Trends in clinical reproductive medicine research: 10 years of growth

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Objective: To study the most important metrics of publication in the field of reproductive medicine over the decade 2003–2012 to aid in discerning the clinical, social, and epidemiologic implications of this relatively new but rapidly emerging area in medical sciences.
Design: Bibliometric analysis of most-cited publications from Web of Science databases.
Setting: Not applicable.
Patient(s): None.
Intervention(s): None.
Main Outcome Measure(s): Most productive and frequently cited investigators, institutions, and countries and specific areas of research, scientific collaborations, and comparison of the growth of reproductive medicine research compared with other areas of medical investigation such as obstetrics and gynecology and related science categories.
Result(s): We found that 90 investigators with more than 1,000 citations had jointly published 4,010 articles. A continued rise in the impact factor of reproductive medicine journals was seen. The number of publications in reproductive medicine grew more rapidly compared with other science categories. Presently 22% of highly cited articles in reproductive medicine research are published in journals belonging to science categories outside reproductive medicine. The most-cited study groups are situated in the Netherlands, Belgium, Spain, the United States, and the United Kingdom, and collaborative studies have been increasing.
Conclusion(s): Reproductive medicine research and subsequent clinical development have attained scientific growth and maturity. High-quality research is increasingly being published in high-impact journals. The increase in (inter)national collaborations seems to be key to the field's success. (Fertil Steril® 2015;104:131–7. ©2015 by American Society for Reproductive Medicine.)
Key Words: Bibliometrics, citation analysis, impact factor, network analysis, reproductive medicine, scientific collaboration

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Reproductive medicine, which has been a rapidly developing area of medical science, is now coming to maturity. Its progress can be attributed largely to the introduction of novel techniques such as radioimmunoassays for the assessment of reproductive hormones, along with novel compounds for ovarian stimulation such as the antiestrogen clomiphene citrate and exogenous gonadotropin hormones during the 1960s followed by the direct clinical application of methods developed in reproductive science laboratories. Integration of knowledge culminated in 1978 in the first live birth from a human embryo generated in vitro using in vitro fertilization (IVF) (1), which paved the way to the development of a very successful and common treatment for human infertility globally. This pioneer work by Robert Edwards was awarded the Nobel prize in 2010. Now more than 5 million human beings have been born using this technology (2). According to statistics from Europe, more than half a million of IVF cycles are performed annually, resulting in 100,000 newborns

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and accounting for 1.5% of all European babies (3). Additional technologies extending the use of IVF have subsequently been developed and implemented, such as intracytoplasmic sperm injection (ICSI), preimplantation genetic diagnosis (PGD), and cryotechnology, which allows the freezing and storage of sperm, oocytes, embryos, and testicular and ovarian tissue.

For the development of such outstanding achievements, clinical medicine requires high-quality research and key publications, which become widely cited by other scientists (4). Indeed, analyses have identified the most widely cited articles in journals for the area of reproductive medicine (4–7). The geographical distribution of articles (8, 9) and the collaboration patterns (10) also have been investigated to some extent.

An increasing number of journals have appeared in the field of reproductive medicine, and the total number of articles published has grown each year (11). The established journals in the category of reproductive medicine show an ongoing trend toward rising impact factors (12), for the higher quartile journals ranging between 3 and 9. Moreover, reproductive medicine research is increasingly published in journals devoted to other science categories, such as endocrinology and metabolism, and general and internal medicine; it also has, at least to some extent, expanded into the highly ranked journals in other science categories such as genetics and immunology. Although this expansion into other areas of medicine has yet to be analyzed, the potential highlights the diversification of reproductive medicine research.

We have identified the most frequently cited investigators and institutions in reproductive medicine over the most recent 10-year period, and we have identified their specific areas of research and collaboration. Our current and comprehensive analysis [1] assesses highly cited reproductive medicine research published in the reproductive medicine science category supplemented with other relevant science categories; [2] identifies specific areas of successful research and collaboration in reproductive medicine among groups and countries; [3] identifies areas of research that have significantly influenced recent developments and may guide future developments of the field; and [4] compares reproductive medicine research with other areas of medical research of comparable size.

MATERIALS AND METHODS

To identify and assess reproductive medicine research, we used a methodology that includes the following steps (see also Supplemental Fig. 1, available online).

Bibliographic Research

All the articles we selected were published in journals in the first quartile of the Reproductive Biology category of the *Journal Citation Report* during the 2003–2012 period. The search was performed in Web of Science (WOS) and was limited to "articles" and "reviews" accessible on June 13, 2013. The search resulted in 21,909 articles (20,332 articles and 1,577 reviews). The citation data were updated on November 18, 19, and 20, 2013. This analysis was performed independently by the first author (R.A.-B.).

