table 5b and Fig. 5D), *Fertility and Sterility* (36), *Human Reproduction* (24), *Journal of Clinical Endocrinology Metabolism* (17), *American Journal of Obstetrics and Gynaecology* (13), and *Biology of*

Table 4
The top 20 journals contributing to publication.

Rank	Jounrals	Articles	IF
1	Fertility And Sterility	99	7.329
2	Human Reproduction	51	6.918
3	American Journal Of Obstetrics And Gynecology	20	8.661
4	Journal Of Clinical Endocrinology Metabolism	19	5.958
5	Gynecological Endocrinology	15	2.26
6	Biology Of Reproduction	13	4.285
7	Obstetrics And Gynecology	12	7.661
8	Theriogenology	11	2.74
9	Reproductive Biomedicine Online	10	3.828
10	Clinical And Experimental Obstetrics Gynecology	9	0.146
11	Seminars In Reproductive Medicine	9	1.303
12	Contraception Fertilite Sexualite	8	N/A
13	Endocrinology	8	4.736
14	Hormone Research	8	N/A
15	Journal Of Assisted Reproduction And Genetics	8	3.412
16	Medicine And Science In Sports And Exercise	8	5.411
17	Current Opinion In Obstetrics Gynecology	7	1.927
18	European Journal Of Obstetrics Gynecology And Reproductive Biology	7	2.435
19	Human Reproduction Update	7	15.61
20	International Journal Of Fertility	7	1.595

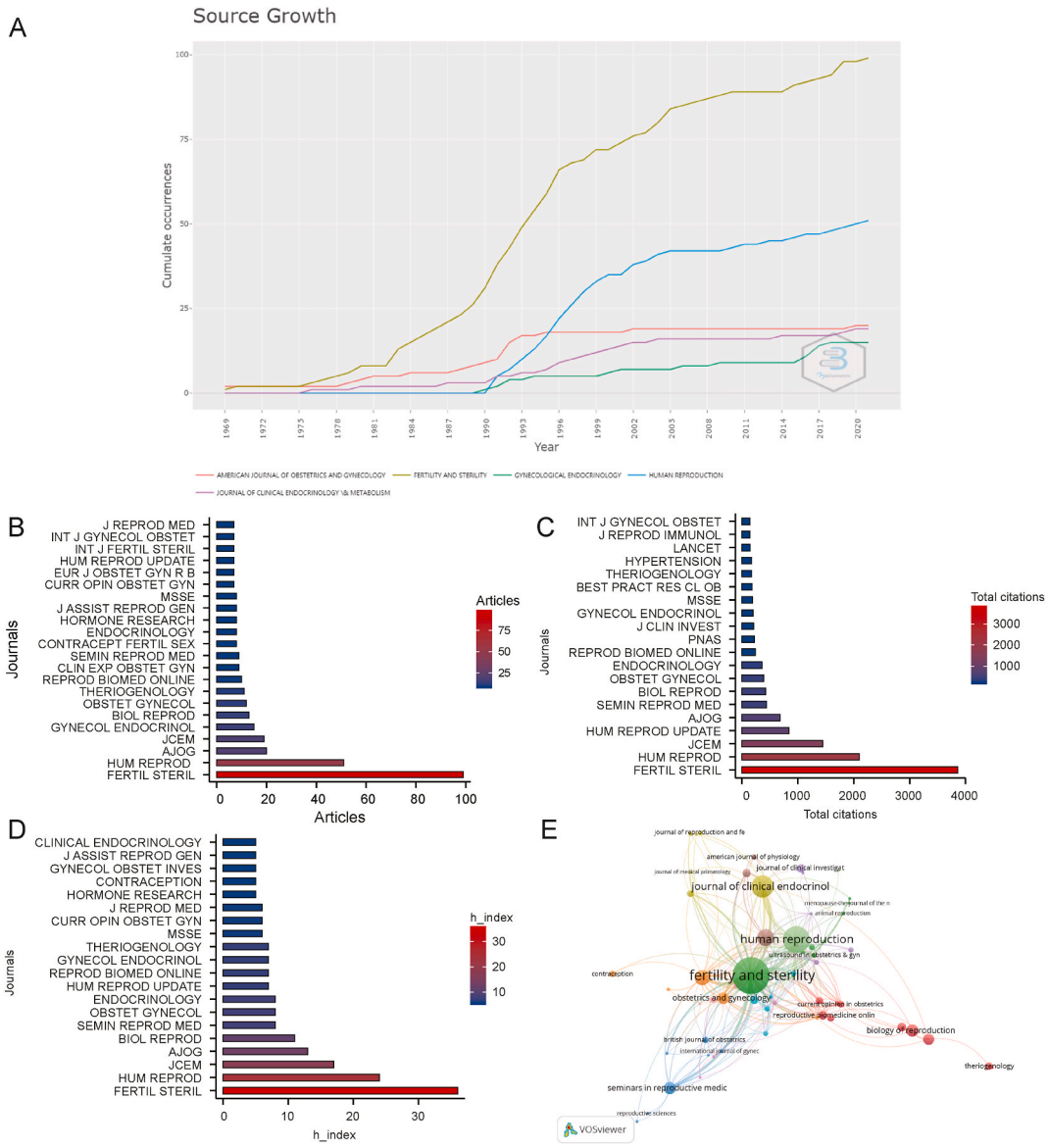

Fig. 5. Distribution by journal. **(A)** The cumulative number of articles published by the top 10 journals from 1969 to 2021. **(B)** The top 20 most productive journals in the field of LPD. **(C,D)** The top 20 journals by the total number of times their LPD publications were cited and their h-indices. **(E)** Network map of journals with more than two publications generated by the VOS viewer. Each node represents a publication, and its size is the total number of times that the publication was cited.

Reproduction (11) were the top five journals. VOSviewer was used to analyse the 200 total journals. Seventy-seven journals met the thresholds of more than two publications (Fig. 5E). Each node represents a publication, and its size is the total number of times that the publication was cited.

3.5. *Influential articles*

The top 20 most influential articles in the field of LPD are presented in Table 6. The top article was "Human Leptin Deficiency Caused by a Missense Mutation: Multiple Endocrine Defects, Decreased Sympathetic Tone, and Immune System Dysfunction Indicate New Targets for Leptin Action, Greater Central than Peripheral Resistance to the Effects of Leptin, and Spontaneous Correction of Leptin-Mediated Defects" by Ozata M with 502 citations, and it was published in *J Clin Endocrinol Metab* in 1999 (https://doi.org/10.1210/jc.84.10.3686). The article "Integrins as markers of uterine receptivity in women with primary unexplained infertility" by Lessey Ba et al., which was published in *Fertil Steril* in 1995 (https://doi.org/10.1016/S0015-0282(16)57422-6), ranked second with 304 citations. The article "Recurrent miscarriage: aetiology, management and prognosis" by Li Tc et al., published in *Hum Reprod Update* in

Table 5a
Top 20 cited journals by total citations.

Rank	Jounral	Total citations	IF
1	Fertility And Sterility	3860	7.329
2	Human Reproduction	2099	6.918
3	Journal Of Clinical Endocrinology Metabolism	1447	5.958
4	Human Reproduction Update	839	15.61
5	American Journal Of Obstetrics And Gynecology	678	8.661
6	Seminars In Reproductive Medicine	437	1.303
7	Biology Of Reproduction	424	4.285
8	Obstetrics And Gynecology	387	7.661
9	Endocrinology	357	4.736
10	Reproductive Biomedicine Online	241	3.828
11	Proceedings Of The National Academy Of Sciences Of The United States Of America	219	11.205
12	Journal Of Clinical Investigation	212	14.808
13	Gynecological Endocrinology	200	2.26
14	Medicine And Science In Sports And Exercise	188	5.411
15	Best Practice Research Clinical Obstetrics Gynaecology	182	5.237
16	Theriogenology	173	2.74
17	Hypertension	172	10.19
18	Lancet	149	79.321
19	Journal Of Reproductive Immunology	141	4.054
20	International Journal Of Gynecology Obstetrics	140	3.561

Table 5b
Top 15 cited journals by h_index citations.

