Original Article

Emerging trends and frontier research on recurrent implantation failure: a bibliometric analysis

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Background: Recurrent implantation failure (RIF) has been recognized to be a major obstacle to the successful application of artificial reproduction technologies. In this study, the trends in RIF research were examined through a bibliometric analysis evaluating relevant literature quantitatively and qualitatively.

Methods: A total of 1,764 publications from 2000 to 2020 were downloaded from the Web of Science Core Collection (WoSCC). Relevant articles were searched using the term "recurrent implantation failure" and other synonyms of this term. Using Excel 2013, CiteSpace V, and VOSviewer 1.6.10 software, data extracted from the literature, including countries/regions, institutions, journals, keywords, and trends, were analyzed. Next, a clustered network was constructed based on 46,718 references cited by the 1,764 publications to determine the top 10 cocited articles.

Results: The annual number of publications on RIF progressively increased over time. The highest number of publications were from the United States. Analysis of the cocited reference cluster showed that "endometrial injury", "platelet-rich plasma", "chronic endometritis" and "extracellular vesicles" were the hotspots in RIF research. Burst detection analysis of the top keywords showed that "hysteroscopy" and "improvement" are emerging research foci.

Conclusions: This study clarifies the current research status and evolution of research in the field of RIF. New therapeutic interventions designed to improve pregnancy outcomes are the focus of current research and are expected to dominate future research in the field of RIF.

Keywords: Recurrent implantation failure (RIF); emerging trends; research foci; burst detection; cocitation analysis

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Introduction

Recurrent implantation failure (RIF) refers to repeated unsuccessful pregnancy after several transfers of good-quality embryos. However, no internationally recognized definition for RIF has been established. Now, the widely accepted definition for RIF is the failure to achieve a clinical pregnancy in women under the age of 40 after at least four transfers of high-quality embryos in a minimum of three frozen or fresh cycles (1,2). RIF presents a significant clinical challenge for patients undergoing in vitro fertilization (IVF). Despite recent advances in IVF, RIF remains significantly high. Currently, the rate of successful IVF for frozen embryos is only 37.3% for women under the age of 35 years and 29.2% for those aged 41–42 years (3).

Many different risk factors can lead to RIF, and it is necessary to establish a standardized evaluation for these patients. Appropriate action and interventions are formulated based on the assessment results, and personalized treatments are provided. The two leading factors in RIF are the mother as a host and the embryo. There are several types of uterine pathology, including fibroids, polyps, and adhesions, that can affect implantation rates in patients receiving IVF (4). Hydrosalpinx refers to fluid-filled fallopian tubes. It is now recognized that women with hydrosalpinges undergoing IVF have only half the live birth rate (LBR) of women without hydrosalpinx (5). Ultrasonography, hysteroscopy, sonohysterography, combined hysteroscopy and laparoscopy, hysterosalpingography, and hydrosalpinges are used investigational tools in women with RIF (1). Correction of intra-uterine pathologies and salpingectomy/tubal occlusion procedures in some cases have been shown to increase implantation success in IVF cycles (6,7). The endometrium itself may also be the etiology of implantation failure. Endometrial damage, impaired uterine blood flow, and long-term contraceptive use are potential causes of a thin endometrium (4). Ultrasound examination of endometrial thickness and appearance is an easily performed means of assessing changes in endometrial morphology during the follicular phase. These RIF women with thin endometrium should be offered all available treatments (high-dose estrogen, aspirin, vaginal estrogen pills, and other drugs that may increase endometrial blood flow) (8). Failure to transfer embryos into the recipient endometrium during the appropriate implantation window has been implicated as a cause of RIF (9). The use of endometrial receptivity array (ERA) to assess endometrial receptivity and determine the window of implantation (WOI) may help improve outcomes for multiple implantation failure patients (10). RIF is mainly caused by uterine factors. However, there will inevitably be some cases due to embryonic factors. Embryo quality is affected by oocyte quality, sperm quality, parental chromosomal anomalies, etc. The ovarian response to gonadotrophin stimulation should be reviewed to select an appropriate ovarian stimulation protocol (1). Based on sperm DNA integrity testing results, providing medical treatment and selecting sperm with more minor DNA damage may be considered to improve sperm quality (1). RIF patients have a high percentage of chromosomally abnormal embryos, and the use of preimplantation genetic screening (PGS) and selection of chromosomally normal embryos for transfer can improve the implantation rate of RIF (8). However, even embryos that are defined as good quality may stop developing in utero. This may be due to intrinsic embryonic factors or suboptimal local conditions. It has been confirmed that blastocyst transfer, sequential embryo transfer (ET), embryo co-culture and zygote intrafallopian transfer can effectively overcome these obstacles (11). The hatching of blastocysts through the zona pellucida is an important step before implantation. Assisted hatching has been suggested increasing implantation rates in patients who have previously failed IVF cycles (11). Some of the newly introduced diseases and factors, such as chronic endometritis (CE), immunologic profile, and vaginal microbiota, maybe help pave the way toward new diagnostic and therapeutic strategies for RIF. CE as a contributing factor needs to be investigated in RIF. It is histologically defined by plasma cell infiltration in the endometrial stroma but can also be diagnosed by the use of hysteroscopy (12). A recent meta-analysis evaluating the relationship between CE and RIF concluded that treatment of CE may improve IVF outcomes in RIF women (13). If all tests for the embryo and the mother are normal, it is recommended to consider the possible contribution of immune factors to implantation failure. The test indicators to assess the patient's immune balance include an abnormal tumor necrosis factor-α (TNF-α)/interleukin-10 (IL-10) ratio, elevated natural killer (NK) cells, T helper 1 (Th1)/Th2 ratio, and auto-antibodies (4,14). Immunological therapy has also been regarded as a potential intervention for repeated implantation failure. Peripheral blood mononuclear cell (PBMC) therapy has been reported to improve pregnancy outcomes for women with at least three previous IVF-ET failures (3). In recent years, it has been found that vaginal microbiota dysbiosis may be involved in RIF at different stages, such as gamete

formation, implantation and delivery (15,16). The vaginal microbiota of pregnant women appears to be exclusively colonized by the Firmicutes phylum, with the *Lactobacillus* species (*L. iners* and *L. crispatus*) being the main species within this phylum. In contrast, women with implant failure after undergoing an assisted reproductive technology (ART) displayed a richer vaginal ecosystem and greater biodiversity (17). The IVF or IVF-intracytoplasmic sperm injection (ICSI) population with low levels of Lactobacillus in the vaginal sample were less likely to have successful embryo implantation (18). Fu *et al.* confirmed that vaginal microbiota could affect embryo implantation, and vaginal lactobacilli in unexplained RIF patients were significantly positively correlated with pregnancy rate (19). The change of vaginal microbial composition in RIF patients brings into the change of metabolite composition, which may be one of the important mechanisms leading to the pathogenesis of RIF. Fu *et al.* also found that 37 metabolites were significantly different between patients with unexplained RIF and those who achieved clinical pregnancy after the first ET cycle, and, among the 37 metabolites, inositol phosphate and 2',3-cyclic uridine monophosphate (UMP) were the top two metabolites (19). They were higher in the RIF group, while benzopyran and glycerophospholipids were lower in the RIF group. The metabolites may be essential for the implantation and maintenance of pregnancy. However, the relationship between the microbiome and RIF remains largely unknown, and further research is needed, which has clinical value for proposing meaningful interventions to improve RIF outcomes. There are other influential factors, such as maternal age, body mass index (BMI), smoking, and stress. Lifestyle interventions such as a healthier diet and regular exercise, smoking cessation, and taking care of mental health may positively impact people with RIF.