Identification of Articles from the Most-cited Investigators

Our next step was to identify excellent research by selecting investigators publishing in journals in the first quartile of the reproductive biology category whose articles had more than 1,000 citations. A total of 90 investigators was selected. We then extended the search from these 90 most-cited investigators for more articles published in journals in first quartile of other science categories, such as obstetrics and gynecology; medicine, general and internal; and endocrinology and metabolism. We selected these three science categories because they are the most frequently used by researchers in reproductive medicine when publishing their articles. Moreover, general and internal medicine is the area that includes the most-cited multidisciplinary journals and the journals with the highest impact factors. As a result, we collected 4,010 articles. All data included in our tables and figures were extracted from these 4,010 articles.

Number of Articles, Journals, and Science Categories

Total number of articles published on reproductive medicine in the highest impact factor quartile journals per science category are shown in Table 1. Two tables provided as additional supplementary material complement these data. Supplemental Table 1 (available online) compares the

TABLE 1

Total number of papers published on reproductive medicine over a 10-year period (2003–2012) in the highest impact factor quartile journals, per science category.

No. of papers	Journal	Science category
980	*Human Reproduction*	RB
891	*Fertility & Sterility*	RB
385	*Reproductive BioMedicine Online*	RB
288	*Journal of Clinical Endocrinology & Metabolism*	E&M
175	*Biology of Reproduction*	RB
145	*Human Reproduction Update*	RB
94	*Molecular Human Reproduction*	RB
77	*British Journal of Obstetrics and Gynaecology*	OG
72	*American Journal of Obstetrics & Gynecology*	OG
54	*Obstetrics & Gynecology*	OG
54	*Reproduction*	RB
51	*Endocrinology*	E&M
48	*Placenta*	RB
45	*Seminars in Reproductive Medicine*	RB
39	*Current Opinion in Obstetrics and Gynecology*	OG
37	*Cochrane Database*	MGI
36	*Contraception*	OG
35	*Reproductive Sciences*	RB
34	*New England Journal of Medicine*	MGI
31	*British Medical Journal*	MGI
27	*Gynecological Oncology*	OG
22	*Menopause*	OG
21	*The Lancet*	MGI
21	*Ultrasound in Obstetrics and Gynecology*	OG

Note: Total number of papers published (in journals with >20 articles): 3,662, of which 78% were published in RB journals, 9% in E&M, 9% in O&G, and 3% in MGI. E&M = endocrinology and metabolism; MGI = medicine, general and internal; OG = obstetrics and gynecology; RB = reproductive biology.

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number of journals and the impact factors (top impact factor, at the 10th percentile and at the 25th percentile) in reproductive medicine with other science categories. Supplemental Table 2 (available online) shows the annual growth of the number of publications in three science categories: reproductive medicine, obstetrics and gynecology, and pediatrics.

Productivity, Citations, Collaboration Patterns, and Key Words of Institutions

To identify institutions whose articles received a greater number of citations and their research topics (Table 2), we used both "author key words" as "key word plus," which are automatically assigned by WOS from the titles of the references of the articles. The combination of both has proven to be highly effective in representing the conceptual content of articles (13, 14). We collected 47,667 different words that were corrected unifying grammatical variants and using only one key word for singulars and plurals, adjectives, and nouns, acronyms, and developed names of the same concept, among others. We also removed from this list words with vague meanings such as "syndrome," "disease," "trial," "mouse," "rat," "complication," "mice," "cohort," "parameters," "sheep," "care," "biopsy," "patient," "disorders," "patterns," "index," "protocol," and "definitions." We identified the five key words in highly cited research articles with the highest increase or decline over the decade, which allowed the creation of trend graphs. Supplemental Figure 2 (available online) provides the five key words with the most distinct upward and downward trends over time. Supplemental Figure 3 (available online) illustrates the trends in institutional collaboration based on three levels of analysis: national cooperation, international cooperation, and lack of cooperation.

Maps of Collaboration between Institutions and Countries

One of the best ways for the visual representation of the extent of collaboration is creating maps through social network analysis. To construct networks of institutional and country collaborations (Figs. 1 and 2), we used the Pajek program (version 3.00) (15). For editing the graphics we used the Inkscape program (version 0.48.4) (16). In these figures, the thickness of the spheres represents the total number of citations received from each institution or country, and the thickness of the lines connecting two spheres represents the number of articles published in collaboration between two institutions or countries.

Remarks on Methodology

To facilitate the identification of the investigators and prevent errors, three different searches in WOS were performed. The chosen criterion for the first search was to use the investigator's name. To avoid the loss of records, the name of the investigator was written together with all the possibilities using truncation operators. For example, the investigator "Tan, Seang Lin" was written as "a:*Tan Sean Lin OR Tan S* Lin OR Tan SL* OR Tan S**." Our second search used the name of the investigator (also with truncation) and the location (city and country) where the investigator usually works. Afterward, our third search was an advanced search performed to detect articles in which the investigator's affiliation was different from the usual, which was checked against each of these articles to confirm that they belonged to the proper investigator. The result of these verifications revealed the articles that had been written by other investigators with the same surname and/or initials who worked at institutions that differed from those of the investigators we were including in our study. Thus, it was necessary to check all the articles to exclude those written by other people.

