Global Hotspots and Frontier Landscapes of DNA Methylation in Reproductive Medicine (1993-2020): A Scientometric Analysis

Yuan Li
Fang Lian
Ying Guo
Haicui Wu
Shan Xiang

Yuan Li, Shan Xiang The First Clinical School, Shandong University of Traditional Chinese Medicine, Jinan 250011, Shandong Province, China, Yuan Li, Fang Lian, Ying Guo, Haicui Wu The Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan 250011, Shandong Province, China, *Correspondence to: Fang Lian, Address : Reproductive and Genetic Center, The Affiliated Hospital of Shandong University of Traditional Chinese Medicine, No. 42 Wenhuaxi Road, Jinan 250011, Shandong Province, China. Email: quyatao1731@163.com lianfangbangong@163.com, Telephone: +86-531-68617980*

BACKGROUND: DNA methylation is a major epigenetic modification of genomes in mammals, involving the regulation of many cellular processes. Increasing study focus on the correlation between DNA methylation and reproductive medicine. Thus, it is meaningful to systematically review the latest knowledge domain and provide a hallmark of DNA methylation in reproductive medicine. This study aimed to quantitatively analyze the intellectual structure, hot topics and emerging trends of DNA methylation-related studies in reproductive medicine using visualization software.
METHODS: In the present study, we perform a qualitatively and quantitatively evaluation on publications about DNA methylation in reproductive medicine, using a visual exploration tool CiteSpace, to identify emerging trends and transient patterns in scientific literature.
RESCULTS: A total of 660 records relating DNA methylation in reproductive medicine were retrieved the Web of Science core collection from 1993 to 2020. The number of the annual publications gradually increased. CiteSpace 5.3 was used to comprehensively analyze the publication information. Fertility and Sterility published the highest number of studies on DNA methylation. Nature and New England Journal of Medicine ranked the first in the frequency and centrality of cited journal. Among countries, the United States was the publication leader, and the top institute was Chinese Academy of Sciences with the most productions. Haaf T was the most representative author. Gene expression, epigenetics, in vitro fertilization, assisted reproductive technology, fertilization, and beckwith wiedemann syndrome were the hot spots, and endocrine disruptor, genome-wide analysis, and the safety of assisted reproductive technology represented research frontiers.
CONCLUSION: Scientometric analysis identifies that DNA methylation is still a hot topic in reproductive medicine, and provides valuable information for researchers to identify new perspectives on potential collaborators and cooperative institutions and shape the future research directions.

Keywords: DNA methylation; reproductive medicine; scientometric analysis; CiteSpace; visualization analysis; Web of Science
Tob Regul Sci.™ 2021;7(6): 6484-6498
DOI: doi.org/10.18001/TRS.7.6.124

Core tip: DNA methylation is the main epigenetic modification of mammalian genome, which involves the regulation of many cellular processes. More and more attention has been paid to the relationship between DNA methylation and reproductive medicine. It is of great significance to systematically study the latest knowledge of DNA methylation in germ cells and provide markers of DNA methylation in germ cells. This study shows that DNA methylation is still a hot issue in the field of reproductive medicine, which provides valuable information for researchers to find new perspectives of potential collaborators and cooperative institutions and determine the future research direction.

DNA methylation is a major epigenetic modification of genomes that usually represses transcription without changing DNA sequence[1]. In mammals, DNA methylation primarily occurs on cytosine residues of CpG dinucleotides[2], and the process is mediated by a conserved group of DNA methyltransferases. Genomic patterns of DNA methylation are closely related to the gene regulation and chromatin organization during embryogenesis and gametogenesis[3]. Moreover, it plays a critical role in many cellular processes, such as tissue specific gene expression, transcriptional regulation, X chromosome inactivation, mammalian imprinting, and embryonic development[4,5]. Growing evidence has pointed towards the association of changes in DNA methylation with the pathogenesis of several diseases, such as type 2 diabetes, neurodegenerative disease, cardiovascular disease, and cancer[6-9]. Systematic interrogation of DNA methylation may substantially improve our understanding of underlying etiology.

Reproductive medicine is a medical discipline concerning the morphology, physiology, biochemistry, and pathology of human reproductive systems. It involves a variety of reproductive conditions, including ovulation induction, infertility, endocrine disorders, recurrent spontaneous abortion, as well as assisted reproductive techniques. Evidence has identified epigenetic reprogramming as a crucial event in embryonic development, maintenance of pluripotency, X-chromosome inactivation and genomic imprinting[10]. DNA methylation, as the best understood epigenetic reprogramming cycle, is considered as a component of epigenetic memory with a critical role during embryo development. Evidence suggests that assisted reproduction techniques can cause epigenetic disruption that is responsible for some phenotypic and gene expression abnormalities in their offspring[11,12]. There is increasing studies that focus on the correlation between DNA methylation and reproductive medicine. Thus, it is meaningful to systematically review the latest knowledge domain and provide a hallmark of DNA methylation in reproductive medicine.

Scientometrics focuses on quantitative research assessment of academic outputs in a specific field, and has been considered as a possible auxiliary tool in research process[13]. With advance in technology, current scientometric study has realized the visualization of the knowledge domain with reduced complexity and costs. In the present study, we perform a qualitatively and quantitatively evaluation on publications about DNA methylation in reproductive medicine, using a visual exploration tool CiteSpace, to identify emerging trends and transient patterns in scientific literature. This work will contribute to understanding historical perspective and potential prospects in the field of epigenetic reproductive medicine.

MATERIALS AND METHODS

Data collection

The Web of Science Core Collection (WoSCC) is a widely used database in academia, which provides a comprehensive and standardized set of data for export. Here, the WoSCC was used to compile the literature dataset for the scientometric analysis. The first article on DNA methylation in reproductive medicine was published in 1993[14], thus the timespan for the retrieval in this study was from 1993 to 2020. The topic search consists of index words as follows: “DNA methylation OR DNA methylations” AND “reproductive medicine OR reproduction”. The topic retrieval resulted in 666 records published between 1993 and 2020.

Scientometric analysis

CiteSpace is a freely available tool based on Java platform for visualizing and analyzing trends and patterns in scientific literature[15], and is considered as an optimal means for collaboration network analysis, including co-authors, co-citation references, and co-occurring keywords. It can connect all kinds of publication characteristics to facilitate the delivery of knowledge domain, and identify critical points by recognizing the nodes with high centrality. In the map, different nodes represent elements, such as an author, country, institution, and cited reference, and links between nodes are relationships of collaboration or co-citations. Critical points are highlighted with a purple ring in the visualized network[16]. Based on Kleinberg’s burst-detection algorithm[17], the current research front is identified according to burst terms from titles, abstracts, descriptors, and identifiers of scientometric records. In this study, CiteSpace 5.3.R8 was employed to perform the scientometric analysis based on records retrieved from the WoSCC. From 1993 to 2020, we set the “years per slice” to 2.

RESULTS AND DISCUSSION

Analysis of publication outputs

The first article on DNA methylation in reproductive medicine was published in 1993. The publications on DNA methylation in reproductive medicine show an accelerating growth trend from 2006 to 2011. Thereafter, the number of published articles showed increasing tendency in fluctuation, indicating that DNA methylation is still a hot spot in the field of reproduction and is still in the development stage. Figure 1 shows the distribution of annual publications from 1993 to 2020. Among 660 publications, almost all the retrieved articles were in English (99%), the other 1% were mainly in French, German, and Spanish.

Journal analysis

All the article records on DNA methylation in reproductive medicine were distributed in 277 journals. Fertility and Sterility (IF_{2018} 5.411) published the highest number of studies on DNA methylation (88 articles, 13.33%), followed by Reproduction (IF_{2018} 3.125, 25 articles, 3.79%), Human Reproduction (IF_{2018} 5.506, 22 articles, 3.33%) and PLoS One (IF_{2018} 2.776, 22 articles, 3.33%). DNA methylation-related studies in reproductive medicine are more likely to be accepted by these active journals, which can provide reference information for new researchers.