Due to the attention of researchers and clinical workers to RIF patients, the studies have increased rapidly related to RIF, and a series of original articles and literature reviews have been published. The review by Pirtea *et al.* focused on whether the endometrial and embryonic assessments available today is helpful in treating RIF women (20). Moustafa *et al.* reviewed the diagnostic and therapeutic options in RIF emphasizing disorders of endometrial receptivity (21). Zohni *et al.* summarized the knowledge of normal human embryonic development, molecular aspects of endometrial-embryo interactions, and preimplantation genetic assessment, which will pave the way for new diagnostic and therapeutic strategies for RIF (22). Busnelli *et al.* conducted a systematic review and meta-analysis to assess the impact of different therapeutic approaches for RIF patients on subsequent IVF cycle outcomes (23). Although these articles provide valuable insights and research directions for RIF in general, the syntheses and analyses do not provide a complete picture of global RIF research. For example, useful knowledge about developments in the field, such as which are the most productive countries, institutions and journals; what national and institutional collaboration networks exist in the field; what are the narrative clusters in the research domain; and what are the hot research trends in the RIF field, are questions which difficult to answer utilizing traditional review methodologies. However, such information is handy for researchers to understand the past evolution of RIF and the structure of the RIF research field and identify the emerging research areas within the RIF domain. We introduce bibliometric analysis for additional analysis of all published literature on RIF over the last 20 years, which can provide additional insights and answer the above questions. Therefore, it may be beyond meta-analyses that do not highlight relationships between publications in the field or mere literature reviews that are not necessarily comprehensive enough.

Evaluative bibliometrics is a scientific quantitative analysis technique that combines mathematical and statistical methods to evaluate research performance. Bibliometric analysis utilizes published data to identify novel findings and current research trends in specific fields (24). Therefore, clinical practitioners and investigators are updated on the new practices that evoke new research ideas (25). Bibliometrics was first introduced in 1969 by Alan Richard, a famous British scientist, who first proposed the replacement of "statistical bibliography" with this method (26). In recent years, bibliometrics has attracted the attention of many researchers, resulting in the publication of numerous bibliometric studies in high-impact journals. Through this method, Sugimoto *et al.* performed a bibliometric analysis to identify sex-related reporting in medical research and found an increased probability of reporting sex in articles with female first and last authors (27). In their study, Zhai *et al.* conducted a bibliometric analysis to investigate trends of spinal ultrasound research and found that anesthesia use and adolescent idiopathic scoliosis are the major research foci in the foreseeable future (28). Bibliometric studies have extended to several other scientific fields, including obstetrics (29), health care (30,31), gastrointestinal diseases (32), tumors (33,34), cardiovascular disease (35), and

ophthalmology (36,37).

To the best of our knowledge, bibliometric analyses on RIF are limited (none). CiteSpace and VOSviewer are currently the most common tools for visualizing and analyzing trends and patterns in scientific literature. In the present study, we used these tools to analyze the current trend in RIF-related research. Collaboration network analysis, reference cocitation analysis, and keyword co-occurrence and burst analyses were also performed.

Methods

Data source and search strategy

We searched through the Web of Science Core Collection (WoSCC) databases for recent articles on RIF. The papers had to have been published between 2000 and 2020. The key search words included (I) in vitro fertilization, IVF, intracytoplasmic sperm injection, ICSI, embryo transfer, etc.; (II) failed implantation, implantation failure, recurrent implantation failure, and repeated implantation failure. Only "articles" and "reviews" were considered. The search generated 1,764 articles and reviews. The papers were coded and input into scientometric software, including Microsoft Office Excel 2013 (Microsoft Corporation, Redmond, WA, USA), CiteSpace V (Drexel University, Philadelphia, PA, USA), and VOSviewer 1.6.10 (Leiden University, the Netherlands). Any disagreements were resolved through discussion. The data were collected and organized by two independent researchers.

Statistical analysis

The trend in RIF researches was analyzed using the WoSCC literature analysis tool. The number of publications in future years was predicted using the polynomial model expressed as $f(x) = ax^3 + bx^2 + cx + d$, where f(x) is the number of publications and x is the year of publication. VOSviewer was used to construct a network map of countries/regions and organizations. CiteSpace V was used to construct a dual-map overlay of journals, identify cocited references, and capture keywords with strong burst strength. The CiteSpace was set as follows: link retaining factor (LRF) =2, look back years (LBY) =−1, e for top N(e) =2, period = (2000–2020), years per slice =2, and links (strength: cosine, scope: within slices), and criteria for the selection of items (country, keywords, and references) were adopted based on the situations.

Results

Annual publications and increased publication prediction

Our search generated 1,764 research papers on RIF, which included 1,477 articles and 287 reviews. Overall, we observed a gradual and steady increase in publications on RIF from 18 articles in 2000 to 262 articles in 2020. A sudden jump in the publication of papers occurred from 2019, peaking in 2020. The polynomial curve fitting revealed a strong positive correlation between the year of publication and the number of published articles and reviews [coefficient of determination (R^2) =0.9715]. The specific numbers of papers per year are shown in *Figure 1*.

Country/region and institutional analysis

The 1,764 articles were from 78 countries/regions (*Figure 2*). The top 10 countries/regions published a total of 1,447 (82%) articles. The top three countries/regions were the United States (n=336; 19%), China (n=300; 17%), and England (n=169; 9.6%). Additionally, 1,764 studies were performed by 2,195 research institutions (*Figure 3*). The top five leading universities in RIF research were the University of Valencia (n=45; 2.55%), Tel Aviv University (n=31; 1.76%), Tehran University of Medical Sciences (n=27; 1.53%), the Chinese University of Hong Kong (n=26; 1.47%), and the Academic Center for Education, Culture, and Research (Genetic Laboratory of Tabriz Branch of ACECR) (n=25; 1.42%).