RESULTS

The 90 investigators with more than 1,000 citations jointly published 4,010 articles (3,583 articles and 427 reviews) (see Supplemental Fig. 1). These publications were signed by 15,072 different institutions and 29,085 investigators. All data included in our tables and figures were extracted from these 4,010 articles. The number of reproductive medicine articles published in the highest impact factor quartile for the four different science categories was 3,662 (see Table 1). *Human Reproduction* was the journal with most articles (n = 980), followed by *Fertility & Sterility* (n = 891). The first non–reproductive medicine journal was the *Journal of Clinical Endocrinology and Metabolism* (n = 288), and the second was the *British Journal of Obstetrics and Gynaecology* (n = 77).

The number of journals included in the reproductive biology science category was fairly small. However, a continued rise in the impact factor of these journals can be observed, resulting at present in similar impact factors compared with the other science categories such as geriatrics, respiratory systems, ophthalmology, obstetrics and gynecology, and pediatrics (see Supplemental Table 1). Moreover, the number of publications in reproductive medicine has grown more rapidly compared with the other science categories, as shown in Supplemental Table 2. Although obstetrics and gynecology increased 10-fold the number of articles in reproductive medicine and pediatrics increased as well, the growth during the period was much higher in reproductive medicine, multiplying by 12 the percentage.

We found that 67% of the citations received by the 4,010 articles were generated in reproductive medicine, 19% in endocrinology and metabolism, 11% in general and internal medicine, and 3% in obstetrics and gynecology. Fauser was the leader in the number of citations in all areas (n = 7,451), followed by Azziz (n = 6,347) and Devroey (n = 6,104). The number of published articles highlighted Devroey (n = 221), Mol (n = 184), and Pellicer (n = 164). Fauser also led the citations in reproductive biology (n = 5,457), followed by Devroey (n = 5,263) and Agarwal (n = 3,638), and the number of published articles in this area highlighted Devroey (n = 205), Pellicer (n = 135), and Fauser (n = 108). In obstetrics and gynecology, the leader

TABLE 2

Most cited institutions in reproductive medicine (n > 3,000 citations), and the 10 most frequently used key words per center.

			10 Most frequently used key words (used >10 times)									
Institution	**Citations**	**Articles**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Erasmus University Medical Center, Rotterdam (Netherlands)	9,006	218	IVF	Infertility	FSH	Pregnancy	AMH	PCOS	Subfertility	Menstrual cycle	Ovarian stimulation	Fertility
University Medical Center Utrecht (Netherlands)	7,108	259	IVF	FSH	Pregnancy	Infertility	AMH	PCOS	ART	Menstrual cycle	RCT	Ovarian reserve
Vrije Universiteit Brussels (Belgium)	6,846	280	IVF	ICSI	Pregnancy	PGD	Infertility	GnRH antag	hCG	FSH	Cycles	LH
VU University Medical Center Amsterdam (Netherlands)	6,333	220	IVF	Pregnancy	Infertility	RCT	Meta analysis	IUI	Subfertility	Prediction	FSH	Risk
Academic Medical Center Amsterdam (Netherlands)	5,858	257	Pregnancy	IVF	Infertility	RCT	Risk	Meta analysis	Subfertility	Diagnosis	IUI	Prediction
Cleveland Clinics (OH, U.S.)	5,098	124	Male infertility	Oxidative stress	Sperm	Infertility	IVF	Spermatozoa	Apoptosis	Antioxidants	Semen	DNA damage
IVI (Spain)	4,670	227	IVF	Pregnancy	Implantation	In vitro	ICSI	ART	hCG	Oocyte	FSH	Oocyte donation
University of Adelaide (Australia)	4,628	99	PCOS	IR	Metabolic syndrome	Pregnancy	Lifestyle	Infertility	Diabetes	Clomiphene	BMI	IVF
Cedars-Sinai Medical Center (Los Angeles, CA, U.S.)	4,386	71	PCOS	IR	Prevalence	HA	Hirsutism	DHEAS	Testosterone			
Pennsylvania State University (State College, PA, U.S.)	3,383	71	PCOS	IR	Prevalence	HA	Hirsutism	DHEAS	Testosterone			
Copenhagen University Hospital (Denmark)	3,262	115	IVF	Pregnancy	ART	Cryopreservation	AMH	FSH	Infertility	ART	ICSI	hCG
University of Pennsylvania (Philadelphia, PA, U.S.)	3,205	120	Ectopic pregnancy	Pregnancy	Diagnosis	RCT	hCG	PCOS				
Université catholique de Louvain (Belgium)	3,079	103	Cryopreservation	Endometriosis	Transplantation	Ovarian tissue	Fertility preservation	Cancer	Fertility	Primordial follicle	Tissue	Laparoscopy

Note: AMH = antimüllerian hormone; ART = assisted reproductive technologies; BMI = body mass index; FSH = follicle-stimulating hormone; GnRH = gonadotropin releasing hormone; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; IR = insulin resistance; IUI = intrauterine insemination; HA = hyperandrogenemia; hCG = human chorionic gonadotropin; LH = luteinizing hormone; PCOS = polycystic ovary syndrome; PGD = preimplantation genetic diagnosis; RCT = randomized controlled trial.