Rank	Jounral	h_index	IF
1	Fertility And Sterility	36	7.329
2	Human Reproduction	24	6.918
3	Journal Of Clinical Endocrinology Metabolism	17	5.958
4	American Journal Of Obstetrics And Gynecology	13	8.661
5	Biology Of Reproduction	11	4.285
6	Seminars In Reproductive Medicine	8	1.303
7	Obstetrics And Gynecology	8	7.661
8	Endocrinology	8	4.736
9	Human Reproduction Update	7	15.61
10	Reproductive Biomedicine Online	7	3.828
11	Gynecological Endocrinology	7	2.26
12	Theriogenology	7	2.74
13	Medicine And Science In Sports And Exercise	6	5.411
14	Current Opinion In Obstetrics Gynecology	6	1.927
15	Journal Of Reproductive Medicine	6	0.142
16	Hormone Research	5	N/A
17	Contraception	5	3.375
18	Gynecologic And Obstetric Investigation	5	2.031
19	Journal Of Assisted Reproduction And Genetics	5	3.412
20	Clinical Endocrinology	5	3.478

2002 (https://doi.org/10.1093/humupd/8.5.463), ranked third with 288 citations. Fig. 6 shows the 102 LPD documents that met the threshold of being cited >50 times.

3.6. Influential Authors and Studies in LPD

The University of Medicine And Dentistry of New Jersey School is a pioneer in the field of LPD and has the largest number of publications and coauthorship analyses conducted by the authors. *Fertility and Sterility* has the largest number of local citations and the top rank for the h-index.

Jones GS, a pioneer in reproductive endocrinology from Johns Hopkins Hospital, was the first scientist to propose the concept of luteal phase defect and has the largest number of local citations (88). Lessey, BA and Li, TC have the top two publications, rank first and second in terms of total citations and have the top rank for the h-index and m-index. These data suggest that Jones GS was the originator of this field, and that these other scholars are the next outstanding scientists in this field.

In 1949, Jones presented a study of 255 cycles in 98 patients on the Department of Obstetrics and Gynaecology of the American Medical Association [1]. In this study, 33 patients were considered to have defects in luteal function. In 1978, Jones retired from Johns Hopkins University and was appointed professor of Obstetrics and Gynaecology at the East Virginia School of Medicine. Together with her husband, they established the first in vitro fertilization (IVF) project in the United States and successfully induced the first IVF baby in the United States in 1981.

Table 6
The top 20 most influential papers in the field of LPD.

Rank	Author	Title	Jounral	DOI	Total Citations	Year
1	Ozata M	Human Leptin Deficiency Caused by a Missense Mutation: Multiple Endocrine Defects, Decreased Sympathetic Tone, and Immune System Dysfunction Indicate New Targets for Leptin Action, Greater Central than Peripheral Resistance to the Effects of Leptin, and Spontaneous Correction of Leptin-Mediated Defects	J CLIN ENDOCRINOL METAB	10.1210/jc.October 84, 3686	502	1999
2	Lessey Ba	Integrins as markers of uterine receptivity in women with primary unexplained infertility	FERTIL STERIL	10.1016/S0015-0282(16)57422-6	304	1995
3	Li Tc	Recurrent miscarriage: aetiology, management and prognosis	HUM REPROD UPDATE	10.1093/humupd/8.5.463	288	2002
4	Sugiura-Ogasawara M	Exposure to bisphenol A is associated with recurrent miscarriage	HUM REPROD	10.1093/humrep/deh888	274	2005
5	Jones Gs	The luteal phase defect	FERTIL STERIL	10.1016/S0015-0282(16)41769-3	233	1976
6	Brannstrom M	Involvement of leukocytes and cytokines in the ovulatory process and corpus luteum function[J]. Human Reproduction	HUM REPROD	10.1093/oxfordjournals.humrep.a137929	231	1993
7	Green Dn	Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study.	AM J OBSTET GYNECOL	10.1067/mob.2002.126643	219	2002
8	Pritts Ea	Luteal phase support in infertility treatment: a meta-analysis of the randomized trials	HUM REPROD	10.1093/humrep/September 17, 2287	205	2002
9	Hu Yc	Subfertility and defective folliculogenesis in female mice lacking androgen receptor	PROC NATL ACAD SCI U S A	10.1073/pnas.0404372101	203	2004
10	Coutifaris C	Histological dating of timed endometrial biopsy tissue is not related to fertility status	FERTIL STERIL	10.1016/j.fertnstert.2004.03.069	197	2004
11	Murray Mj	A critical analysis of the accuracy, reproducibility, and clinical utility of histologic endometrial dating in fertile women	FERTIL STERIL	10.1016/j.fertnstert.2003.11.030	190	2004
12	Torry Ds	Therapeutic Effects of VEGF Gene-Transfected BMSCs Transplantation on Thin Endometrium in the Rat Model	FERTIL STERIL	10.1016/S0015-0282(16)58390-3	182	1996
13	Germain Am	Endothelial dysfunction: a link among preeclampsia, recurrent pregnancy loss, and future cardiovascular events?	HYPERTENSION	10.1161/01.HYP.0000251522.18094.d4	172	2007
14	Lessey Ba	Endometrial progesterone receptors and markers of uterine receptivity in the window of implantation	FERTIL STERIL	10.1016/S0015-0282(16)58140-0	162	1996
15	Seppala M	Hyperprolactinæmia And Luteal Insufficiency	LANCET	10.1016/S0140-6736(76)91343-X	149	1976
16	Smitz J	A prospective randomized comparison of intramuscular or intravaginal natural progesterone as a luteal phase and early pregnancy supplement	HUM REPROD	10.1093/oxfordjournals.humrep.a137611	143	1992
17	Dickey Rp	Development, pharmacology and clinical experience with clomiphene citrate	HUM REPROD UPDATE	10.1093/humupd/2.6.483	136	1996
18	Barreiro Ml	Ghrelin and reproduction: a novel signal linking energy status and fertility?	MOL CELL ENDOCRINOL	10.1016/j.mce.2004.07.015	128	2004
19	Fatemi Hm	An update of luteal phase support in stimulated IVF cycles	HUM REPROD UPDATE	10.1093/humupd/dmm021	124	2007
20	De Souza Mj	High prevalence of subtle and severe menstrual disturbances in exercising women: confirmation using daily hormone measures	HUM REPROD	10.1093/humrep/dep411	118	2010

The United States, Japan, the United Kingdom, Germany and Canada have published the most articles in the field of LPD. American scholars have conducted numerous clinical and basic studies in the field of LPD. Pfister et al. [2] studied 2171 menstrual cycles in 755 women and found that hormone dysfunction in the early follicular phase may contribute to LPD in women of older reproductive age.

3.7. Cocitation analysis of highly cited references

The top 20 most highly cited references in the LPD publications are summarized in Table 7. Fig. 7 shows the clustering results of these highly cited references. Among the 15513 references cited in the 631 LPD publications, 24 references (each cited ≥20 times by the 631 articles) were selected to construct the cocitation map of highly cited references. An article by Noyes et al. (1950, *Fertil Steril*) had the largest number of citations (147), followed by articles by Jones et al.(1976, *Fertil Steril*, 60), Mcneely et al. (1988, *Fertil Steril*, 57), Jones et al. (1949, *J Am Med Assoc*, 46), and Jordan et al. (1994, *Fertil Steril*, 37).