Journal analysis

Journal citation analysis shows the distribution of knowledge sources in the RIF field. *Table 1* shows the top 15 most active journals in RIF research. The top four journals include *Fertility and Sterility* (114 publications), *Reproductive Biomedicine Online* (112 publications), *American Journal of Reproductive Immunology* (111 publications), and *Human Reproduction* (103 publications). The impact factor (IF) for 11 (73.3%) of the 15 most influential journals was >3.000. The dual-map overlay of the journals is shown in *Figure 4*. The lines running from left to right represent the citation links. Four main citation paths are also shown. The two yellow paths indicate that articles published in molecular/biology/genetics journals and health/nursing/medicine journals are mainly cited in the studies published in molecular/biology/immunology journals. The two green paths indicate that articles published in molecular/biology/

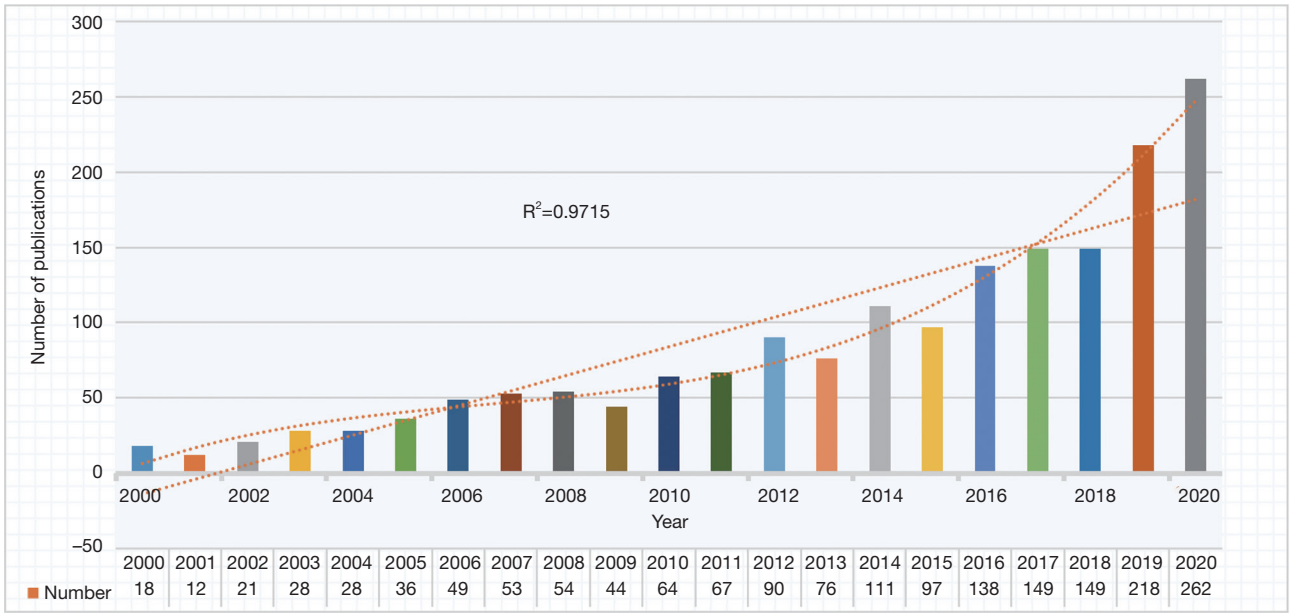
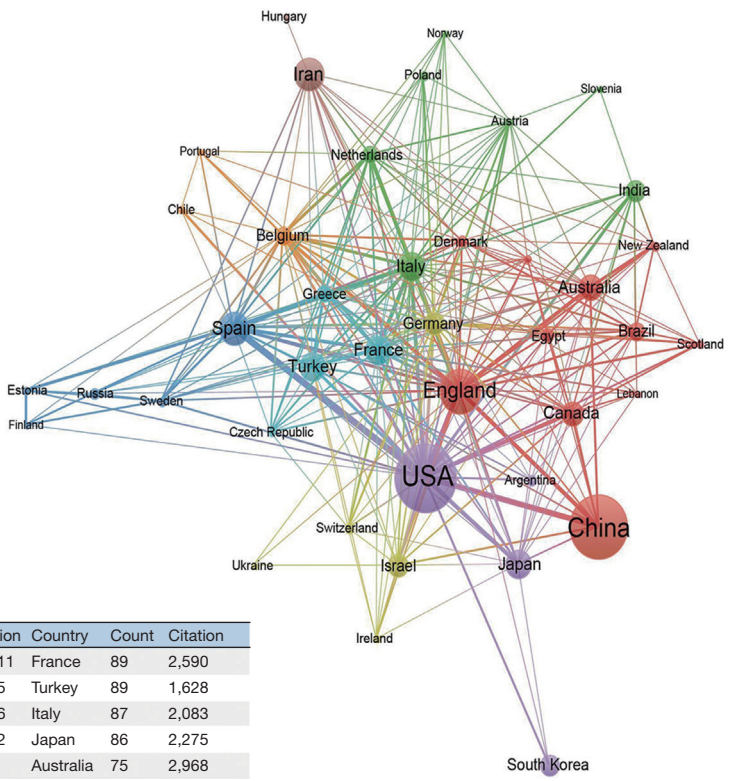
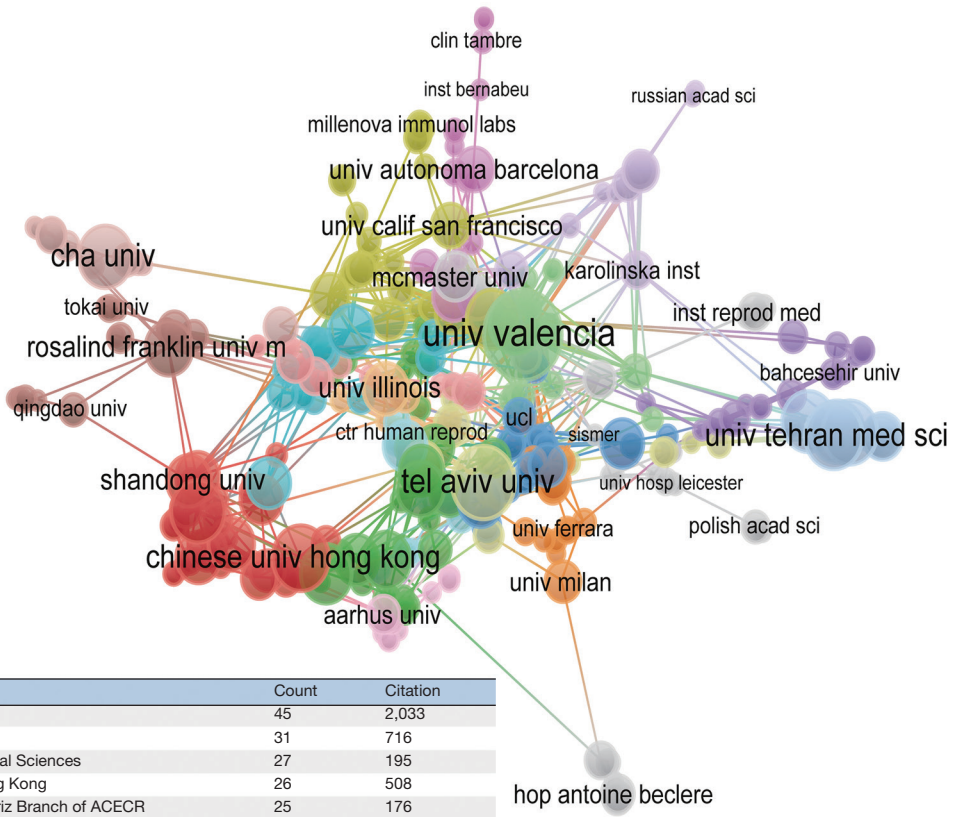


Figure 1 Time-trend distribution of articles in the field of RIF. RIF, recurrent implantation failure.