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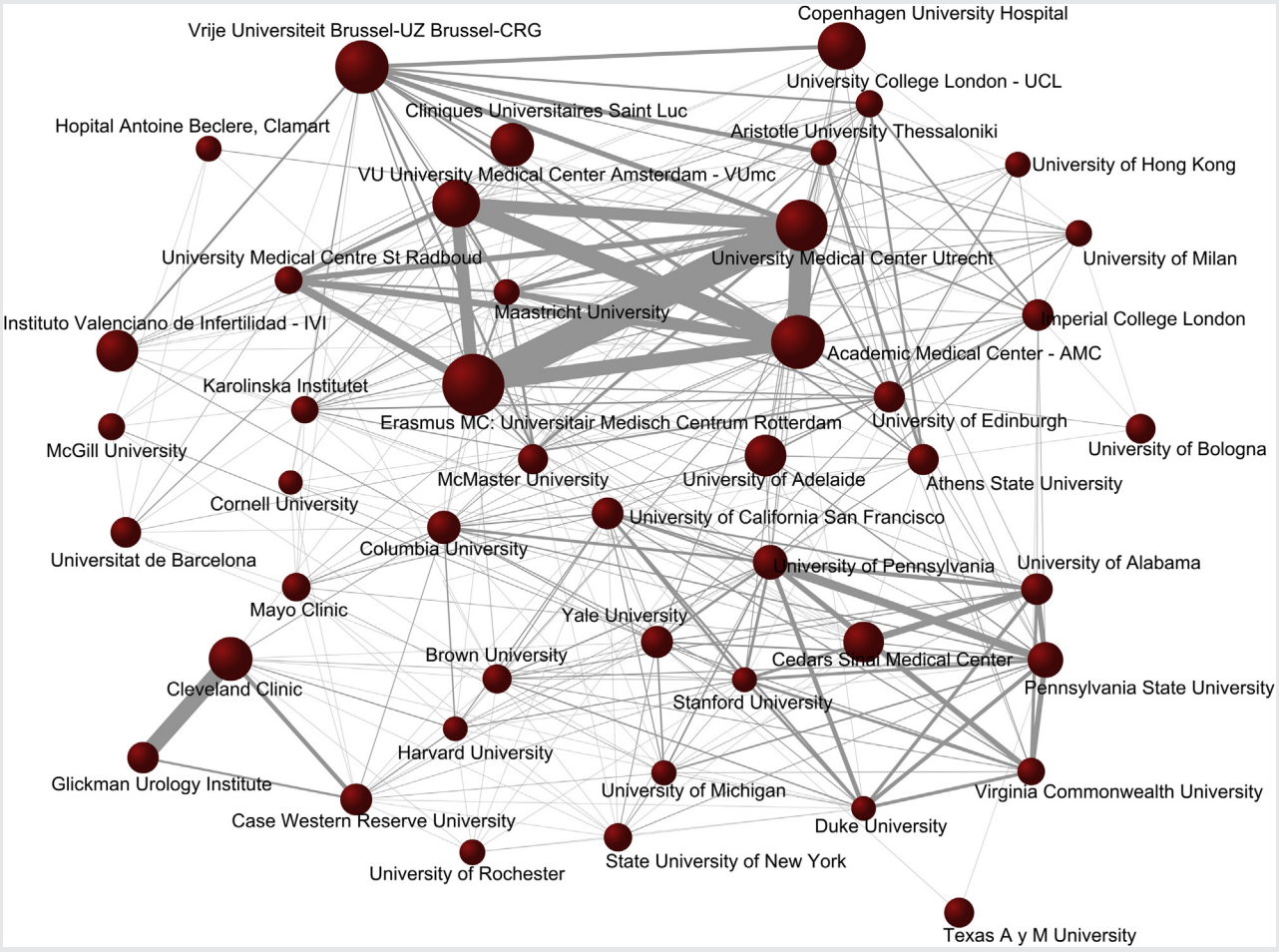
FIGURE 1



Network of collaboration among the most-cited institutions.

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in both citations and number of published articles was Mol (727 citations and 73 articles).