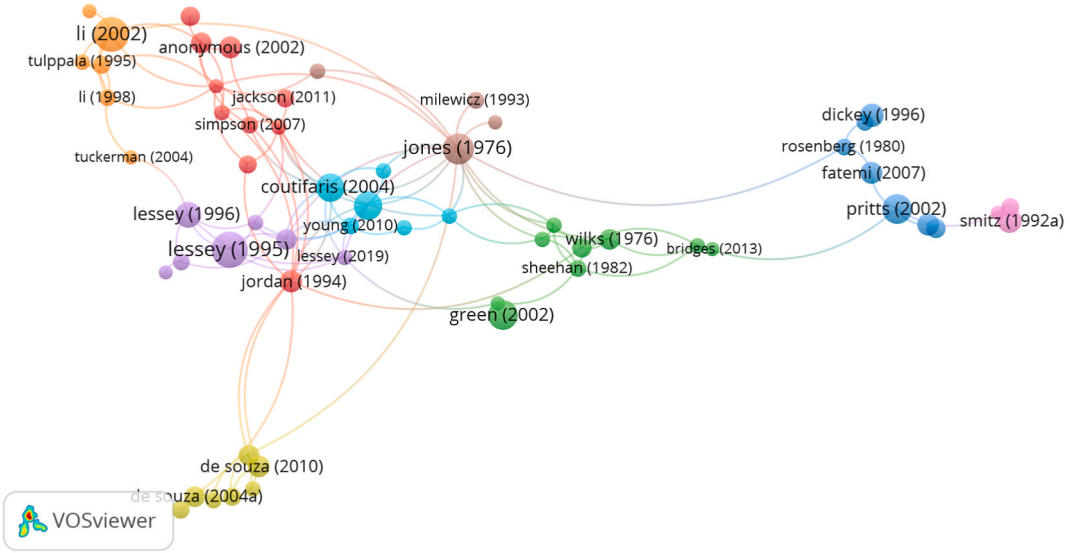

Fig. 6. The highly-cited documents.Network map of documents cited with more than 50 times generated by the VOS viewer. Each node represents a document, and its size is the total number of times that the document was cited.

3.8. Analysis of keywords

Keyword analysis is an important research topic in bibliometrics. New valuable bibliometric indicators or methods can be deduced through keyword analysis, which is very important for promoting further development of this field. To further understand the research hotspots across all research years, an analysis and summarization of keywords was conducted from 1969 to 2021 (Fig. 8). The 50 most common keywords in associated publications are shown in Table 8. The most frequent keywords, from most to least common, were "women", "progesterone", "menstrual cycle", "corpus luteum", "diagnosis", "luteinizing hormone", "pregnancy", "deficiency", "expression", and "ovulation". These keywords represent the research hotspots in the field of luteal insufficiency. The word cloud and word tree map in Fig. 8A and **B** highlight the combinations of keywords. The thematic evolution of the network pharmacology research hotspots over time is shown in Fig. 8C.

3.9. Analysis of keyword Co-occurrence clusters

To identify the most popular research hotspots in the LPD field and the trends in keywords over time, a keyword co-occurrence analysis was performed utilizing the "overlay visualization" feature in VOSviewer. Fig. 9 shows the overall distribution of the co-occurrence of the keywords. Of the 2343 keywords, analysis was conducted on the subset of 191 keywords that appeared more than five times. Each node in the "network visualization" shown in Fig. 9A represents a keyword, and its size represents its frequency. The colours in the "overlay visualization" shown in Fig. 9B indicate the most common publication year of each keyword; according to this, the majority of the keywords were related to articles published after 2000 (green/yellow colours). The "density visualization" of all identified keywords presented by frequency is shown in Fig. 9C.

4. Discussion

4.1. Overview

Luteal insufficiency (or luteal phase defect, LPD) refers to luteal dysfunction, including abnormal formation of follicles after ovulation, a lack of progesterone secretion, or premature degeneration of the corpus luteum, resulting in a decreased secretory response of the endometrium. LPD is associated not only with certain diseases but also with the menstrual cycle and fertility in women. Clinically, the main pathological features are delayed development of the endometrium in the secretory phase and nonsynchronous development of the endometrium and embryonic development, which are closely related to infertility, recurrent miscarriage and irregular menstruation.

4.2. Pathogenesis of luteal phase defects

Luteal phase defect (LPD), first proposed by Jones in 1949, is characterized by abnormal luteal development and function after ovulation, insufficient synthesis and secretion of progesterone, or a decreased responsiveness of the endometrium to progesterone. Such insufficient progesterone exposure results in poor secretion of the endometrium, leading to inadequate endometrial

Table 7
Top 20 co-citation analysis of cited reference on network pharmacology.

Rank	Author	Title	DOI	Journals	Citations	Year
1	Noyes Rw	Dating the Endometrial Biopsy	10.1016/S0015-0282(16)30062-0	FERTIL STERIL	147	1950
2	Jones Gs	The luteal phase defect.	10.1016/s0015-0282(16)41769-3	FERTIL STERIL	60	1976
3	Mcneely Mj	The diagnosis of luteal phase deficiency: a critical review	10.1016/s0015-0282(16)59999-3	FERTIL STERIL	57	1988
4	Jones Ges	Some newer aspects of the management of infertility	10.1001/JAMA.1949.02910160013004	JAMA-J AM MED ASSOC	46	1949
5	Jordan J	Luteal phase defect: the sensitivity and specificity of diagnostic methods in common clinical use	10.1016/s0015-0282(16)56815-0	FERTIL STERIL	37	1994
6	Davis Ok	The incidence of luteal phase defect in normal, fertile women, determined by serial endometrial biopsies	10.1016/s0015-0282(16)60603-9	FERTIL STERIL	36	1989
7	Filicori M	Neuroendocrine regulation of the corpus luteum in the human. Evidence for pulsatile progesterone secretion	10.1172/JCI111370	J CLIN INVEST	36	1984
8	Strott Ca	The short luteal phase	10.1210/JCEM-30-2-246	J CLIN ENDOCR METAB	34	1970
9	Wentz Ac	Endometrial biopsy in the evaluation of infertility	10.1016/s0015-0282(16)44530-9	FERTIL STERIL	32	1980
10	Soules Mr	Luteal phase deficiency: characterization of reproductive hormones over the menstrual cycle	10.1210/JCEM-69-4-804	J CLIN ENDOCR METAB	30	1989
11	Abraham Ge	Evaluation of ovulation and corpus luteum function using measurements of plasma progesterone		OBSTET GYNECOL	27	1974
12	Sherman Bm	Measurement of plasma LH, FSH, estradiol and progesterone in disorders of the human menstrual cycle: the short luteal phase	10.1210/JCEM-38-1-89	J CLIN ENDOCR METAB	27	1974
13	Soules Mr	The diagnosis and therapy of luteal phase deficiency		FERTIL STERIL	27	1977
14	Downs Ka	Clomiphene citrate therapy for luteal phase defect	10.1016/s0015-0282(16)46754-3.	FERTIL STERIL	26	1983
15	Balasch J	Corpus luteum insufficiency and fertility: a matter of controversy	10.1093/OXFORDJOURNALS.HUMREP.A136589	HUM REPROD	24	1987
16	Shoupe D	Correlation of endometrial maturation with four methods of estimating day of ovulation		OBSTET GYNECOL	24	1989
17	Noyes Rw	Accuracy of endometrial dating; correlation of endometrial dating with basal body temperature and menses	10.1016/s0015-0282(16)31446-7.	FERTIL STERIL	23	1953
18	Scott Rt	The effect of interobserver variation in dating endometrial histology on the diagnosis of luteal phase defects	10.1016/s0015-0282(16)60367-9.	FERTIL STERIL	23	1988
19	Andrews Wc	Luteal phase defects	10.1016/s0015-0282(16)44348-7.	FERTIL STERIL	22	1979
20	Daya S	Progesterone profiles in luteal phase defect cycles and outcome of progesterone treatment in patients with recurrent spontaneous abortion	10.1016/0002–9378(88)90127-5	AM J OBSTET GYNECOL	22	1988

transformation or heterogeneous transformation [3]. This document is also the fourth most highly cited document and is a landmark in the field of luteal insufficiency.

However, the mechanism of LPD remains unclear. Many scholars believe that its pathogenesis mainly includes the following aspects: 1) a decreased level of follicle-stimulating hormone (FSH) in the follicular phase, 2) an abnormally fluctuating luteinizing hormone (LH) level, 3) decreased levels of LH and FSH during ovulation peak, 4) decreased endometrial response to progesterone, and 5) increased levels of prolactin [4]. The above mechanisms may be due to endocrine abnormalities or complications, such as hyperprolactinemia or stress [5]. Additionally, abnormal follicular development, defective neovascularization, or insufficient production of yolk cell steroids have all been related to LPD [6].