The impact factor (IF) of a journal is an important factor in evaluating its academic value. In this article, we explored the relationship between the journal’s IF_{2018} and the quantity of articles. Among the top 15 most productive journals, 4 journals had an IF>5, including Human Reproduction Update (IF_{2018} 12.878), PNAS (IF_{2018} 9.58), Human Reproduction (IF_{2018} 5.506), and Fertility and Sterility (IF_{2018} 5.411); 5 journals had 3<IF<5; and 6 showed an IF<3. The publications of relevant research were mainly published in journals with IF>3 (60%, 9/15). However, only one journal Human Reproduction Update had an IF>10, which means that publishing relevant papers in high-scoring journals remains a challenge.

Figure 2 shows the network organized by the cited journal, with 160 nodes and 364 edges. It is apparent that the journal with the largest explosion of citations was “Nature”, followed by “Proceedings of the National Academy of Sciences of United States”, “Science”, “Cell”, and “PLoS One”. Table 1 shows the top 5 most-cited journals and top 5 journals with the highest centrality in this study. These journals represent high quality of research and great impact in the field of DNA methylation in reproductive medicine. The best-classified journal by citation count was Nature, with 471 records, thus being considered the best source for scientists to develop and disseminate papers on the subject. The most outstanding journal by centrality was New England Journal of Medicine, with a centrality of 0.57.

Country and institution analysis

The origin analysis of the authors of the publications contributes to understand the geographic distribution of the countries and institutions with the highest publication indices on methylation-related studies in reproductive medicine. Figure 3 summarizes the information on the number of citations and cooperation network between countries. The thickness of the connecting lines between countries demonstrates the intensity of cooperation. Research teams from 37 countries published 660 articles. The top ten countries (5 European countries, 2 Asian countries, 2 American countries, and Australia) published 650 articles, accounting for 98% of the total publications. China is the only developing country in the group, indicating significant progress in the life sciences over the past few years. The publication leader was the United States, followed by China, Germany, England, and France. The United States (199) and China (139) were the two countries with the most publications, accounting for 51% of the total publications. The United States, Japan and France valued cooperation. The top 5 countries in terms of volume and centrality are shown in Table 2.

These 660 articles were generated by many institutions from different countries worldwide. CtieSpace software visually presented the most productive institutions as well as their connection among each other (Figures 4). Chinese Academy of Sciences was the most productive institution with 21 recorded, followed by Northwest A&F University and Zhejiang University. Among these prolific institutions, Chinese Academy of Sciences, China Agricultural University and SciUniv Missouri had close cooperation with each other. It's worth noting that, Chinese Academy of Sciences not only generated high publication number, but also showed the highest centrality, suggesting that Chinese Academy of Sciences is an authoritative institution in this field. It mainly focused on the DNA methylation patterns in oocytes and liver of female mice and their offspring[18], with emphasis on cooperation with other institutions. Table 3 presents the top 5 most productive and influential institutions in DNA methylation-related studies in reproductive medicine field, based on the publication and centrality.

Author analysis

The 660 publications related to DNA methylation in reproductive medicine were involved in 163 authors. The most productive authors were Haaf T with 8 articles, followed by Chen X with 7 articles, Li L with 8 articles, Carrell DT with 6 articles, and Zhang Y with 6 articles. In Haaf T's studies[19,20], the epigenetic changes in reproductive medicine were reported. Chen X and colleagues focused on the association between DNA methylation abnormity and the risk of human spontaneous abortion after assisted reproduction techniques[21,22]. Li's team identified the impairments of di-(2-ethylhexyl) phthalate and bisphenol A exposures to primordial follicle assembly by preventing or delaying DNA demethylation[23]. The collaboration network for the productive authors is shown in Figure 5. However, the annual citation frequency of these productive authors was not included in the top 15, suggesting that these productive authors should consider not only the quantity of articles, but also the quality of their articles.

Furthermore, we analyzed the co-citation relationship of authors in DNA methylation studies. Figure 6 shows the network map of co-citated authors. Reik W (127 co-citations) ranked first in the co-cited authors, followed by Kobayashi H (112 co-citations), Marques CJ (84 co-citations), and Maher ER (68 co-citations), demonstrating their critical roles in DNA methylation-related studies in reproductive medicine.

Publication co-citation analysis

Figure 7 shows the co-citation network of references, in which each node represents an article, and the line between two nodes represents the co-reference. Through the ranking analysis of citation frequency and centrality, 5 "classic literatures" were identified. These literatures laid a theoretical and practical foundation for the related research of DNA methylation in reproductive medicine, which might be landmark research.

The work of Marques CJ *et al*[24] published in 2008 was the most cited reference. They investigated the methylation patterns of H19 and MEST imprinted genes in sperm of control and oligozoospermic patients by bisulphite genomic sequencing, and found an explanation of the cause of Silver-Russell syndrome in children born with H19 hypomethylation after assisted reproductive technologies. Additionally, unmethylation of the CTCF-binding site could lead to inactivation of the paternal IGF2 gene, and be linked to decreased embryo quality and birth weight, often associated with ART. The second most cited reference was the article published in 2007 by Sato *et al*[25], which focused on the aberrant DNA methylation of imprinted loci in superovulated oocytes. This work suggested that superovulation can lead to the production of oocytes without their correct primary imprint and highlight the need for more research into ARTs.

When ranked by centrality, the first was the article published by Heijmans BT *et al*[26] in 2008, which investigated the epigenetic changes in individuals prenatally exposed to adverse environments relative to those unexposed, and revealed that early-life environmental conditions can cause epigenetic changes in humans that persist throughout life. Feil R *et al*[27] performed a systematic review on epigenetics and the environment, and indicated that chemical pollutants, dietary components, temperature changes and other external stresses had long-lasting effects on phenotypic and epigenetic regulation, sometimes even in subsequent generations. Meanwhile, genetic heterogeneity of individuals can influence epigenetic regulation and genetic susceptibility to environment stresses. These results provide critical implications for the involvement of epigenetics in environmentally triggered phenotypes and diseases.

Keyword co-occurrence analysis

Keyword is considered as one of the most important points of a publication, providing a reasonable description of research hotspots. The knowledge map of keyword co-occurrence analysis can be used to identify emerging trends and transient patterns in a certain knowledge domain.

Utilizing Citespace software, the keyword co-occurrence map (containing 199 items and 278 links) was recognized from the publications related to DNA methylation in reproductive medicine, as shown in Figure 8. The top keywords were as follows: gene expression (136 counts), epigenetics (128 counts), *in vitro* fertilization (103 counts), assisted reproductive technology (50 counts), beckwith wiedemann syndrome (69 counts), embryo (33 counts). Moreover, the keywords generated 7 clusters based on the log-likelihood ratio test. The major clusters showed in Figure 9 presented the most representative keywords in the field of DNA methylation in reproductive medicine, with the mean silhouette of 0.679-0.895. The mean silhouette is an indicator to evaluate the clusters of the network, and the silhouette >0.5 means that the clustering result of the network is rational[16]. The detailed information of the 5 clusters are summarized in Table 4.

DNA methylation is one of the most important epigenetic mechanisms during the mammalian life cycle. In the preimplantation embryo, DNA methylation forms the basic epigenetic barrier that guides and limits cell differentiation and prevents the regression to an undifferentiated state. DNA methylation plays a critical role in the maintenance of genomic stability and the coordinated expression of imprinting genes[28].

During embryonic development, adverse prenatal environmental effects may result in persistent epigenomic changes, such as loss of imprinting of insulin-like growth factor 2 (IGF2), and hypermethylation or hypomethylation on CpG sites, leading to an increased risk of adult onset diseases[29]. Epigenetics focuses on the study of epigenetic modification in gene expression. Epigenetic variations can be replicated during somatic cell mitosis and present transgenerational inheritance stability, without changing the DNA sequence[30]. Accumulating evidence indicates that inappropriate epigenetic reprogramming during early embryonic development may contribute to common diseases of fetal origin, such as type 2 diabetes and prostate cancer[31,32].

