

# Research trends and Hotspots of Thrombophilia with recurrent pregnancy loss: a Bibliometric Analysis

**Ying-jun Deng**

Xiyuan Hospital of China Academy of Chinese Medical Sciences

**Sheng-Jing Liu**

Xiyuan Hospital of China Academy of Chinese Medical Sciences

**Ming Zhao**

Xiyuan Hospital of China Academy of Chinese Medical Sciences

**Feng Zhao**

Xiyuan Hospital of China Academy of Chinese Medical Sciences

**Jun Guo**

Xiyuan Hospital of China Academy of Chinese Medical Sciences

**Yu-xiao Huang** (✉ [13581922080@139.com](mailto:13581922080@139.com))

Xiyuan Hospital of China Academy of Chinese Medical Sciences

---

## Research Article

**Keywords:** Thrombophilia, Recurrent Pregnancy Loss, Bibliometric Analysis

**Posted Date:** July 27th, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-1782428/v1>

**License:** © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

**Background:** Thrombophilia is a group of disorders that result in a blood hypercoagulable state and induce thrombosis, which was found widely existed in recurrent pregnancy loss (RPL). More and more research about thrombophilia has been conducted but the association between thrombophilia and RPL remains uncertain. Thus, it's necessary to combine relevant literature to find the research hotspots and analyze the internal link between different study points, and then predict the development trend in RPL with thrombophilia.

**Methods:** Relevant articles between 1990 and 2022 were obtained from the Web of Science (WoS) database. Software VOSviewer and CiteSpace were used to perform the analysis and conduct visualization of scientific productivity and emerging trends.

**Results:** 742 articles published in recent 30 years by 3205 authors from 1139 organizations and 68 countries were analyzed. 37 authors, 38 countries, and 53 organizations published papers  $\geq 5$ . The USA was the most productive country and Univ Amsterdam was the most productive institution. Journal *thrombosis and haemostasis* had the most total citations. In keyword and clusters, factor-v-Leiden, inherited thrombophilia, activated protein-c, low-dose aspirin, molecular-weight heparin, polymorphism had high-frequency focus on its etiology, diagnostics, and therapeutics. The strongest keyword bursts showed the research hotspots changed over time.

**Conclusions:** By Bibliometric Analysis, we comprehensively reviewed publications related to thrombophilia and RPL during the past 30 years. The research in the relationship between thrombophilia and RPL suggested that there could be differences in the clinical relevance of the different types of thrombophilia. And we should attach more attention to this relationship in in-vitro fertilization.

## 1. Introduction

Thrombophilia, which is a group of disorders that result in a blood hypercoagulable state and induce thrombosis [1,2], tends to resemble a prethrombotic state (PTS) and is associated with the risk of deep venous thrombosis and/or venous thromboembolism. Thrombophilia can be divided into hereditary thrombophilia and acquired thrombophilia [3], primary disorders or genetic causes of thrombophilia include factor V Leiden mutation, deficiency of antithrombin III, protein C or S, histidine-rich glycoprotein deficiency, and prothrombin-related thrombophilia [4]. Sometimes the thrombosis occurs in uncommon sites, such as the splanchnic veins, cerebral veins, and retinal veins. It was believed that thrombophilia was more closely related to vascular diseases, such as Arterial Ischemic Stroke, Alzheimer's disease, pulmonary embolism, etc [5-8]. Furthermore, thrombophilia was found widely existed in recurrent pregnancy loss (RPL) and cause pregnancy complications [9-15]. Different types of thrombophilia cause difference in different pregnancy stage. There is a large scale of research in this area, involving diagnostic markers, mechanisms, and treatments. One study showed that at least one thrombophilic defect was found in most patients with RPL [16]. But the association between thrombophilia and RPL

remains uncertain [17,18]. Therefore, it is necessary to combine relevant literature to find the research hotspots and analyze the internal link between different study points, and then predict the development trend in RPL with thrombophilia.