4.2.1. Endocrine changes

Given that both luteal defects and reduced ovarian reserve function can manifest as abnormalities in luteal function, scholars have speculated about the correlation between reduced ovarian reserve capacity and LPD. Pfister et al. [2] investigated this hypothesis for the first time by studying the correlation between the menstrual cycle and serum anti-Müllerian hormone (AMH), FSH, oestradiol (E2), and inhibin B levels in 755 women. They found that although decreased ovarian reserve (DOR) was not related to LPD, low FSH levels and high E2 levels in the early follicular phase increased the probability of luteal bleeding (LB). Furthermore, the increase in levels of inhibin B reduced the risk of shortening the luteal phase. These results suggest that one of the causes of LPD in elderly women is hormonal dysfunction in the early follicular period, thereby providing a reference for follow-up clinical medication.

It has also been reported that poor folliculation is a precursor of impaired luteal function [7]. The GnRH/TRH stimulation test was

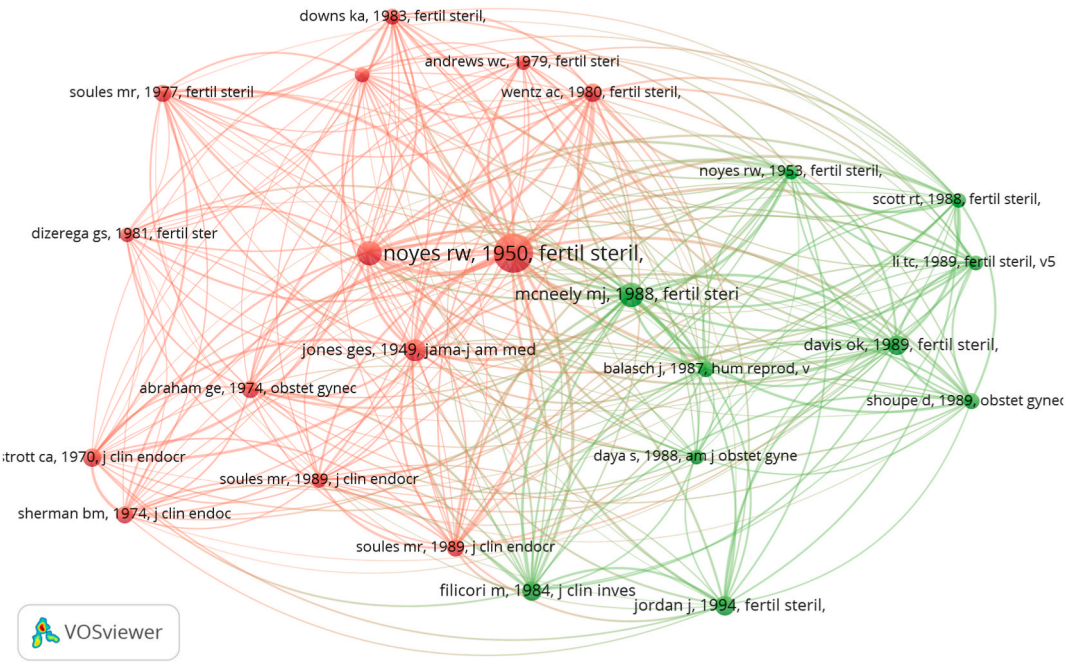

Fig. 7. The highly cited references in the 631 LPD publications.Network map of references cited with more than 20 times generated by the VOS viewer. Each node represents a reference, and its size is the total number of times that the reference was cited.

conducted in the middle luteal phase (MLP) to determine the responsiveness of the pituitary gland and ovary, as the test can dynamically and accurately evaluate not only the pituitary-ovary function in the luteal phase but also the development of LPD.

4.2.2. Stress and energy

Short-term stress can interfere with the normal menstrual cycle by affecting ovulation and luteal function. Berga [8] found that psychological stress, as a potentially important factor that may activate the central nervous regulatory mechanism, can interfere with normal periodic function and cause functional hypothalamic anovulation. Xiao et al. [9] selected 11 female rhesus monkeys for a stress test, and the results showed that the first clinical stage of stress damage to the normal menstrual cycle was luteal insufficiency, which can continue to have harmful effects on the menstrual cycle even after relieving the stress. This basic research provides new insights into the occurrence of LPD [9]. Some studies suggest that LPD may be related to oxidative stress. Previous studies found that melatonin can promote the production of progesterone by granulosa cells during the luteinization of follicles [10–12]. Toshiaki et al. [13,14] confirmed in 2008 that melatonin, as an antioxidant, plays a role in protecting follicular oocytes from free radicals during ovulation, thereby protecting granulosa cells from ROS and allowing them to continue to produce progesterone. Additionally, some studies have shown that low energy availability (EA) can also cause menstrual disorders, including subclinical LPD, hypomenorrhea, and amenorrhea [15,16]. Low EA may cause the pulse frequency of LH to slow down, thus causing menstrual disorders [17]. Low LH is a substitute index for the pulsatile decrease in GnRH levels [18].

4.3. Diagnosis of LPD

There are no uniform, accurate diagnostic criteria for LPD. The more commonly used methods include basal body temperature (BBT) measurement, mid-luteal progesterone level measurement, and endometrial biopsy and pathological examination [3,4,19]. In 1949, Jones first proposed combining BBT charts, urinary progesterone diol levels, and an endometrial biopsy to describe LPD [3]. BBT and progesterone levels are often used to evaluate the luteal phase. Ultrasound measurement of endometrial thickness and endometrial biopsy have unique advantages.

4.3.1. Serum progesterone level and duration of luteal phase

For the diagnosis of clinical LPD (luteal phase is shorter than 10 days) and biochemical LPD (progesterone $\leq$5 ng/ml), Schliep et al. [20] conducted a prospective study of 259 women aged 18–44 years in West New York in 2013 (2005–2007) for up to two menstrual cycles. The level of oestradiol in an LPD cycle was low, but LH and FSH levels were only related to the shortening of the luteal phase (i.e., clinical LPD), indicating that clinical and biochemical LPD may reflect different potential mechanisms. Therefore, combining timely progesterone measurement to determine ovulation can be used as a specific cost-effective tool by clinicians and researchers to evaluate LPD [20]. At present, the serum progesterone level on the second day of the mid-luteal phase provides a convenient method for evaluating luteal function.

