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The 100 most-cited articles on prenatal diagnosis

A bibliometric analysis

Meilian Zhang, MD[a], Yu Zhou, PhD[b], Yanfang Lu, MM[c], Suhui He, MM[a], Min Liu, MM[a,*]

Abstract

Background: The number of citations a published article receives can be used to demonstrate its impact on a field of study. The objective of this study was to identify and characterize the 100 most-cited research articles (T100) published on prenatal diagnosis.

Methods: The Web of Science (WOS) database was searched for papers on prenatal diagnosis published between 1900 and 2018. The 100 most-cited original articles and reviews were recorded. Each eligible paper was reviewed for authors, journal name, year of publication, country, institution, total citations, citation density, H-index, research field, article type, and keywords.

Results: The T100 were published between 1972 and 2015 with a mean of 332.7 citations per paper (range: 196–1254). Most of the T100 were published between 1990 and 2005, in 35 journals led by *New England Journal of Medicine* (n = 14) followed by *Lancet* (n = 10), and *Proceedings of The National Academy of Sciences of the United States of America* (n = 8). Studies on method application, which promotes field development, were the majority article type. The team of Lo YM featured prominently in the field, and the United States of America, United Kingdom, and Hong Kong, China were the leading countries/regions. Frequency of cooperation was also highest among these 3 regions. Hierarchical cluster analysis produced 4 groups of keywords.

Conclusion: Our analysis provides a historical perspective on scientific progress in prenatal diagnosis and may assist clinicians and researchers in assessing the quality of research over the past 50 years. It also provides concise information to guide future research.

Abbreviations: β-hCG = β-human chorionic gonadotrophin, ISI = Institute for Scientific Information, NIPT = non-invasive prenatal testing, PAPP-A = pregnancy-associated plasma protein-A, PNAS = Proceedings of the National Academy of Sciences, WOS = Web of Science.

Keywords: academic influence, bibliometric analysis, citations, prenatal diagnosis, Web of Science

1. Introduction

Prenatal examination and diagnosis have played an important role in raising the quality of population for nearly 2 centuries. They allow parents to make informed decisions about a pregnancy, healthcare professionals to optimize antenatal care, and families to prepare for the birth of the baby. A large volume of research is published annually giving new insights into the development of safe and valuable prenatal diagnostic techniques.[1–3]

Bibliometrics is a type of statistical and quantitative analysis of the academic impact and characteristics of publications within a research field.[4] Citation analysis is a bibliometric analysis method used to quantify the relative importance of a scientific publication by examining the citations attributed to published research. Although there are obvious disadvantages in assessing the quality of a study simply based on the quantity of citations, it is widely accepted that this is the best method currently available for judging the merit of a paper or a journal.[5] Bibliometric studies have been published in several medical fields, including diabetes,[6] obesity,[7] gastrointestinal medicine,[8] asthma,[9] and coronary heart disease.[10] However, to the best of our knowledge, this type of identification has not been used in the field of prenatal diagnosis, and articles with significant findings that have contributed considerably to the development of antenatal diagnosis have not been identified and summarized comprehensively.

In this study, we aimed to analyze the characteristics of the 100 most-cited articles in antenatal diagnosis (T100) during the last 50 years, from a bibliometric perspective. We also intended to identify factors, such as journal and country/region, that contribute to successful citation.

2. Methodology

The expanded citation index of the database of the Institute for Scientific Information (ISI) Web of Science (WOS) was used to identify the most-cited papers in prenatal diagnosis research between 1900 and July 16, 2018. Searches were conducted on a

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[a] Department of Ultrasound, Fujian Provincial Maternity and Children's Hospital Affiliated Hospital of Fujian Medical University, [b] Department of Clinical Pharmacy and Pharmacy Administration, School of Pharmacy, Fujian Medical University, [c] Clinical Laboratory, Fujian Provincial Maternity and Children's Hospital Affiliated Hospital of Fujian Medical University, Fuzhou, China.

[*] Correspondence: Min Liu, Department of Ultrasound, Fujian Provincial Maternity and Children's Hospital, No. 18 Daoshan Road, Gulou District, Fuzhou 350001, Fujian, China (e-mail: fycsliumin@163.com).

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single day to avoid changes in citation rate as far as possible. Ethical approval was not required as no human subjects were enrolled and our data were from publicly available sources. The search terms were the "topic" (title, abstract, author's keywords, and KeyWords Plus) with the following strategy: TS = (prenatal OR antepartum OR predelivery OR antenatal OR fetus OR fetus OR embryo) AND TS = (diagnos* OR test* OR detect* OR examin* OR screen*). The search was restricted to papers in the English language. Papers published as "article" or "review" were selected for further analysis. The search results retrieved 2 010 266 published articles and these were listed in descending order of number of citations. The data extraction process was performed independently by 2 reviewers (MLZ and YZ). In cases of discrepancy between the reviewers, consensus was achieved with the help of a third independent reviewer (YFL). The abstract of each search result was read thoroughly to ensure that prenatal diagnosis was the major subject of the research. At last, the 100 most-cited articles were obtained and reviewed.

For the selected 100 articles, the following information was recorded: author names, journal name, country/region of authors, year of publication, institution, total number of citations, H-index of authors, citation density (defined as citations per year after publication), article type, research field, and keywords. Each article was categorized by type as follows:

(i) studies of method application;
(ii) observational clinical trials, including prospective/retrospective studies and case reports;
(iii) molecular level trials, including bench-top laboratory research of clinical samples or research involving animal models;
(iv) reviews, including literature reviews and meta-analyses;
(v) epidemiological studies; and
(vi) guidelines.