## 2. Materials And Methods

### *2.1 Data Source and Search Strategy*

We searched the Web of Science (WoS) database to collate recurrent pregnancy and Thrombophilia studies between 1970 and 2022. The database source was limited to Science Citation Index Expanded (SCIE) and publication types to “article”, and the language of publications was limited to English. We use Boolean Operator [AND] to retrieve papers related. The main search terms were as described below: “recurrent miscarriage”, “Recurrent Abortions”, “habitual abortion”, “recurrent pregnancy loss”, and “Thrombophilia”. All eligible data from the WoS were downloaded for further analysis by scientometric tools.

After that, we derived a full record of all documents, and merged multiple exported files to the same file. Then use Citespace 5.1 software to remove the duplicates.

### *2.2 Statistical Analysis*

Two reviewers skimmed the titles and removed the useless literature. Data cleaning was performed prior to analysis, and meaningless keywords and synonyms of search terms were deleted.

VOSviewer (1.6.16) was used to identify keywords, author keywords, productive countries, organizations, and the main co-cited journals, related visual networks were also constructed. CiteSpace (5.0. R1) was used to construct cluster analysis of high-frequency keywords based on the clustering function and annual burst keywords. We managed the data and analyzed the publication tendency using Microsoft Office Excel 2019 (Microsoft Corporation, Redmond, WA, United States). In the VOSviewer network maps, the size of the nodes reflects the number of studies or co-occurrence frequencies, the links between nodes represent the co-occurrence relationships, and the size of the links indicates the cooccurrence frequencies of two nodes. The impact factors(IFs) of the academic journals were collected from the 2022 Journal Citation Reports (JCR) (Clarivate Analytics, Philadelphia, USA).

## 3. Results

### *3.1 Analysis on the Amount of Published Papers*

A total of 1347 articles were retrieved, and 745 of them were left after removing duplicates by the established retrieval strategy. Finally, 742 papers remained after weeded by reading the title and abstract. As we can see in Fig. 1, the first article about thrombophilia and RPL was published in 1995 [19]. Then the number of published articles began to increase after that and maintained an average annual publication

volume of 30 globally. The trend of the number of documents issued conforms to the logarithmic function as  $y=11.658\ln(x)-1.7653$ .

### 3.2 Authors, organizations, and countries

Fig. 2 showed the connections between 37 authors' published papers  $\geq 5$  of the total 3205 authors in adopted articles (1.15%). As can be seen in Fig. 2A, 2B, and 2C, all the authors came from 1139 organizations and 68 countries and were from different research teams. In order to see the relationship among them, we reserved the documents  $\geq 5$  in the Fig. 2A and Fig. 2B, 38 countries and 53 institutions miss the requirement. We then listed the rank of author, country, institution by their productions and citations to see the industry power and internal relationship among them. The top 10 most contributed countries and institutes about thrombophilia and RPL were shown in Table 1 and institutions in Table 2. The USA was the top1 of all the countries and the Univ Amsterdam was the top1 in all the institutions. The sizes of nodes reflected the publications quantity and the width of lines reflects the collaborations between them in the figure.

### 3.3 Papers and journals

All the 1347 articles were published in 226 journals, set Boundary value as 5,33 journals reserved in Fig. 2D. The top 10 co-cited journals and articles about thrombophilia with RPL were listed in Table 3 and Table 4. *Thrombosis and haemostasis* had the most total citations, and the most cited article was Rey (2003) "Thrombophilic disorders and fetal loss: a meta-analysis". How thrombophilia leads to RPL is still a critical question and the diagnosis and treatment of it is ongoing in the world.

**Table 1** The top 10 countries and institutes contributed to publications about thrombophilia with RPL.

Rank	Country	Document	Citations	Institution/Country	Documents	Citations
1	USA	103	3632	Univ Amsterdam/ Netherlands	28	1531
2	German	70	1755	Rambam Med Ctr/Israel	25	1413
3	England	66	3496	Tel Aviv Univ/Israel	15	982
4	Israel	66	3392	Leiden Univ/Holland	15	654
5	Italy	64	2652	Technion Israel Inst /Israel	13	556
6	Netherlands	48	2384	Univ Ottawa Hosp/Canada	11	490
7	France	43	1697	King Edward Mem Hosp/India	10	137
8	Turkey	38	297	Chaim Sheba Med Ctr/Israel	9	683
9	Spain	32	1466	Univ Foggia/Italy	9	228
10	China	31	260	Univ Belgrade/Serbia	9	31

