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Ectopic pregnancy – exploration of its global research architecture using density-equalizing mapping and socioeconomic benchmarks

Short title: Global architecture of ectopic pregnancy research

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ABSTRACT

Objective: About 2% of all pregnancies are complicated by the implantation of the zygote outside the uterine cavity and termed ectopic pregnancy. Whereas a multitude of guidelines exists and related research is constantly growing, no thorough assessment of the global research architecture has been performed yet. Hence, we aim to assess the associated scientific activities in relation to geographical and chronological developments, existing research networks and socio-economic parameters.

Design: retrospective, descriptive study

Setting: On the basis of the NewQIS platform, scientometric methods were combined with novel visualizing techniques such as density equalizing mapping to assess the scientific output on ectopic pregnancy. Using the Web of Science, we identified all related entries from 1900 to 2012.

Results: 8,040 publications were analyzed. The United States (US) and the United Kingdom (UK) were dominating the field in regards to overall research activity (2,612 and 723 publications), overall citation numbers and country-specific H-Indices (US: 80, UK: 42). Comparison to economic power of the most productive countries demonstrated that Israel invested more resources in ectopic pregnancy-related research than other nations (853.41 ectopic pregnancy-specific publications per 1000 Bio USD GDP), followed by the UK (269.97). Relation to the GDP per capita index revealed 49.3 ectopic pregnancy-specific publications per 1000 USD GDP per capita for the US in contrast to 17.31 for the UK. Semi-qualitative indices such as country-specific citation rates ranked Switzerland first (24.7 citations per ectopic pregnancy-

specific publication), followed by the Scandinavian countries Finland and Sweden. Low-income countries did not exhibit significant research activities.

Conclusions: This is the first in-depth analysis of global ectopic pregnancy research since 1900. It offers unique insights into the global scientific landscape. Besides the US and the UK, Scandinavian countries and Switzerland can also be regarded as leading nations with regard to their relative socioeconomic input.

KEY MESSAGE

This is the first in-depth analysis of global ectopic pregnancy research since 1900. It offers unique insights into global landscape that reveals that next to the US or the UK, also Scandinavian countries and Switzerland can be regarded as leading nations with regard to their relative socioeconomic input.

KEY WORDS

ectopic pregnancy; density equalizing mapping; female health; reproduction biology

STRENGTH AND LIMITATIONS

- We compiled the first concise depiction of the worldwide scientific productivity related to ectopic pregnancies.
- The NewQIS platform was used to evaluate the scientific output regarding quantitative and qualitative aspects, geographical and chronological developments, existing research networks and socio-economic benchmarks.

The method combines scientometric methods and “density equalizing mapping projections in a reliable and standardized way.

- The WoS focuses on English journals. It is a weakness that non-English articles are underrepresented in our analysis.
- We analysed citation-based parameters, which rather reflect the recognition of the research in the scientific community than truly measure quality.

INTRODUCTION

Around 2% of zygotes implant outside the uterine lining and form an ectopic gestation [1]. Frequently, the products of conception grow in the fallopian tube. Other implantation sites are the ovaries or the cervix. Affected patients may face significant morbidity or even mortality [1]. During the last decades, transvaginal ultrasound and beta-human chorionic gonadotropin (beta-HCG) levels became part of the clinical routine[2-6] leading to the timely detection of ectopic pregnancies and better patient outcomes [7-9]. First scientific publications describing therapeutic measures for ectopic pregnancies date back to the 16th century. Since then, thousands of studies tackled the most pressing questions in the field [1, 10-12]. Numerous discoveries improved diagnosis and management, and shaped the clinical guidelines we are using today [13]. Despite these hallmark advances in clinical care, ectopic pregnancies pose a significant burden on million women around the globe: In the United States of America (US) alone, costs related to the condition were estimated at around $1 billion in 1990 [14]. Although the mortality associated with ectopic gestations was halved in industrialized countries since the 1980s [15], the condition constitutes a major cause of death continents like Asia and Africa [16].