Research field was categorized according to study field classification on WOS. Keywords included the author's keywords, KeyWords Plus, and high frequency words (Articles were read in full and 3–5 high frequency words were summarized according to topic and frequency of occurrence.) To eliminate duplication and improve accuracy, we took synonyms into consideration, for example, "Mutation Screening", "Genetic Analysis", and similar terms were classified as "DNA/Gene Analysis", and "Chromosome Breakpoints", "Chromosome Deletion", and similar terms were classified as "Chromosomal Defects".

BibExcel software (designed by Persson and available at homepage.univie.ac.at/juan.gorraiz/bibexcel/index.html) was used to analyze the text data downloaded from WOS. VosViewer (Leiden University, Leiden, Netherlands) was used to construct co-occurrence networks of important terms (authorship, country/region, and keywords). SPSS 19.0 (SPSS Inc., Chicago, IL) was used for statistical analysis, with Pearson's correlation coefficient used to determine the relationship between dependent and independent variables. A dendrogram based on morphological traits was plotted using hierarchical cluster analysis and the between-group linkage method. Distance values were computed by dissimilarity cosine, rescaled between 0 and 1. Results were considered significant when $P < .05$.

3. Results

3.1. Total citations and citation density

The T100 published between 1972 and 2015, identified from 2 010 266 publications, are listed in descending order in Table 1. Total citations for each article ranged from 196 to 1254, and the mean number of citations per article was 332.7. Most of the articles (n = 93) received more than 200 citations; however, only 11 articles had more than 500. Citation density ranged from 5.0 to 71.7, with a mean density of 20.7. Citation density was positively correlated with total citations (Pearson's correlation coefficient = 0.511, $P < .01$), with articles with a higher citation density tending to have more total citations. The most cited paper was published in the *Lancet* in 1997,[11] an article that first reported that fetal DNA was found in maternal plasma and could be used for non-invasive prenatal diagnosis. The article with the highest citation density was a meta-analysis from 2015[12] reporting that screening for trisomy 21 by analysis of cell-free DNA in maternal blood is superior to traditional screening methods, with higher detection rates and lower false-positive rates.

3.2. Year of publication, article type, and journal

More than 80% of the articles were published after 1990. In terms of article type, method application studies and observational clinical trials contributed the largest proportion (33 and 31 articles, respectively), closely followed by molecular basis studies (24 articles). The total share of reviews, epidemiological studies, and guidelines was a low 12%. Distribution by publication year and article type is shown in Figure 1.

The T100 were published in 35 journals. Table 2 presents the journals that contributed more than 2 articles to the T100, led by *New England Journal of Medicine* (n = 14) followed by *Lancet* (n = 10). *Proceedings of the National Academy of Sciences of the United States of America (PNAS)* was third on the list with eight articles. We found a positive correlation between journal impact factor and the number of T100 articles (Pearson's correlation coefficient = 0.761, $P < .01$), with journals with a higher impact factor tending to have more T100 articles.

3.3. Authorship, country/region, and cooperation networks

A total of 13 authors contributed more than 3 articles to the T100 and were listed as the first author or corresponding author (Table 3). Lo YM authored the most classic papers (n = 16) followed by Lau TK, who authored 14 classic papers. Lo YM and Nicolaides KH ranked highest as first or corresponding authors, co-authoring 16 and 6 articles, respectively. Nicolaides KH, Lo YM and Cantor CR were the 3 authors with the highest H-index ranking. H-index was not obviously correlated with the number of articles published by these authors ($P > .05$). Almost all of the authors in Table 3 are from Hong Kong, China and the United States of America (USA). Networks of author cooperation are documented and their analysis presented visually in Fig. 3A. The most frequent cooperation was between Lo YM and Lau TK (n = 14), followed by Lo YM–Leung TN (n = 8), Lau TK–Leung TN (n = 8), Lo YM–Chan KC(n = 7), and Lau TK–Chan KC (n = 7).

The articles originated from 25 different countries/regions. The USA contributed the most articles (n = 58), followed by the United Kingdom (UK) (n = 29), and Hong Kong (n = 16) (Fig. 2). Bilateral cooperation was most frequent between the USA and UK (n = 7), followed by the USA and Hong Kong (n = 6), and the UK and Hong Kong (n = 6) (Fig. 3B). The UK (n = 35) and USA (n = 31) contributed to the majority of bilateral cooperation (Fig. 3B).

Table 1

The 100 most-cited articles on prenatal diagnosis.

