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Research trends and perspectives of male infertility: a bibliometric analysis of 20 years of scientific literature

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SUMMARY

To carry out an in-depth analysis of the scientific research on male infertility, we performed the first bibliometric analysis focusing on studies involving male infertility worldwide during the period 1995–2014. Analysis of 6357 articles in the field of male infertility showed a significant increasing trend in the number of publications over the period 1995–2014. Obstetrics and Gynecology was an important subject category and Multidisciplinary Sciences was the newest interest. Authors were mainly from Europe and USA, with researchers from Cleveland Clinic producing the most articles, and those from the Tel Aviv Sourasky Medical Center and the University of Utah having the highest-quality articles. The USA contributed the most independent and international collaborative articles. The Cleveland Clinic and the University of Munster were the most productive institutions. The Cleveland Clinic and the University of Giessen had the most international collaboration publications. Harvard University had the most collaborators. The most common interests were pathogenesis and therapy, and new interests were hypogonadism, obesity, and cryopreservation. In conclusion, rapid development of the male infertility field was observed. Overall, collaborative and multidisciplinary science research has become more popular. The USA and its institutions play a dominant role, followed by European countries. Thanks to the common research focus worldwide, more insight into male fertility has been gained in the scientific literature over the past 20 years. [Correction added on September 21, 2016, after online publication: the term "institute" has been replaced by the term "institution" throughout the text.]

INTRODUCTION

Infertility is a disease of the reproductive system, defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (Venkatesh *et al.*, 2014). It affects approximately 10–15% of couples, even up to 30% in some regions of the world (Inhorn & Patrizio, 2015). Although male infertility contributes to more than half of all cases of global childlessness, infertility remains a woman's social burden, as the scientific literature and other media have neglected the male component of reproduction other than its sexual nature for a long time (Cassatella *et al.*, 2013; Petok, 2015). In recent years, male infertility has been attracting increasing interest because of evidence in decline in semen quality among young healthy men worldwide, broader public awareness, psychological health, and the continuous development of assisted reproduction techniques (ART) which solicit attempts to identify a precise diagnosis, in particular for idiopathic infertile couples and those currently undergoing ART cycles (Milewski *et al.*, 2013; Alrabeeah *et al.*, 2014; Stuppia *et al.*, 2015).

Male infertility has been a rapidly developing area of medical science. Great interest has been raised by novel insight on numerous of male infertility, including pathogenesis, personalized therapeutic protocols, molecular changes and social effects (Nikzad *et al.*, 2015). An increasing number of journals have appeared dealing with male infertility medicine, and the total number of published articles has grown each year. By the end of 2014, the PubMed database included 31,770 articles classified according to the medical subject heading (MeSH) terms 'male infertility' and 'human'. Of these articles,

1650 articles reported clinical trials, including 728 randomized controlled trials, 5309 review articles and 149 meta-analyses. Moreover, there has been an exponential growth in this research field: only 1 study from 1960 was included in the database, while there were 574 by 1990, by 2012, this figure rose to 866. Nevertheless, despite the increased productivity in male infertility research, there have been few attempts at gathering systematic data on the global scientific production in male infertility. A suitable tool to evaluate the large amount of information present in the literature is, the bibliometric method, which has been widely applied to examine scientific production and research status in many scientific disciplines (Daly *et al.*, 2015; Rondanelli & Perna, 2015). Up to now, only Gonzalez-Alcaide *et al.* (2008) analyzed co-authorship networks and institutional collaboration patterns in reproductive biology using the bibliometric method. Aleixandre-Benavent *et al.* (2015b) analyzed trends in clinical reproductive medicine research. To date, there has been no systematic evaluation of male infertility data based on bibliometric analysis. Given the importance of the male infertility research field, global systematic analysis of male infertility is necessary.

Our study is the first bibliometric analysis focusing on male infertility research at the global level. The purpose of this research was to carry out an in-depth analysis on the scientific study of male infertility covering the period 1995–2014 present in the Web of Science (WoS) database, which is the most important and most frequently used source reporting scientific and technological achievements. This comprehensive analysis (i) assesses the increasing trend in publications and the relationship between the number of articles and the global gross domestic product (GDP); (ii) identifies core journals, productive countries, productive authors, productive institutions and international collaborations; and (iii) identifies distribution of output in subject categories and hot issues by analysis of keyword frequencies. We attempted to visualize the research state and trends in male fertility research using improved bibliometric methods.

MATERIALS AND METHODS

Data sources

The items under study were taken from the online version of the WOS, which is published by Thomson Router International Scientific Index (ISI), operated by Thomson Scientific, Philadelphia, PA, USA. The main benefit of the ISI journals is that they consist of the most important journals (in terms of scientific impact) from all over the world. According to the Journal Citation Report (JCR), as of 2014, it indexed 11,149 major journals with citation references across 237 scientific disciplines in the world. Documents published from 1995 to 2014 were downloaded from the database and analyzed. The impact factor (IF) of WoS journals in 2014 was determined by the JCRs, which is currently the latest data available. GDP data was obtained from the website of the World Bank (www.worldbank.org).

Publications retrieval strategies

Based on the search rules of the WoS, we performed our retrieval strategy as follows:

TS = (Male AND (infertility OR Sterility OR Sub*fertility)) AND TS = (Human*OR Homo sapiens OR Modern Man OR Man OR People).

Hence, the word 'Sub*fertility' might retrieve 'Sub fertility' or 'Sub-fertility'; and 'Human*' might retrieve 'Humans' or 'Human being'.

Data analyses

In this study, we thoroughly analyzed the distribution of the publishing years, keywords, languages, subject categories, publication outputs of articles from countries/territories and institutions, manuscript types, and collaborations. Articles originating from England, Scotland, Northern Ireland, and Wales were reclassified as from the United Kingdom (UK). Articles from Hong Kong were not included in China (mainland) (Han & Ho, 2011). We performed keyword analysis based on the frequency that a term appeared in the authors' keywords. Otherwise, in order to avoid the influence of synonymy and polysemy, we substituted all the author's keywords matching the Medical Subject Headings (MeSH) database to a MeSH term (http://www.ncbi.nlm.nih.gov/mesh). Based on the information derived from the authors' addresses, we used ARCGIS software v. 9.2 (ESRI, Redlands, CA, USA) to visualize the geographic distribution of authors and research institutions. The GEPHI program (version 0.9) was used to construct networks of collaborations and keywords. The size/degree of a node depended on the number of edges adjacent to the node, and was calculated using the SCI² TOOL v. 1.1 (Terre Haute, IN, USA). Otherwise, we calculated the correlation between GDP and the number of publications using SPSS v.16.0 (SPSS Inc., Chicago, USA).

RESULTS

Characteristics of article outputs

Based on our inclusion criteria, we retrieved a total of 8096 unduplicated research publications in the field of male infertility. Twelve document types were identified, for a total of 1226 publications over a period of 20 years. Research articles were the most frequently observed document type (6357 articles; 79% of the total number of publications), followed distantly by reviews (911 articles; 11%), editorial material (180 articles; 2%), and proceedings papers (148 articles; 1.8%). The detailed results are shown in Table S1. Finally, 6357 articles were used for further analyses, while all publications of other types were discarded.

The characteristics of publication outputs during the period 1995–2014 are shown in Table 1. In the 20 years of the analysis, the average number of journal articles published and the number of journals devoted to the field of male infertility research increased more than threefold. In particular, the number of articles published increased from 162 in 1995 to 527 in 2014, and the number of journals increased from 56 in 1995 to 193 in 2014. Figure 1 shows the trend in the number of male infertility articles; it indicates a steady increase in the number of articles published over the 20 years period evaluated ($y = 19.614x + 111.9$).