Country	Count	Citation	Country	Count	Citation
United States	336	13,911	France	89	2,590
China	300	3,645	Turkey	89	1,628
England	169	5,756	Italy	87	2,083
Spain	109	3,222	Japan	86	2,275
Iran	107	916	Australia	75	2,968

Figure 2 Knowledge map of country/region co-occurrence in research on RIF during 2000–2020. RIF, recurrent implantation failure.



Institution	Count	Citation
University of Valencia	45	2,033
Tel Aviv University	31	716
Tehran University of Medical Sciences	27	195
Chinese University of Hong Kong	26	508
Genetic Laboratory of Tabriz Branch of ACECR	25	176
Shanghai Jiao Tong University	24	197
CHA University	24	148
Shahid Beheshti University Medical Sciences	24	136
Stanford University	23	1,413
Tabriz University of Medical Sciences	23	203

Figure 3 The distribution of organizations involved in RIF research. RIF, recurrent implantation failure.

genetics journals and health/nursing/medicine journals are mainly cited in the studies published in medicine/medical/clinical journals.

Cocitation analysis

Knowledge of current RIF research was evaluated using the most cocited reference network. The network is composed of 933 unique nodes and 3,621 links (*Figure 5A*). The top 10 most cocited articles related to RIF are shown in *Table 2*. Each was cocited at most 108 times, and they include Coughlan [2014] published in *Reproductive BioMedicine Online* (108 cocitations), Cicinelli [2015] published in Human Reproduction (59 cocitations), Nastri [2015] published in *The Cochrane Database of Systematic Reviews* (53 cocitations), and Potdar [2012] published in *Reproductive BioMedicine Online* (53 cocitations). Clustering of the cocited references was performed using loglikelihood tests (LLR). In total, 110 clusters with a Q-value of 0.8345 and a weighted mean silhouette-value of 0.9444 (*Figure 5B*) were obtained. The largest cluster was the "preimplantation genetic screening" group, with a total of 79 references. The silhouette of this cluster was 0.921. The number of members in the second cluster, including "integrin" and "endometrial injury", was 77, and their silhouettes were 0.949 and 0.981, respectively. Other active clusters include "platelet-rich plasma", "granulocyte colony-stimulating factor", "vascular endothelial growth factor", "aneuploidy", "chronic endometritis", "extracellular vesicles", "heparin", and "uterine flushing". From the timeline view (*Figure 6*), cluster #2 "endometrial injury", cluster #3 "platelet-rich plasma", cluster #7 "chronic endometritis", and cluster #8 "extracellular vesicles" represented by the bright color were the latest studies in RIF.

Table 1 The top 15 journals that have published the most papers on RIF

Journal	Count	JCR	IF	Country	Main ideas
Fertility and Sterility	114	Q1	7.329	United States	Infertility and human reproductive disorders
Reproductive BioMedicine Online	112	Q1	3.828	England	The formation, growth and differentiation of the human embryo
American Journal of Reproductive Immunology	111	Q3	3.886	Denmark	The presentation of current information in all areas relating to reproductive immunology
Human Reproduction	103	Q1	6.918	England	The clinical science and medical aspects of reproductive physiology, pathology and endocrinology
Journal of Assisted Reproduction and Genetics	65	Q2	3.412	United States	The biology and underlying mechanisms from gametogenesis to offspring health
Journal of Reproductive Immunology	55	Q2	4.054	Netherlands	Experimental, animal and clinical reproductive immunobiology
Gynecological Endocrinology	38	Q3	2.26	England	The control and function of the different endocrine glands in females, the effects of reproductive events on the endocrine system, and the consequences of endocrine disorders on reproduction.
Molecular Human Reproduction	32	Q1	4.025	United States	The basic science of reproduction
European Journal of Obstetrics & Gynecology and Reproductive Biology	31	Q2	2.435	United States	Obstetrics, prenatal diagnosis, maternal-fetal medicine, perinatology, general gynecology, gynecologic oncology, urogynecology, reproductive medicine, infertility, reproductive endocrinology, sexual medicine and reproductive ethics
Archives of Gynecology and Obstetrics	28	Q2	2.344	Germany	Maternal fetal medicine, general gyneocology, gynecologic oncology, gynecologic endocrinology and reproductive medicine, and urogynecology
Journal of Obstetrics and Gynecology Research	28	Q3	1.73	Japan	The fields of obstetrics and gynecology
Reproductive Sciences	28	Q2	3.06	Germany	The advancement of knowledge in reproductive biology
Reproductive Biology and Endocrinology	26	Q2	5.211	England	Gametogenesis, fertilization, early embryonic development, embryo-uterus interaction, reproductive development, pregnancy, uterine biology, endocrinology of reproduction, control of reproduction, reproductive immunology, neuroendocrinology, and veterinary and human reproductive medicine
Human Reproduction Update	24	Q1	15.61	England	Human reproductive physiology and medicine
Biology of Reproduction	21	Q1	4.285	United States	The field of reproductive biology

RIF, recurrent implantation failure; JCR, journal citation reports; IF, impact factor.

Analysis of keywords

Keywords for constructing the knowledge map were extracted using CiteSpace. The words and the relationships among them were represented by 108 nodes and 742 links (*Figure 7*). The size of the circle is directly proportional to the co-occurring frequencies of a keyword, whereas the lines between the two circles reflect the strength of their co-occurrence relationship. The four most frequently used keywords were "in vitro fertilization" (n=487), "implantation failure" (n=462), "pregnancy" (n=319), and "women" (n=319). The topmost keywords based on centrality were "leukemia inhibitory factor" (0.54), "mice" (0.52), "aneuploidy" (0.51), and "expression" (0.49). Eighteen keywords had citation bursts. *Figure 8* shows the

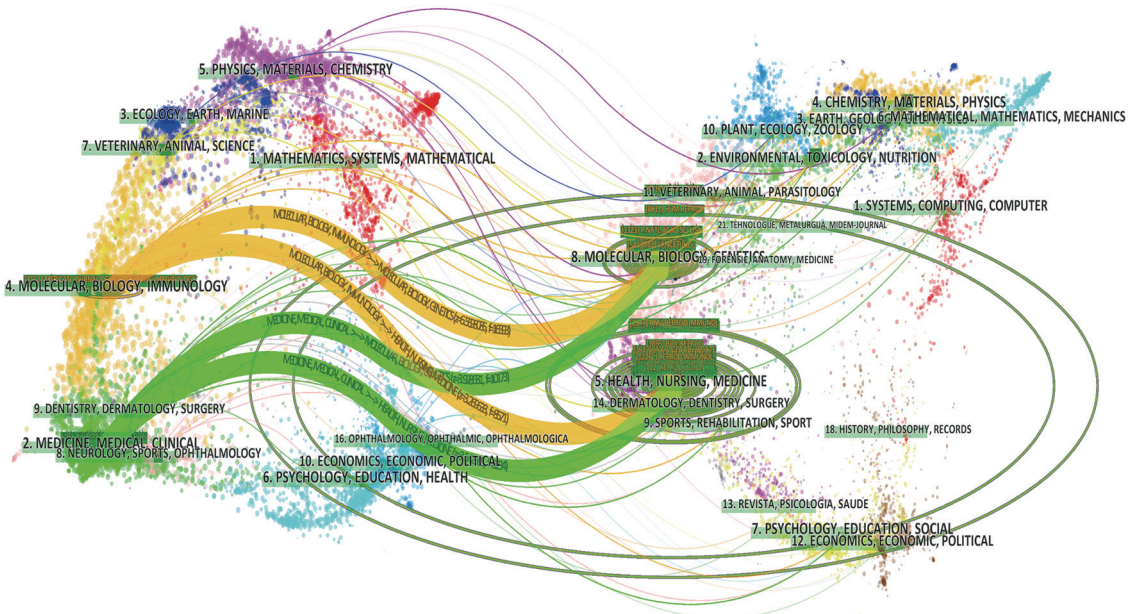


Figure 4 The dual-map overlay of journals publishing studies on RIF (left: citing journals; right: cited journals). RIF, recurrent implantation failure.