Preliminary evidence indicates that the manipulation to embryo can alter the cell lineage differentiation, making cells be allocated preferentially to the trophoectoderm[33]. As a result, a placenta larger than the normal placenta is formed, leading to the abnormal growth and development of the fetus. Presumably, this interference is caused by environmental-induced changes in early gene expression regulation, which is related to the disruptions to nucleocytoplasmic interaction and maternal-embryonic signaling[33].

Epigenetic changes are also related to assisted reproduction. Evidence suggests that *in vitro* conception is associated with the DNA methylation differences that are implicated to expression differences of imprinted and non-imprinted genes[34]. Several of the genes with significant differences between children conceived by assisted reproduction and children conceived in vivo have been linked to chronic metabolic disorders, such as obesity and type 2 diabetes[34]. It is admonished that even minimal manipulation in assisted reproduction technologies, such as embryo transfer, can adversely affect genomic imprinting during post-implantation development[35]. Assisted reproduction technology may influence epigenetics in global patterns of DNA methylation and gene expression in early embryogenesis[34]. Superovulated oocytes can influence the sex-specific epigenetic modifications that are imposed during gametogenesis[25]. With the development of epigenetics, the safety of assisted reproductive technology has been paid increasing attention[36,37].

A citation burst detection is an indicator of the most active field, which provides the items with a sharply increased frequency change in a short time[38]. The keywords were analyzed in a timespan from 2001 to 2019, and the top 30 keywords with the strongest bursts were chosen (Figure 10). Meanwhile, CiteSpace also provides a time-zone visualization of the keyword co-occurrence map (Figure 11)，which shows keywords occurred for the first time in chronological order. Notably, the keywords endocrine disruptor, metabolism, epigenetic inheritance, genome wide, and pregnancy with strongest burst were identified, which represented the emerging trends in DNA methylation.

Endocrine disruptors, as environment chemicals, can cause adverse effects in homeostasis, reproduction and development by interfering with hormone system[39]. Endocrine disruptors can cause effects in germ line reprograming and epigenetic transgenerational actions[40], which has significant implications for evolutionary biology and disease etiology. Current effort focuses on the exploration of underlying mechanisms of endocrine disruptor actions in epigenetic reproductive medicine.

Exposure to endocrine disruptors is also associated with dysfunctions of metabolism and reproduction. One-carbon metabolism function is a key biochemical conduit between prenatal environment and epigenetic regulation of early development[41]. It is indicated that maternal obesity has adverse effects on reproduction and the health of the offspring[42]. Moreover, DNA methylation patterns of several metabolism-related genes have been identified to be altered in oocytes of obese mice and their offspring[42].

Despite of the advance in assisted reproduction, its adverse outcomes has resulted in increasing attention of epigenetic risk of assisted reproduction[43]. Assisted reproduction can induce epigenetic variation that might be transmitted to the offspring. Thus, the field of epigenetic inheritance of an individual and between generations is growing.

Next generation sequencing promotes the development of genome-wide DNA methylation analysis to identify imprinted genes[44], which provides significant insights into the molecular processes in the mammalian embryo for normal development. Genome-wide methylation data and insights into epigenetic reprogramming of embryos allows us to view epigenetic modification from a new angle.

CONLUSION

This study performs a comprehensive review of the various aspects of DNA methylation in reproductive medicine using a scientometric method and results in information on the structure and subjects of this field. In total, 666 articles related to DNA methylation in reproductive medicine between 1993 and 2020 have been analyzed. The number of published articles showed increasing tendency. The United States and China are the leading countries for research. Cooperation between countries and institutions still needs to be strengthened in the future. Keyword occurrence and co-occurrence analyses showed the hotspot (including the effects of superovulation and adverse prenatal environmental on DNA methylation and gene expression, and assisted reproductive technology and its safety) and the frontiers (endocrine disruptors and metabolism, epigenetic risk of assisted reproduction, and genome-wide methylation analysis technology).

In conclusion, this scientometric analysis shows that DNA methylation is still a hot topic in the field of reproduction, especially assisted reproductive technology-related DNA methylation, endocrinology and metabolism. As a burgeoning discipline, reproductive medicine needs deeper research and more collaboration. The findings from the scientometric analysis are expected to provide valuable information for researchers in this field to discover new ideas and shape the future research directions.

Author contributions: Li Y designed the study; Li Y, Guo Y, Wu HC and Xiang S contributed surgical treatment and follow-up data collection; Li Y wrote the paper; Lian F revised the manuscript; all authors read and approved the final manuscript.

Supported by Major Science and Technology Innovation Project of Shandong Province (2018CXGC1302).

Informed consent statement: This study does not involve human and animal experiments.

Data share statement: All data generated or analyzed during this study are included in this published article.

Conflict-of-interest statement: The authors declare no conflict of interest.