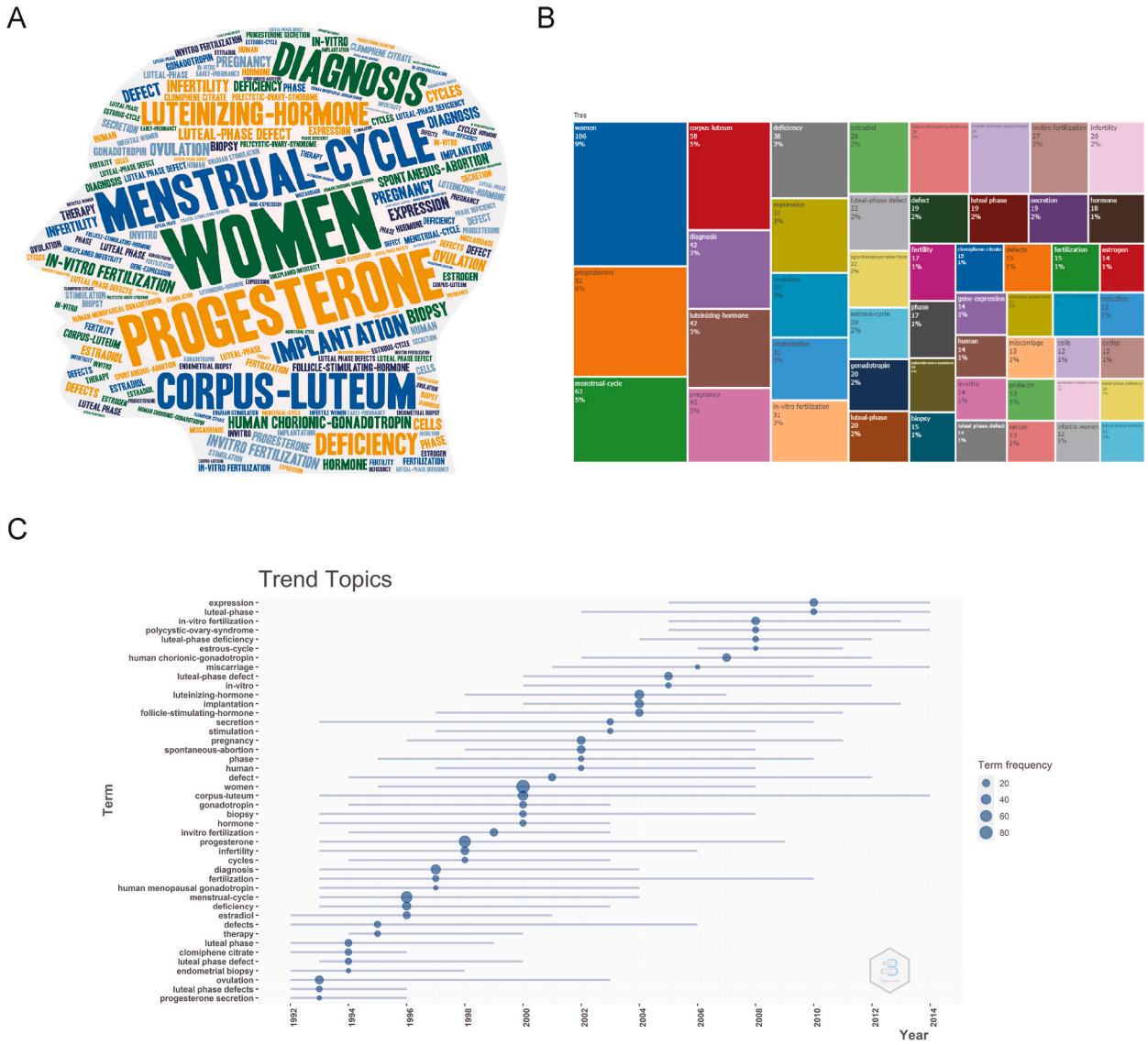

Fig. 8. The keywords distribution. **(A, B)** Keywords cloud map and tree map related to LPD research. **(C)** The thematic evolution of the network pharmacology research hotspots over time.

LPD is also considered to be more likely the result of an abnormal reaction of the endometrium to progesterone than the result of a lower-than-normal level of progesterone produced by the corpus luteum [21]. Therefore, improving the responsiveness of the endometrium to progesterone may be more beneficial than supplementing progesterone.

4.3.2. Endometrial biopsy

In 1953, Noyes and Haman [22] proposed the theory of endometrial biopsy and proposed detailed evaluation rules (Highly Cited Literature Rank 17). In the second most highly cited literature [23], Jones GS et al. concluded that a properly obtained and carefully diagnosed endometrial biopsy can diagnose luteal function defects, rather than using basal thermograms, urinary pregnenolone, or even plasma progesterone monoassay. The timing of the biopsy is defined differently by different scholars [24].However, Jordan et al. [25] developed a new gold standard by collecting daily blood samples throughout the entire luteal phase to calculate the total amount of progesterone produced during that phase; the optimal sensitivity and specificity of endometrial biopsy were approximately 50 %.

As early as 1996, a study pointed out that the delay in histology conforming to LPD was related to a failure of the downregulation of the progesterone receptor and a lack of normal markers of endometrial receptivity [26]. The avf33 integrin can also be used as a marker protein to detect altered uterine function in infertile patients [27]. In the same year, another study determined the luteal phase of patients with recurrent spontaneous abortion (RSA) by endometrial biopsy. The study found that the serum progesterone level in patients with recurrent spontaneous abortion related to LPD was significantly lower than that in patients with RSA with normal

Table 8
Keywords of LPD research hotspots.

Rank	Terms	Frequency
1	women	106
2	progesterone	81
3	menstrual-cycle	63
4	corpus-luteum	58
5	diagnosis	42
6	luteinizing-hormone	42
7	pregnancy	40
8	deficiency	38
9	expression	37
10	ovulation	32
11	implantation	31
12	in-vitro fertilization	31
13	estradiol	28
14	follicle-stimulating-hormone	28
15	human chorionic-gonadotropin	28
16	invitro fertilization	27
17	infertility	26
18	luteal-phase defect	22
19	spontaneous-abortion	22
20	estrous-cycle	20
21	gonadotropin	20
22	luteal-phase	20
23	defect	19
24	luteal phase	19
25	secretion	19
26	hormone	18
27	fertility	17
28	phase	17
29	polycystic-ovary-syndrome	16
30	biopsy	15
31	clomiphene citrate	15
32	defects	15
33	fertilization	15
34	estrogen	14
35	gene-expression	14
36	human	14
37	in-vitro	14
38	luteal phase defect	14
39	endothelial growth-factor	13
40	human menopausal gonadotropin	13
41	induction	13
42	miscarriage	13
43	prolactin	13
44	serum	13
45	cells	12
46	cycles	12
47	gonadotropin-releasing-hormone	12
48	infertile women	12
49	luteal-phase deficiency	12
50	luteal phase defects	12

endometrial biopsy in almost the entire luteal phase [28].

Some studies indicate that it is not accurate to diagnose LPD by endometrial biopsy for histological determination of the endometrium alone. Endogenous progesterone levels can be considered, and the endometrial response to hormone therapy in fertility treatment can be monitored. At least three points of detection before, during, and after the luteal phase can more accurately assess the progesterone level [29–31]. Subsequently, Coutifaris et al. [32] conducted a prospective study and collected a large amount of data in 2004. The results showed that LPD may theoretically be a pathological entity leading to infertility, but an endometrial biopsy may not be the first choice for diagnosis. This is because the incidence rate of endometrial biopsy in the abnormal stage is very high, and the positive predictive value of choosing endometrial biopsy as a diagnostic test may only be between 7% and 10 % [32]. More studies have shown that histological endometrial measurement does not have the accuracy or precision required to provide an effective method for diagnosing luteal phase deficiency or to guide the clinical management of women with reproductive failure [33].

In addition to the above methods, the number of endometrial glandular openings can also be evaluated by using software that can provide objective counting. Gland openings can be seen throughout the menstrual cycle but are more obvious during the secretory phase. The changes in gland openings are related to reproductive status and prognosis [34]. Some studies have found that glycodelin PP14 can prevent fertilization by preventing the interaction between sperm and the zona pellucida. This protein has been detected as a