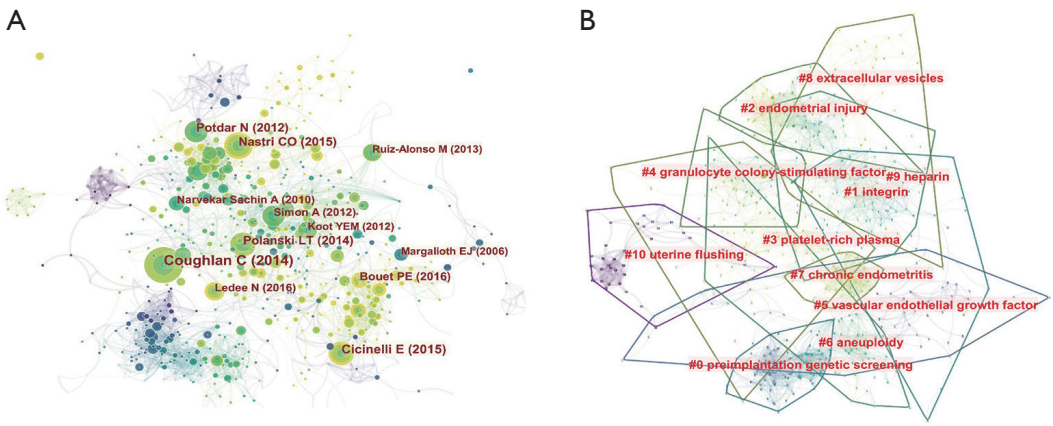


Figure 5 The analysis of references. (A) Network map of document cocitations for RIF; (B) clustered network of cocited articles on RIF. RIF, recurrent implantation failure.

base timeline (blue line) and the burst duration of a subject (red part). The top three keywords with the highest burst strength included "preimplantation genetic diagnosis" (15.92), "receptivity" (15.73), and "cytokine" (13.83) from 2000 to 2011, 2012 to 2017, and 2004 to 2011, respectively. In terms of the end year, citation bursts on "hysteroscopy" [2014–2020] and "improvement" [2016–2020] continued until 2020.

Discussion

General information

Herein, we used visual tools to analyze recent trends in RIF research based on studies published from 2000 through 2020. We found a steady increase in the annual number of published studies on RIF over the past 20 years, underlining the global significance of RIF. In general, RIF has been

Table 2 The top 10 cocited references of RIF studies

Authors	Years	Title	Cited frequency	Journal	IF [2020]	Term
Coughlan C	2014	Recurrent implantation failure: definition and management	108	*Reproductive Biomedicine Online*	3.828	Definition and management
Cicinelli E	2015	Prevalence of chronic endometritis in repeated unexplained implantation failure and the IVF success rate after antibiotic therapy	59	*Human Reproduction*	6.918	Prevalence of CE
Nastri CO	2015	Endometrial injury in women undergoing assisted reproductive techniques	53	*Cochrane Database of Systematic Reviews*	9.266	Endometrial injury
Potdar N	2012	Endometrial injury to overcome recurrent embryo implantation failure: a systematic review and meta-analysis	53	*Reproductive Biomedicine Online*	3.828	Endometrial injury
Polanski LT	2014	What exactly do we mean by 'recurrent implantation failure'? A systematic review and opinion	53	*Reproductive Biomedicine Online*	3.828	The basis for defining RIF
Bouet PE	2016	Chronic endometritis in women with recurrent pregnancy loss and recurrent implantation failure: prevalence and role of office hysteroscopy and immunohistochemistry in diagnosis	40	*Fertility and Sterility*	7.329	Diagnosis of CE
Simon A	2012	Repeated implantation failure: clinical approach	37	*Fertility and Sterility*	7.329	Female and embryonic factors
Lédée N	2016	The uterine immune profile may help women with repeated unexplained embryo implantation failure after in vitro fertilization	35	*American Journal of Reproductive Immunology*	3.886	The uterine immune profile
Narvekar SA	2010	Does local endometrial injury in the nontransfer cycle improve the IVF-ET outcome in the subsequent cycle in patients with previous unsuccessful IVF? A randomized controlled pilot study	34	*Journal of Human Reproductive Sciences*	2.100	Local endometrial injury in the nontransfer cycle
Margalioth EJ	2006	Investigation and treatment of repeated implantation failure following IVF-ET	32	*Human Reproduction*	6.918	Investigation and treatment

RIF, recurrent implantation failure; IF, impact factor; IVF, in vitro fertilization; ET, embryo transfer; CE, chronic endometritis.

reported by 78/230 (34%) of the countries/regions in the world. RIF has been reported most often in the United States, which may be related to the high uptake of IVF in the country. China ranks second and may be related to the recent spur in research in the country. For example, the National Natural Science Foundation Project Guide for 2021 mentioned the study of maternal-fetal metabolic interactions and pregnancy-related diseases (38). Based on the institutional knowledge map, universities are the main institutions performing studies on RIF. Four of the 10 most productive institutions include Tehran University of Medical Sciences [27], Genetic Laboratory of Tabriz Branch of ACECR [25], Shahid Beheshti University Medical Sciences [24], and Tabriz University of Medical Sciences [23], all in Iran, which developed collaborative research on IVF. Sometimes, network analysis between countries and institutions does not yield consistent results, which is mainly attributed to differences in institutional and technological advancement. For instance, Iranian scholars and research institutions have formed close cooperation in RIF research, whereas the United States and China have many institutions scattered around the country, with most performing independent research. Journal analysis provides important information on high-impact journals. In most