A multitude of disciplines such as OB/GYN, Family Medicine, Internal Medicine and Surgery are involved in the management of ectopic pregnancies. Hence, related research attracts the interest of scientists worldwide addressing the issue from a clinical, basic science and Public Health perspective. To carry out research according to identified shortcomings, establish global networks and allocate funds, scientists and funding institutions have to be aware of the global scientific landscape related to ectopic pregnancy research. Thus, this study provides a first comprehensive assessment of the research performance in the field and identifies trends in the

related literature by a scientometric approach [17, 18]. Therefor we identified all ectopic pregnancy-related publications indexed in the Web of Science until 2012. These items were (1) analysed in reference to their content and citations describing geographical and historical developments, (2) research networks were identified and (3) the country-specific productivity was related to socioeconomic variables. Furthermore, we present the most cited publications related to ectopic pregnancies. These studies cover key discoveries in the field and provide the scientific fundament for many clinical decisions made daily around the globe.

MATERIALS AND METHODS

NewQIS study protocol

We employed the 'New Quality and Quantity Indices in Science' (NewQIS) platform to assess global ectopic pregnancy research in a standardized, reliable and objective way [17, 18]. This tool combines scientometric techniques to assess scientific productivity and density equalizing mapping [19] to generate global maps according to analysed parameters [20-23].

Data source

The database Web of Science (WoS, Thomson Scientific) was used to conduct this study. We selected this data source because it allows the assessment of publication activity similar to the PubMed database, but facilitates a thorough citation analysis for the research in focus [24, 25].

Search strategy

The following search term was used: *"ectopic pregnanc*" OR "ovarian pregnanc*" OR "cervical pregnanc*" OR "tubal pregnanc*" OR "abdominal pregnanc*" OR "extrauterine pregnanc*" OR "ectopic gestation*" OR "ovarian gestation*" OR "cervical gestation*" OR "tubal gestation*" OR "abdominal gestation*" OR "extrauterine gestation*"*. We performed a "Topic" search, and the term was inserted into the WoS search fields "title", "abstract" and "key words" to identify the total number of published items related to ectopic pregnancies.

Timeframe

The analysed timeframe for research on ectopic pregnancy encompassed the years between 1900 (01-01) and 2012 (31-12). Results from 2013 onwards were not considered due to incomplete data acquisition (i.e. citation rate) at the time the study was performed.

Data analysis and categorization

Metadata were retrieved in Plain Text Format (S1 File) as described in previously published NewQIS studies [26, 27]. Bibliometric details were analysed with respect to quantitative and semi-qualitative aspects such as originating countries, languages, citations, cited references, year published and subject categories. Subject categories are assigned to every journal and its publications by the Journal Citation Reports (provided by the Institute of Scientific Information) and can be retrieved via WoS. As semi-qualitative items describing the recognition of publications by the scientific

community, the number of citations, citation rates and the modified H-Indices (HI) were investigated, as previously described [28]. Therefore the citation numbers were retrieved for each publication and the average citations per item (citation rate) were calculated. Regression analysis was used to investigate the timely evolution of ectopic pregnancy research.

After the transformation of the raw data to excel program charts and analysis, the findings were illustrated in numerous diagrams and visualized by the use of density-equalizing mapping projections (DEMP). The algorithm for this procedure was published by Gastner and Newman [19]. In DEMPs, the territories of the different countries were resized in proportion to our selected variables such the distribution of country-specific numbers of published items, average citation rates and H-Indices.

Socioeconomic analysis

In order to assess research output with regard to the economic power of the most active countries, the publication activity was related to the Gross Domestic Product (GDP) and the GDP per capita in current USD, as described earlier [29]. According to the World Bank, the GDP at purchaser's prices is the sum of gross value added by all resident producers in the economy plus any product taxes and minus any subsidies not included in the value of the products. It is calculated without making deductions for depreciation of fabricated assets or for depletion and degradation of natural resources. Data are in current U.S. dollars. Dollar figures for GDP are converted from domestic currencies using single year official exchange rates. For a few countries where the official exchange rate does not reflect the rate effectively applied to actual

foreign exchange transactions, an alternative conversion factor is used (http://data.worldbank.org/indicator/NY.GDP.MKTP.CD).