REFEARENCE

1. Reik W, Kelsey G. Epigenetics: Cellular memory erased in human embryos. Nature 2014; 511: 540-541 [PMID: 25079550 DOI: 10.1038/nature13648]
2. Goldberg AD, Allis CD, Bernstein E. Epigenetics: a landscape takes shape. Cell 2007; 128: 635-638 [PMID: 17320500 DOI: 10.1016/j.cell.2007.02.006]
3. Goll MG, Bestor TH. Eukaryotic cytosine methyltransferases. Annu Rev Biochem 2005; 74: 481-514 [PMID: 15952895 DOI: 10.1146/annurev.biochem.74.010904.153721]
4. Senner CE. The role of DNA methylation in mammalian development. Reprod Biomed Online 2011; 22: 529-535 [PMID: 21498123 DOI: 10.1016/j.rbmo.2011.02.016]
5. Reik W, Dean W, Walter J. Epigenetic reprogramming in mammalian development. Science 2001; 293: 1089-1093 [PMID: 11498579 DOI: 10.1126/science.1063443]
6. Berson A, Nativio R, Berger SL, Bonini NM. Epigenetic Regulation in Neurodegenerative Diseases. Trends Neurosci 2018; 41: 587-598 [PMID: 29885742 DOI: 10.1016/j.tins.2018.05.005]
7. Nebbioso A, Tambaro FP, Dell'Aversana C, Altucci L. Cancer epigenetics: Moving forward. PLoS Genet 2018; 14: e1007362 [PMID: 29879107 DOI: 10.1371/journal.pgen.1007362]
8. Rosa-Garrido M, Chapski DJ, Vondriska TM. Epigenomes in Cardiovascular Disease. Circ Res 2018; 122: 1586-1607 [PMID: 29798902 DOI: 10.1161/CIRCRESAHA.118.311597]
9. Zhou Z, Sun B, Li X, Zhu C. DNA methylation landscapes in the pathogenesis of type 2 diabetes mellitus. Nutr Metab (Lond) 2018; 15: 47 [PMID: 29988495 DOI: 10.1186/s12986-018-0283-x]
10. Paoloni-Giacobino A. Epigenetics in reproductive medicine. Pediatr Res 2007; 61: 51R-57R [PMID: 17413849 DOI: 10.1203/pdr.0b013e318039d978]
11. Denomme MM, Mann MR. Genomic imprints as a model for the analysis of epigenetic stability during assisted reproductive technologies. Reproduction 2012; 144: 393-409 [PMID: 22956517 DOI: 10.1530/REP-12-0237]
12. Fauque P. Ovulation induction and epigenetic anomalies. Fertil Steril 2013; 99: 616-623 [PMID: 23714436 DOI: 10.1016/j.fertnstert.2012.12.047]
13. Leydesdorff L, Milojević S. Scientometrics. arXiv preprint arXiv:12084566. 2012.
14. Chigira M, Watanabe H. Is 'senescence'of diploid cells an ad hoc mechanism suppressing 'replicon'or not? Medical hypotheses. 1993;41(4):384-9. DOI: 10.1016/0306-9877(93)90090-D
15. Chen C, Chen Y, editors. Searching for clinical evidence in CiteSpace. AMIA Annual Symposium Proceedings; 2005: American Medical Informatics Association.
16. Chen C. CiteSpace II: Detecting and visualizing emerging trends and transient patterns in scientific literature. Journal of the American Society for information Science and Technology. 2006;57(3):359-77.[DOI: 10.1002/asi.20317]
17. Kleinberg J. Bursty and hierarchical structure in streams. Data Mining and Knowledge Discovery. 2003;7(4):373-97.[DOI: 10.1023/A:1024940629314]
18. Ge ZJ, Luo SM, Lin F, Liang QX, Huang L, Wei YC, Hou Y, Han ZM, Schatten H, Sun QY. DNA methylation in oocytes and liver of female mice and their offspring: effects of high-fat-diet-induced obesity. Environ Health Perspect 2014; 122: 159-164 [PMID: 24316659 DOI: 10.1289/ehp.1307047]PMID:24316659]
19. El Hajj N, Haaf T. Epigenetic disturbances in in vitro cultured gametes and embryos: implications for human assisted reproduction. Fertil Steril 2013; 99: 632-641 [PMID: 23357453 DOI: 10.1016/j.fertnstert.2012.12.044PMID:23357453]
20. Haaf T. Imprinting defects in reproductive medicine. Medizinische Genetik. 2010;22(4):424-8.DOI: 10.1007/s11825-010-0248-6
21. Liu Y, Zheng H, Guo P, Feng S, Zhou X, Ye D, Chen X, Chen S. DNA methyltransferase 3A promoter polymorphism is associated with the risk of human spontaneous abortion after assisted reproduction techniques and natural conception. J Assist Reprod Genet 2017; 34: 245-252 [PMID: 27817038 DOI: 10.1007/s10815-016-0837-7PMID:27817038]
22. Zheng HY, Tang Y, Niu J, Li P, Ye DS, Chen X, Shi XY, Li L, Chen SL. Aberrant DNA methylation of imprinted loci in human spontaneous abortions after assisted reproduction techniques and natural conception. Hum Reprod 2013; 28: 265-273 [PMID: 23042795 DOI: 10.1093/humrep/des358PMID:23042795]
23. Zhang T, Li L, Qin XS, Zhou Y, Zhang XF, Wang LQ, De Felici M, Chen H, Qin GQ, Shen W. Di-(2-ethylhexyl) phthalate and bisphenol A exposure impairs mouse primordial follicle assembly in vitro. Environ Mol Mutagen 2014; 55: 343-353 [PMID: 24458533 DOI: 10.1002/em.21847PMID:24458533]
24. Marques CJ, Costa P, Vaz B, Carvalho F, Fernandes S, Barros A, Sousa M. Abnormal methylation of imprinted genes in human sperm is associated with oligozoospermia. Mol Hum Reprod 2008; 14: 67-74 [PMID: 18178607 DOI: 10.1093/molehr/gam093PMID:18178607]
25. Sato A, Otsu E, Negishi H, Utsunomiya T, Arima T. Aberrant DNA methylation of imprinted loci in superovulated oocytes. Hum Reprod 2007; 22: 26-35 [PMID: 16923747 DOI: 10.1093/humrep/del316PMID:16923747]
26. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proceedings of the National Academy of Sciences. 2008;105(44):17046-9.DOI: 10.1073/pnas.0806560105
27. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, Slagboom PE, Lumey LH. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A 2008; 105: 17046-17049 [PMID: 18955703]

28. Feil R, Fraga MF. Epigenetics and the environment: emerging patterns and implications. Nat Rev Genet 2012; 13: 97-109 [PMID: 22215131 DOI: 10.1038/nrg3142PMID:22215131]
29. Messerschmidt DM, Knowles BB, Solter D. DNA methylation dynamics during epigenetic reprogramming in the germline and preimplantation embryos. Genes Dev 2014; 28: 812-828 [PMID: 24736841 DOI: 10.1101/gad.234294.113PMID:24736841]
30. Waterland RA. Is epigenetics an important link between early life events and adult disease? Horm Res 2009; 71 Suppl 1: 13-16 [PMID: 19153498 DOI: 10.1159/000178030PMID:19153498]
31. Skinner MK. Environmental epigenetic transgenerational inheritance and somatic epigenetic mitotic stability. Epigenetics 2011; 6: 838-842 [PMID: 21637037 DOI: 10.4161/epi.6.7.16537PMID:21637037]
32. Martin-Gronert MS, Ozanne SE. Programming of appetite and type 2 diabetes. Early Hum Dev 2005; 81: 981-988 [PMID: 16257499 DOI: 10.1016/j.earlhumdev.2005.10.006PMID:16257499]
33. Ho SM, Tang WY, Belmonte de Frausto J, Prins GS. Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. Cancer Res 2006; 66: 5624-5632 [PMID: 16740699 DOI: 10.1158/0008-5472.CAN-06-0516PMID:16740699]
34. Walker S, Hartwich K, Seamark R. The production of unusually large offspring following embryo manipulation: concepts and challenges. Theriogenology. 1996;45(1):111-20. DOI: 10.1016/0093-691X(95)00360-K
35. Katari S, Turan N, Bibikova M, Erinle O, Chalian R, Foster M, Gaughan JP, Coutifaris C, Sapienza C. DNA methylation and gene expression differences in children conceived in vitro or in vivo. Hum Mol Genet 2009; 18: 3769-3778 [PMID: 19605411 DOI: 10.1093/hmg/ddp319PMID:19605411]
36. Rivera RM, Stein P, Weaver JR, Mager J, Schultz RM, Bartolomei MS. Manipulations of mouse embryos prior to implantation result in aberrant expression of imprinted genes on day 9.5 of development. Hum Mol Genet 2008; 17: 1-14 [PMID: 17901045 DOI: 10.1093/hmg/ddm280PMID:17901045]
37. Fauque P, Jouannet P, Lesaffre C, Ripoche MA, Dandolo L, Vaiman D, Jammes H. Assisted Reproductive Technology affects developmental kinetics, H19 Imprinting Control Region methylation and H19 gene expression in individual mouse embryos. BMC Dev Biol 2007; 7: 116 [PMID: 17949482 DOI: 10.1186/1471-213X-7-116PMID:17949482]
38. Market-Velker BA, Zhang L, Magri LS, Bonvissuto AC, Mann MR. Dual effects of superovulation: loss of maternal and paternal imprinted methylation in a dose-dependent manner. Hum Mol Genet 2010; 19: 36-51 [PMID: 19805400 DOI: 10.1093/hmg/ddp465PMID:19805400]
39. Chen C. The citespace manual. College of Computing and Informatics; Drexel University: Philadelphia, PA, United States. 2014.
40. Sharma RP, Schuhmacher M, Kumar V. Review on crosstalk and common mechanisms of endocrine disruptors: Scaffolding to improve PBPK/PD model of EDC mixture. Environ Int 2017; 99: 1-14 [PMID: 27697394 DOI: 10.1016/j.envint.2016.09.016PMID:27697394]
41. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 2005; 308: 1466-1469 [PMID: 15933200 DOI: 10.1126/science.1108190PMID:15933200]
42. Clare CE, Brassington AH, Kwong WY, Sinclair KD. One-Carbon Metabolism: Linking Nutritional Biochemistry to Epigenetic Programming of Long-Term Development. Annu Rev Anim Biosci 2019; 7: 263-287 [PMID: 30412672 DOI: 10.1146/annurev-animal-020518-115206PMID:30412672]
43. Ge ZJ, Luo SM, Lin F, Liang QX, Huang L, Wei YC, Hou Y, Han ZM, Schatten H, Sun QY. DNA methylation in oocytes and liver of female mice and their offspring: effects of high-fat-diet-induced obesity. Environ Health Perspect 2014; 122: 159-164 [PMID: 24316659 DOI: 10.1289/ehp.1307047PMID:24316659]
44. van Montfoort AP, Hanssen LL, de Sutter P, Viville S, Geraedts JP, de Boer P. Assisted reproduction treatment and epigenetic inheritance. Hum Reprod Update 2012; 18: 171-197 [PMID: 22267841 DOI: 10.1093/humupd/dmr047PMID:22267841]
45. Maeda N, Hayashizaki Y. Genome-wide survey of imprinted genes. Cytogenet Genome Res 2006; 113: 144-152 [PMID: 16575174 DOI: 10.1159/000090826PMID:16575174]

FIGURES

Figure 1.
Time distribution of annual publications in WoSCC.