Based on data from the World Bank, the world GDP increased from $30,631 billion dollars in 1995 to $77,869 billion dollars in 2015. Correlation analysis indicated a significant relationship between the number of articles and log2-transformed GDP

Table 1 Characteristics of male infertility evaluated by number of articles output by year of publication from 1995 to 2014

Year	No. articles	Growth rate, %	No. authors	No. journals	Total citations	Total pages
1995	162	–	716	56	7306	1061
1996	182	12.35	906	73	8726	1216
1997	207	13.74	997	71	8921	1381
1998	230	11.11	1105	80	9105	1571
1999	195	−15.22	1062	77	8745	1281
2000	269	37.95	1325	97	8815	1848
2001	230	−14.50	1269	89	9103	1518
2002	253	10.00	1376	96	7667	1756
2003	247	−2.37	1352	102	6731	1741
2004	267	8.10	1637	96	7861	1754
2005	255	−4.49	1465	95	7301	1840
2006	282	10.59	1527	106	8495	1989
2007	315	11.70	1809	131	6572	2278
2008	376	19.37	2108	148	6430	2711
2009	385	2.39	2373	161	5950	2860
2010	403	4.68	2409	173	4979	3172
2011	510	26.55	2984	209	4101	3896
2012	550	7.84	3564	203	3006	4311
2013	512	−6.91	3533	203	1515	4291
2014	527	2.93	3611	193	361	4457
Total	6357	–	37,128	–	131,690	46,932

($r = 0.959$, $p < 0.001$, Fig. 2A and B). Moreover, we chose the USA and China for further analysis. Results showed a significant relationship between the number of articles and the GDP ($r = 0.971$, $p < 0.001$) for China, while, correlation analysis showed an apparent correlation between the number of articles and the GDP (r = 0.871, $p < 0.001$) for the USA (Fig. 2C and D).

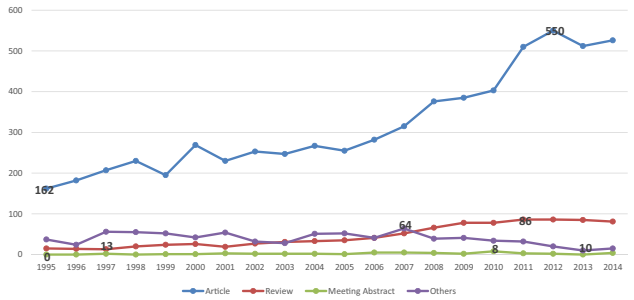
Furthermore, almost all articles were published in English (6149 articles; 96.9%), followed by French (77 articles), and German (65 articles) (Table S2). English was obviously the most widely used language for international scientific communication. The results indicated that authors whose native language was not English submitted their papers in English.

Distribution of journals and subject categories

All papers were published in 954 journals, of which 15 journals published more than 50 articles. The top six journals had more than 180 articles (Table 2). Approximately 34% of the WoS papers were published in these most productive top six journals (*Human Reproduction*, *Fertility and Sterility*, *Andrologia*, the *Journal of Andrology*, *Systems Biology in Reproductive Medicine*, and the *International Journal of Andrology*), which are considered the core journals of male infertility research under the Bradford Law (Yao *et al.*, 2013). The journal that published the largest share of articles was *Human Reproduction* ($n = 673$ articles). There were three other journals that published more than 200 articles each: *Fertility and Sterility* ($n = 632$ articles), *Andrologia* ($n = 274$ articles) and the *Journal of Andrology* ($n = 208$ articles). *Human Reproduction* received the greatest number of citations ($n = 23{,}531$), followed by *Fertility and Sterility* ($n = 15{,}190$) and the *Journal of Andrology* ($n = 5{,}707$). However, the ratio of citations (C) per article (A) in the most productive journals was greater for the *Proceedings of The National Academy of Sciences of The United States of America*, (PNAS, C/A = 74.4), followed by *Human Molecular Genetics* (C/A = 52.6), the *Journal of Clinical Endocrinology & Metabolism* (C/A = 49.49), *Human Reproduction* (C/A = 34.96) and the *Biology of Reproduction* (C/A = 30.16). It should be noted that some less-productive journals had a higher C/A ratio, such as *Nature*, which only published 11 papers (C/A = 321.2) and *Cell*, publishing only four papers (C/A = 319.8). More importantly, the top 19 most productive journals were mainly from the USA ($n = 8$) and the UK ($n = 7$), which are both developed countries, while only one journal was from a developing country (China).

There were 309 subject categories identified by the JCR during the past 20 years, and the top four categories were *Obstetrics & Gynecology*, *Reproductive Biology*, *Endocrinology & Metabolism*, and *Urology & Nephrology*. Figure 3 shows the growth trends of the four most productive categories in male infertility from 1995 to 2014. Moreover, the top 4 categories over 5-year intervals were calculated. The results showed *Obstetrics & Gynecology*, *Reproductive Biology*, and *Urology & Nephrology* were still the top categories based on all 5-year intervals. Interestingly, *Multidisciplinary Sciences* appeared in the top four subject categories in 2010–2014 (Table S3).

Figure 1 Trend in the number of the male infertility publications by year.

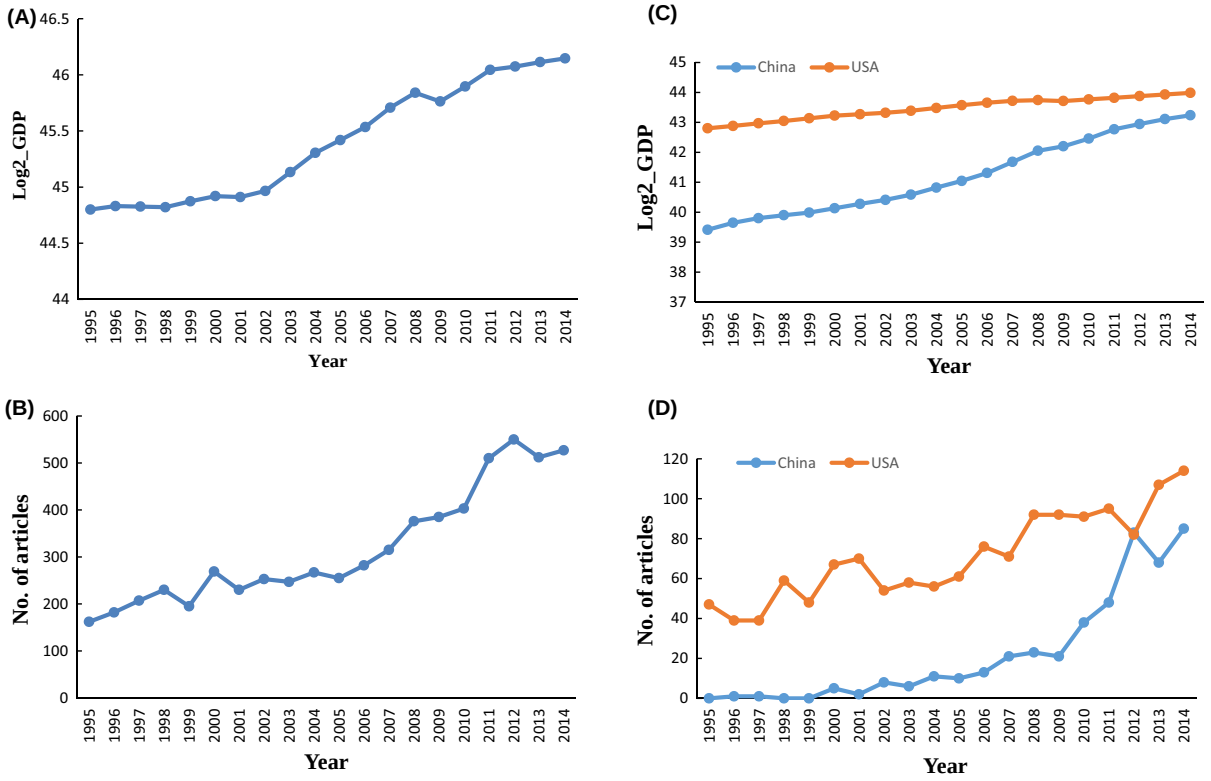


Author performance and geographic distribution

Based on the author's addresses, we plotted a global geographic distribution map using color shadings to represent the number of articles, and the intensity of spots to represent the geographic distribution of authors. As shown in Fig. 4, most investigators were gathered in Europe and the USA, followed by East Asia, South Asia, and Australia. The intensity of spots in the corresponding area was much 'hotter' and denser than the remaining regions. Africa, South America, West Asia, Central Asia, and Southeast Asia did relatively less research.