The GDP per capita is defined as gross domestic product divided by midyear population. GDP is the sum of gross value added by all resident producers in the economy plus any product taxes and minus any subsidies not included in the value of the products. It is calculated without making deductions for depreciation of fabricated assets or for depletion and degradation of natural resources. Data are in current U.S. dollars (http://data.worldbank.org/indicator/NY.GDP.PCAP.CD).

Analysis of international ectopic pregnancy research collaborations

To investigate international research collaborations, the affiliations of all identified ectopic pregnancy-related publications were screened as described earlier [30, 31]. In brief, if at least two authors, who were working in different countries, contributed to one ectopic pregnancy-related publication, this relationship was defined as a collaborative publication. To visualize the productivity of collaborations for each pair of countries, a vector was calculated. Its line width and shade of grey is proportional to the number of depicted collaborations [24, 32].

RESULTS

Global ectopic pregnancy research activity

We identified 8,040 ectopic pregnancy-related publications issued from 1900 to 2012; these were cited 86,680 times. 92.4% of these items were written in English and published by researchers from 76 different countries. US-American researchers

authored 2612 publications accounting for 32% of all ectopic pregnancy-related publications. The US was identified as the country with the highest number of publications worldwide (Fig 1A). The United Kingdom (UK) was positioned second with 723 ectopic pregnancy publications, followed by Germany (370 publications), France (366 publications), Israel (248 publications), Canada (215 publications), Australia (203 publications), Italy (179 publications), Japan (169 publications), Turkey (162 publications), China (159 publications), Sweden (151 publications), the Netherlands (134 publications), Austria (124 publications) and Taiwan (122 publications). Since North America, Western Europe and Australia were responsible for the majority of research output associated with “ectopic pregnancy”, their country sizes appear inflated in the DEMP-analysis (Fig 1A). Major parts of Asia (except China and Taiwan), Russia, Africa and South America occupied only small areas on the cartogram. The analysis of the timely evolution led to a regression coefficient of 0.6793 for the period from 1900 until 2012 and of 0.8105 for the period from 1970 until 2012 (Fig 1B). This indicated a strong increase of global research activity in the past 40 years.

Socioeconomic analysis of ectopic pregnancy research

In order to assess the relative magnitude of the countries research activities in relation to their economic wealth, the two indicators GDP and GDP per capita were used for our evaluation. The analysis of publication activity in relation to the most productive countries´ GDP demonstrated that Israel published the highest amount of ectopic pregnancy-specific research relative to its GDP: 853.41 publications per 1000 bn USD GDP. It was followed by the UK with 269.97 ectopic pregnancy-specific

publications per 1000 bn USD GDP, Turkey (196.79 publications per 1000 bn USD GDP) and the US (155.77 publications per 1000 bn USD GDP) (Table 1).

When the ectopic pregnancy publication activity was related to the GDP per capita, the US again gained the leading position with a level of 49.3 ectopic pregnancy specific publications per 1000 USD GDP per capita. This benchmarking largely resembled the total publication activity analysis with the exception of Turkey, which climbed from tenth to third position due to its extremely low GDP per capita (Table 1).

Table 1. Socio-economic analysis of ectopic pregnancy research of the ten most active countries. Sources for GDP and GDP per capita in 2013: http://data.worldbank.org/indicator/NY.GDP.PCAP.CD

Country	Number of publications	GDP in 1000 bn US-$	Publications / GDP in 1000 bn US-$	GDP per capita in 1000 US-$	Publ. / GDP per Capita in 1000 US-$
Israel	248 (5)	0.2906 (10)	853.41 (1)	36.05 (8)	6.88 (6)
United Kingdom	723 (2)	2.6781 (5)	269.97 (2)	41.78 (6)	17.31 (2)
Turkey	162 (10)	0.8232 (9)	196.79 (3)	10.99 (10)	14.75 (3)
United States	2612 (1)	16.7681 (1)	155.77 (4)	52.98 (2)	49.30 (1)
France	366 (4)	2.8102 (4)	130.24 (5)	42.63 (5)	8.59 (4)
Australia	203 (7)	1.5604 (8)	130.09 (6)	67.47 (1)	3.01 (10)
Canada	215 (6)	1.8389 (7)	116.92 (7)	52.31 (3)	4.11 (9)
Germany	370 (3)	3.7303 (3)	99.19 (8)	46.26 (4)	8.00 (5)
Italy	179 (8)	2.1369 (6)	83.77 (9)	35.48 (9)	5.05 (7)
Japan	169 (9)	4.9195 (2)	34.35 (10)	38.63 (7)	4.37 (8)