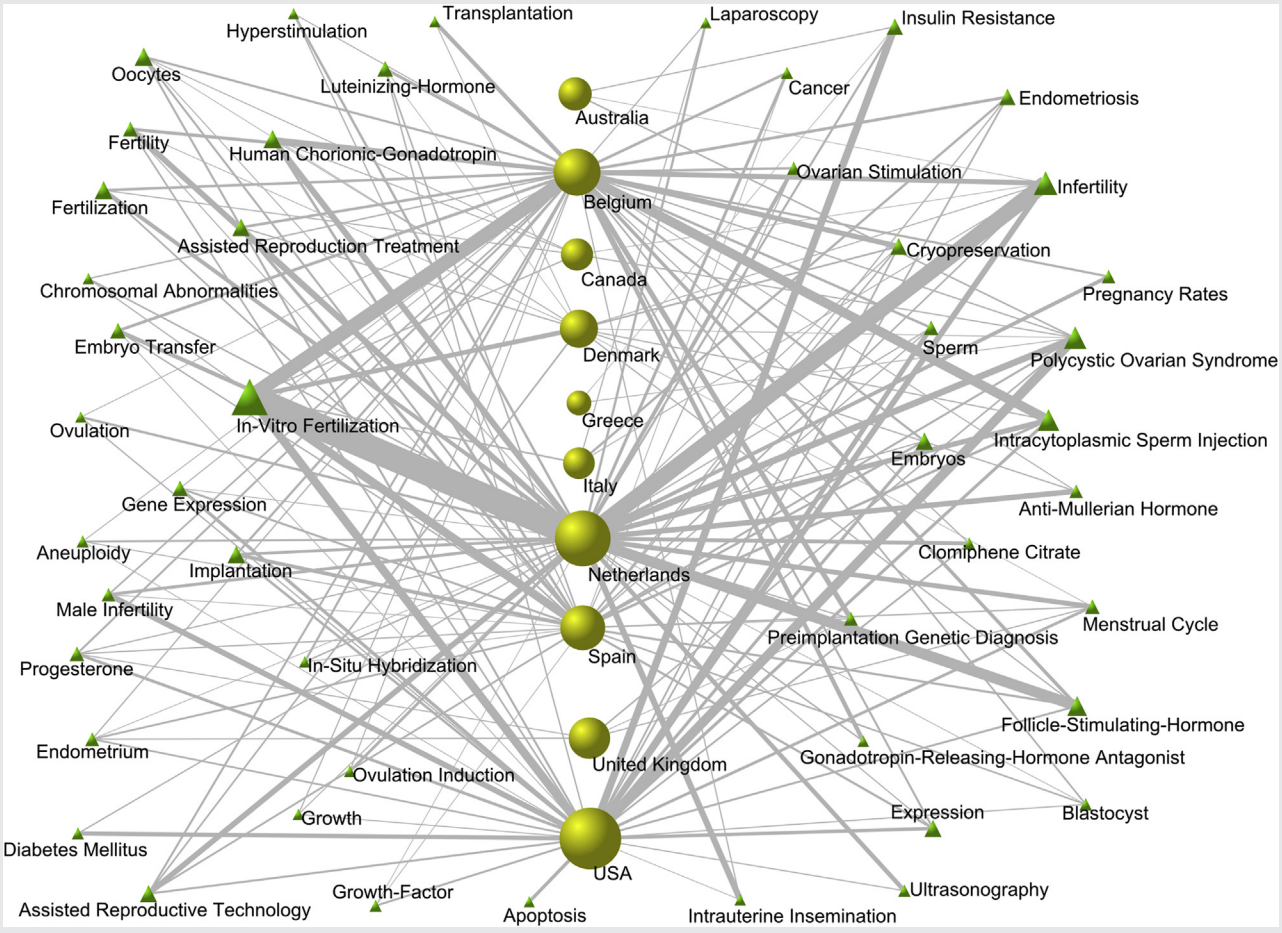
The most-cited institutions in reproductive medicine and the most frequently used key words are shown in Table 2. Erasmus University Medical Center (Rotterdam, the Netherlands) was the most-cited institution (n = 9,006 citations), followed by the University Medical Center Utrecht (the Netherlands) (n = 7,108) and Vrije Universiteit Brussels (Belgium) (n = 6,846). Networks of the 50 most-cited institutions are depicted in Figure 1, in which institutions are placed in the center for their greater number of collaborations, such Erasmus MC (Rotterdam), the Academic Medical Center Amsterdam, the University Medical Center Utrecht, and the VU University Medical Center Amsterdam. Other institutions with significant interinstitutional collaborations were the Cleveland Clinic in Ohio with its Glickman Urological & Kidney Institute and Center for Advanced Research in Human Reproduction, Infertility, and Sexual Function; Rigshospitalet, the Copenhagen University Hospital; and the Cliniques Universitaires Saint-Luc at the Université Catholique de Louvain in Belgium, among others.

The evolution of international versus domestic collaboration can be observed in Supplemental Figure 3. The number of articles published by these institutions with international collaboration has doubled from 2003 to 2007, while domestic collaboration has grown to a lesser extent and decreased the articles signed without collaboration (only by a single institution).

The most-cited countries and the associated key words are presented in Figure 2. In this figure, the thickness of the lines represents the number of times a key word appears in the articles of each country, the thickness of the yellow spheres represents the total number of citations of each country, and the thickness of the green spheres are the number of occurrences of key words.

Supplemental Figure 2 shows how the field has developed during the decade based on its keywords. The most frequent keywords with an upward trend (Supplemental Fig. 2A) were in vitro fertilization, pregnancy, infertility, polycystic ovarian syndrome, and assisted reproductive technology. Keywords with an upward trend (Supplemental Fig. 2B) were follicle-stimulating hormone, intracytoplasmic sperm

FIGURE 2



Network of countries of origin of most-cited institutions and international collaborations.

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injection, luteinizing hormone, ovulation induction, and preimplantation genetic diagnosis.