Rank	Year	First author	No. of citations	Citation density	New* rank	Rank	Year	First author	No. of citations	Citation density	New* rank
1	1997	Lo YM	1254	59.71	6	51	1994	Hohlfeld P	258	10.75	72
2	1998	Snijders RJ	1019	50.95	8	52	2006	Mills PB	256	21.33	30
3	1993	Noguchi M	992	39.68	15	53	2002	Bonduelle M	256	16.00	46
4	1998	Lo YM	957	47.85	11	54	1985	Adzick NS	256	7.76	87
5	1996	Bianchi DW	778	35.36	17	55	2007	Lo YM	255	23.18	24
6	1987	Kogan SC	773	24.94	22	56	2008	Lun FM	251	25.10	21
7	1972	Brock DJ	584	12.70	64	57	1988	Kazazian HH	251	8.37	84
8	1993	Chelly J	582	23.28	23	58	2000	Ringpfeil F	250	13.89	57
9	1991	Rousseau F	547	20.26	31	59	2003	Ng EK	248	16.53	45
10	2002	Bobadilla JL	536	33.50	18	60	2007	Lo YM	246	22.36	27
11	2008	Fan HC	503	50.30	9	61	1993	Toda T	245	9.80	76
12	2011	Palomaki GE	494	70.57	3	62	1990	Kazazian HH	245	8.75	80
13	1991	Warburton D	485	17.96	40	63	1985	Adzick NS	237	7.18	90
14	2008	Chim SS	474	47.40	12	64	2007	Jani J	236	21.45	29
15	2000	Yoon BH	460	25.56	20	65	1992	Wald NJ	236	9.08	78
16	2008	Chiu RW	442	44.20	14	66	1979	Golbus MS	236	6.05	93
17	1998	Lo YM	440	22.00	28	67	1997	Bleyl SB	233	11.10	71
18	1992	Speiser PW	397	15.27	49	68	1985	Bakker E	227	6.88	91
19	2012	Wapner RJ	391	65.17	4	69	1999	Bull C	226	11.89	68
20	1996	Metkus AP	385	17.50	42	70	1976	Simpson NE	225	5.36	98
21	2012	Bianchi DW	378	63.00	5	71	1993	Brown WT	224	8.96	79
22	1993	Driscoll DA	377	15.08	50	72	2001	Chiu RW	223	13.12	62
23	1999	Wiemels JL	376	19.79	34	73	2005	Chim SS	221	17.00	44
24	1999	Bonnet D	376	19.79	35	74	1984	Moser AE	218	6.41	92
25	1999	Spencer K	372	19.58	37	75	2007	Malinger G	217	19.73	36
26	1992	Handyside AH	354	13.62	59	76	1997	Lipshutz GS	217	10.33	74
27	1989	Rhoads GG	350	12.07	67	77	2015	Gil MM	215	71.67	1
28	2011	Chiu RW	346	49.43	10	78	2000	Skari H	214	11.89	69
29	2001	Crawford DC	342	20.12	32	79	2015	Norton ME	213	71.00	2
30	2001	Tworetzky W	340	20.00	33	80	2010	Limperopoulos C	213	26.63	19
31	1995	Yoon BH	337	14.65	54	81	2003	Nolin SL	213	14.20	55
32	2003	Botto LD	336	22.40	26	82	2006	Chan KC	212	17.67	41
33	1978	Kan YW	335	8.38	83	83	2002	Finning KM	211	13.19	61
34	1997	Gale KB	324	15.43	48	84	1991	Chitty LS	210	7.78	86
35	2004	Chan KC	319	22.79	25	85	1980	Kleinman CS	210	5.53	96
36	1993	Hamosh A	314	12.56	65	86	2003	DeVore GR	209	13.93	56
37	2011	Ehrich M	312	44.57	13	87	1980	Kan YW	209	5.50	97
38	2001	Cicero S	309	18.18	39	88	2004	Sermon K	208	14.86	53
39	2012	Palomaki GE	306	51.00	7	89	1991	Clemens PR	208	7.70	88
40	2000	Chong SS	306	17.00	43	90	1994	Zerres K	204	8.50	82
41	1998	Adzick NS	301	15.05	52	91	2003	Spencer K	203	13.53	60
42	1999	Grandjean H	295	15.53	47	92	1984	Boue A	202	5.94	94
43	1995	Wang W	295	12.83	63	93	1978	Orkin SH	200	5.00	100
44	2010	Lo YM	290	36.25	16	94	1999	Lo YM	198	10.42	73
45	1990	Ransley PG	289	10.32	75	95	1995	Merz E	197	8.57	81
46	1997	Bianchi DW	287	13.67	58	96	1991	Price JO	197	7.30	89
47	1995	Ledbetter DH	282	12.26	66	97	1983	Pirastu M	197	5.63	95
48	1983	Woo SL	274	7.83	85	98	2005	Souka AP	196	15.08	51
49	2003	Wald NJ	273	18.20	38	99	2001	Mahle WT	196	11.53	70
50	1990	Old JM	260	9.29	77	100	1981	Auerbach AD	196	5.30	99

* Sorted by citation density.

3.4. Research fields and keywords

The largest number of studies were in "Medicine, General and Internal" (n=29), and "Obstetrics and Gynecology" (n=17). Additionally, a considerable proportion of research was in "Genetics and Heredity", "Multidisciplinary Science", and "Pediatrics", according to the WOS study field classifications (Table 4).

Table 5 presents a list of the most frequently used (used more than once) T100 keywords. The keyword DNA/Gene Analysis occurred the most (n=59), followed by Peripheral Blood (n=28), Non-invasive Testing (n=27) and Fetal DNA (n=24). The hierarchical clustering results are presented as a dendrogram in Figure 4, and provide insight into the relationships between keywords. The 42 keywords occurring more than twice were classified to 4 clusters. The first cluster included Cystic Fibrosis, Fragile X Syndrome, Congenital Muscular Dystrophy, Thalassemia, and Chromosomal Defects, described as "prenatal diagnosis of diseases associated with chromosomal defects"; the second cluster included Non-invasive Testing, Polymerase Chain Reac-