**Table 2** Author contributed to publications about thrombophilia with RPL.

Rank	Author	Organization	Documents	Citations
1	Brenner	Rambam Med Ctr/Israel	23	1440
2	Middeldorp	Univ Amsterdam /Netherlands	17	796
3	Regan	Univ London Imperial Coll/England	10	963
4	Goddijn	Univ Amsterdam/Netherlands	10	547
5	Grandone	Casa Sollievo Della Sofferenza/Italy	9	94
6	Blumenfeld	Rambam Med Ctr/Israel	8	781
7	Rogenhofer	Klinikum Der Ludwig-Maximilians-Universität München/Germany	8	242
8	Ghosh	KEM Hospital/India	8	100
9	Shetty	KEM Hospital/India	8	100
10	Kovac	Blood Transfusion Institute of Serbia/Serbia	8	35

**Table 3** The top 10 co-cited journals about thrombophilia with RPL.

Rank	Journal	IF	Country	Documents	Citations
1	<i>Thrombosis and Haemostasis</i>	5.249	Germany	33	2219
2	<i>Human Reproduction</i>	6.918	England	39	1617
3	<i>Lancet</i>	60.39	England	5	1375
4	<i>American journal of Reproductive Immunology</i>	3.886	USA	35	1128
5	<i>Fertility and Sterility</i>	7.329	USA	23	859
6	<i>Journal of Thrombosis and Haemostasis</i>	5.824	England	31	797
7	<i>Blood</i>	17.543	USA	12	577
8	<i>British Journal of Haematology</i>	5.518	England	8	563
9	<i>Seminars in Thrombosis and Hemostasis</i>	2.892	USA	18	451
10	<i>Thrombosis Research</i>	2.869	USA	40	447

**Table 4** The top 10 highly cited articles about thrombophilia with RPL.

Rank	Document	Title	Journal	Citations
1	Rey (2003)	Thrombophilic disorders and fetal loss: a meta-analysis	<i>Lancet</i>	585
3	Regan (2000)	Recurrent miscarriage - an aspirin a day?	<i>Human Reproduction</i>	322
4	Kaandorp (2010)	Aspirin plus Heparin or Aspirin Alone in Women with Recurrent Miscarriage	<i>New England Journal of Medicine</i>	289
5	Keeling (2012)	Guidelines on the investigation and management of antiphospholipid syndrome	<i>British Journal of Haematology</i>	278
6	Haverkate (1995)	Familial dysfibrinogenemia and thrombophilia. Report on a study of the SSC Subcommittee on Fibrinogen	<i>Thromb Haemost</i>	264
7	Martinelli (2000)	Mutations in coagulation factors in women with unexplained late fetal loss	<i>New England Journal of Medicine</i>	253
8	Brenner (2000b)	Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxaparin	<i>Thrombosis and Haemostasis</i>	239
9	Laskin (2009)	Low Molecular Weight Heparin and Aspirin for Recurrent Pregnancy Loss: Results from the Randomized, Controlled HepASA Trial	<i>Journal of Rheumatology</i>	232
10	grandone (1997)	Factor V Leiden is associated with repeated and recurrent unexplained fetal losses	<i>Thrombosis and Haemostasis</i>	231

### 3.4 Keywords and clusters

There were 2096 keywords in 742 articles that were analyzed. For a better understanding of the relationship among them, the keywords meaning to correlative subject headings were removed from the list, and the keywords with similar meanings were merged for analysis. The frequencies of keywords greater than or equal to 5 ( $T \geq 5$ ) were used to construct the co-occurrence network map, as shown in Fig. 3A. (The nodes size reflects the frequency of keywords, and the lines between nodes reflects the correlation between keywords.). The significant keywords include factor-v-Leiden, inherited thrombophilia, activated protein-c, low-dose aspirin, molecular-weigh heparin, polymorphism, etc. All the keywords indicated that research about thrombophilia and RPL focused on its etiology, diagnostics, and therapeutics.