The 20 most productive authors are shown in Table 3, A. Agarwal from Cleveland Clinic published the most articles ($n = 104$), followed by C. Foresta from the University of Padua ($n = 69$), E. Nieschlag from University of Munster ($n = 68$), P.N. Schlegel from Cornell University ($n = 62$), and X.R. Wang from the Nanjing Med University ($n = 52$). We also quantified whether these authors published as either the first author or the corresponding author (FCA). Clearly, the FCA, A. Agarwal still ranked first ($n = 71$) in the male infertility field. Considering the fact that older articles are likely to have higher citations, the h-index and 5-year citations per articles, which were used to estimate the academic impact of authors, were only investigated in a 5-year window from 2010 to 2014. The h-index of R. Hauser from Tel Aviv Sourasky Medical Center and D.T. Carrell from the University of Utah tied for first place with a score of 10. Moreover, D.T. Carrell from University of Utah ranked first in CPP and total citations (TC) (5-year TC) ($n = 399$), with a CPP of 26.60, which indicated D.T. Carrell published more high-quality articles in male infertility research.

Figure 2 Relationship between the gross domestic product and articles published on male infertility. (A) Log_2-transformed global gross domestic product (GDP) from 1995 to 2014. (B) Trend in the number of the male infertility articles published. (C) Log_2-transformed GDP of China and the USA from 1995 to 2014. (D) Trends in the number of the male infertility articles from China and the USA.



Countries, Institute performances, and international collaborations

We extracted 99 countries/territories as well as 3283 institutions in the male infertility research field to evaluate the publication activity. The top 10 countries ranked by the number of publications are reported in Table S4. Five European countries, three Asian countries, and two North and Central American countries were ranked in the top 10 for WoS papers. There were no African countries in the top 10. The countries with the most published papers were the USA (n = 1417), followed by Germany (n = 543), and Italy (n = 509). Other countries that surpassed 300 papers were China (n = 444), the UK (n = 396), France (n = 387), and Japan (n = 301). The seven major industrialized nations of the world (G7 countries (Gomes, 2013)), the USA, France, Germany, Italy, UK, Japan, and Canada, were among the top 10 countries. Furthermore, China, India, and Japan have the highest population densities in the world. The result overlapped that of the geographic distribution of authors.

In addition, the top 10 countries for publications for each of the 5-year intervals were also calculated (Table S5). We found China appeared among the top most-productive countries in last 10 years (2005–2014), and even ranked second in 2010–2014, during which the number of publications increased more than fourfold.

The top 20 most productive institutions are presented in Table 4. The Cleveland Clinic, USA, ranked first with a total of 114 publications, followed by the University of Munster, Germany (n = 99), the Nanjing Medical University, China (n = 95), the University of Padua, Italy (n = 83), and Baylor College of Medicine, USA (n = 83). More importantly, seventeen institutions came from developed countries (USA, Germany, Canada, Italy, Denmark, Israel, Italy, Spain, France and Australia) and only three institutions came from developing countries (China, Egypt, and Iran). Moreover, the number of institutions from the USA ranked first of seven institutions in the top 20.

Of all publications from 1995 to 2014, 29.7% were international collaboration papers and 70.3% were single country publications. Moreover, the USA had the greatest number of international collaboration publications (n = 471), followed by Germany (n = 217), the UK (n = 172) and France (n = 152). The network of the 30 most productive countries is shown in Fig. 5A; the larger the size of the nodes, the higher the number of international collaborators. The USA still took the core position in international collaboration on male infertility research. It collaborated with the most countries (n = 58), and was the main partner of the other nine top most productive countries (Table S4). Furthermore, there were numerous collaborations among European countries. Germany, France, the UK, and Italy were in the core position. Asia was another research hot area. It is worth noting that China had the most collaboration articles with the USA.

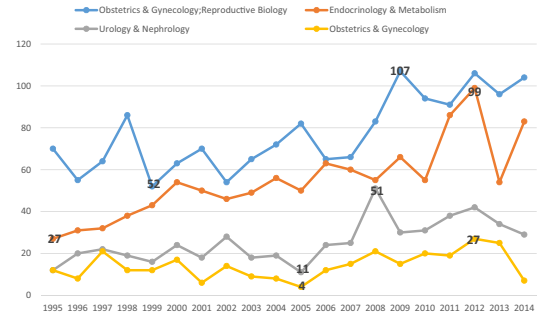
At the institution level, the USA also was dominant in male infertility research. Among the Top 20 most productive institutions in Table 4, six were in the USA, two were in Germany, two were in Italy, two were in Canada, and other eight institutions were from China, Spain, Denmark, Australia, Iran, Israel, France and Egypt, respectively. Moreover, the Cleveland Clinic, USA had the most international collaboration publications

Table 2 The top 19 most productive journals on male infertility research from 1995 to 2014

Journal	Country	No. of articles (R)	Citations (R)	C/A (R)	IF
Human Reproduction	UK	673 (1)	23,531 (1)	34.96 (4)	4.569
Fertility and Sterility	USA	632 (2)	15,190 (2)	24.03 (8)	4.59
Andrologia	Germany	274 (3)	2400 (10)	8.76 (16)	1.63
Journal of Andrology (until 2012)	USA	208 (4)	5707 (3)	27.44 (7)	2.473
Systems Biology in Reproductive Medicine	UK	193 (5)	1754 (12)	9.09 (15)	1.6
International Journal of Andrology (until 2012)	UK	181 (6)	3355 (7)	18.54 (10)	3.695
Journal of Urology	USA	177 (7)	4248 (4)	24 (9)	4.471
Journal of Assisted Reproduction and Genetics	Netherlands	164 (8)	1320 (14)	8.05 (17)	1.718
Molecular Human Reproduction	UK	133 (9)	3953 (5)	29.72 (6)	3.747
Asian Journal of Andrology (from 1999)	China	130 (10)	1264 (15)	9.72 (14)	2.596
Reproductive Biomedicine Online	Netherlands	115 (11)	1743 (13)	15.16 (12)	3.015
PLoS One (from 2006)	USA	93 (12)	628 (17)	6.75 (18)	3.234
Biology of Reproduction	USA	86 (13)	2594 (9)	30.16 (5)	3.318
Journal of Clinical Endocrinology & Metabolism	USA	67 (14)	3316 (8)	49.49 (3)	6.209
Urology	USA	59 (15)	1031 (16)	17.47 (11)	2.188
Proceedings of the National Academy of Sciences of the United States of America	USA	48 (16)	3571 (6)	74.4 (1)	9.674
Andrology (from 2013)	UK	46 (17)	107 (19)	2.33 (19)	2.298
BJU International (from 1999)	UK	41 (18)	461 (18)	11.24 (13)	3.533
Human Molecular Genetics	UK	40 (19)	2104 (11)	52.6 (2)	6.393

R, rank; C/A, the ratio of citations per article; IF, impact factor of 2014. [Correction added on October 13, 2016, after online publication: The dates listed in Table 2 for Journal of Andrology, International Journal of Andrology, and Andrology have been corrected from 2009 and 2012 to 2012 and 2013.]