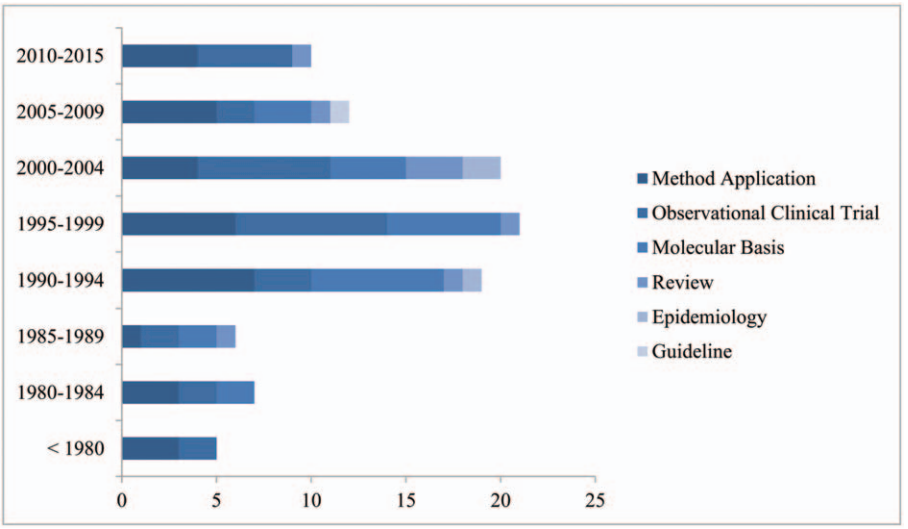

Figure 1. Publication year and article type of the 100 most-cited papers.

tion, Down Syndrome, Trisomy, Aneuploidy, Parallel Shotgun Sequencing, Peripheral Blood, First Trimester, and DNA/Gene Analysis, described as "non-invasive diagnosis via maternal peripheral blood"; the third cluster included HCG, Maternal Age, Fetal Nuchal Translucency, and Ultrasonography, described as "prenatal diagnosis via ultrasonography joint serum indexes and maternal age"; and the fourth cluster included Fetal Surgery, Malformations, and Congenital Heart Disease, described as "fetal therapy of partial congenital malformations".

4. Discussion

Identification of classic citations can facilitate the recognition of academic advances in a particular discipline, as well as help to identify emerging topics and future directions.[13] The aim of this bibliometric analysis was to provide insight into the development over time and the circumstances of prenatal diagnosis research.

The T100 in our study were cited between 196 and 1254 times. This number lags far behind citation classics in asthma studies,[9] (701–2947 citations) and coronary heart disease[10] (1157–7829 citations) during the time periods covered by those studies. Citation rates differ between specialties and depend on the size of the research field. Hotter scientific fields, such as cancer and neurodegenerative disorders tend to be have a higher number of classic citations. However, the assessment of classic citations is inherently limited, as citations accumulate over time and recently published articles will be underestimated irrespective of their true impact.[14] Citations gradually reach their peak numbers 3 to 10 years after publication and tend to decrease afterwards.[15] To overcome this limitation, we analyzed citation density. Most of the T100 were published between 1990 and 2005, but the top 5 ranked articles for citation density were focused on the period from 2011 to 2015, indicating an increasing focus on the field of prenatal diagnosis in more recent years and improved availability of resources for research.

Table 2

Journals contributing more than 2 papers to the 100 most-cited articles.

Journal	No. of articles	2017 impact factor
New England Journal of Medicine	14	79.258
Lancet	10	53.254
Proceedings of The National Academy of Sciences of The United States of America	8	9.504
American Journal of Obstetrics and Gynecology	7	5.732
Clinical Chemistry	6	8.636
Ultrasound in Obstetrics & Gynecology	6	5.654
Journal of Pediatric Surgery	5	2.128
American Journal of Human Genetics	5	8.855
Pediatrics	4	5.515
Genetics in Medicine	3	9.937
Nature Genetics	3	27.125
Circulation	3	18.880

Outstanding articles tend to be published in journals with high impact factors, and high impact factor journals facilitate the academic influence of articles.[16] Our results support this. The 3 journals that ranked highest for citations, *New England Journal of Medicine*, *Lancet*, and *PNAS*, have an impact factor of higher than 50 or the peak level in the subspecialty. Most of the highly cited articles were studies of method application, which suggests that prenatal diagnostic and screening options are rapidly increasing, largely pushed by technological advances. Several methodologies for performing reliable prenatal diagnostic testing, ranging from basic biomolecular methods (qPCR, QF-PCR, COLD-PCR coupled with Sanger sequencing and MEMO qPCR)[17–19] to highly sophisticated and costly methodology, such as MALDI-TOF mass spectrometry,[20] array primer single-base extension,[21] and PCR/LDR/capillary electrophoresis,[22] have been documented in the literature. Similarly, the large majority of the T100 in the field of imaging have been relatively recently published "methods-type" articles.[23] Our findings also revealed that high quality observational clinical trials and molecular-based research gave impetus to the development of prenatal diagnosis.

The majority of our T100 originated from developed countries in Europe and North America; the voice from Asia, Africa, and South America was relatively quiet. The USA ranked highest for quality of scientific production in prenatal diagnosis research,

Table 3

Authors contributing more than 3 papers to the 100 most-cited articles.