DISCUSSION

Our current analysis provides, to the best of our knowledge, the first comprehensive global analysis of high-quality published research in the field of reproductive medicine. We have identified the most-cited investigators, institutions, and key words in reproductive medicine based on publications from the years 2003 to 2012 in the highest impact factor quartile journals in the science category of reproductive biology supplemented with the three most relevant additional science categories: obstetrics and gynecology, endocrinology and metabolism, and general and internal medicine. This analysis complements and expands the perspective of previous studies that analyzed highly cited articles in the area of reproductive medicine (4–7), the geographical distribution of articles (8, 9), and the collaboration patterns (10).

Our analysis reveals that 22% of highly cited reproductive medicine research is published in journals belonging to science categories outside reproductive biology, accounting for 33% of all citations. Additional citations were mainly obtained from the science categories of endocrinology and metabolism, and general and internal medicine. Highly cited investigators in the area of reproductive medicine generated from 5% to 52% of their total citation score from articles published in areas other than reproductive medicine. We acknowledge that owing to the search strategy chosen (as outlined in Supplemental Fig. 1) we may have missed some high-quality basic science researchers primarily publishing their work on more fundamental aspects of reproductive sciences in other, more general high-impact journals along with clinical research published in other science categories such as immunology, surgery, or cardiovascular health. It should be noted that in the citation count for institutions and countries, the total citations received by an article were assigned to each of the participating institutions on the work, so some institutions and countries may have benefited from published collaborations.

The most-cited groups are situated in the Netherlands, Belgium, Spain, the United States, and the United Kingdom,

and collaborative studies are increasing. Different characteristics can be observed among the big-five countries as identified by their scientific productivity: The number one country (the Netherlands) mainly featured four major centers with strong collaborations among them; in other countries, one or two centers were mainly responsible for their performance in the field (Belgium and Spain). For the other countries, many different medium-sized centers were jointly responsible for their collective impact (United States and United Kingdom).

We have analyzed the key words that characterize the research focuses of these centers and their collaborations, both national and international. These most-cited institutions published research using key words such as IVF/assisted reproductive technologies (ART), infertility, pregnancy, hyperandrogenemia, polycystic ovary syndrome (PCOS), follicle-stimulating hormone (FSH), metabolic dysfunction, and semen/male. To understand how the field has developed over the last decade, we examined the evolution of key words used by the most-cited groups over time. The most important keywords with an upward trend—indicating that the research field continues to grow—involve areas such as ART (mainly IVF), pregnancy outcomes, and the future health of IVF children and mothers. It is laudable that interest is shifting from merely developing novel infertility interventions toward more detailed analyzes of the health implications for women and their offspring. Judging from sound publications, the most studied illness in reproduction is PCOS, a heterogeneous condition that affects up to 10% of all women; this supports the increasing awareness that this condition is associated with many general health risks beyond reproduction per se. The keywords with a downward trend reveal that research interest in ovarian stimulation protocols (which had attracted much attention in the previous two decades) is currently diminishing, as is interest in the two main glycoprotein hormones involved, follicle-stimulating hormone and luteinizing hormone. Intracytoplasmatic/intracytoplasmic sperm injection sperm injection represented a breakthrough in 1993, allowing the couples with severe male factor infertility to have their own genetic offspring. As this is now an accepted treatment, scientific interest has decreased. Preimplantation genetic diagnosis, which allows chromosomal analysis of the preimplantation embryo, has suffered from insufficient randomized studies, which has diminished interest; however, newly developed technologies have been helping the focus on additional clinical trials increase again.

Despite the rapidly increasing clinical and scientific relevance of reproductive medicine, up to now no highly ranked general journals have devoted a special section to this field, nor are specific (inter)national research funds being made available (in for instance, the 7th European Union framework). Each country independently sponsors some of the work performed by scientists working in this area, with huge variability (17).

In conclusion, the current comprehensive and thorough global analysis provides compelling evidence of the scientific growth and maturity of reproductive medicine research and subsequent clinical development. High-quality research is increasingly published in high-impact journals outside the field of reproductive medicine and increasing (inter)national collaborations seem key to success. Areas with increasing interest and science output involve ART, infertility, IVF, PCOS, and pregnancy. Rapid technological advances leading to treatment modifications and the introduction of newly developed treatment modalities require national and international monitoring of their efficacy and safety for both the patients and the infants conceived with their use.