Global citation analysis

Citation analysis of all country-specific publications demonstrated a leading position of the US. US-American publications dedicated to ectopic pregnancy research received a total of 39,404 citations (Fig. 2A). It was followed by the UK with over 8,000 citations, France (4,423 citations), Canada (3,578 citations), Israel (3,057 citations) and Sweden (3,349 citations). DEMP analysis regarding the citation activity was similar to the cartogram reflecting absolute publication numbers: The map represents nearly no citations for African, South American or Asian countries leading to a minimized appearance of these areas whereas North America and Europe are depicted increased in size (Fig 2A).

The calculation of the country-specific H-Index (Fig 2B) showed a leading position of the US with 80 ectopic pregnancy-related publications being cited at least 80 times. The US was followed by the UK with a country-specific H-Index of 42, Canada (H-Index: 36), France (H-Index: 35), Israel (H-Index: 31), Sweden (H-Index: 30), Finland (H-Index: 29), the Netherlands (H-Index: 29), Belgium (H-Index: 25) and Germany (H-Index: 25). Again, countries from Africa, Eastern Europe, Latin America or Russia exhibited very low rates.

The results of the country-specific citation rate (Fig 2C) contrasted all other benchmarks since Switzerland ranked first with a citation rate (CR) of 24.7, followed by the Scandinavian countries Finland and Sweden with CR of 20.9 and 20.2, respectively.

Cooperation articles

Out of the 8,040 ectopic pregnancy-related publications, only 397 were published within international collaborations. This equates a relatively small percentage of 4.9%. With 82.1% (326 publications), bilateral collaborations were the most common type of established collaborative efforts, followed by trilateral (51) co-operations. The US was the leading country with 156 collaborations followed by the UK with 127 international relationships. The most frequent bilateral collaboration was set up between the UK and Belgium with 37 joint studies. Interestingly, 51 out of the 111 total studies from Belgium arose from international collaborations, which equals a percentage of 45.9% (Fig 3A). In comparison, the US was characterized by a ratio of 156 collaborative publications out of 2,612 (6%), the UK by 17.6% and Germany by 10.3%. A continuous increase in the numbers of collaborations was present until 2010 with 34 collaborative publications in this year (Fig 3B).

Subject area analysis

The timely evolution in subject categories of ectopic pregnancy-related publications was analysed since 1973 and the proportion of the different subject areas was investigated (Fig 4A). Articles can be assigned to more than one category, hence percentages of more than 100 were possible. From the beginning until 2012, “Obstetrics & Gynecology“ remained the most prominent category. “Reproductive Biology” gained importance after 1988. The field diversified in 1978 when research was also published in the categories of “Emergency Medicine” (since 1978) and “Pathology” (since 1983). Overall, the percentages of all assigned subject categories remained relatively constant with no rapid increase of one particular area within the

past 20 years. A small but constant proportion of publications was attributed to the area of “Public, Environmental & Occupational Health”, which indicates that scientists also focused upon Public Health issues related to ectopic pregnancy.

We identified the leading, most impactful publication categories based on item and citation count (Fig 4B). The primary areas of ectopic pregnancy-research were “Obstetrics & Gynecology” and “Reproductive Biology”. The 5,100 publications assigned to “Obstetrics & Gynecology” were cited 57,879 times. “Reproductive Biology” with 1,496 publications was cited 22,545 times. When citation rates were analysed, the highest rate was present for the subject area “Infectious Diseases” with 24.02 citations per ectopic pregnancy-related publication. The frequently assigned subject areas “Reproductive Biology” and “Obstetrics & Gynecology” were characterized by citation rates of 15.07 and 11.37 respectively.