Figure 3 The growth trends of the four most productive categories on male infertility from 1995 to 2014.



(n = 57), followed by the University of Giessen, Germany (n = 36) the University of Munster, Germany (n = 33), the University of Copenhagen, Denmark (n = 31) and Harvard University, USA (n = 26). However, there was not always a correction between the productivity ranking and the measures of centrality. The network of the 30 most international institutions showed Harvard University, the University of Munster, and the Karolinska Institute were the top three inter-institution collaborative research institutions (Fig. 5B). In contrast, those institutions with a high productivity index, such as China, India, Turkey, Iran, or Brazil, all among the 20 most productive countries, did not have an important role in the centrality of the institution network. [Correction added on September 21, 2016, after online publication: The information in this paragraph has been updated to reflect the corrected data in Table 4.]

Although both single-institution articles and inter-institution articles increased over the 20 years, the annual percentage of single- institution articles decreased from 59.2% in 1995 to 27.3% in 2014. In contrast, the annual proportion of inter-institution articles increased from 40.8% in 1995 to 72.7% in 2014 (Fig, 5C). In particular, the number of inter- institution articles exceeded the number of single-institute articles as of 2001. Furthermore, inter-institutional collaborations in the same country were more prevalent than those of different countries (Fig. 5C). Among the collaboration publications, international, and domestic collaborations both maintained steady-state growth during the 20 years (30.2% ± 4.4% vs. 69.8% ± 4.4%), and collaborations in the same country played a dominant role.

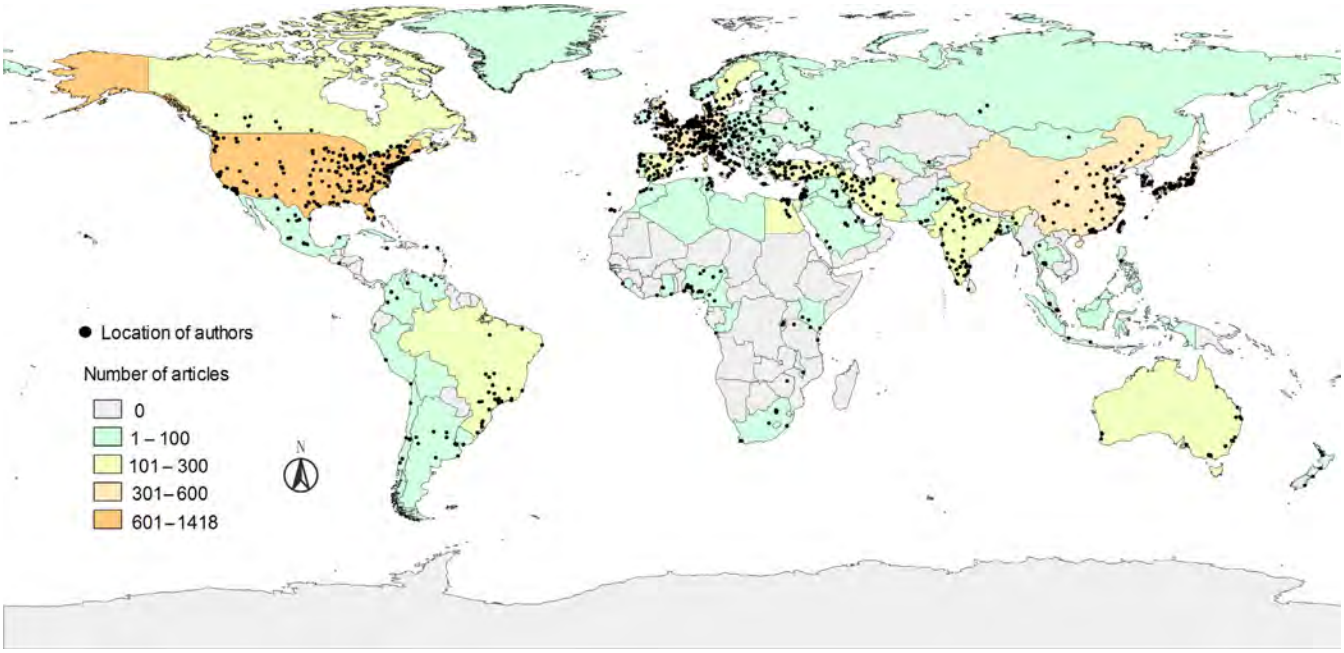
Citation of articles

The number of citations cannot always be used to judge the quality of a paper, but it is a measure of its impact on male infertility research (Rondanelli & Perna, 2015). The top 18 most frequently cited articles (>300 times) from 1995 to 2014 are shown in Table 5. The most frequently cited article was 'Atm-deficient mice: A paradigm of ataxia telangiectasia' published in 1996 by C. Barlow. It was cited 947 times as it was first published in *Cell*, which vastly exceeds the citation of other articles on male infertility. The top cited papers were all authored by scientists from institutions in high GDP countries. The USA contributed 12, Canada contributed 3 and France, Germany, Spain, and UK contributed 1 each, respectively. There were 12 articles published before 2000 and the remainder published between 2000 and 2006. Moreover, the main subject category of the top 18 most frequently cited articles was *Science & Technology – Other Topics*.

Hot issues analyzed by keyword frequencies

There were 7395 keywords used for the male infertility research field. Among these, only 314 keywords appeared more than ten times. The Top 30 high-frequency keywords for each of the 5-year intervals from 1995–2014 are given in Table S6. We also drew Venn diagrams to illustrate the detailed relationships between these hot keywords (Fig. 6A). Indeed, there were 16 keywords, which remained hot issues for over 20 years. Eight keywords appeared in the first 5-year interval (i.e. 1995–1999) as hot issues but not on the list in the following three 5-year intervals. For male infertility, researchers focused on 'Infertility, Male', 'Infertility', 'Sperm Injections, Intracytoplasmic' 'Spermatozoa', 'Testis', 'Semen', 'Azoospermia' 'Semen Analysis', 'Spermatogenesis', 'Fertility', 'Reactive Oxygen Species', 'Sperm Motility', 'Oligospermia', 'Varicocele', 'Y Chromosome' and 'Male' over the 20 years of the analysis. The co-occurrence relationships

Figure 4 Global geographic distribution map showing authors and output of per each particular country.



among the top high-frequency keywords over the 20 years periods were visualized, using the Gephi program (Fig. 6B). 'Infertility, Male', 'Infertility', 'Spermatozoa' and 'Spermatogenesis' were the most frequently used words. 'Polymorphism, Genetic', 'Apoptosis', appeared since 1999 and continued to be the hottest issues from then on. 'Oxidative Stress', 'DNA Fragmentation', 'Testosterone' and 'DNA Damage' became hot issues after the third 5-year interval. In the more recent 5-years intervals, 'Hypogonadism', 'Obesity', 'Reproductive Techniques, Assisted', 'Cryopreservation', as well as 'semen parameters' have received considerable attention.