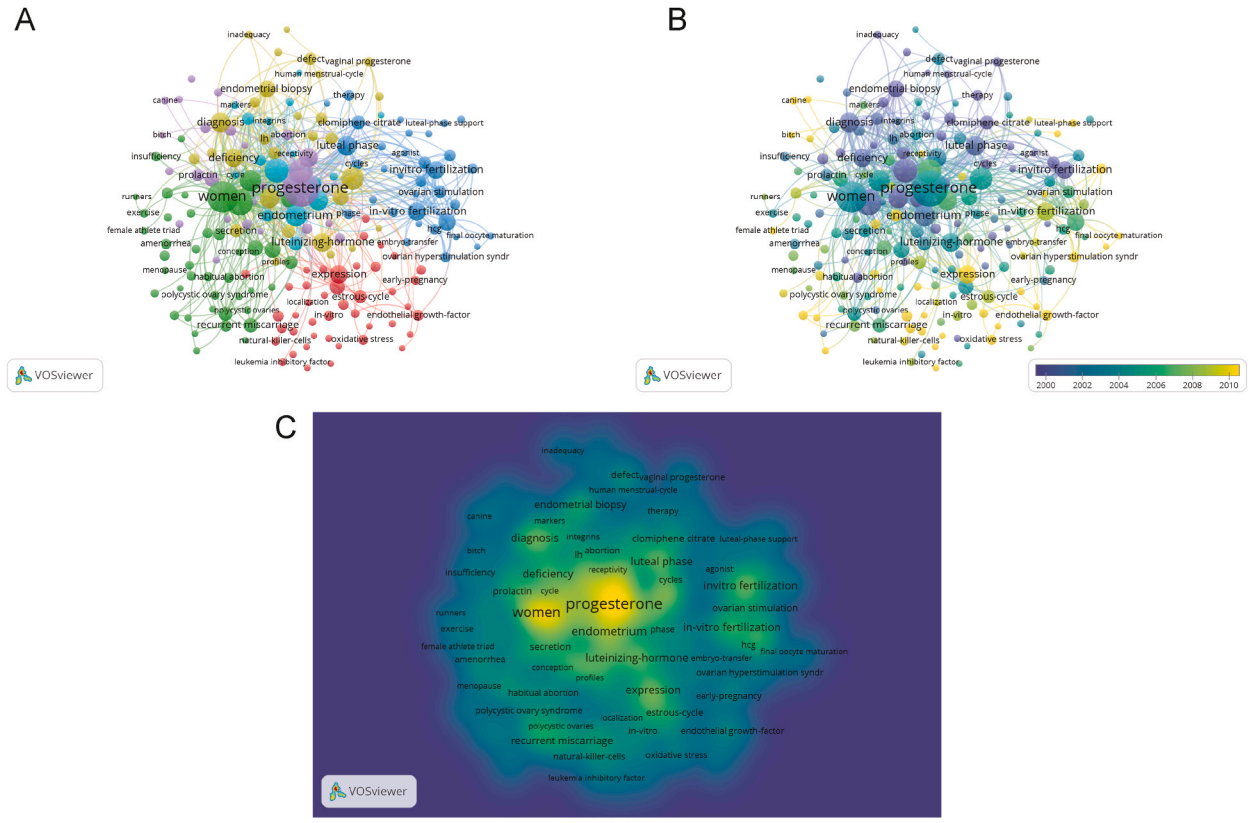

Fig. 9. The overall distribution of the co-occurrence of the keywords. **(A)** Mapping of keywords of studies. **(B)** VOSviewer overlay visualization of co-occurring author keywords by time (blue:earlier, yellow: later). **(C)** Distribution of keywords according to the mean frequency of appearance. The deeper the color of a node, the more frequently keywords appear.

marker of uterine receptivity because its expression is related to progesterone levels and luteal function [35].

In general, endometrial biopsy has some drawbacks: (1) the judgement criteria tend to be subjective, and the results obtained do not have high reliability, even if the same observer performs observations on the same sample several times; (2) endometrial biopsy is an invasive test that may cause side effects such as excessive vaginal bleeding, fever, pain, vasovagal reaction, and uterine perforation. These factors make the clinical application of endometrial biopsy limited.

4.3.3. Colour Doppler ultrasound

Whether monitoring the BBT, endometrial histology, or measuring the plasma progesterone level, there is not enough sensitivity to diagnose luteal phase dysfunction. The lack of reliable laboratory tools to assess luteal function is an important clinical limitation in the evaluation of the normal menstrual cycle and luteal defects, implantation defects, and endocrinology of early pregnancy loss. In recent years, ultrasound, especially three-dimensional ultrasound based on colour Doppler blood flow pulse technology, has been proposed as a new tool to evaluate the corpus luteum in the human body. The advantage of this noninvasive method is that the endometrium and corpus luteum can be evaluated simultaneously throughout the luteal phase [36].

In 1995, Glock and Brumsted [37] preliminarily found that colour Doppler ultrasound can be an auxiliary method for diagnosing luteal function. They found that the resistance index can be used to quantify the blood flow impedance in the ovary and evaluate the degree of vascularization in the corpus luteum. There were significant differences in ovarian blood flow impedance between LPD cycles and normal weeks. Thus, the physiological and pathological reasons for luteal defects are clarified: insufficient vascularization of the corpus luteum may be the reason for the insufficient production of progesterone and the lack of luteal phase. The study suggests that abnormal blood flow in the ovary occurs in the early follicular phase and lasts until the luteal phase [37]. In the following two years, a prospective study on B-mode ultrasound and endometrial staging was conducted [38]. The study found that colour and pulsed Doppler analysis of small vessels in the corpus luteum and endometrium may help assess the adequacy of the luteal phase. In an article published in 2005 by the American Association of Reproductive Medicine [39], it was also noted that VEGF-dependent angiogenesis is crucial for endometrial development in the luteal phase. The level of progesterone in the corpus luteum was negatively correlated with ovarian, uterine, and spiral blood flow.

4.4. Clinical manifestations of LPD

4.4.1. Sterility

LPD is one of the causes of infertility observed in the clinic [40]. Approximately 3 %–10 % of patients with primary or secondary infertility show abnormal luteal function. The current view is that progesterone secretion is too low or for too short of a duration due to luteal defects, which leads to insufficient endometrial transformation or transformation reversal, preventing embryo implantation. A study also found that serum lipid peroxidation (a manifestation of hypoxia-induced damage to cells under all oxidation stress conditions) in patients with infertility is related to the hormonal environment of the LPD and to sympathetic nerve activity [41].

In 1992, many scholars studied and discussed the causes of LPD-associated infertility. There may be three potential pathogenic mechanisms of LPD. The most common is transient hyperprolactinemia, which is characterized by normal follicular development and a significant or transient increase in prolactin, which inhibits luteal function. Another reason is a high LH syndrome due to an improper proportion of LH/FSH and a relatively low FSH level, leading to luteal dysfunction. The third reason is due to a lack of corpus luteum itself. Although LH increases, progesterone secretion decreases [42]. Liu et al. [43] discussed the cause of infertility and spontaneous abortion in women with LPD from a pathological point of view and proposed that the expression of integrins in the endometrium of women with LPD and the formation of pinopodes change the expression of oestrogen and progesterone, thereby exacerbating the low fertility rate of the cycle and the high rate of embryo loss. Liu and Hong and other researchers believe that infertility caused by LPD is mainly related to the function of the pituitary GnRH receptor [44]. From a genetic perspective, some scientists found that Lgr4 plays a key role in female reproduction by regulating EGFR–ERK-mediated granulosa-lutein cell differentiation and corpus luteum function [45].

The relationship between LPD and infertility is complex. In the treatment of LPD, due to the lack of a clear diagnostic basis, it is difficult to determine the treatment plan. In early 1992, a statistical study showed that the use of progesterone suppositories or oral progesterone treatment had no significant effect on the pregnancy rate [46]. After further research, different views have emerged. In 2016, Check proposed a view contrary to that of the ASRM Practice Committee by stating that, compared to the use of follicle maturation-promoting drugs to treat patients with LPD and low fertility, it is more appropriate to use empirical progesterone therapy in the luteal phase for patients with "unexplained infertility" [47]. At present, for infertility of unknown cause, treatment methods (such as induced ovulation and assisted reproduction) have successfully induced pregnancy in women with LPD [4]. Clomiphene citrate has been successfully used in anovulatory cycles and LPD correction [48]. However, due to the small study sample and the lack of consensus on LPD diagnosis, the efficacy of such treatment methods needs to be further verified [49].

In the case of traditional Chinese medicine treatment, Zhou et al. [50,51] found that *Bushen Zhuyun* Decoction can reduce oestrogen and progesterone receptor levels and improve the expression of integrins α5 and β3, thereby improving the receptivity of the endometrium during embryo implantation and increasing the pregnancy rate. Based on this, they further studied the effect of cerebrospinal fluid (CSF) containing *Bushen Zhuyun* Decoction on the synthesis and secretion of GnRH in the anterior pituitary. The results showed that the decoction could increase the levels of GnRH receptors, transcription factors, and secretory vesicles and promote the secretion of FSH β and LH β [52]. Later, other studies found that *Bushen Zhuyun* Decoction had two effects on luteal function: first, it regulates the uterus and ovary downstream of the reproductive axis; second, it regulates the secretion of GnRH in the pituitary gland at the centre of the reproductive axis [53]. These studies support a promising candidate drug for the treatment of LPD and infertility.