Cluster analysis using the K-means algorithm was conducted and identified 10 distinct clusters as shown in Fig. 3B. The Q value was 0.43 (Q value is the clustering module value,  $Q > 0.3$  means that the clustering

result is significant), and the  $s$  value was 0.64 ( $s$  value is the average contour value of clustering,  $s > 0.5$  means that the clustering is reasonable). Cluster 1, 5, and 9 showed the association between inherited thrombophilia and RPL. Cluster 3, 6, and 7 showed acquired thrombophilia with RPL. Cluster 0 emphasized the application of anticoagulants in thrombophilia in RPL.

As shown in Fig. 3D, the strongest keyword bursts were analyzed according to the year of publication, which made it possible to find the research hotspots changes over time.

## 4. Discussion

Since the first article about thrombophilia and RPL was published in 1995 [19], 742 articles were published by 3205 authors from 1139 organizations and 68 countries. The knowledge domain and emerging trends in thrombophilia and RPL have been analyzed by scientometric research based on VOSviewer and CiteSpace to offer a better understanding of its development in the past 30 years for researchers.

The annual output of thrombophilia and RPL related publications was steady. The USA kept the lead in publications and citations, followed by Germany and England. The important journals in this area came from these countries such as *thrombosis and haemostasis*, *human reproduction*, *lancet*, and *American journal of reproductive immunology*. The *Univ Amsterdam* and *Rambam Med Ctr* were the most important institutions in thrombophilia and RPL with considerable publications and citations. So as the influential authors were from these research teams, such as Brenner from Rambam Med Ctr in Israel, Middeldorp from Univ Amsterdam in the Netherlands. The two institutions combined as two centers in the research of thrombophilia and RPL. Both the research teams and countries needed more communication with each other.

Factor V Leiden was found earlier as can be seen in Fig. 3A and Fig. 3C, and it was the most common genetic risk factor in thrombophilia [20]. The most cited paper was a meta-analysis about Thrombophilic disorders and fetal loss published in *Lancet*. Their finding showed limited data were available on the association between maternally inherited thrombophilia and RPL [20]. It was still necessary to suggest that the assessment of women with early recurrent fetal loss should include screening for factor V Leiden, activated protein C resistance, PTm, and protein S deficiency, whereas women with late fetal loss should be tested for factor V Leiden, PTm, and protein S deficiency [21]. Later research shows that inherited thrombophilia or gene polymorphism include the factor V Leiden, methylenetetrahydrofolate reductase (MTHFR), and prothrombin G20210A (PTm) mutations, and deficiencies of protein C, protein S, and antithrombin [18,22,23] still showed relevance between them.

The association between acquired thrombophilia with RPL attract more attention in recent years. Antiphospholipid syndrome (APS) is the only proven thrombophilia that is associated with adverse pregnancy outcomes [24]. APS is an autoimmune disease characterized by the presence of antiphospholipid antibodies (aPLs), such as lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti- $\beta$ 2-glycoprotein 1 antibodies ( $\beta$ 2GPI) [25]. These aPLs are the main laboratory criteria. But the

role of classical serological markers is limited in the assessment of the thrombotic risk [26]. aPLs positive is not the only diagnostic criteria, but the APS diagnostic criterion is not clear up to now.

The presence of aPLs was a major acquired thrombophilia and predisposes to venous thrombosis, arterial thrombosis, and microvascular thrombosis [26]. It was widely accepted that aPL caused placental thrombosis, and APLs might change the number of cytokines and hormones and result in inflammation and change in the function of the trophoblast, which led to infertility, RPL, and recurrent implantation failure(RIF) [27,28]. The application of anticoagulants and immune agents was the research hotspot of APS and RPL. Aspirin or heparin or both for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and RPL [29,30]. And the antimalarial hydroxychloroquine (HCQ) is currently the center of attention in thrombotic APS and is recognized as safe [27]. But more research is expected to prove the effectiveness of these drugs.

## 5. Conclusion

As we are unlikely to have introduced important selection bias by excluding non-English-language studies, there must be some deficiencies in this study. We can still draw some conclusions that both inherited and acquired thrombophilia are related to RPL. The assessment of women with RPL is limited at present. So, the research on the relationship between thrombophilia and RPL suggests that there could be differences in the clinical relevance of different types of thrombophilia [30]. More clinical trials and basic research are needed in the future and we should attach more attention to in-vitro fertilization.