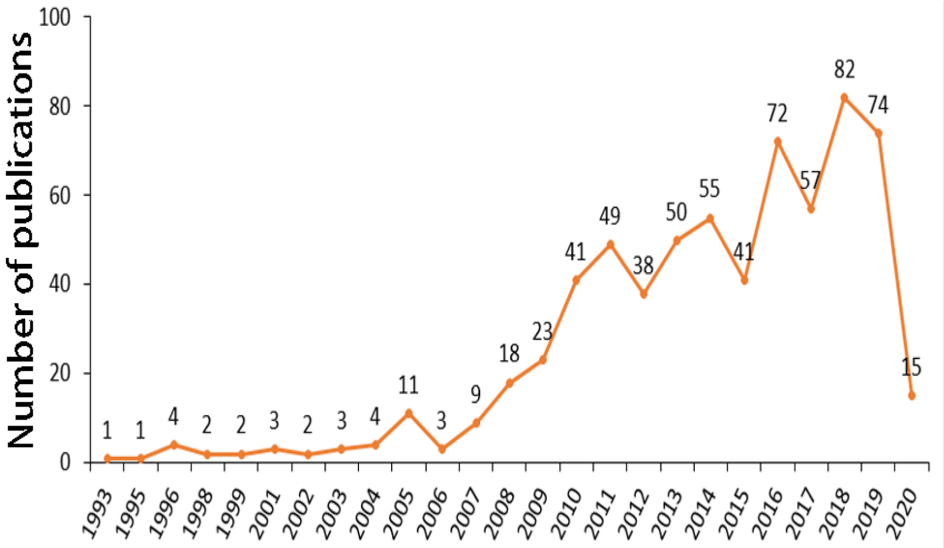


Figure 2.
The network organized by the cited journal.

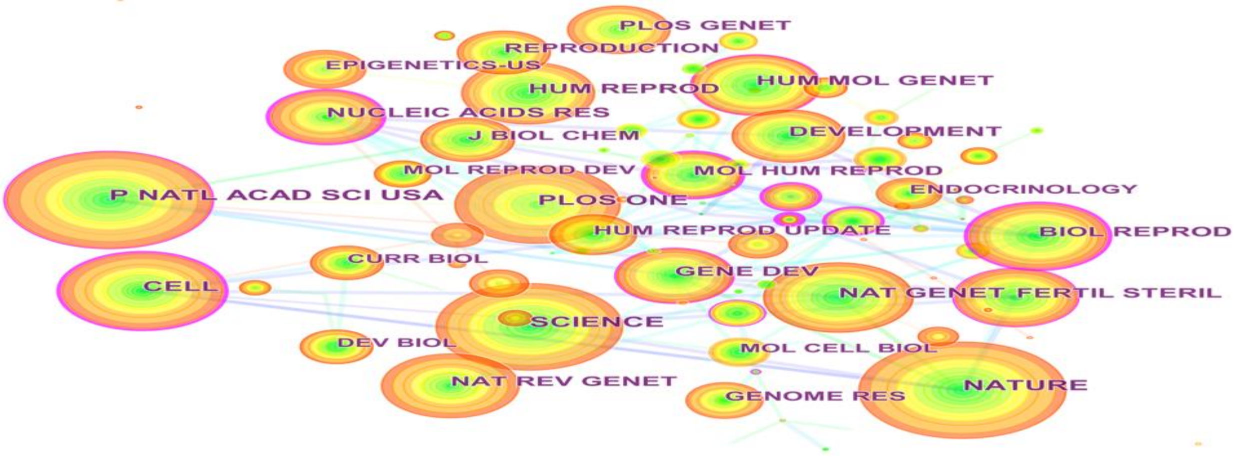


Figure 3.
Network map of productive countries.

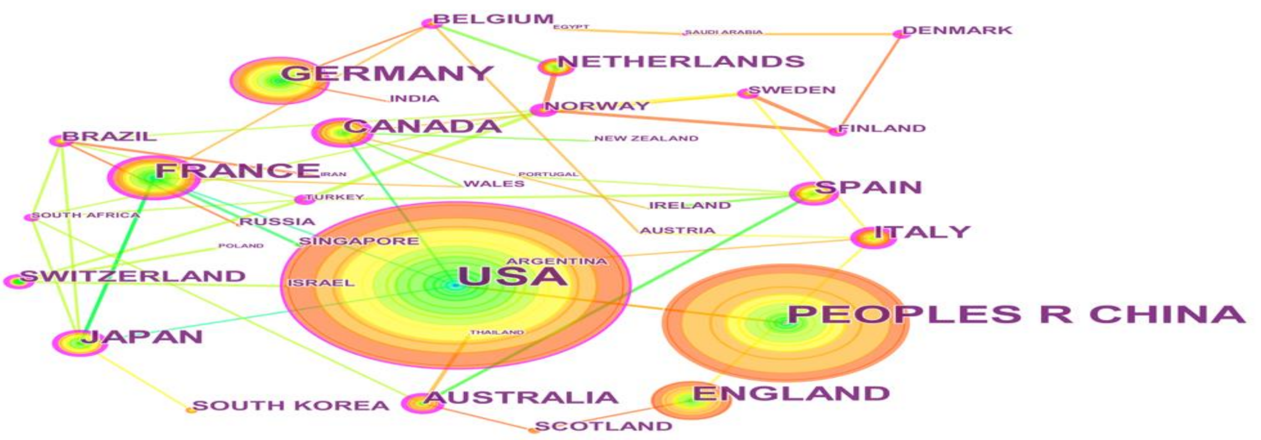


Figure 4.
Network map of productive institutions.

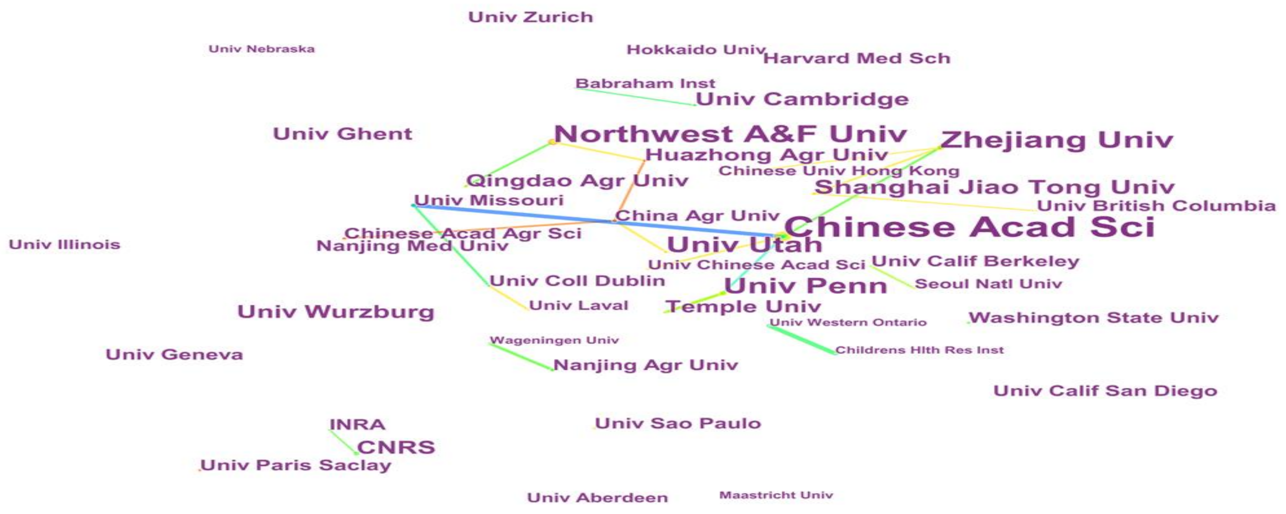


Figure 5.
Cooperation network of productive authors.