We performed a subject area analysis for the most productive countries aiming to pinpoint the particular focus researchers are working on in these nations: In France, a high volume of “Public Health”-related work was published. This finding underlines the nation’s interest to allocate considerable resources to Public Health issues in context with ectopic pregnancies. A relatively high percentage of Public Health-related ectopic pregnancy research originated from the US when compared to other countries, e.g. Japan. Also, US-American scientists focused more on emergency medicine aspects of ectopic pregnancy research than researchers from all other countries. This is reflected by a high percentage of allocated publications originating from the US to that category (Fig 5). Also, we identified the key publications in the field of ectopic pregnancy research, which were cited 200 times or more.

Table 2. Key publications in the field of ectopic pregnancy research. These articles were published since 1900 and cited 200 times or more.

Title	Publication Year	Country	Citations	Journal
WHO analysis of causes of maternal death: a systematic review *Khan KS et al.* [33]	2006	Switzerland, United Kingdom, Argentina	534	LANCET
Comparative genomes of Chlamydia pneumoniae and C-trachomatis *Kalman S et al.* [34]	1999	United States	457	NAT GENET
Pelvic inflammatory disease and fertility *Weström L et al.* [35]	1992	United States	347	SEX TRANSM DIS
Genital chlamydial infections - epidemiology and reproductive sequelae *Cates W et al.* [36]	1991	United States	345	AM J OBSTET GYNECOL
Current methods of laboratory diagnosis of Chlamydia	1997	United States	293	CLIN MICROBIOL

trachomatis infections *Black CM et al.* [37]				REV
Prevalence of chlamydial and gonococcal infections among young adults in the United States *Miller WC et al.* [38]	2004	United States	270	JAMA-J AM MED ASSN
The epidemiology of smoking during pregnancy *Cnattingius S* [39]	2004	Sweden	250	NICOTINE TOB RES
Single-dose methotrexate - an expanded clinical-trial *Stovall TG and Ling FW* [40]	1993	United States	238	AM J OBSTET GYNECOL
A method of screening for ectopic pregnancy and its indications *Kadar N et al.* [41]	1981	United States	235	OBSTET GYNECOL
Maternal age and fetal loss: population based register Linkage study *Nybo Andersen AM et al.* [42]	2000	Denmark	234	BRIT MED J
Treatment of interstitial ectopic pregnancy with methotrexate - report of a successful case *Tanaka T et al.* [43]	1982	Japan	233	FERTIL STERIL
Discriminatory HCG zone - its use in the sonographic evaluation for ectopic pregnancy *Kadar N et al.* [44]	1981	United States France	229	OBSTET GYNECOL
Conservative laparoscopic treatment of 321 ectopic pregnancies *Pouly JL et al.* [45]	1986	France	228	FERTIL STERIL
Incidence, trends, and risks of ectopic pregnancy in a population of woman *Westström L et al.* [46]	1981	Sweden	214	BRIT MED J
Early termination of pregnancy with mifepristone (RU-486) and the orally active prostaglandin misoprostol *Peyron R et al.* [47]	1993	France	216	N ENGL J MED

DISCUSSION

Accounting for a percentage of 2% of all first-trimester pregnancies in the US, ectopic gestation is a very common complication of pregnancy. It should therefore merit a high degree of interest within the scientific community. Hence, this NewQIS study [17, 18] is focused on this condition and presents the first multifaceted analysis of the related global research architecture using density equalizing mapping analysis tools [19]. Additionally, we selected 15 publications that were defined as key articles in the field based on 200 and more citations. These key publications provide relevant background information for individual scholarship, practice and research endeavours.