## Abbreviations

LA: Lupus anticoagulant;

RPL: Recurrent Pregnancy Loss;

APS: Antiphospholipid syndrome;

PTS: Prethrombotic state;

MTHFR: Methylenetetrahydrofolate reductase;

aPLs: Antiphospholipid antibodies;

aCL: Anticardiolipin antibodies;

$\beta$ 2GPI: Anti- $\beta$ 2-glycoprotein 1 antibodies;

RIF: Recurrent implantation failure.

## Declarations

## **Acknowledgements**

Not applicable.

## **Authors' contributions**

YJD: data collection, data analysis and manuscript writing. SJL and MZ: data collection and data analysis. FZ: manuscript writing. JG and YXH: manuscript revising. All authors read and approved the final manuscript.

## **Authors' information**

JG and YXH are employed by Xiyuan Hospital of China Academy of Chinese Medical Sciences. YJD and SJL are Ph.D of this institution, FZ is a postgraduate student in this institution. MZ is a Ph.D of Beijing University of Chinese Medicine. The National Natural Science Foundation Program provided funding for this study.

## **Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## **Ethics approval and consent to participate**

Not applicable.

## **Consent for publication**

Not applicable.

## **Competing interests**

The authors have no conflicts of interest to declare.

## **Author details**

Xiyuan Hospital of China Academy of Chinese Medical Sciences, Beijing 100091, China.

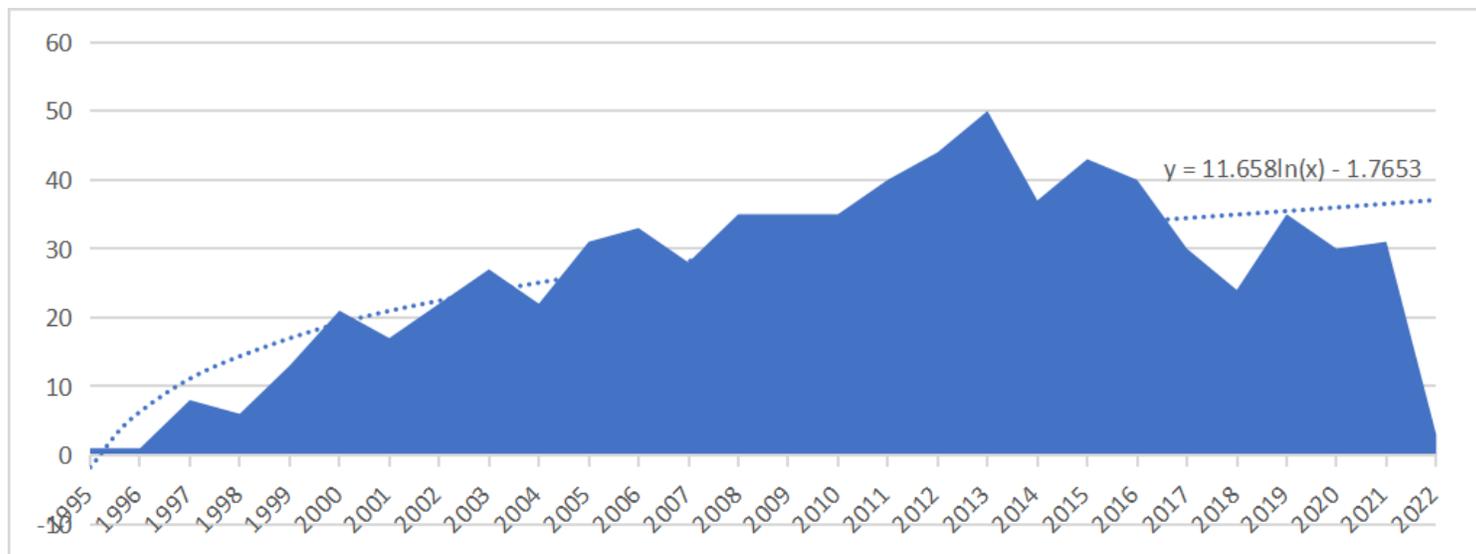
## **References**

1. Middeldorp S. Inherited thrombophilia: a double-edged sword. Hematology Am Soc Hematol Educ Program. 2016;2016:1-9, doi: 10.1182/asheducation-2016.1.1.