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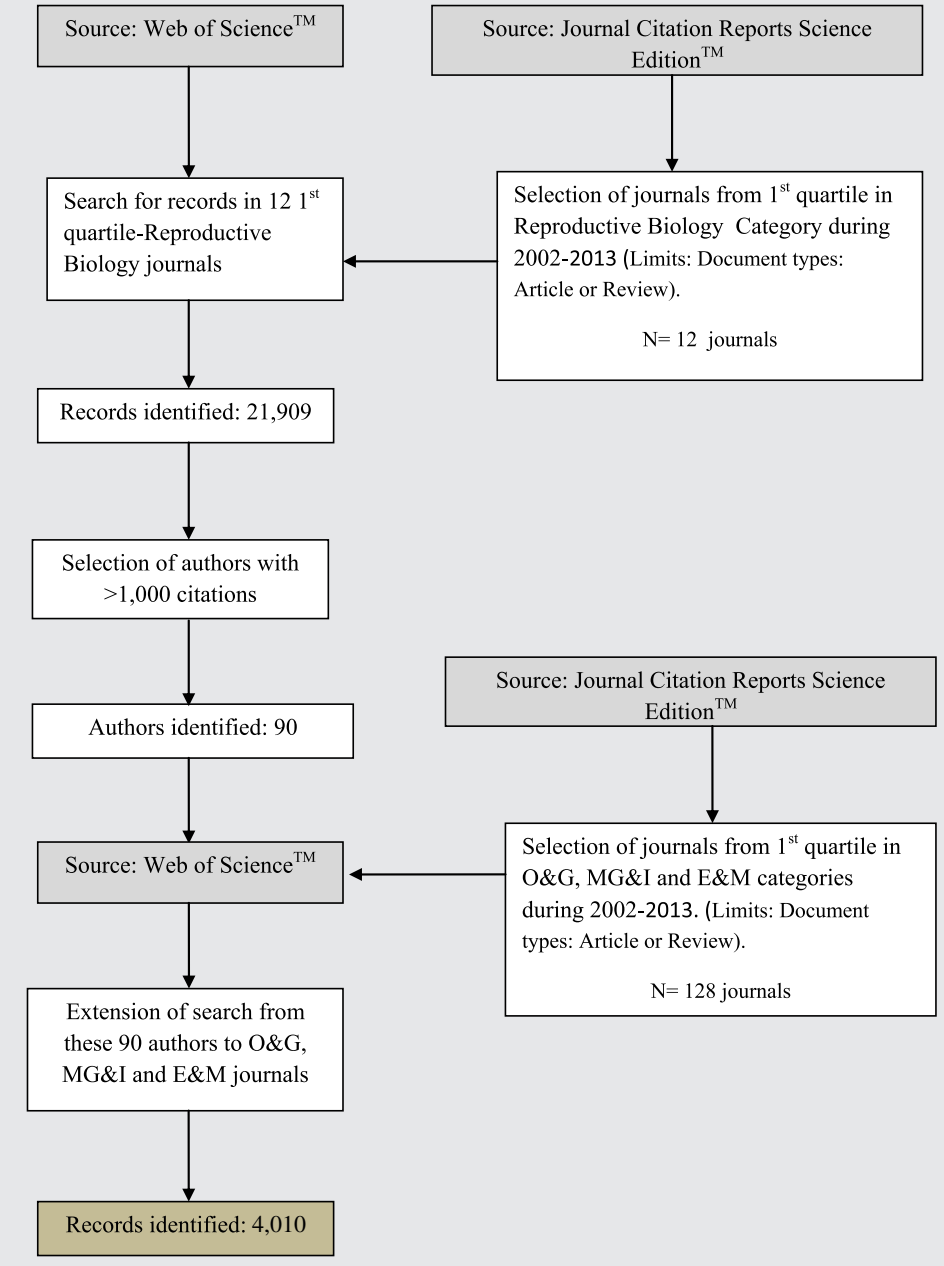
SUPPLEMENTAL FIGURE 1



O&G: Obstetrics and Gynecology; MG&I: Medicine General and Internal; E&M: Endocrinology and Metabolism.

Flow diagram of search criteria and the publication selection process.