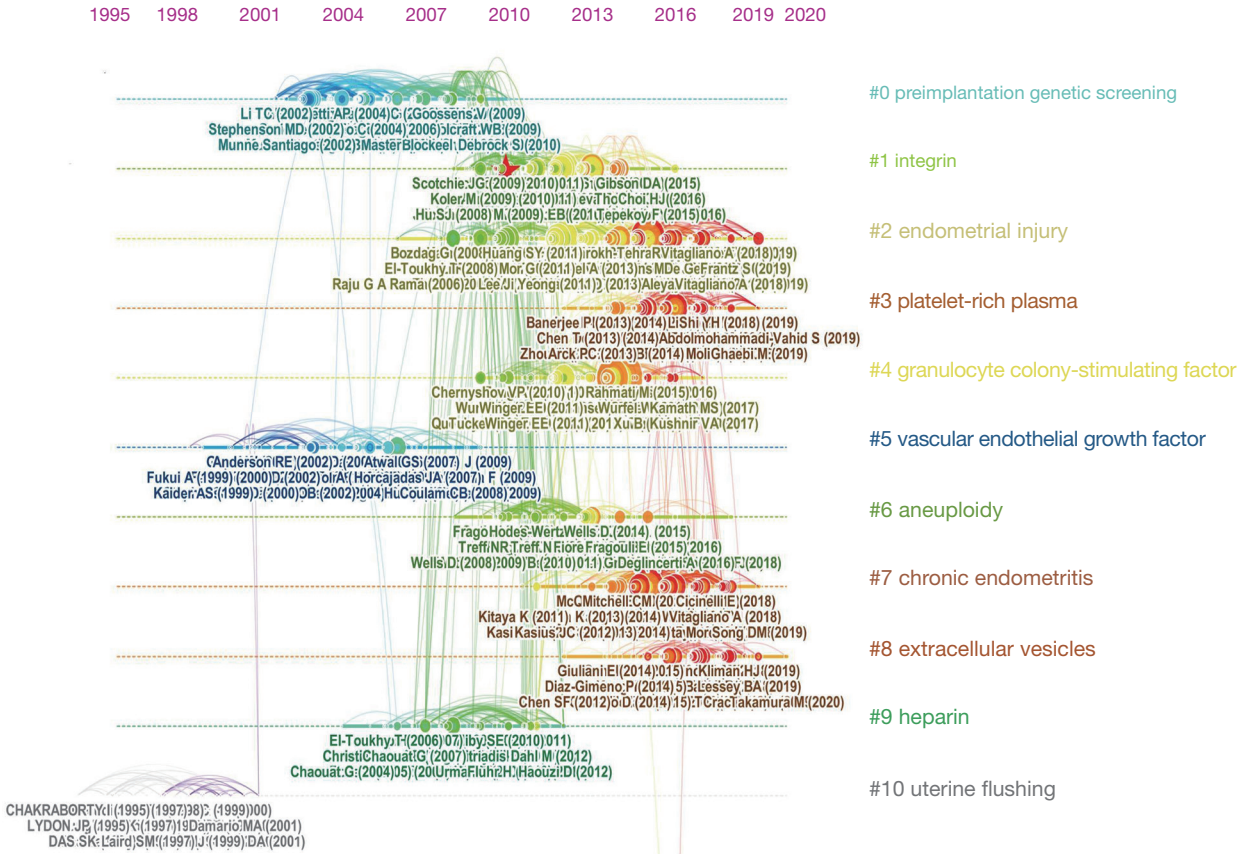
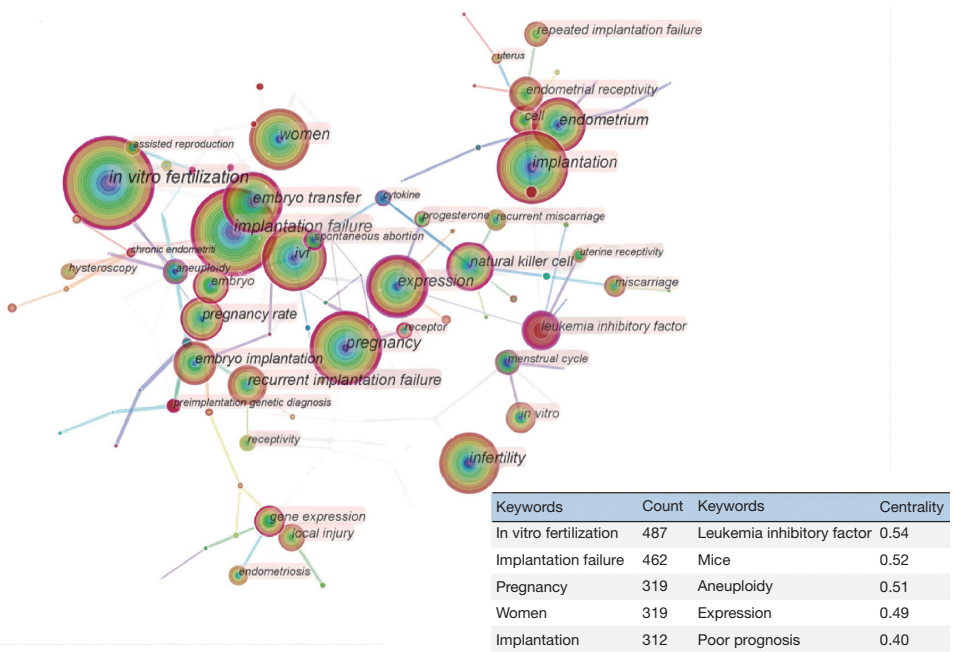


Figure 6 Timeline view of cocited references on RIF research. RIF, recurrent implantation failure.



Keywords	Count	Keywords	Centrality
In vitro fertilization	487	Leukemia inhibitory factor	0.54
Implantation failure	462	Mice	0.52
Pregnancy	319	Aneuploidy	0.51
Women	319	Expression	0.49
Implantation	312	Poor prognosis	0.40

Figure 7 Knowledge map of keyword co-occurrence in the field of RIF. RIF, recurrent implantation failure.