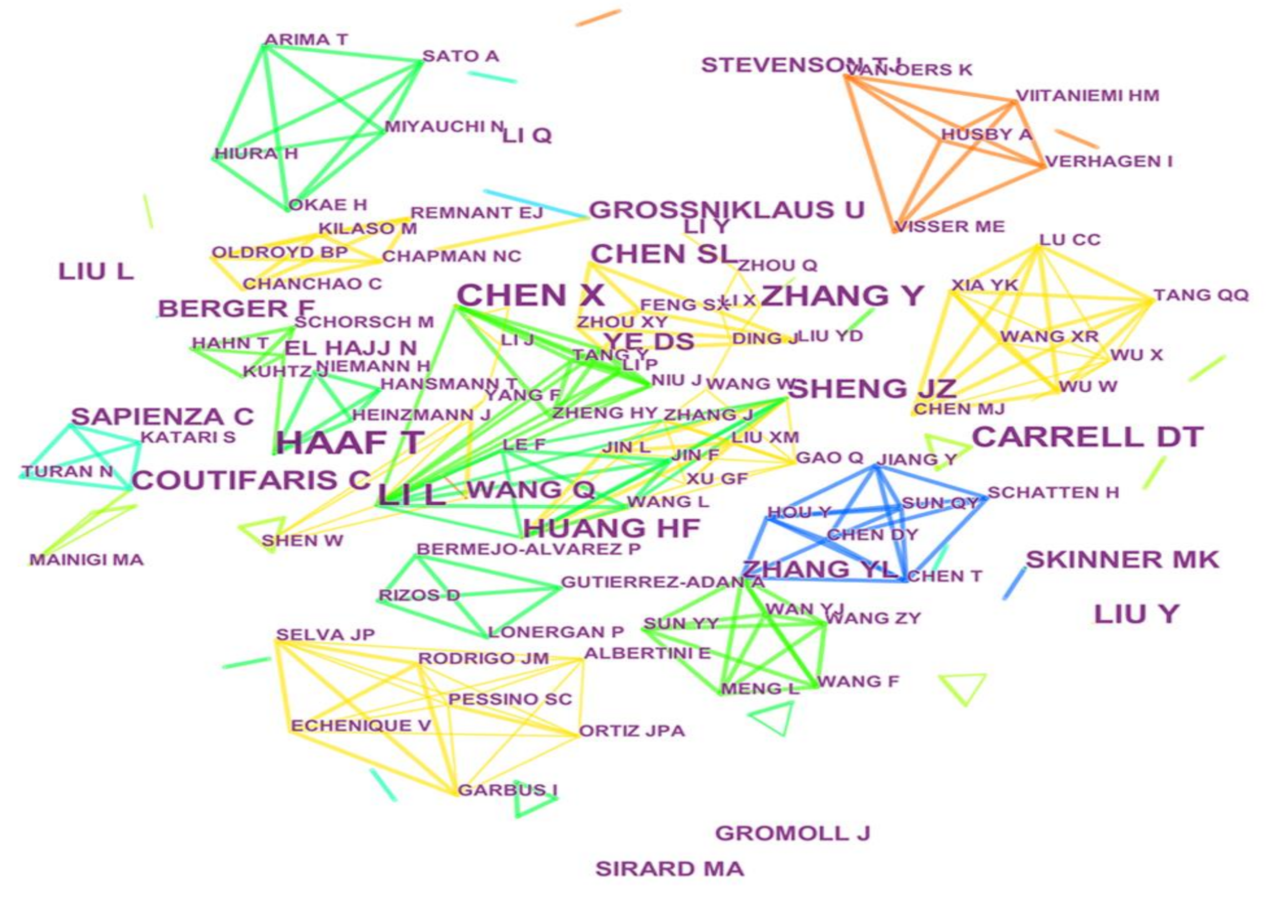


Figure 6.
Network map of co-cited authors.

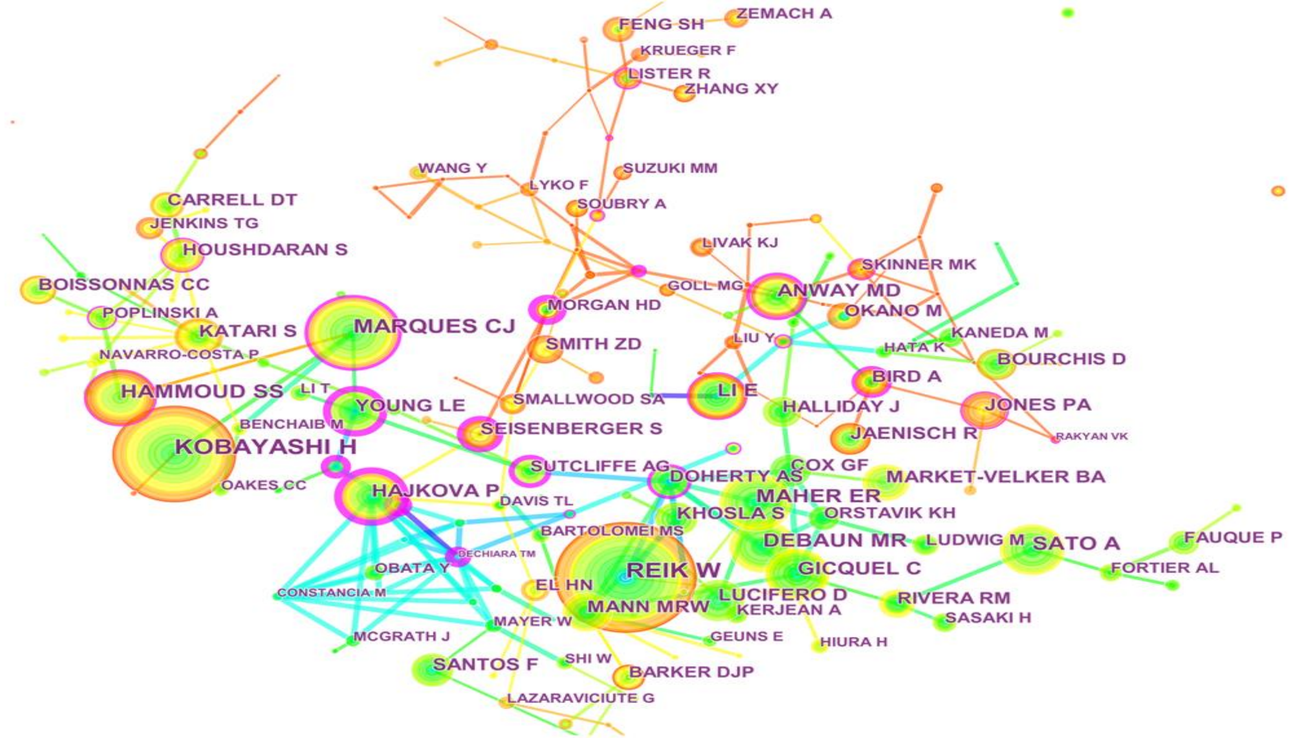


Figure 7.
Co-citation network of references.