Author	No. of articles	No. of first or corresponding authors	H- index	Affiliation	Country/region
Lo YM	16	16	82	Chinese University of Hong Kong	Hong Kong, China
Lau TK	14	0	54	Chinese University of Hong Kong	Hong Kong, China
Chiu RW	11	4	50	Chinese University of Hong Kong	Hong Kong, China
Nicolaides KH	10	6	105	King's College School of Medicine	UK
Leung TN	8	0	39	Chinese University of Hong Kong	Hong Kong, China
Chan KC	7	2	43	Chinese University of Hong Kong	Hong Kong, China
Harrison MR	6	3	81	University of California	USA
Leung TY	6	0	37	Chinese University of Hong Kong	Hong Kong, China
Lun FM	5	1	13	Chinese University of Hong Kong	Hong Kong, China
Cantor CR	5	2	82	University of Boston	USA
Adzick NS	4	4	76	University of California /Children's Hospital of Philadelphia	USA
Bianchi DW	4	4	57	Harvard Medical School/Tufts University School of Medicine,	USA
Tsui NB	4	1	21	Chinese University of Hong Kong	Hong Kong, China

followed by the UK and Hong Kong, and the frequency of cooperation among these 3 country/regions was also highest. The visualization of our geographic analysis clearly showed a regional imbalance in development in this field. A similar phenomenon is apparent in other fields, including gastrointestinal medicine,[8] asthma,[9] and coronary heart disease.[10] Biomedical research productivity is largely dependent on a country's per capita gross national product, which influences the funding allocated for research and development.[24] Gains in quality of life and survival made through improved prenatal examination and diagnosis have yet to reach globally.

Lo YM and team[11] made the important discovery of free fetal DNA in the maternal circulation in 1997, creating a precedent for non-invasive prenatal testing (NIPT). They featured prominently in our T100, with further work published in 2003 and 2007 demonstrating that the placenta is the main source of fetal RNA in maternal plasma[25] and that fetal RNA in maternal plasma could be used for detection of Down syndrome with over 90% accuracy.[26] The use of NIPT potential avoids or reduces the need for invasive techniques, such as chorionic villus sampling and amniocentesis. Although Lo YM's discovery of free fetal DNA in the maternal peripheral blood was more than 2 decades ago, the transfer of NIPT from research into clinical practice has been rather fragmented. Despite advances in the translation of methods, a lack of sensitivity and low reproducibility in distinguishing between fetal and maternal sequences remain challenges.[2] Moreover, the techniques are cumbersome and prone to contamination, presenting a conspicuous dependence on the handling expertise of the technicians. Thus, NIPT has yet to be routinely applied in clinical diagnostics and the detection of genetic diseases. More than 60 years since its application to obstetrics, ultrasonography has played important roles in modern prenatal care, including assessment of gestation age, fetal viability, multiple pregnancy, placental location, fetal morphology and growth.[27] After entering the 1990s, screening for aneuploidies has focused on the first trimester of pregnancy. Which is an algorithm based on the combination of maternal age, fetal nuchal translucency thickness and maternal serum indexes including free β-human chorionic gonadotrophin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A).[28,29] In the last decade, several additional sonographic markers have been described that improve the detection rate of malformations and

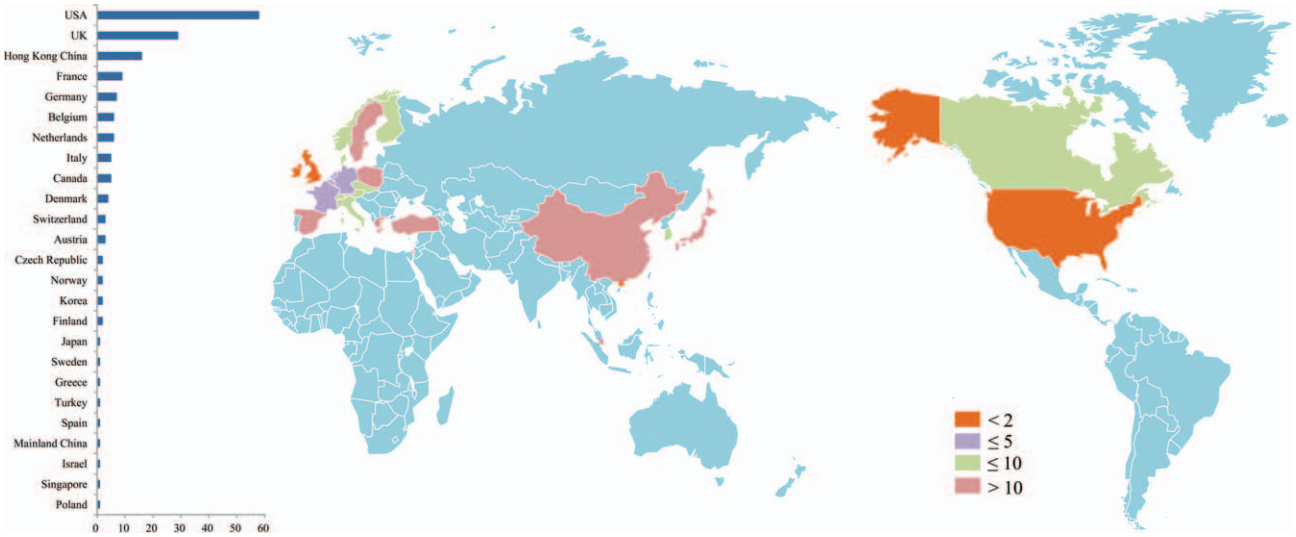

Figure 2. Geographical distribution of countries/regions in 100 top-cited papers.