DISCUSSION

This study showed an increase in the number of publications involving male infertility over the period 1995–2014. Further analysis indicated that the average annual growth rate of publication was approximately 7.15%. This was probably because of different reasons. First, reproductive medicine has become a rapidly developing area of medical science, and is now coming to maturity. Its progress can be attributed largely to the introduction of novel approaches in diagnosis and treatment, such as ART and intracytoplasmic sperm injection (ICSI) (Aleixandre-Benavent *et al.*, 2015b). Second, there has been greater social awareness in the contribution of male factors as a cause of infertility. Hence, infertility is increasingly becoming a source of concern for affected couples given the expected social and psychological consequences and the potential of threatening relationships (Chukwunyere *et al.*, 2015). Third, the development of the global economy has accelerated the number of publications to maintain this increasing trend (Zyoud *et al.*, 2015). Our correlation analysis also indicated a significant relationship between the number of articles and the GDP. Fourth, undoubtedly the important measures taken by the World Health Organization (WHO) to improve the male fertility have made a major contribution (Havrylyuk *et al.*, 2015). Finally, the continuous interest in the field and the incorporation of new journals in the WoS may have contributed to this linear increase. In this sense, some new journals related to the study of male infertility have been launched in recent years: the *Asian Journal of Andrology* was created in 1999, the *British Journal of Urology* International was created in 1999, and *PLoS One* was established in 2006. These journals are playing a major role in the area with a strong research activity.

Publications have mainly been published in professional journals and in a few comprehensive journals. Of the top 20 most productive journals, *PLoS One* and *PNAS,* are comprehensive journals, while the other journals are professional journals. We will emphatically discuss the role of *PNAS* and *Human Reproduction.* The IF of the *PNAS* journal was the highest of the top 19 most productive journals. As one of the world's most-cited multidisciplinary scientific serials, *PNAS* was established in 1915 and continues to publish cutting-edge research reports, commentaries, reviews, perspectives, colloquium papers, and actions of the Academy. We observed that *PNAS* published a total of 48 articles, received 3571 citations, and covered biological, physical, and social sciences areas. Meanwhile, the C/A ratio of *PNAS* was the first of the top 19 most productive journals. As a professional journal, *Human Reproduction,* which is a core journal, has published the most articles in the male infertility field. In fact, according to the citations and C/A ratio, we can estimate that the two journals have the greatest influence on the field of male infertility. Moreover, although journals like *Nature* and *Cell* only published a few articles, they received a high number of citations. There is no doubt that the ratio of C/A is closely linked to the quality of the articles. In addition, articles in the earlier years will get higher citations because they had more years to be cited (Ye *et al.*, 2014), although it should be mentioned that some of the manuscripts with lower citations will likely see an increase in the number of citations over time.

Table 3 The top 20 most productive authors on male infertility research from 1995 to 2014

Author	TP	FCA (R)	In 5-year window		
			TC (R)	CPP (R)	h-index (R)
A. Agarwal, Cleveland Clinic, USA	104	71 (1)	247 (3)	7.3 (12)	8 (5)
C. Foresta, University of Padua, Italy	69	56 (2)	195 (7)	8.1 (11)	8 (5)
E. Nieschlag, University of Munster, Germany	68	32 (4)	14 (20)	2.3 (20)	2 (20)
P.N. Schlegel, Cornell University, USA	62	27 (6)	135 (12)	6.1 (16)	6 (11)
X.R. Wang, Nanjing Medical University, China	52	27 (6)	243 (4)	6.2 (15)	6 (11)
Y.K. Xia, Nanjing Medical University, China	50	10 (13)	216 (5)	5.7 (17)	5 (15)
A. Ferlin, University of Padua, Italy	46	17 (10)	107 (16)	10.7 (7)	9 (3)
A. Garolla, University of Padua, Italy	43	9 (15)	168 (9)	9.3 (9)	9 (3)
R.K. Sharma, Cleveland Clinic Foundation, USA	41	7 (18)	73 (18)	14.6 (4)	8 (5)
W. Weidner, University of Giessen, Germany	41	10 (13)	65 (19)	3.8 (19)	4 (17)
A. Giwercman, Malmo University Hospital, Sweden	40	8 (17)	200 (6)	14.3 (5)	8 (5)
T. Mostafa, Cairo University, Egypt	40	40 (3)	147 (11)	7 (13)	6 (11)
R. Hauser, Tel Aviv Sourasky Medical Center, Israel	39	9 (15)	274 (2)	19.6 (3)	10 (1)
L.I. Lipshultz, Baylor College Medicine, USA	39	7 (18)	131 (14)	9.4 (8)	5 (15)
J. Gromoll, University of Munster, Germany	39	6 (20)	135 (12)	8.4 (10)	4 (17)
D.T. Carrell, University of Utah, USA	37	30 (5)	399 (1)	26.6 (1)	10 (1)
A. Zini, Mt Sinai Hospital, Canada	37	27 (6)	165 (10)	13.8 (6)	7 (9)
K. Jarvi, University of Toronto, Canada	34	12 (11)	130 (15)	6.5 (14)	7 (9)
C. Krausz, University of Florence, Italy	34	23 (9)	179 (8)	19.9 (2)	6 (11)
J.H. Sha, Nanjing Medical University, China	34	11 (12)	96 (17)	4.6 (18)	3 (19)

TP, total articles; FCA, the number of articles published as the first author or the corresponding author; TC, 5-year citations; CPP, 5-year citations per articles; h-index, 5-year h-index. [Correction added on September 21, 2016, after online publication: A typographical error in W. Weidner's name has been corrected.]

Table 4 Top 20 most productive institutions on male infertility research from 1995 to 2014