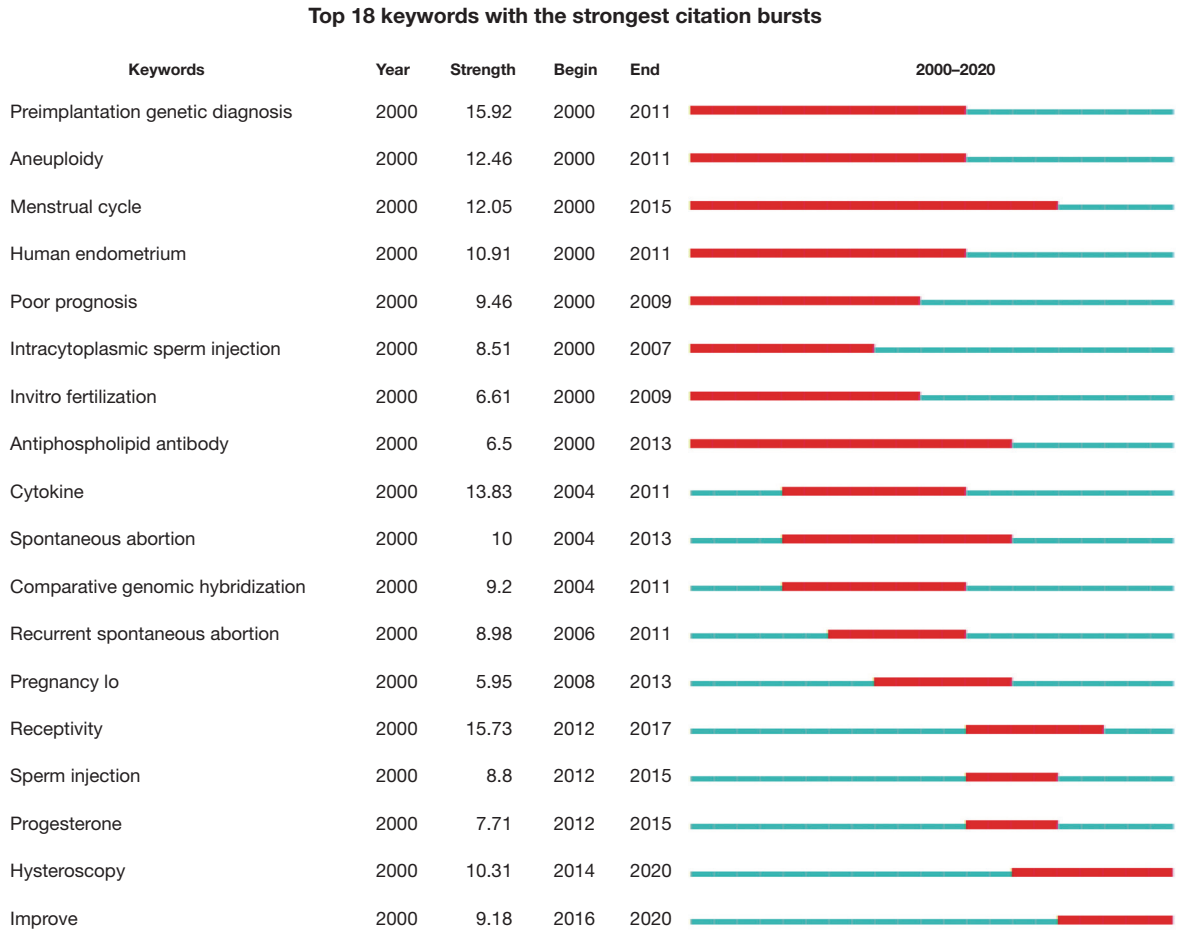


Figure 8 Top 18 keywords with the strongest citation bursts in the research on RIF between 2000 and 2020. RIF, recurrent implantation failure.

cases, the journals with the most publications in a field take precedence when researchers make decisions on how to disseminate their findings. Our analyses revealed that the top 10 most active journals published approximately half (46%) of the total research outputs on RIF, underlining the relatively centralized distribution of RIF research findings. More than 100 research outputs have been published in the four most active journals, including the *Fertility and Sterility*, *Reproductive Biomedicine Online*, *American Journal of Reproductive Immunology*, and *Human Reproduction journals*. The IF for most of the top 10 most active journals in RIF was >3.000, and only one had an IF <2.000.

Intellectual base

Cocitation is a measure of the frequency of jointly cited documents (39). Cocitation analysis identifies the most recognized scholarly or intellectual works in a given field or subject. Therefore, we focused on the top 10 cocited studies to assess trends, patterns, and knowledge regarding RIF. Among them, two papers highlighted the definition and underlying causes of RIF and further described major therapeutic strategies for improving successful pregnancy and delivery (1,8). Three studies reported how endometrial injury impacts RIF after IVF. In their systematic review and meta-analysis, Potdar *et al.* reported that induction of endometrial injury in the cycle preceding ovarian stimulation improves the outcome of pregnancy in patients with regular RIF (40). A separate randomized controlled pilot study revealed that endometrial injury caused by Pipelle sampling increases the chances of successful implantation and pregnancy in women with a history of RIF (41). Nastri *et al.* reported comparable findings, where local endometrial injury between day 7 of the previous

cycle and day 7 of the ET cycle was shown to increase the chance of successful pregnancy and live birth. In the same research, whether endometrial injury causes adverse events such as miscarriage, bleeding, or multiple pregnancies was uncertain (42). Two papers investigated the incidence and impact of CE on RIF patients after IVF. Bouet *et al.* found that CE promotes RIF. They further reported that office hysteroscopy complemented by an endometrial biopsy is a useful tool for CE diagnosis (43). Cicinelli and colleagues further underlined how untreated CE diminished the chances of successful IVF. However, they found that successful treatment restored the normal endometrial pattern and increased the chances of pregnancy (44). In addition, Polanski *et al.* reported a systematic review and provided an up-to-date overview of current definitions of RIF following these key features: (I) the number of unsuccessful cycles; (II) the number of embryos transferred; and (III) additional factors including ovarian reserve, the day of ET, the stage of embryo development, and outcomes of treatment (45). Lédée *et al.* found that 81.7% of RIF patients suffered from a spectrum of endometrial immune disorders, including overactivation and underactivation. However, treatment increases the likelihood of a LBR among these patients (46). Simon *et al.* revealed that female factors (including anatomical causes, endometrium, and thrombophilia) and embryonic factors (including genetics, sperm contribution, and immunologic factors) are the most important parameters affecting the outcome of IVF. Effective treatment options for these factors aimed at increasing the success of implantation were also described (11).

Among the top 10 cocited references, three papers by Potdar *et al.* [2012], Narvekar *et al.* [2010], and Nastri *et al.* [2015] belong to cluster #2, whereas two papers by Coughlan *et al.* [2014] and Polanski *et al.* [2014] belong to cluster #4. Two papers by Bouet *et al.* [2016] and Cicinelli *et al.* [2015] belong to cluster #7, whereas the remaining articles by Simon *et al.* [2012], Lédée *et al.* [2016], and Margalioth *et al.* [2006] belong to cluster #1, cluster #3, and cluster #5, respectively. The timeline view of the knowledge map was constructed to analyze the development trends of clusters in specific periods. In our study, we found that cluster #2 "endometrial injury", cluster #3 "platelet-rich plasma", and cluster #7 "chronic endometritis" remained in the spotlight in RIF research. In addition, cluster #8 "extracellular vesicles" has recently attracted the attention of researchers. For cluster #2, the most active citer (1) cited 23 articles of 77 member papers and entitled "*Recurrent implantation failure: definition and management*". This study is also the most cocited paper on RIF research. In this paper, the authors summarize the overall conclusion of randomized controlled trials and systematic reviews on endometrial injury. They suggested that endometrial injury can be treated using hysteroscopy or a Pipelle sampler, which increases the chance of successful IVF. In cluster #3, the most active citing paper cited 11 (47) member papers and entitled "*The role of immunotherapy in in vitro fertilization: a guideline*". This guideline evaluated the role of immunomodulating therapy in ART. Unfortunately, studies on numerous immunotherapies are lacking. Given the lack of robust evidence from well-designed randomized controlled trials, definitive recommendations regarding immunotherapies and IVF were not proposed. The most active citer (48) for cluster #7 cited 12 member papers. In this paper, 14–41% of patients with RIF were reported to suffer from CE, and compared with normal women, these groups of patients have lower implantation success rates after IVF-ET. Molecular microbial technology was further suggested to be able to accurately detect CE in patients intending to undergo IVF to reveal markers for better outcomes. The most active citer (49) in cluster #8 cited 11 member papers and reviewed endometrial factors, including CE, uterine peristalsis, and displacement of the WOI. Although extracellular vesicles have not been directly discussed, several studies show that extracellular vesicles in the normal endometria promote the proliferation of trophoblasts and may thus enhance the success of IVF (50-52). Therefore, alteration of the number of extracellular vesicles can prevent RIF. Cocitation analysis revealed that the knowledge and research development on RIF has primarily covered four aspects: concept or definition, underlying causes, therapeutic strategies, and factors affecting the success of IVF.