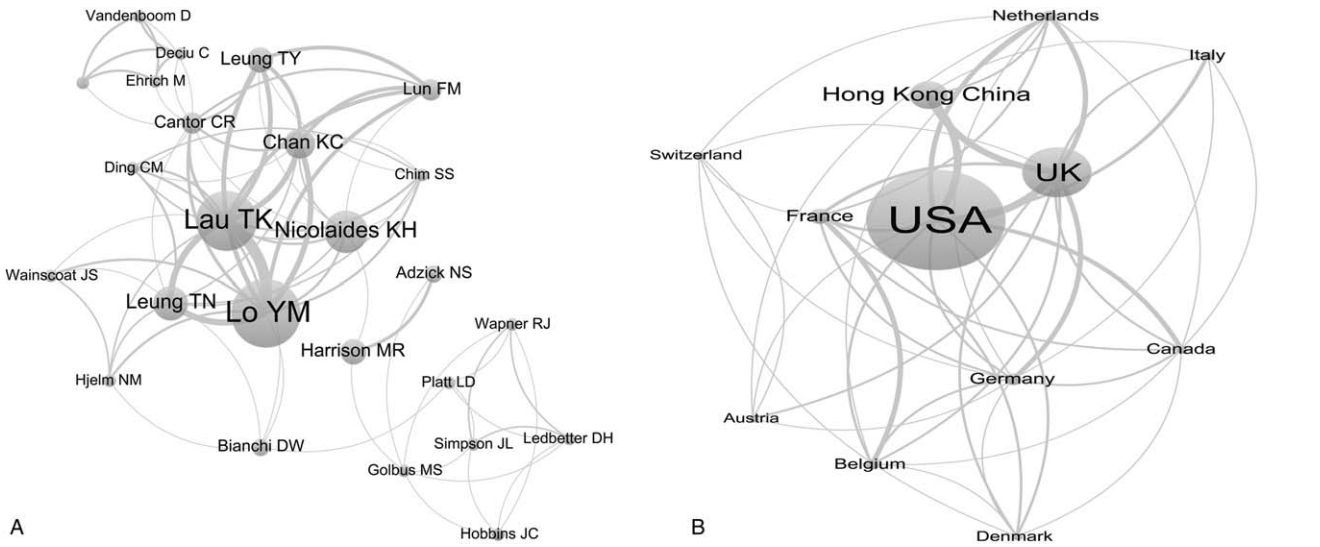

Figure 3. Interactions between authors contributing more than 2 papers and countries/regions that contributed more than 1 paper to the 100 most-cited articles. The size of the circles indicates the importance of an author or country/region in the cooperation network. The thickness of the lines indicates the strength of the connection between the authors or countries/regions.

reduce the false-positive rate.[2] Fetal therapy has tremendous potential to treat a broad range of congenital disorders. The goal of fetal therapy is to provide the best possible outcome for the fetus, while minimizing the risk to the mother.[30] Fetal therapy is not just restricted to the correction of structural anomalies—prenatal stem cell transplantation and gene therapy enjoy a brighter prospect for abnormal genetic conditions.[31] There is still a need for ongoing research to develop novel methods and improve specificity and safety.

Our study has several limitations. First, we confined the search to English language journals and did not include citation counts from PubMed, Scopus, or Google Scholar. Second, inherent bias exists in citation analysis.[32] The total numbers of article citations accumulate over time, meaning that older publications will have received more citations than new ones. Authors are more likely to cite articles in their own language, and English articles are more likely to be cited overall. Third, the possibility of oriented or biased citing, including self-citation, in-house, or negative citation, cannot be ignored. Lastly, bibliometric analysis may omit some publications of high quality or that deserve scientific merit.

5. Conclusion

Although bibliometric analysis has its limitations, it provides an important quantitative method for comparing research in scientific fields. To our knowledge, this study is the first report on the 100 most-cited papers in prenatal diagnosis. It highlights the landmark contributions leading to developments of prenatal

Table 4

Research fields of the 100 most-cited articles.

Research field	No. of articles
Medicine, general and internal medicine	29
Obstetrics and gynecology	17
Genetics and heredity	16
Multidisciplinary sciences	10
Pediatrics	9
Acoustics	6
Medical laboratory technology	6
Radiology, nuclear medicine, and medical imaging	6
Surgery	5
Cell biology	4
Biochemistry and molecular biology	4
Medicine, research and experimental	4
Hematology	4
Cardiac and cardiovascular systems	3
Peripheral vascular disease	3
Urology and nephrology	1
Public, environmental and occupational health	1
Reproductive biology	1

Table 5

Keywords occurring more than once in the 100 most-cited articles.

Keywords	Frequency	Keywords	Frequency
DNA/gene analysis	59	HCG	3
Peripheral blood	28	Malformations	3
Non-invasive Testing	27	Cystic fibrosis	3
Fetal DNA	24	Fetal surgery	3
Ultrasonography	20	Cytokines	2
Chromosomal Defects	20	Detection rate	2
Down syndrome	14	Invasive testing	2
First trimester	13	Intra-amniotic Inflammation	2
Polymerase chain reaction	12	Pediatrics	2
Trisomy	10	Fmr1	2
Amniocentesis	9	False-positive rate	2
Fetal nuchal translucency	7	Epidemiology	2
Thalassemia	7	Molecular basis	2
Congenital heart disease	6	Fetal RhD status	2
Congenital diaphragmatic hernia	5	Fetal infection	2
Aneuploidy	4	Second trimester	2
Fragile X Syndrome	4	Clinical validation	2
Karyotype	3	Chorioamnionitis	2
Parallel shotgun sequencing	3	Amplification reaction	2
Maternal age	3	Chorionic villus sampling	2
Congenital muscular dystrophy	3	Acute leukemia	2