2. Dautaj A, Krasi G, Bushati V, Precone V, Gheza M, Fioretti F, et al. Hereditary thrombophilia. *Acta Biomed.* 2019;90:44-6, doi: 10.23750/abm.v90i10-S.8758.
3. Stevens SM, Woller SC, Bauer KA, Kasthuri R, Cushman M, Streiff M, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. *J Thromb Thrombolysis.* 2016;41:154-64, doi: 10.1007/s11239-015-1316-1.
4. Dautaj A, Krasi G, Bushati V, Precone V, Gheza M, Fioretti F, et al. Hereditary thrombophilia. *Acta Biomed.* 2019;90:44-6, doi: 10.23750/abm.v90i10-S.8758.
5. Chiasakul T, De Jesus E, Tong J, Chen Y, Crowther M, Garcia D, et al. Inherited Thrombophilia and the Risk of Arterial Ischemic Stroke: A Systematic Review and Meta-Analysis. *J Am Heart Assoc.* 2019;8:e12877, doi: 10.1161/JAHA.119.012877.
6. Obaid M, El-Menyar A, Asim M, Al-Thani H. Prevalence and Outcomes of Thrombophilia in Patients with Acute Pulmonary Embolism. *Vasc Health Risk Manag.* 2020;16:75-85, doi: 10.2147/VHRM.S241649.
7. Green D. Thrombophilia and stroke. *Top Stroke Rehabil.* 2003;10:21-33, doi: 10.1310/L9KD-N5N8-69X0-08QK.
8. Stern RM, Al-Samkari H, Connors JM. Thrombophilia evaluation in pulmonary embolism. *Curr Opin Cardiol.* 2019;34:603-9, doi: 10.1097/HCO.0000000000000668.
9. Liu X, Chen Y, Ye C, Xing D, Wu R, Li F, et al. Hereditary thrombophilia and recurrent pregnancy loss: a systematic review and meta-analysis. *Hum Reprod.* 2021;36:1213-29, doi: 10.1093/humrep/deab010.
10. Bennett SA, Bagot CN, Arya R. Pregnancy loss and thrombophilia: the elusive link. *Br J Haematol.* 2012;157:529-42, doi: 10.1111/j.1365-2141.2012.09112.x.
11. McNamee K, Dawood F, Farquharson RG. Thrombophilia and early pregnancy loss. *Best Pract Res Clin Obstet Gynaecol.* 2012;26:91-102, doi: 10.1016/j.bpobgyn.2011.10.002.
12. Kupferminc MJ. Thrombophilia and pregnancy. *Curr Pharm Des.* 2005;11:735-748, doi: 10.2174/1381612053381855.
13. Simcox LE, Ormsher L, Tower C, Greer IA. Thrombophilia and Pregnancy Complications. *Int J Mol Sci.* 2015;16:28418-28, doi: 10.3390/ijms161226104.
14. Carp HJ. Thrombophilia and recurrent pregnancy loss. *Obstet Gynecol Clin North Am.* 2006;33:429-2, doi: 10.1016/j.ogc.2006.05.012.
15. Coumans AB, Huijgens PC, Jakobs C, Schats R, de Vries JI, van Pampus MG, et al. Haemostatic and metabolic abnormalities in women with unexplained recurrent abortion. *Hum Reprod.* 1999;14:211-4, doi: 10.1093/humrep/14.1.211.
16. Sarig G, Younis JS, Hoffman R, Lanir N, Blumenfeld Z, Brenner B. Thrombophilia is common in women with idiopathic pregnancy loss and is associated with late pregnancy wastage. *Fertil Steril.* 2002;77:342-7, doi: 10.1016/s0015-0282(01)02971-5.