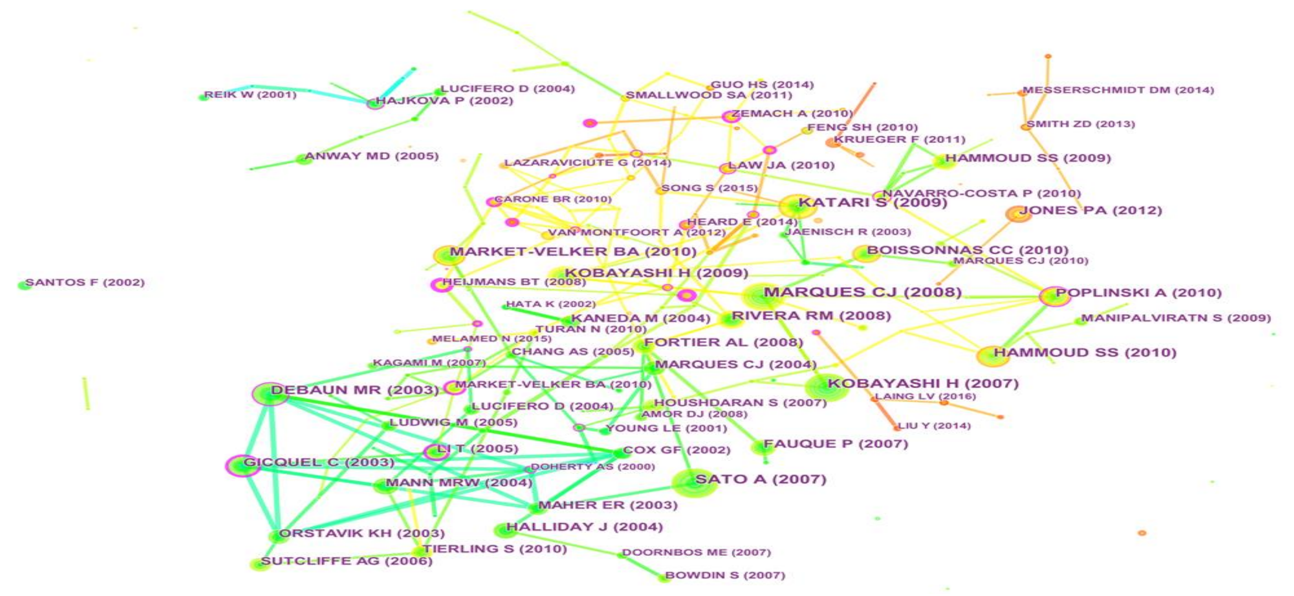


Figure 8.
Network map of co-occurring keywords.

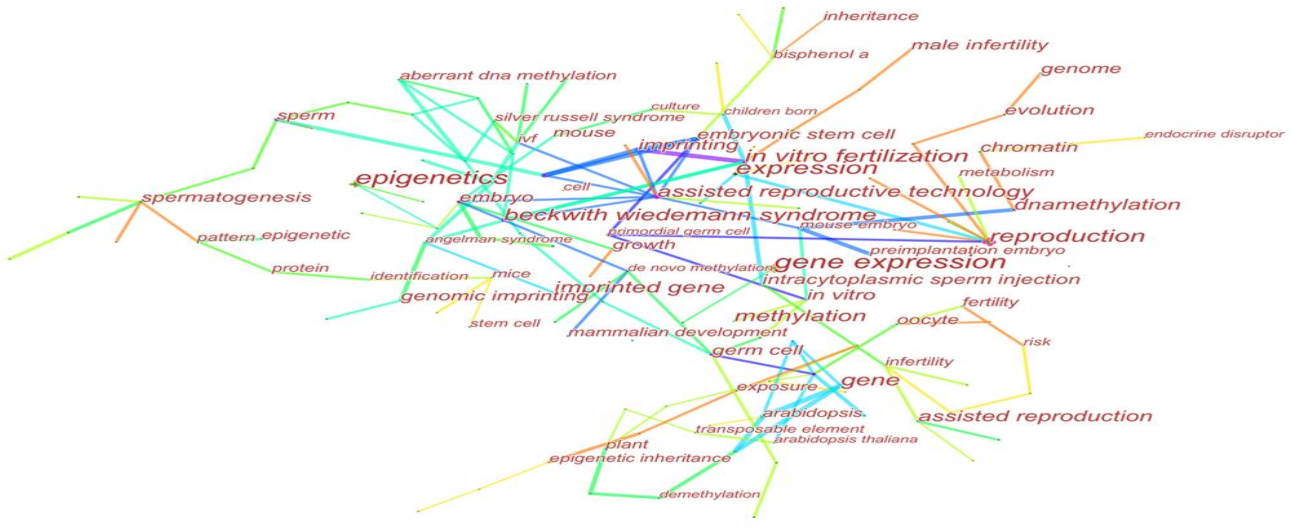
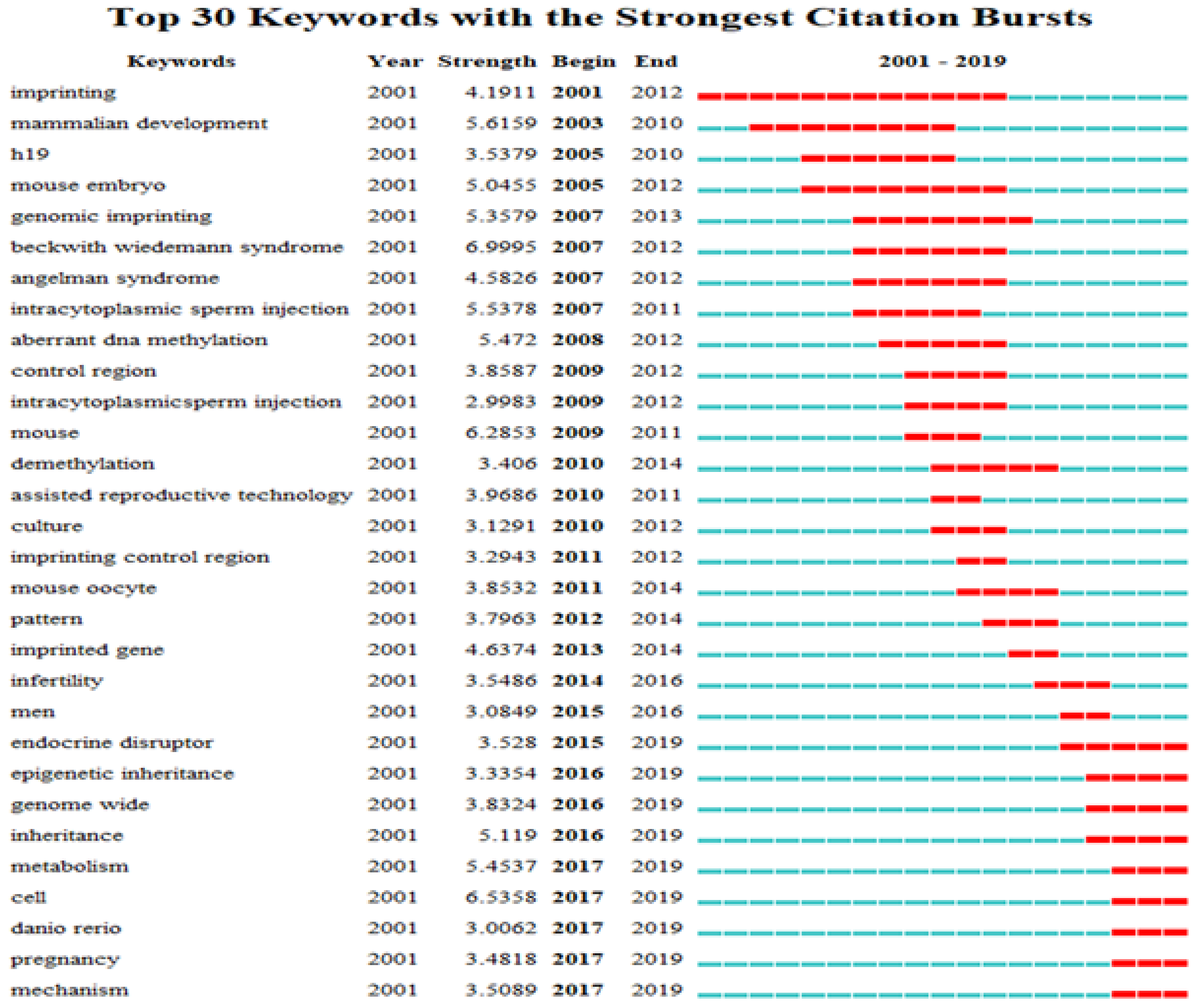


Figure 9.
Clusters of keyword co-ocurrence.