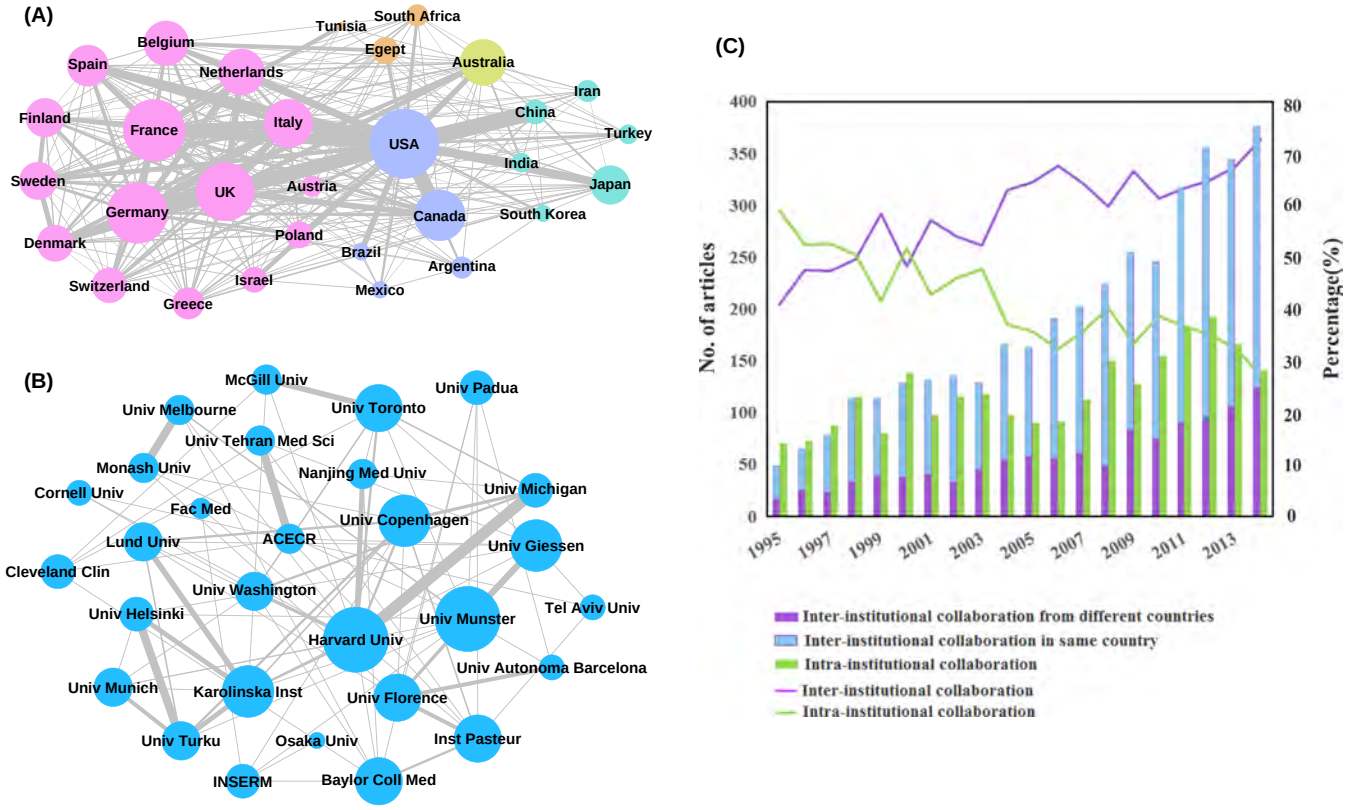
Institution	TP	% (R)	SP	% (R)	IP	% (R)
Cleveland Clinic (USA)	114	1.8 (1)	57	0.9 (5)	57	0.9 (1)
University of Munster (Germany)	99	1.56 (2)	66	1.04 (3)	33	0.52 (3)
Nanjing Medical University (China)	95	1.49 (3)	71	1.12 (1)	24	0.38 (6)
Baylor College Medicine (USA)	83	1.31 (4)	62	0.98 (4)	21	0.33 (8)
University of Padua (Italy)	83	1.31 (4)	71	1.12 (1)	12	0.19 (13)
University of Giessen (Germany)	81	1.27 (6)	45	0.71 (10)	36	0.57 (2)
Harvard University (USA)	69	1.09 (7)	43	0.68 (13)	26	0.41 (5)
University of Toronto (Canada)	68	1.07 (8)	53	0.83 (6)	15	0.24 (9)
McGill University (Canada)	65	1.02 (9)	52	0.82 (7)	13	0.2 (12)
Tel Aviv University (Israel)	57	0.9 (10)	46	0.72 (9)	11	0.17 (15)
Cairo University (Egypt)	55	0.87 (11)	47	0.74 (8)	8	0.13 (18)
University of Florence (Italy)	53	0.83 (12)	31	0.49 (18)	22	0.35 (7)
University of Copenhagen (Denmark)	52	0.82 (13)	21	0.33 (20)	31	0.49 (4)
Cornell University (USA)	52	0.82 (13)	45	0.71 (10)	7	0.11 (19)
University California San Francisco (USA)	52	0.82 (13)	45	0.71 (10)	7	0.11 (19)
University of Washington (USA)	51	0.8 (16)	37	0.58 (15)	14	0.22 (10)
University Tehran Medical Science (Iran)	48	0.76 (17)	38	0.6 (14)	10	0.16 (17)
Monash University (Australia)	45	0.71 (18)	31	0.49 (18)	14	0.22 (10)
University Autonoma Barcelona (Spain)	44	0.69 (19)	32	0.5 (16)	12	0.19 (13)
Pasteur Institute (France)	43	0.67 (20)	32	0.5 (16)	11	0.17 (15)

TP, total publication output; %, the percentage of the institute in the study field; (R), rank; SP, single-country publication; IP, international-institution collaborative publication. [Correction added on September 21, 2016, after online publication: The original version of this table had the Cleveland Clinic and Foundation listed as two separate institutions. This has been corrected, and the table now reflects the Cleveland Clinic as the most productive institution.]

It is not surprising that the USA was the leading country in publication output on male infertility, a fact that has also been described for other biomedical fields. G7 countries published more publications (49.37% articles in total) than lower GDP countries. Notably, the top 20 most productive institutions and top 20 most productive authors on male infertility research were mainly from the highest GDP areas. There were seven most productive institutions from the USA in top 20 most productive institutions, and the Cleveland Clinic was ranked first. Interestingly, three institutions (the Nanjing Medical University, China; Cairo University, Egypt; the University of Tehran Medical Science, Iran) in the top 20 most productive institutions and four authors in the top 20 most productive authors did not come from developed countries. Three authors (X.R. Wang, Y.K. Xia, and J.H. Sha) were from China and one author (T. Mostafa) was from Egypt. Importantly, China had published more and more papers in the latest 5-year intervals. This could be attributed to the development of the country's scientific research platform and to the development of the economy. Of interest, the center for reproductive medicine have been founded following the management approach established for ART by the National Health and Family Planning Commission of People's Republic of China in 2001 (http://www.nhfpc.gov.cn/).

The h-index simultaneously measures the quality and quantity of the entire scientific output of a researcher, and is one of the

Figure 5 Characteristics of research institutions and countries. (A) Co-occurrence network for top 30 countries of international collaborations. (B) Co-occurrence network for the top 30 institutions with scientific collaborations. (C) Trends in the number of inter-institutional and single-institutional articles from 1995 to 2014. The size of the nodes is proportional to the occurrence frequency. The lines represent the relationship between two countries/institutions, the thickness of which indicates the strength of the connection.



most commonly used indicators of research quality (Sweileh *et al.*, 2015). Consistently, we could conclude that R. Hauser and D.T. Carrell, who had the highest h-index, could be considered authorities in the male infertility field. It should be underlined that both researchers come from areas with a high GDP. Moreover, the top 18 most frequently cited articles all originated from developed countries. Although citations do not reflect the quality of a paper comprehensively, in a sense, they reflect a difference in scientific output between developed countries and developing countries.

We cannot ignore that collaboration articles increased over the 20 years of the analysis. It has been suggested that the academic communities of male infertility research in different countries or institutions have gradually became more cooperative. The USA is in the core position in international collaboration, and its dominance in male infertility research has extended to the institutional level. European countries have also played a vital role in male infertility research. Many European countries appeared in the top 20 most productive countries, and many shared collaborations among them. In general, more collaboration allows a greater exchange of ideas, knowledge, and workload for different research groups. Developing countries can benefit more from the research conducted in the most scientifically advanced countries, e.g. the USA was the main partner of China, and these countries can also benefit from their funding sources (Aleixandre-Benavent *et al.*, 2015a). It would be reasonable to suppose that more collaboration would lead to more scientific output. Furthermore, we should point out that institutions in the same country tended to have a higher rate of collaboration.

Otherwise, based on our subject category statistic results, the published articles mainly focused on *Obstetrics & Gynecology*, *Reproductive Biology*, *Endocrinology & Metabolism*, *Urology & Nephrology, and Obstetrics & Gynecology*. It can thus be concluded that the keyword 'male infertility' was mostly present in the field related to the subject category of *Obstetrics* and *Gynecology*. More importantly, subject categories of the top 18 most cited WoS papers in the most recent 10 years of the analysis mainly focused on *Science & Technology – Other Topics*. Thus, we suppose this may be considered a hot topic. In contrast, *Multidisciplinary Sciences,* which appeared in the top four categories in the latest 5-year intervals, were also important and this suggests that multidisciplinary research has become popular in male infertility. These results provided a current view on the research focuses of male infertility. More importantly, subject categories can represent a suitable guide for future research directions.