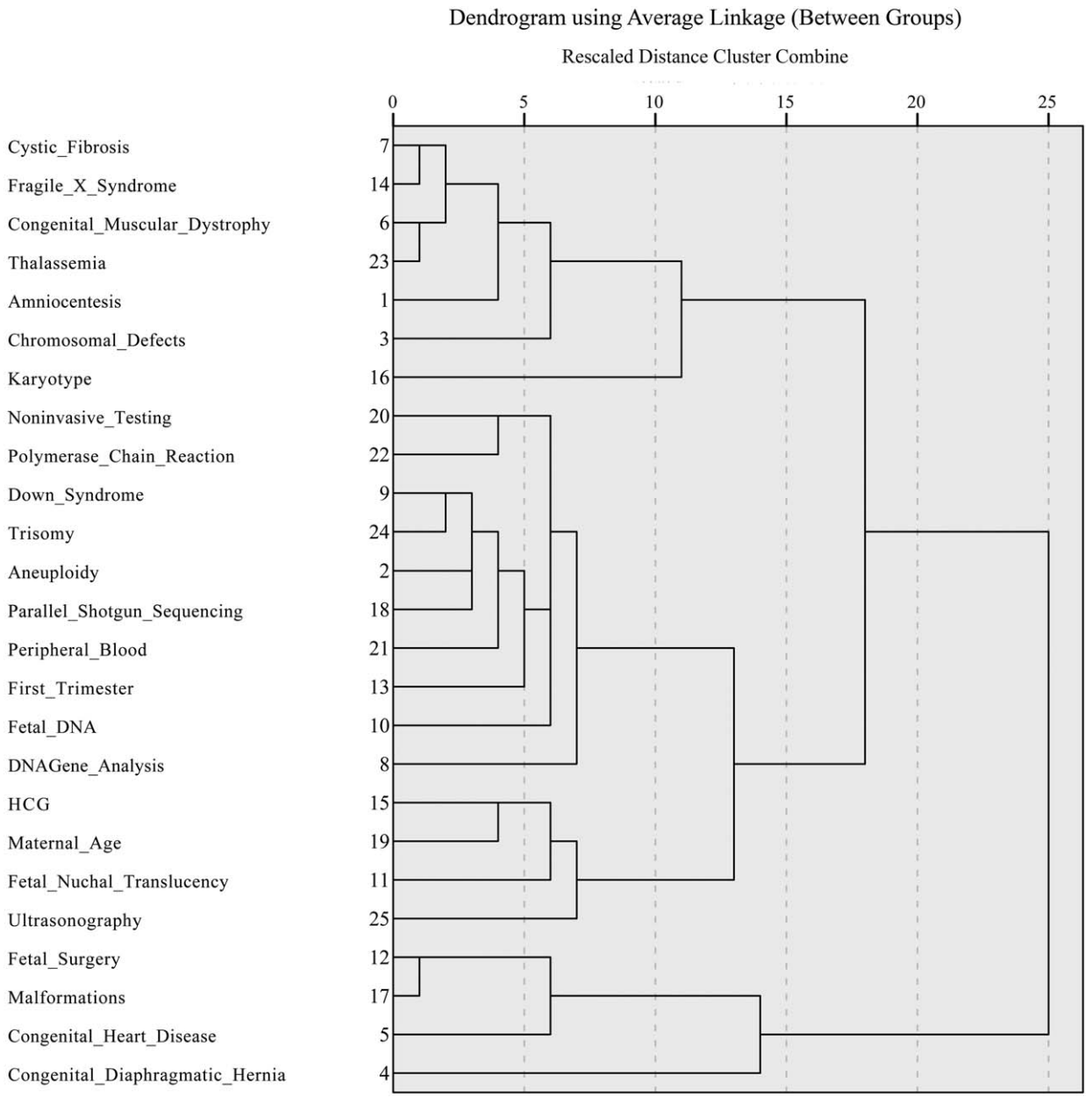

Figure 4. Hierarchical clustering of keywords occurring more than twice in the 100 most-cited papers.

diagnosis, and is instructive for researchers who are new to the field. The results of this report emphasize the quality of prior research of prenatal diagnosis and could stimulate new approaches and thoughts. Additionally, it provides a historical perspective on progress in prenatal diagnosis research and serves as a source for future academic pursuit.

Author contributions

Conceptualization: Meilian Zhang, Min Liu.
Data curation: Meilian Zhang, Yu Zhou, Yanfang Lu, Min Liu.
Formal analysis: Meilian Zhang, Yanfang Lu.
Funding acquisition: Meilian Zhang, Min Liu.
Investigation: Yanfang Lu.
Methodology: Meilian Zhang, Yanfang Lu, Min Liu.
Project administration: Meilian Zhang, Yu Zhou.
Resources: Meilian Zhang.
Supervision: Yu Zhou, Suhui He, Min Liu.
Validation: Yu Zhou.
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References

[1] Collins SL, Impey L. Prenatal diagnosis: types and techniques. Early Hum Dev 2012;88:3–8.
[2] Ferrari M, Carrera P, Lampasona V, et al. New trend in non-invasive prenatal diagnosis. Clin Chim Actay 2015;451(Pt A):9–13.
[3] Beaudet AL. Using fetal cells for prenatal diagnosis: history and recent progress. Am J Med Genet C Semin Med Genet 2016;172:123–7.