In total, we analysed 8,040 publications related to ectopic pregnancies. The US was identified as the country dominating the field. With regard to total publishing activities, it is important to compare ectopic pregnancy research to other disease entities or to the field of OB/GYN in general: A recent study by Aleixandre-Benavent et al. focused on trends in reproductive medicine research over a period of 10 years [48]. It was the authors' objective to study the publication activity metrics from 2003 to 2012 and to shed a light on the clinical, social, and epidemiologic implications of this relatively new but rapidly emerging field. As outcome measures, they analysed most productive and frequently cited investigators, institutions, and countries as well as specific areas of research and scientific collaborations. The authors found that 90 investigators with more than 1,000 citations had jointly published 4,010 articles. The most-cited study groups were located in the Netherlands, Belgium, Spain, the US, and the UK, and collaborative studies have been increasing. It was concluded that reproductive medicine research has attained scientific interest and importance. Also, the increase in (inter)national collaborations seems to be the key to the field's success. In contrast to Aleixandre-Benavent et al., we focused on a single disease

entity and encompassed more than one hundred years of research. Besides monitoring the scientific output we also related the numbers to the economic power of investigated countries in order to dissect the real interest of single nations in research related to a particular condition. Therefore, we related the ectopic pregnancy-related research activities to the total GDP and the GDP per capita. We found that the US still dominated when GDP per capita index was used. However, when related to the total GDP index, Israel exhibited the highest contribution of ectopic pregnancy research in relation to its overall economic power.

We compared the present data to other OBGYN entities such as polycystic ovary syndrome (PCOS) or ovarian cancer [49, 50]: A published study on PCOS that covered the years between 1900 and 2014 reported a total of 6261 PCOS-specific publications and 703 international research collaborations in the Web of Science. As in the present study, the USA was identified as the most active country in total and collaborative research activity [49]. In the socioeconomic analysis, the USA was also ranked first concerning PCOS-related publications per gross domestic product, followed by the UK, Italy and Greece [49]. For ovarian cancer research 23,378 reports were identified for the period 1900 - 2014. Denmark was positioned at the first place with a total of 1293.2 calculated ovarian cancer-specific articles per 1000 billion US-$ GDP [50]. Other gynecological topics, which have been screened for scientific productivity, were predominantly related to breast cancer [51-54]: Glynn et al. presented an in-depth evaluation of breast cancer research. The authors screened publications from 1945 to 2008 also using the NewQIS platform [54]. They identified 180,126 breast cancer-associated items; these had been cited 4,136,224 times. In comparison to our data on ectopic pregnancies encompassing a time span of 112 years, breast cancer research has produced a more than 20 times greater scientific output in a period of

slightly over 60 years. One reason for this discrepancy is that breast cancer accounts for the most common malignancy among women, with an estimated 231,840 new cases diagnosed in the US in 2015 alone [55]. Hence, this disease receives large amounts of public awareness. Also, significant volumes of scientific resources are allocated to support research in this area. In breast cancer, the US produced the greatest publication output (n = 77,101; 42.8%), followed by the UK (n = 18,357; 10.2%) and Germany (n = 12,529, 7%) [54]. This ranking of the most productive nations was similar to ectopic pregnancy research with 32.5% ectopic pregnancy-related publications originating from the US, around 9% from the UK and 4.6% from Germany. The percentage of total global research activity exhibited by US-American institutions is higher in breast cancer research than in ectopic pregnancy research.

"Smoking in pregnancy" is another area of OB/GYN research that was studied [56]. Here, 10,043 related publications were identified in a period from 1900 to 2012. As in our investigation and the presented breast cancer study, the highest number of scientific works was published by the US (35.5%), followed by the UK (9.9%). For both countries, we documented similar percentage values and the highest modified H-Indices of 128 (US) and 42 (UK) for ectopic pregnancy research activities. When citation performance is compared, it is evident that research in "smoking and pregnancy" receives a higher attention in the scientific community than scientific endeavours related to "ectopic pregnancy" since the 10,043 publications in the field of "smoking and pregnancy" were cited 112,136 times (11.2 citations per publication) versus 8,040 ectopic pregnancy-related publications that received 86,680 citations (10.8 citations per publication).