Author keywords provide important information about research trends that may have concern researchers. Among the core keywords, the most frequently used word for across all periods was 'Infertility, Male' which was also a keyword used for searching the literature in this study. Apart from the latter, most keywords were related to 'semen'. As is well-known, sperm is an essential part of male fertility. To date, diagnosis of male infertility is commonly based on standard semen analysis. The male partner is considered a patient when an abnormality in semen

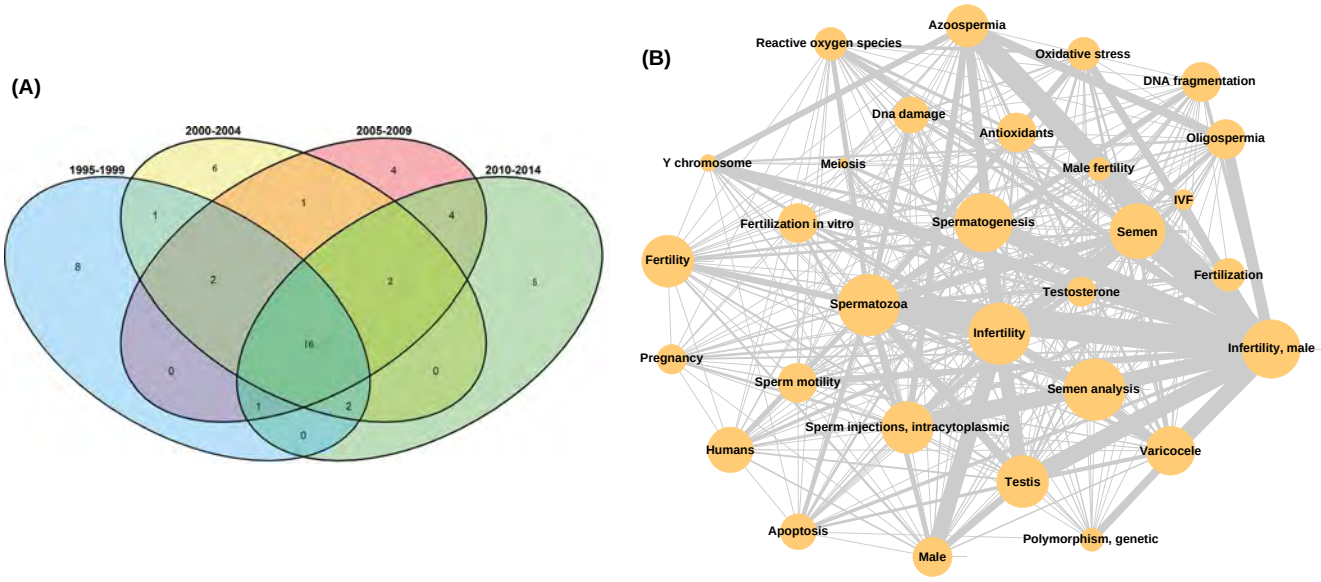
Table 5 Top 18 most cited WOS papers [Correction added on September 21, 2016, after online publication: The author name in row 2 has been corrected.]

No.	Citations	Authors	Title	Journal	Year	Country	Institution	Subject categories
1	947	C. Barlow	Atm-deficient mice: A paradigm of ataxia telangiectasia	Cell	1996	USA	Natl Inst Health	Biochemistry & Molecular Biology; Cell Biology
2	867	R. Reijo-Pera	Diverse Spermatogenic Defects In Humans Caused By Y-Chromosome Deletions Encompassing A Novel RNA-Binding Protein Gene	Nature Genetics	1995	USA	Massachusetts Institute of Technology	Genetics & Heredity
3	669	M. Guo	Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin	Nature	2006	USA	Univ Calif Los Angeles	Science & Technology - Other Topics
4	597	G.J. Hannon	A germline-specific class of small RNAs binds mammalian Piwi proteins	Nature	2006	USA	Watson Sch Biol Sci	Science & Technology - Other Topics
5	597	M. Chillón	Mutations in the cystic fibrosis gene in patients with congenital absence of the vas deferens	New England Journal Of Medicine	1995	Spain	Cancer Research Institute	General & Internal Medicine
6	569	R.A. Hess	A role for oestrogens in the male reproductive system	Nature	1997	USA	Univ Illinois	Science & Technology - Other Topics
7	532	D.P. Evenson	Utility of the sperm chromatin structure assay as a diagnostic and prognostic tool in the human fertility clinic	Human Reproduction	1999	USA	S Dakota State Univ	Obstetrics & Gynecology; Reproductive Biology
8	466	G.B. Witman	Proteomic analysis of a eukaryotic cilium	Journal Of Cell Biology	2005	USA	Univ Massachusetts, Worcester	Cell Biology
9	450	M.R. Sairam	Impairing follicle-stimulating hormone (FSH) signaling in vivo: Targeted disruption of the FSH receptor leads to aberrant gametogenesis and hormonal imbalance	PNAS	1998	Canada	Univ Montreal	Science & Technology - Other Topics
10	442	J.G. Sun	Detection of deoxyribonucleic acid fragmentation in human spermatozoa: Correlation with fertilization in vitro	Biology of Reproduction	1997	Canada	University of Toronto	Reproductive Biology
11	440	D.S. Guzick	Sperm morphology, motility, and concentration in fertile and infertile men.	New England Journal of Medicine	2001	USA	Univ Rochester	General & Internal Medicine
12	417	L.F. Parada	Cryptorchidism in mice mutant for Insl3	Nature Genetics	1999	USA	Univ Texas	Genetics & Heredity
13	415	F. Nantel	Spermiogenesis deficiency and germ-cell apoptosis in CREM-mutant mice	Nature	1996	France	CNRS-INSERM	Science & Technology - Other Topics
14	365	D.S. Irvine	DNA integrity in human spermatozoa: relationships with semen quality	Journal of Andrology	2000	UK	MRC	Endocrinology & Metabolism
15	357	J.A. Blendy	Severe impairment of spermatogenesis in mice lacking the CREM gene	Nature	1996	Germany	German Cancer Research Center	Science & Technology - Other Topics
16	351	D.E. Clapham	A sperm ion channel required for sperm motility and male fertility	Nature	2001	USA	Harvard Univ	Science & Technology - Other Topics
17	315	R.F. Casper	Sperm deoxyribonucleic acid fragmentation is increased in poor quality semen samples and correlates with failed fertilization in intracytoplasmic sperm injection	Fertility and Sterility	1998	Canada	Toronto Gen Hosp	Obstetrics & Gynecology; Reproductive Biology
18	307	J.M. van Deursen	BubR1 insufficiency causes early onset of aging-associated phenotypes and infertility in mice	Nature Genetics	2004	USA	Mayo Clin	Genetics & Heredity

parameters involving motility, morphology, or concentration, has been detected in at least two semen analyses (Garg & Kumar, 2015). Therefore, it is no surprise 'spermatozoa' and 'spermatogenesis' were both hot issues over the 20 year period of this analysis. A better understanding of the biology and mechanisms involved in impaired spermatogenesis is important for the optimization of diagnostic and therapeutic management of both male and couple infertility (Pizzol *et al.*, 2014). Researchers have also focused on 'azoospermia' and 'oligospermia' which are related to male infertility. Azoospermia is observed in 10–15% of infertile men (Gudeloglu & Parekattil, 2013; Elzanaty, 2014). A reduced sperm density (oligozoospermia) is often accompanied by poor motility and morphology reflecting qualitative and quantitative defects in spermatogenesis (McLachlan, 2013). In addition, many studies focused on 'Semen Analysis', which was the most prevalent technique during 1995–2014, and 'Sperm Motility' which was the most important diagnostic parameter.