Figure 10.
Top 30 keywords with thestrongest citation bursts.


Top 30 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End
imprinting	2001	4.1911	**2001**	2012
mammalian development	2001	5.6159	**2003**	2010
h19	2001	3.5379	**2005**	2010
mouse embryo	2001	5.0455	**2005**	2012
genomic imprinting	2001	5.3579	**2007**	2013
beckwith wiedemann syndrome	2001	6.9995	**2007**	2012
angelman syndrome	2001	4.5826	**2007**	2012
intracytoplasmic sperm injection	2001	5.5378	**2007**	2011
aberrant dna methylation	2001	5.472	**2008**	2012
control region	2001	3.8587	**2009**	2012
intracytoplasmicsperm injection	2001	2.9983	**2009**	2012
mouse	2001	6.2853	**2009**	2011
demethylation	2001	3.406	**2010**	2014
assisted reproductive technology	2001	3.9686	**2010**	2011
culture	2001	3.1291	**2010**	2012
imprinting control region	2001	3.2943	**2011**	2012
mouse oocyte	2001	3.8532	**2011**	2014
pattern	2001	3.7963	**2012**	2014
imprinted gene	2001	4.6374	**2013**	2014
infertility	2001	3.5486	**2014**	2016
men	2001	3.0849	**2015**	2016
endocrine disruptor	2001	3.528	**2015**	2019
epigenetic inheritance	2001	3.3354	**2016**	2019
genome wide	2001	3.8324	**2016**	2019
inheritance	2001	5.119	**2016**	2019
metabolism	2001	5.4537	**2017**	2019
cell	2001	6.5358	**2017**	2019
danio rerio	2001	3.0062	**2017**	2019
pregnancy	2001	3.4818	**2017**	2019
mechanism	2001	3.5089	**2017**	2019

Figure 11.
Time-zone visualization of keywords.

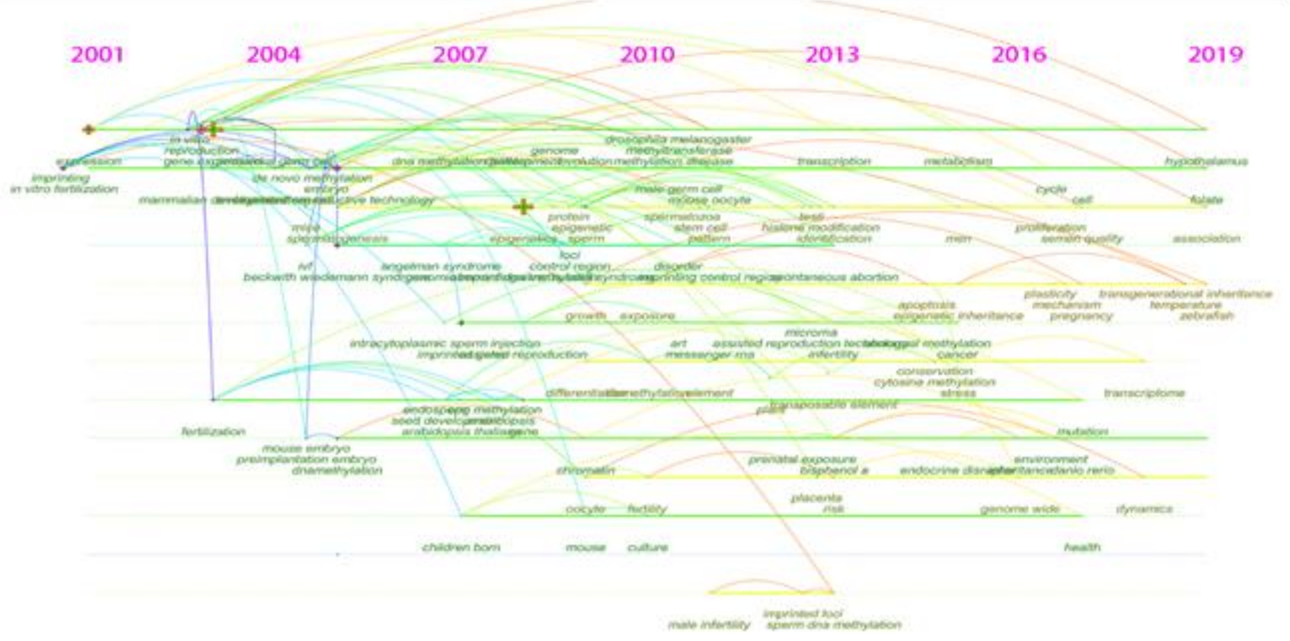


Table 1.
Top 5 journals in terms of frequency and centrality

Rank	Journal	Frequency	Rank	Journal	Centrality
1	Nature	471	1	New England Journal of Medicine	0.57
2	Proceedings of the National Academy of Sciences of United States	460	2	Biology of Reproduction	0.34
3	Science	411	3	Molecular Human Reproduction	0.31
4	Cell	374	4	Molecular and Cellular Endocrinology	0.25
5	PLoS One	354	5	Lancet	0.22

Table 2.
The top 5 most productive and influential countries in the field of DNA methylation in reproductive medicine

Rank	Country	Frequency	Rank	Country	Centrality
1	United States	199	1	Norway	0.57
2	China	139	2	Turkey	0.43
3	Germany	56	3	Sweden	0.37
4	England	54	4	Japan	0.35
5	France	50	5	Canada	0.32

Table 3.
The top 5 most productive and influential institutions in the field of DNA methylation in reproductive medicine.

Rank	Institution	Frequency	Rank	Institution	Centrality
1	Chinese Acad Sci	21	1	Chinese Acad Sci	0.09
2	Northwest A&F Univ	12	2	Qingdao Agr Univ	0.07
3	Zhejiang Univ	11	3	Northeast Agr Univ	0.07
4	Univ Utah	9	4	Northwest A&F Univ	0.06
5	Univ Penn	9	5	Huazhong Agr Univ	0.06

Table 4.
The top 5 most representative keywords in the field of DNA methylation in reproductive medicine

Cluster ID	Silhouette	keyword	Label
0	0.887	Imprinting, protein, gene expression, maternal and paternal effects, ransgenerational effects, early development, epigenetic reprogramming, epigenetic resetting, offspring, sex determination, gene regulation	Imprinting
1	0.563	assisted reproductive technology, human embryos, embryonic development, blastocysts, superovulation, embryo culture, art laboratory, ovarian stimulation, fertility treatment, in vitro	assisted reproductive technology
2	0.857	Oocyte, intracytoplasmic sperm injection (icsi), human embryo, preimplantation embryo, tripronuclear zygote, gonadotropin, mitochondria, in vitro maturation (ivm), postovulatory oocyte aging, blastocysts	Oocyte
3	0.803	h19, lgf2r, peg3, snrpn gene, dnmt3 family, pem homeobox gene, gene expression, transcription factor	h19
4	0.748	Infertility, human sperm, recurrent spontaneous miscarriage, fertilization, spermatogenesis, peg1/mest, endocrine disruptors	Infertility