Research hotspots and frontiers

Current trends in RIF research were identified using burst detection methods. As shown in *Figure 8*, in the past 20 years, most studies have focused on "preimplantation genetic diagnosis", "receptivity", and "cytokines" in prospective women before IVF. "Hysteroscopy" and "improvement" have been among the new research foci since 2016.

Preimplantation genetic diagnosis (PGD)

Chromosomal abnormalities have been implicated in implantation failure. Among them, aneuploidy is the most frequent in normally developing embryos (53). PGD for

aneuploidy screening (PGD-AS) has been developed to detect numeric aneuploidy in embryos of RIF couples (54). At present, PGD-AS is performed using fluorescence in situ hybridization (FISH) or comparative genomic hybridization (CGH). Wilton *et al.* found that CGH was more effective than FISH in identifying chromosomally normal embryos (55). However, not all individuals with a history of RIF who undergo ART may benefit from PGS. Wilding *et al.* reported that PGS significantly increased the rate of successful pregnancy in women with a history of RIF (56). Taranissi *et al*. reported comparable findings (57). In contrast, randomized controlled trials have shown that PGS does not improve LBRs after IVF or ICSI (58). A separate randomized controlled trial revealed that PGS does not increase the successful implantation rates in women with repeated implantation failure (54). The conflicting evidence on the clinical value of PGS may be related to the heterogeneity of the patient population, study design, and other factors yet to be identified.

Receptivity

Endometrial receptivity is the period in which endometrial tissue allows normal embryo implantation and therefore pregnancy initiation (59,60). The common factors affecting endometrium receptivity include hysteromyoma, endometriosis, endometritis, hydrosalpinx, adenomyosis, changes in endogenous hormone levels, etc. (61,62). Some scholars believe that RIF is mainly related to poor endometrial receptivity (61). Optimal endometrial receptivity allows for normal implantation and stable pregnancy. Therefore, endometrial receptivity is important to evaluate. Most recently, the ERA was thought to accurately stratify the endometrium into 'receptive' or 'nonreceptive' groups based on the expression profile of 238 genes (59). However, a retrospective cohort study in RIF patients on the clinical usefulness of ERA revealed that this procedure does not improve pregnancy outcomes (10). In a related prospective controlled cohort study, the ERA test of endometrial biopsies revealed that there was no significant difference in the prevalence of a displaced ERA test result between the RIF and non-RIF groups (63). Overall, further studies are needed to identify endometrial factors associated with RIF.

Cytokines

Cytokines are small proteins secreted by immune cells and nonimmune cells. They mediate cellular and humoral immune responses and inflammatory responses related to tissue damage, participate in repair, and regulate the functioning of the endometrium, decidua, and cytotrophoblasts (64). After successful IVF-ET, implantation failure may be related to locally secreted cytokines, particularly those resulting from an imbalance in the secretion of Th1/Th2-based cytokines (65). Th1 cytokines are detrimental to pregnancy, whereas Th2 cytokines promote successful pregnancy. Overexpression of Th1-based cytokines promotes the Th2/Th1 transition, which affects the immunological response at the embryo implantation stage and may be the main reason for implantation failures (66-68). Ng *et al.* found that the numbers of $CD3^+/CD4^+$ TNF-α-producing cells and $CD3^+/CD8^+$ IL-10-producing cells were significantly high before pregnancy in the blood of women who experienced implantation failure after IVF (69). A separate randomized trial showed that after endometrial biopsy, a massive secretion of cytokines in the wound healing process might improve uterine receptivity and thus might have an additional favorable effect on the implantation of the blastocyst (70).

Hysteroscopy

Hysteroscopy is the direct observation of pathological and physiological disorders in the endometrium, as well as the treatment of abnormalities if any (71). A randomized controlled trial demonstrated that hysteroscopy findings are closely related to pregnancy success or failure and that routine office hysteroscopy before ICSI can detect infertility even in patients with normal ultrasound (72). In his meta-analysis, Cao *et al.* revealed that clinical pregnancy rate (CPR) and LBR were both significantly higher in RIF patients who underwent hysteroscopy than in those who did not (73). Endometrial injury and CE are the most recent attractive areas in RIF research (*Figure 6*), with hysteroscopy being central to research. Additionally, adding endometrial scratching to diagnostic hysteroscopy has been revealed to enhance implantation and pregnancy success rates in women with RIF (74,75). Numerous studies have found that hysteroscopy and immunohistochemistry offer superior CE diagnosis in RIF patients compared with other diagnostic techniques, such as transvaginal sonography, saline infusion/gel instillation sonography, 3D ultrasound scan, and hysterosalpingography. They also guide on the antibiotic treatment (43,76,77).

Improvement

RIF remains the major setback for IVF. Accordingly, IVF outcomes urgently need to be improved. In their

systematic analysis, Yakin *et al.* summarized the current RIF treatments targeting either the embryo, the maternal immune system, the endometrium, or the sperm (78). During the last decade, researchers have focused on the effect of endometrial injury and immunotherapy on RIF and pregnancy outcomes. Based on a prospective and randomized controlled trial, endometrial injury improves the successful implantation and LBRs in RIF patients (75). Recently, Maleki-Hajiagha *et al.* in their systematic review, revealed that PBMCs increased the successful pregnancy rate in patients with a previous history of RIF and can be a useful therapeutic target for RIF (79). However, RIF is a complex phenomenon with numerous etiologies and pathophysiologies. Conflicting findings have been reported for these treatments and ART outcomes. For instance, one randomized controlled trial revealed that endometrial injury did not improve the pregnancy success rates in women with RIF (80). A separate systematic review found no association between the administration of PBMCs and LBRs in women with RIF (78). Therefore, how to improve ET outcomes for RIF patients remains unresolved.

Strengths and limitations

Compared to traditional reviews, this bibliometric analysis provided better insight into the knowledge, patterns, trends, and evolution of RIF research. Regarding limitations, however, first, given that we only searched through the WoSCC database for articles published between 2000–2020, some studies on RIF may have been missed. Second, bibliometric analysis usually favors older published articles but may fail to appreciate novel findings of recently published high-quality papers because of low citation frequency. Third, the number of citations alone may not fully quantify the benefits of research because citation rates are affected by many factors, such as the quality of citation, the IF of a given journal, author self-citation, and omission bias (25).

Conclusions

In the present bibliometric study, we identified a gradual and steady increase in publications on RIF since 2000. The United States was the leading country in RIF research, and most of the RIF studies were published in the journal of *Fertility and Sterility*. Notably, "hysteroscopy" and "improvement" reflected the latest foci and should be closely followed in RIF research.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-703/coif). The authors have no conflicts of interest to declare.

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

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