It is worth mentioning that a common genitourinary system disease named 'varicocele', a condition that impairs production and decreases the quality of sperm (Aquila *et al.*, 2015), was also a hot keyword for twenty years. Varicocele is the most common cause of male infertility affecting about 15–20% of the general population and 35–40% of men presenting for an infertility evaluation (Esteves *et al.*, 2011; Shiraishi *et al.*, 2012; Masson & Brannigan, 2014). To date, the exact mechanisms that ultimately lead to infertility are not fully understood despite the fact that varicocele pathophysiology has been discussed for close to five decades (Esteves *et al.*, 2015b). Many researchers have reported

Figure 6 Characteristics of the top keywords from published articles of the male infertility field. (A) Venn diagram illustrating the detailed relationships between the hot keywords in the male infertility field. (B) Co-occurrence network of the top 30 keywords.



that oxidative stress and elevated sperm DNA fragmentation have been associated with varicocele-mediated infertility (Blumer *et al.*, 2012; Wright *et al.*, 2014; Esteves *et al.*, 2015a). 'Oxidative stress' was a hot keyword resulting from our study. Furthermore, also the 'Y chromosome' could be considered a hot topic. Many researchers have reported that spermatogenesis is regulated by numerous Y chromosome-specific genes (Krausz *et al.*, 2015; Yu *et al.*, 2015).

With regard to therapy, 'ICSI', which was one the three highest ranking terms, appeared to be the main measure for treatment. From the time Palermo *et al.* (1992) first used this technique, ICSI has been used more and more frequently. After a 5-span dynamic analysis, some changes appear. From 2000, 'gene polymorphism', 'DNA fragmentation' and 'apoptosis' emerged as core themes between 2000 and 2004. It indicates researchers understood that these variations or changes in the DNA sequence may significantly contribute to spermatogenesis and germ cell development, and thus have an impact an individual's response to certain drugs or even influence the risk of developing male infertility (DeAngelis *et al.*, 2014; Palermo *et al.*, 2014; Gunes *et al.*, 2015). In the most recent 5 years, 'ICSI', 'IVF' (i.e. in vitro fertilization), and 'assisted reproductive techniques' are common treatments. In addition, 'testosterone' and 'antioxidants' have received widespread attention in male infertility. Prescribing, the testosterone replacement therapy has become one of the largest growing health care markets over the last 5 years with a 170% increase in sales (Kolettis *et al.*, 2015). A number of antioxidant agents have also been used against oxidative stress and to improve men's fertility in idiopathic male infertility (Agarwal *et al.*, 2014; Showell *et al.*, 2014).

It is worthwhile mentioning that in, the more recent 5 years, 'obesity' was a core theme. Obesity in men has been associated with infertility in numerous studies. The current trend for a decline in semen parameters parallels the increasing prevalence of obesity worldwide. Studies linking the pathology of obesity to male subfertility have been performed, and pathophysiological mechanisms have been proposed (Katib, 2015). Furthermore, during this period 'hypogonadism' also first became a hot keyword in the male infertility research field. Male hypogonadism is a disorder characterized by the absence of pubertal development, or discontinuation or regression of the maturation of secondary sex characteristics, and infertility (Sato *et al.*, 2015). In recent years, public awareness of the signs and symptoms of hypogonadism has increased (Le *et al.*, 2014). Elucidating the endocrine mechanisms underlying human testicular development and spermatogenesis has been challenging (Pitteloud & Dwyer, 2014). 'Cryopreservation' which is connected to ART received the most attention in the five most recent years of the survey and preservation of male fertility has received growing attention in the field of reproductive medicine. With the aim to preserve or restore fertility in patients affected by gonadotoxic treatment (chemotherapy, irradiation) and other diseases (Klinefelter syndrome, Sertoli cell only syndrome), clinical programs have been established to preserve the reproductive potential of males. Sperm cryopreservation has now become a standard procedure. The preservation of testicular tissue is still experimental (Goossens & Tournaye, 2014).

However, there are some limitations in this study. Firstly, in order to ensure a high quality bibliometric analysis, we only selected publications available in the WoS. Thus, some papers published in non-ISI journals were not included for analysis (Han & Ho, 2011). Secondly, the C/A ratio is based on the absolute number of citations that articles received, a calculation that could preferentially favor older articles. Moreover, these are other potential factors that may have influenced citation rates, including incomplete citing, journal and author self-citations, and omission bias (Hennessey *et al.*, 2009).

CONCLUSION

This study provided an alternative perspective on the global research trends in male infertility studies during the period 1995–2014. A total of 6357 articles were published in 954 journals listed in 309 subject categories. Male infertility research presented an upward trend as the production of papers increased

rapidly over the 20-year period of the study. Correlation analysis showed a significant positive correlation with the number of articles and the GDP. About 34% of WoS papers were concentrated in six journals –*Human Reproduction, Fertility and Sterility, Andrologia,* the *Journal of Andrology, Systems Biology in Reproductive Medicine,* and the *International Journal of Andrology*. *Human Reproduction* was responsible for 10.59% of the total articles. The most frequently cited article was 'Atm-deficient mice: A paradigm of ataxia telangiectasia' which was cited 947 times since being published in *Cell* in 1996 by C. Barlow. *Obstetrics & Gynecology*, *Reproductive Biology*, *Endocrinology & Metabolism*, and *Urology & Nephrology* were the top four subject categories over the 20 year study periods. *Multidisciplinary Sciences* emerged in the top four subject categories between 2010 and 2014.

The spatial distribution of authors was determined, and the main study area was founded to be mainly in Europe and the USA, followed by East Asia, South Asia, and Australia. Among the Top 20 productive authors, A. Agarwal from the Cleveland Clinic produced the most articles, R. Hauser from the Tel Aviv Sourasky Medical Center, and D.T. Carrell from the University of Utah had the most high-quality articles.

Ninety-nine countries/territories and 3283 institutions took part in male infertility research between 1995 and 2014. At the country level, it was also notable that the USA, contributing the most independent and international collaborative articles, had the most frequent international partners. At the institutional level, the Cleveland Clinic, the University of Munster, Nanjing Medical University, Baylor College of Medicine, and University of Padua were the top five most productive research institutions. The Cleveland Clinic and the University of Giessen had the most international collaboration publications, followed by the University of Munster and the University of Copenhagen. Moreover, Harvard University, the University of Munster, and the Karolinska Institute had the most collaborators. [Correction added on September 21, 2016, after online publication: The information in this paragraph has been updated to reflect the corrected data in Table 4.]

The author keyword analysis indicated that there was a common interest in pathogenesis, therapy, and molecular changes in male infertility. 'Infertility, Male', "Infertility", "Sperm Injections, Intracytoplasmic" "Spermatozoa", "Testis", "Semen", "Azoospermia" "Semen Analysis", "Spermatogenesis", "Fertility", "Reactive Oxygen Species", "Sperm Motility", "Oligospermia", "Varicocele", "Y Chromosome" and "Male" were the invariable hotspots of male infertility research over the 20-year period of this survey. "Hypogonadism", "Obesity", "Reproductive Techniques, Assisted", "Cryopreservation", as well as "Semen parameters", dramatically increased in ranking in the most recent years of the analysis and, might become hotspots in the near future.

This study represents a useful tool for researchers to comprehend the panorama of global male infertility research, and establish directions for further research.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Distribution of types of articles published from 1995 to 2014.
Table S2. Distribution of language of articles published from 1995 to 2014.
Table S3. The top 4 categories based on 5-year intervals.
Table S4. Publication distribution in the top 10 countries
Table S5. The top 10 most productive countries for each of the 5-year intervals during 1995–2014.
Table S6. The top 30 high-frequency keywords for each of the 5-year intervals during 1995–2014.