4.4.2. Recurrent miscarriage (RM)

The local hormonal environment is crucial for embryo attachment and early pregnancy. Granular cells undergo luteinization after ovulation, forming part of the corpus luteum, and then secrete progesterone, causing secretory transformation of the endometrium, thus promoting embryo implantation. Before the placenta starts producing progesterone, the corpus luteum produces progesterone to provide the necessary support for early pregnancy. Hence, LPD will lead to implantation failure and miscarriage [54]. In clinical practice, 35 % of early pregnancy losses and 4 % of recurrent pregnancy losses are caused by luteal insufficiency [55]. Meresma et al. [56] reported for the first time a difference in cell proliferation and cell death levels between heterogeneous and homogeneous endometria in patients with infertility miscarriage. Studies have confirmed that infertility or RM in patients with LPD may be related to the increase in cell death in endometriosis samples [56].

However, the actual existence of LPD and its relationship with miscarriage is still controversial [57]. In 1997, Ogasawara et al. [20,58] raised doubts; they studied 197 RM cases and showed that pregnancy progesterone levels, oestradiol levels, and the progesterone/oestradiol ratio may not predict future pregnancy loss. However, in this study, serum progesterone in the middle segment of the corpus luteum was used as a marker of LPD. Since the diagnosis of LPD is still unclear, further research is needed, and the correlation between LPD and infertility and recurrent pregnancy loss needs further investigation [29].

Although the diagnostic criteria of LPD are still controversial, it seems beneficial to use progesterone in early pregnancy to treat patients with recurrent miscarriage and LPD [5]. The European Progestin Club believes that progesterone supplementation for patients with LPD plays an important role in early pregnancy miscarriage [55,59]. Luteal supplementation may also reduce the incidence of miscarriage in patients with preterm miscarriage [60]. Studies on unexplained recurrent miscarriages have shown that enhanced luteal support may have a protective effect against recurrent miscarriage [51].

4.4.3. Polycystic ovary syndrome (PCOS)

LPD and PCOS are independent diseases with common pathophysiological characteristics, and they both may originate from hyperinsulinaemia, high AMH levels, and corpus luteum angiogenesis defects [6]. Ovulating women with PCOS show defective progesterone secretion during the luteal phase. As a result, these women have low progesterone levels in the early luteal phase,

resulting in infertility. Therefore, LPD may be another possible cause of female infertility in PCOS. Using female rhesus monkeys as an experimental model, McGee et al. [61] also found that testosterone and a Western diet can damage metabolism and ovarian function, increase insulin insensitivity, increase the number of antral follicles in the middle of the cycle, and reduce the progesterone level in the circulating luteal phase.

The cause of progesterone deficiency in the luteal phase in women with PCOS is still unclear; however, this low progesterone expression in the luteal phase may be one of the reasons for early pregnancy loss. Meenakumari et al. [62] revealed the possible endocrine factors of LPD in women with PCOS. The study showed that patients with PCOS had excessive LH secretion in the luteal phase, which is negatively correlated with progesterone levels and positively correlated with insulin levels. This suggests that the high secretion of LH in women with PCOS may be caused by hyperinsulinaemia/insulin resistance and may be the cause of low progesterone levels, which also confirms previous conclusions. This study also clearly reported for the first time that metformin treatment can significantly increase progesterone concentration in the corpus luteum of patients with PCOS [62].

4.4.4. Perimenopausal syndrome

The menopausal transition period is characterized by LPD, an anovulatory cycle, and changes in weight and body composition. During the luteal phase of the menstrual cycle, the resting metabolic rate (RMR) increases. Cagnaci et al. [63] demonstrated that taking progesterone acetate (nomegesterone acetate, NOMAc) can supplement progesterone levels and increase RMR. They showed that periodic administration of NOMAc during the menopausal transition can help reduce negative changes in body composition [63].

4.5. LPD and assisted reproduction

4.5.1. Effect of luteal function and endometrial receptivity on embryo implantation in assisted reproduction

With the increasing application of assisted reproductive technology, some studies have found that controlled super-promoting of ovulation in assisted reproductive technology may cause luteal insufficiency. In human IVF, the control of ovarian hyperstimulation is necessary for the production of mature oocytes. Patients undergoing ART usually have luteal phase deficiency. The use of GnRH analogues and inhalation of granulosa cells during egg retrieval may weaken the ability of the corpus luteum to produce progesterone [54]. Edwards et al. [64] first proposed that ovarian stimulation may lead to LPD, which may lead to in vitro fertilization (IVF) failure. The study found that there were defects in the luteal phase in almost all IVF stimulation schemes.

Luteal phase hormonal supplementation schemes such as luteal hormone, human menopausal gonadotrophin (hMG), GnRH agonist/HMG, GnRH antagonist/HMG and other treatment schemes may reduce the level of LH, thus leading to LPD. The luteal defect in IVF is likely due to the physiological steroid level induced by ovarian stimulation (high oestradiol level in the early luteal phase) directly through the hypothalamic-pituitary-ovarian axis negative feedback loop, thereby inhibiting the release of pituitary LH [65]. The hyperphysiological levels of oestradiol and progesterone in the early luteal phase may lead to late development of the endometrium and poor environmental acceptance of the endometrium, which will lead to asynchrony between the embryo and the endometrium and reduce the pregnancy rate in the IVF cycle. A hormonal environment with a high progesterone level or an altered oestradiol/progesterone ratio may affect the development of the endometrium and ultimately affect embryo implantation [56,66]. Additionally, impaired oocyte maturation or poor-quality embryos may cause insufficient follicle maturation, thereby reducing the production of progesterone in the corpus luteum. Therefore, some scholars believe that the level of corpus luteum progesterone in systemic circulation may not be an indicator of endometrial receptivity but rather an indicator of the quality of oocytes and synthetic progesterone.

4.5.2. Corpus luteum support

It was previously believed that the exogenous use of natural or synthetic progesterone to support the endometrium in the luteal phase of ART would have harmful effects on the foetus. With the progress of research, the effectiveness and safety of exogenous progesterone have been confirmed, and it has become the most commonly used clinical approach (progesterone or HCG luteal phase support) [64]. However, in different cases of embryo transfer, luteal support must be personalized according to the patient [67].

For LPD caused by GnRH agonists during IVF, most clinicians choose the luteal phase to supplement various steroid hormones to improve the reproductive success rate. In general, clinicians have confirmed via evidence-based methods that progesterone is effective for infertility or repeated pregnancy loss caused by LPD, and is therefore recommended for providing luteal support in the IVF cycle [68]. Pritts and Atwood [69] conducted a meta-analysis of several homogeneous randomized controlled trials. The results showed that, considering that the use of HCG would increase the risk of ovarian hyperstimulation syndrome, progesterone injection while supplementing oestrogen in the luteal phase was the preferred treatment scheme. It is also believed that vaginal gel containing microparticle progesterone is better for luteal support [70]. Asada et al. [71] conducted research on the clinical utility of chlormadinone acetate (Lutoral™) in frozen-thawed embryo transfer, and the results showed that chlormadinone acetate has neither androgen nor follicle hormone effects, which is equivalent to the pregnancy rate supported by vaginal progesterone, and will not increase the risk of birth defects or the incidence of hypospadias.

A 2015 Cochrane analysis showed that luteal support in the early luteal phase of ART increased the rate of sustained pregnancy and live birth [72]. A meta-analysis of the effectiveness of luteal support after ovulation induction (OI)/intrauterine insemination (IUI) was conducted in 2017. The results suggested that the clinical pregnancy rate was high in the progestin supplementation group after OI and IUI (RR = 1.34, 95 % CI 1.15–1.57), especially in patients treated with human menopausal gonadotropin (h MG) for ovulation, and the clinical pregnancy rate (RR = 1.56, 95 % CI 1.21–2.02) and live birth rates (RR = 1.77, 95 % CI 1.30–2.42) were higher after progestogen supplementation [73].