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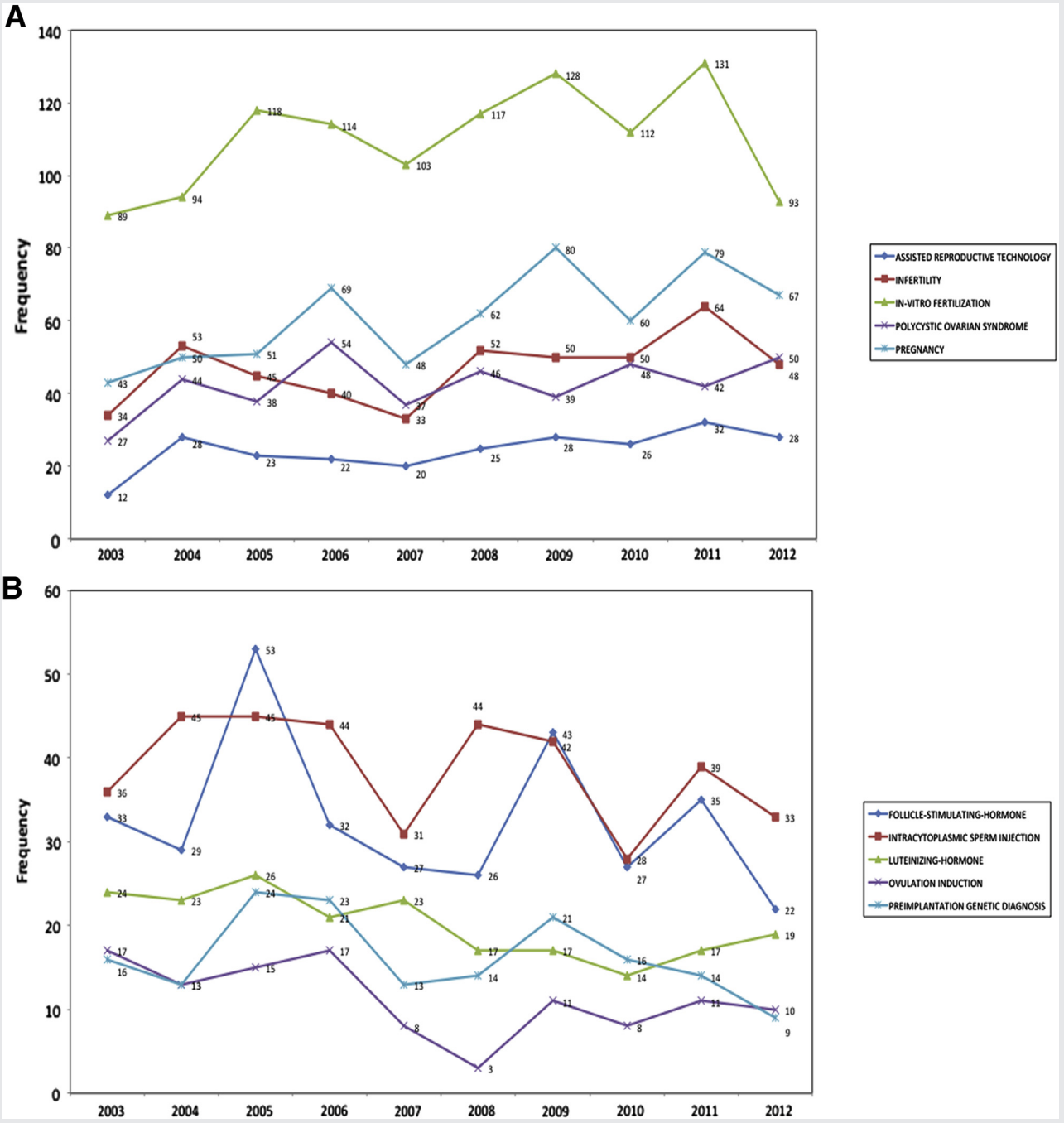
SUPPLEMENTAL FIGURE 2



Five key words with most distinct (**A**) upward and (**B**) downward trends over time (as counted in the total sample size of 4,010 articles).

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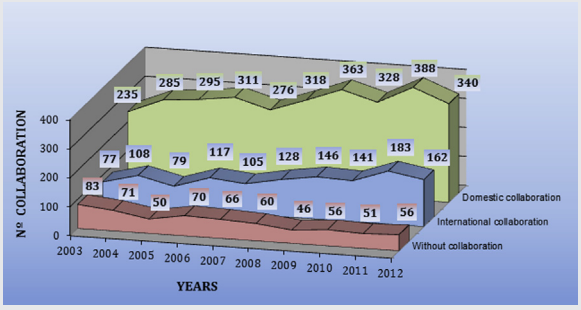
SUPPLEMENTAL FIGURE 3



Collaborations among the most-cited institutions over time.

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SUPPLEMENTAL TABLE 1

Comparison of the area of reproductive biology with other science categories (ISI Web of Knowledge 2012), total number of journals included in each science category and impact factor of journals (top, P_{10}, and P_{25}).

Science category	No. of journals included	Journal impact factor		
		Top	P_{10}[a]	P_{25}[b]
Reproductive biology	28	8.85	4.67	3.32
Geriatrics	47	6.17	5.22	3.52
Respiratory systems	50	11.04	5.11	3.12
Ophthalmology	59	9.44	3.03	2.34
Dermatology	59	6.20	3.58	2.36
Orthopedics	65	4.44	2.95	2.26
Hematology	67	11.86	6.08	4.14
Urology/nephrology	73	10.48	4.79	2.83
Gastroenterology	74	12.82	7.55	2.99
Obstetrics gynecology	78	8.85	3.56	2.51
Pediatrics	122	6.97	2.94	1.24
Endocrinology and metabolism	122	14.87	6.49	4.21
Medicine, general and internal	155	51.66	4.61	2.06

[a] Journal at the 10th percentile of that particular science category.
[b] Journal at the 25th percentile of that particular science category.

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SUPPLEMENTAL TABLE 2

Growth of number of publications in reproductive biology compared to two other science categories: obstetrics and gynecology and pediatrics.

Year	Reproductive biology	Obstetrics and gynecology	Pediatrics
2003	918	11,246	12,918
2004	990	12,360	13,176
2005	1,102	13,600	14,433
2006	1,112	14,852	15,988
2007	1,206	15,152	16,030
2008	1,204	15,407	17,526
2009	1,404	15,816	18,349
2010	1,514	16,399	18,548
2011	1,556	17,588	19,428
2012	1,654	17,769	20,270
Growth rate (2003–2012)	80%	58%	57%

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