[4] Agarwal A, Durairajanayagam D, Tatagari S, et al. Bibliometrics: tracking research impact by selecting the appropriate metrics. Asian J Androl 2016;18:296–309.
[5] Adam D. The counting house. Nature 2002;415:726–9.
[6] Zhao X, Guo L, Lin Y, et al. The top 100 most cited scientific reports focused on diabetes research. Acta Diabetol 2016;53:13–26.
[7] Khan A, Choudhury N, Uddin S, et al. Longitudinal trends in global obesity research and collaboration: a review using bibliometric metadata. Obes Rev 2016;17:377–85.
[8] Tang X, Gong W, Yuan F, et al. Top-cited articles in digestive system disease from 1950 to 2013. J Gastroenterol Hepatol 2016;31:107–11.
[9] Qu Y, Zhang C, Hu Z, et al. The 100 most influential publications in asthma from 1960 to 2017: a bibliometric analysis. Respir Med 2018;137:206–12.
[10] Liao J, Wang J, Liu Y, et al. The most cited articles in coronary heart disease: a bibliometric analysis between 1970 and 2015. Int J Cardiol 2016;222:1049–52.
[11] Lo YMD, Corbetta N, Chamberlain PF, et al. Presence of fetal DNA in maternal plasma and serum. Lancet 1997;350:485–7.
[12] Gil MM, Quezada MS, Revello R, et al. Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol 2015;45:249–66.
[13] Alotaibi NM, Nassiri F, Badhiwala JH, et al. The most cited works in aneurysmal subarachnoid hemorrhage: a bibliometric analysis of the 100 most cited articles. World Neurosurg 2016;89:587–92. e6.
[14] Pepe A, Kurtz MJ. A measure of total research impact independent of time and discipline. PloS One 2012;7:e46428.
[15] Marx W, Schier H, Wanitschek M. Citation analysis using online databases: feasibilities and shortcomings. Scientometrics 2001;52:59–82.
[16] Callaham M, Wears RL, Weber E. Journal prestige, publication bias, and other characteristics associated with citation of published studies in peer-reviewed journals. JAMA 2002;287:2847–50.
[17] Lench N, Barrett A, Fielding S, et al. The clinical implementation of non-invasive prenatal diagnosis for single-gene disorders: challenges and progress made. Prenat Diagn 2013;33:555–62.
[18] Galbiati S, Monguzzi A, Damin F, et al. COLD-PCR and microarray: two independent highly sensitive approaches allowing the identification of fetal paternally inherited mutations in maternal plasma. J Med Genet 2016;53:481–7.
[19] Guissart C, Debant V, Desgeorges M, et al. Non-invasive prenatal diagnosis of monogenic disorders: an optimized protocol using MEMO qPCR with miniSTR as internal control. Clin Chem Lab Med 2015;53:205–15.
[20] Li Y, Di Naro E, Vitucci A, et al. Size fractionation of cell-free DNA in maternal plasma improves the detection of a paternally inherited beta-thalassemia point mutation by MALDI-TOF mass spectrometry. Fetal Diagn Ther 2009;25:246–9.
[21] Papasavva T, Kalikas I, Kyrri A, et al. Arrayed primer extension for the noninvasive prenatal diagnosis of beta-thalassemia based on detection of single nucleotide polymorphisms. Ann N Y Acad Sci 2008;1137:302–8.
[22] Yi P, Chen Z, Yu L, et al. Development of a PCR/LDR/capillary electrophoresis assay with potential for the detection of a beta-thalassemia fetal mutation in maternal plasma. J Matern Fetal Neonatal Me 2010;23:920–7.
[23] Brinjikji W, Klunder A, Kallmes DF. The 100 most-cited articles in the imaging literature. Radiology 2013;269:272–6.
[24] Rahman M, Fukui T. Biomedical research productivity: factors across the countries. Int J Technol Assess Health Care 2003;19:249–52.
[25] Ng EKO, Tsui NBY, Lau TK, et al. mRNA of placental origin is readily detectable in maternal plasma. Proc Natl Acad Sci U S A 2003;100:4748–53.
[26] Lo YMD, Tsui NBY, Chiu RWK, et al. Plasma placental RNA allelic ratio permits noninvasive prenatal chromosomal aneuploidy detection. Nat Med 2007;13:218–23.
[27] Lostchuck E, Poulton A, Halliday J, et al. Population-based trends in ultrasound-indicated prenatal diagnosis from 1994 to 2016: two decades of change. Ultrasound Obstet Gynecol 2018;53:503–11.
[28] Spencer K, Souter V, Tul N, et al. A screening program for trisomy 21 at 10-14 weeks using fetal nuchal translucency, maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 1999;13:231–7.
[29] Spencer K, Spencer CE, Power M, et al. Screening for chromosomal abnormalities in the first trimester using ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three years prospective experience. BJOG 2003;110:281–6.
[30] Graves CE, Harrison MR, Padilla BE. Minimally invasive fetal surgery. Clin Perinatol 2017;44:729–51.
[31] McClain LE, Flake AW. In utero stem cell transplantation and gene therapy: recent progress and the potential for clinical application. Best Pract Res Clin Obstet Gynaecol 2016;31:88–98.
[32] Gisvold SE. Citation analysis and journal impact factors–is the tail wagging the dog? Acta Anaesthesiol Scand 1999;43:971–3.