4.5.3. Ovarian stimulation

Many scholars have different opinions on whether the combination of GnRH agonist and hMG will produce iatrogenic luteal insufficiency. Duffy et al. [74] evaluated the correlation between the use of the GnRH agonist leuprorelin acetate (LA) and the increased incidence of luteal dysfunction in patients receiving controlled ovarian hyperstimulation and intrauterine insemination (IUI). The results showed that pituitary downregulation using LA as an auxiliary hMG superovulation therapy in the mid-luteal phase seemed to be unrelated to luteal phase dysfunction in the IUI cycle. Endometrial biopsy in the late luteal phase and serum hormone determination in the mid-luteal phase also confirmed this point. The study by Stovall et al. [75] demonstrated that preovulatory gonadotropin suppression followed by ovarian stimulation with hMG in women undergoing assisted reproductive techniques (ART) does not result in luteal insufficiency in the majority of women. These are contrary to an earlier study by Smitz et al. [76]. This may also be related to the different pharmacokinetic characteristics caused by the use of different GnRH drugs. The differences in these results may be due to the data extrapolated from IVF cycles not being applicable to hMG, LA, and IUI cycles. In IUI cycles compared to IVF, there is less pronounced follicular development and lower levels of E2. The high E2 levels achieved in superovulation cycles are associated with premature luteolysis [77]. Additionally, the extraction of follicles in IVF removes a significant mass of granulosa cells. This mechanical injury to the follicles may contribute to corpus luteum insufficiency [78].

Intrauterine insemination (IUI) is often performed in conjunction with controlled ovarian hyperstimulation (COH). COH involves the use of fertility medications such as Clomiphene citrate and/or Gonadotropin to stimulate the ovaries and promote the development of multiple follicles [79]. In stimulated cycles it is compromised due to hormonal imbalance and hyperestrogenemic state. Progesterone supplementation is the most commonly used treatment in IUI cycles. Khosravi D et al. [80] found that the effectiveness of oral dydrogestrone as luteal-phase support for women undergoing IUI cycles was comparable to that of vaginal progesterone. Furthermore, the dydrogestrone group exhibited higher mean serum progesterone levels and satisfaction rates than the cyclogest group. However, some studies have shown that there is no significant improvement in the pregnancy rate with luteal phase support in comparison with unsupported cycles in IUI [81,82]. The effectiveness of luteal support in intrauterine insemination (IUI) or gonadotropin ovulation cycles was found to be higher, whereas no significant effect was observed with clomiphene. This variation may be attributed to the different methods of inducing ovulation and the potential differences in endogenous luteal phase function, the underlying mechanism of which remains unknown [79,83].

Luteal phase stimulation will not lead to a premature surge of LH or cause serious complications [84,85]. It is known to be an IVF stimulation scheme that can produce the best pregnancy outcome [86]. The efficacy and safety of low-dose gonadotropin stimulation in non-IVF cycles have been confirmed. The use of GnRH agonists can induce ovulation in patients with multiple follicular developments without causing ovarian enlargement and hyperstimulation syndrome. A low dose of HCG luteal support combined with a GnRH agonist can still prevent ovarian hyperstimulation syndrome and can partially compensate for the harmful effects of a GnRH agonist on luteal function [87]. The application of GnRH agonists in patients with LPD after embryo transfer can increase the level of blood progesterone and increase the chances of pregnancy and fertility [88]. Long-term use of GnRH agonists to support the luteal phase is beneficial to pregnancy after IVF. Using HCG or progesterone, with progesterone as the first choice, to support the luteal phase after assisted reproduction can increase the pregnancy rate. Regarding the route of administration, the intramuscular route seems to be more beneficial than the oral and vaginal routes, but the ideal dose, optimal route, and duration of administration need to be further clarified [89].

5. Directions for future research

Insufficient luteal function is a common female reproductive endocrine disorder. Luteal dysfunction can be caused by various diseases, such as infertility, recurrent miscarriage, polycystic ovary syndrome, and menopausal syndrome. However, the pathogenesis and diagnosis of these conditions are still unclear. Future studies should focus on exploring the following aspects:

(1) Pathogenesis of luteal phase defect (LPD): Current research suggests that LPD is mainly associated with endocrine changes, including luteal deficiency, decreased ovarian reserve function, and short-term stress. Further investigation is needed to clarify the underlying causes and provide evidence for effective treatment.
(2) Diagnosis of luteal insufficiency: Various methods are currently used to evaluate luteal function, such as basal body temperature (BBT) measurement, mid-luteal progesterone level measurement, endometrial biopsy, and pathological examination. Timely measurement of progesterone during the luteal phase can be a convenient method for assessing luteal function. In the future, the expression level of glycodelin PP14, a biomarker of uterine receptivity, could potentially serve as an indicator for evaluating luteal function. Color Doppler ultrasound can also be utilized to assess both the endometrium and corpus luteum, compensating for the limitations of BBT monitoring, endometrial histology, or plasma progesterone levels. Comprehensive auxiliary examinations can improve the assessment of luteal function and guide treatment decisions.
(3) Treatment of luteal insufficiency: Luteal supplementation, particularly with progesterone or HCG, has shown benefits for patients with various conditions, especially infertility and those undergoing assisted reproduction. Progesterone is the preferred choice, with intramuscular administration being potentially more effective than oral or vaginal administration. However, individualized treatment plans should be developed based on each patient's specific condition.

Future studies should aim to further determine appropriate dosages, routes of administration, and treatment durations. Additionally, involving more clinical medical staff in the evaluation, selection, and innovation of current treatment methods will contribute to the development of a comprehensive diagnosis and treatment theory.

6. Conclusion

By systematically analysing the literature on LPD, this study explored the dynamic development process of scientific knowledge on network pharmacology using a scientific knowledge graph. There are several significant advantages in our study. First, this study analysed the global research trends of LPD by using the scientometric method, which can provide research hot spots and future directions. Second, the present study utilized widely adopted scientometric software tools and the "bibliometrix" R package in tandem to carry out the analysis, yielding more comprehensive results. Despite the strengths mentioned above, the limitations of our study should be noted. Since the WoSCC database updates the included research continuously, some recently published and potentially influential papers may not have been included in our study, and the bibliometric analysis results might be missing some of the latest research. In summary, it has been reported that there are many causes of LPD, and although LPD has been considered a cause of infertility and early pregnancy loss for many years, there is still a lack of quality research on the diagnostic criteria and treatment of LPD. Therefore, the aetiology and pathogenesis of LPD still merit further exploration by scholars.

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Data availability statement

Not applicable. Data included in article in article.

Ethics declarations

Approval by an ethics committee was not needed, and informed consent was not required for this study because it does not involve ethical considerations.

For ethics approval

Not applicable.

CRediT authorship contribution statement

Lingli Shi: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Lijuan Cui:** Investigation, Data curation, Conceptualization. **Li Yang:** Methodology. **Lijia He:** Data curation. **Lehan Jia:** Data curation. **Wenxin Bai:** Data curation. **Lihong Wang:** Writing – review & editing, Writing – original draft. **Wenting Xu:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

LPD	Luteal phase defect
ART	Assisted reproductive technology
Gn RH-a	GnRH agonist
TLS	The total link strength
IVF	In vitro fertilization
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone

AMH	Anti-Müllerian hormone
E2	Oestradiol
DOR	Decreased ovarian reserve
LB	Luteal bleeding
MLP	Middle luteal phase
BBT	Basal body temperature
RSA	Recurrent spontaneous abortion
CSF	Cerebrospinal fluid
EA	Energy availability
RM	Recurrent Miscarriage
PCOS	Polycystic Ovary Syndrome
RMR	Resting metabolic rate
hMG	Human menopausal gonadotrophin
NOMAc	Nomegesterone acetate
HCG	Human chorionic gonadotropin
LA	Leuprorelin acetate
IUI	Intrauterine insemination
COH	Controlled ovarian hyperstimulation

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