17. Bennett SA, Bagot CN, Arya R. Pregnancy loss and thrombophilia: the elusive link. *Br J Haematol*. 2012;157:529-42, doi: 10.1111/j.1365-2141.2012.09112.x.
18. Barut MU, Bozkurt M, Kahraman M, Yıldırım E, Imirzalıoğlu N, Kubar A, et al. Thrombophilia and Recurrent Pregnancy Loss: The Enigma Continues. *Med Sci Monit*. 2018;24:4288-94, doi: 10.12659/MSM.908832.
19. Greer IA. Thrombophilia: implications for pregnancy outcome. *Thromb Res*. 2003;109:73-81, doi: 10.1016/s0049-3848(03)00095-1.
20. Kujovich JL. Factor V Leiden thrombophilia. *Genet Med*. 2011;13:1-16, doi: 10.1097/GIM.0b013e3181faa0f2.
21. Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. *Lancet*. 2003;361:901-8, doi: 10.1016/S0140-6736(03)12771-7.
22. Ahangari N, Doosti M, Mousavifar N, Attaran M, Shahrokhzadeh S, Memarpour S, et al. Hereditary thrombophilia genetic variants in recurrent pregnancy loss. *Arch Gynecol Obstet*. 2019;300:777-82, doi: 10.1007/s00404-019-05224-7.
23. Bigdeli R, Younesi MR, Panahnejad E, Asgary V, Heidarzadeh S, Mazaheri H, et al. Association between thrombophilia gene polymorphisms and recurrent pregnancy loss risk in the Iranian population. *Syst Biol Reprod Med*. 2018;64:274-82, doi: 10.1080/19396368.2018.1456576.
24. McNamee K, Dawood F, Farquharson R. Recurrent miscarriage and thrombophilia: an update. *Curr Opin Obstet Gynecol*. 2012;24:229-34, doi: 10.1097/GCO.0b013e32835585dc.
25. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4:295-306, doi: 10.1111/j.1538-7836.2006.01753.x.
26. Gavriş CM, Nedelcu LD, Pascu AM. Thrombotic risk in antiphospholipidic syndrome: From hypothesis to current evidence (Review). *Exp Ther Med*. 2021;21:287, doi: 10.3892/etm.2021.9718. Schreiber K, Hunt BJ. Managing antiphospholipid syndrome in pregnancy. *Thromb Res*. 2019;181 Suppl 1:S41-6, doi: 10.1016/S0049-3848(19)30366-4.
27. Mahdian S, Pirjani R, Favaedi R, Movahedi M, Moini A, Shahhoseini M. Platelet-activating factor and antiphospholipid antibodies in recurrent implantation failure. *J Reprod Immunol*. 2021;143:103251, doi: 10.1016/j.jri.2020.103251.
28. Wang M, Zhang P, Yu S, Zhou G, Lv J, Nallapothula D, et al. Heparin and aspirin combination therapy restores T-cell phenotype in pregnant patients with antiphospholipid syndrome-related recurrent pregnancy loss. *Clin Immunol*. 2019;208, doi: 10.1016/j.clim.2019.108259.
29. Hamulyák EN, Scheres LJ, Marijnen MC, Goddijn M, Middeldorp S. Aspirin or heparin or both for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and recurrent pregnancy loss. *Cochrane Database Syst Rev*. 2020;5:D12852, doi: 10.1002/14651858.CD012852.pub2.
30. Han AR, Han JW, Lee SK. Inherited thrombophilia and anticoagulant therapy for women with reproductive failure. *Am J Reprod Immunol*. 2021;85:e13378, doi: 10.1111/aji.13378.

# Figures



**Figure 1**

**Numbers of articles by year of publication related to Thrombophilia from 1995 to 2022.**

**Figure 2**

**The distribution of countries, institutions, authors, and journals on thrombophilia and RPL research. (A)** Map of countries with publications on thrombophilia and RPL. **(B)** Map of institutions with publications on thrombophilia and RPL. **(C)** Map of authors with publications on thrombophilia and RPL. **(D)** Map of journals with publications on thrombophilia and RPL.

**Figure 3**

Analysis of keywords on thrombophilia and RPL. **(A)** The co-occurrence analysis of keywords on thrombophilia with RPL. **(B)** The cluster map of keywords on thrombophilia with RPL. **(C)** The time zone map of keywords co-occurrence analysis on thrombophilia with RPL. **(D)** The burst keywords of keywords on thrombophilia with RPL.