When the global research activity regarding ectopic pregnancy is compared to other biomedical fields, it can be stated that the observed dominance of the US is also

common in other, non-OB/GYN medical specialties. In a study that analysed 5,527,558 published items authored in all areas of medicine over the last 50 years, the following ranking of total research activity was found [57]: The US was the leading nation, followed by Japan, Germany, the UK, France, and Italy [57]. In our analysis, it can be clearly stated that Japan does not exhibit comparable activities in the field of ectopic pregnancy research with only 169 publications in the present set of data. This finding could be linked to a lower prevalence of ectopic pregnancies in Japan compared with other nations translating into disregard of the topic among local scientists and funding institutions. However, epidemiological data on the exact rates of ectopic pregnancies or pelvic inflammatory disease in Japan are lacking. Also, data on maternal mortality attributed to ectopic pregnancies are sparse. For the early nineties, ectopic pregnancy-related maternal mortality was reported at 4% in Japan compared to 13% in the US (data collected until 1989) [58, 59]. Since this difference could indeed reflect a lower impact of ectopic pregnancies on the public health of Japanese women, this fact may explain a lacking interest of Japanese institutions to foster research on this topic.

We identified a small number of international collaborations in the field of ectopic pregnancy research. The rate of 4.9% is substantially lower than in other fields. Additionally, we documented a very small number of ectopic pregnancy-related publications investigating Public Health aspects. These findings indicate a low awareness of this subject matter in terms of ectopic pregnancy research, which is contrasting the major disease burden this condition poses on women - especially in low-income countries with high rates of pelvic inflammatory diseases and only limited access to diagnostic and treatment procedures. Therefore, future research should pay attention to these problematic issues and focus on fostering collaborative efforts,

involving developing countries in research networks and conducting projects in the field of Public Health.

CONCLUSIONS

The present study is the first combined economic and scientometric study that depicts a sketch of the global research activities on ectopic pregnancies. With regard to other disease entities, it can be stated that a mere total of about 8000 related publications highlights the need to foster research programs on this problematic condition that endangers female health and human reproduction biology all around the globe. The lack of research productivity in low-income countries and their missing presence in international collaborations also exemplifies the need for Public Health approaches to help women in these parts of the world.

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AUTHORS' CONTRIBUTIONS

DB, JK, DQ, MHB, DK, FL, JJ, and DAG have made substantial contributions to the conception and design of the study, acquisition of the data and interpretation. They have been involved in drafting and revising the manuscript. All authors have read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

FUNDING

We did not receive any funding to conduct this study.

SUPPORTING INFORMATAION

S1 File. **Raw data used in analysis**. For our study, metadata were retrieved in Plain Text Format to establish an interim database, which was used to sort and analyse bibliometric data in regards to variables of interest.

FIGURE LEGENDS

Fig 1. Publication output. A) Global Density-equalizing mapping of ectopic pregnancy publications. The area of each country is scaled in proportion to its total number of ectopic pregnancy-related publications. Colours encode numbers of ectopic pregnancy publications. B) Timely evolution of ectopic pregnancy-related publications.

Fig 2. Density-equalizing maps. A) Density-equalizing map of country total citations of ectopic pregnancy-related publications. The area of each country was scaled in proportion to its total number of ectopic pregnancy-related citations. Colours encode numbers of ectopic pregnancy-related citations. B) Density-equalizing map of country specific H-Index of ectopic pregnancy-related publications. The area of each country was scaled in proportion to the countries´ specific H-Index. C) Density-equalizing map of country specific citations per ectopic pregnancy-related publication. Colours encode ectopic pregnancy-related citation rate levels.

Fig 3. International collaboration. A) Net diagram of international ectopic pregnancy-related collaborations. Line width and grey scale encode numbers of ectopic pregnancy-related collaborations. Numbers in brackets indicate: (number of ectopic pregnancy-related publications of a specific country/number of ectopic pregnancy-related collaboration articles of a specific country). B) Timely evolution of number of ectopic pregnancy-related international collaborations per year.

Fig 4. Subject area analysis. A) Timely evolution of subject areas assigned to the ectopic pregnancy-related publications in 5-year periods. Proportion of the 10 most assigned subject areas in 5-year intervals in order to gain insights into the field activity. B) Citation analysis of the 10 most assigned subject areas of all ectopic pregnancy-related publications.

Fig 5. Country-specific analysis of assigned subject categories. Analysis was performed of the 10 most active countries in ectopic pregnancy research in order to identify regional differences in ectopic pregnancy research.

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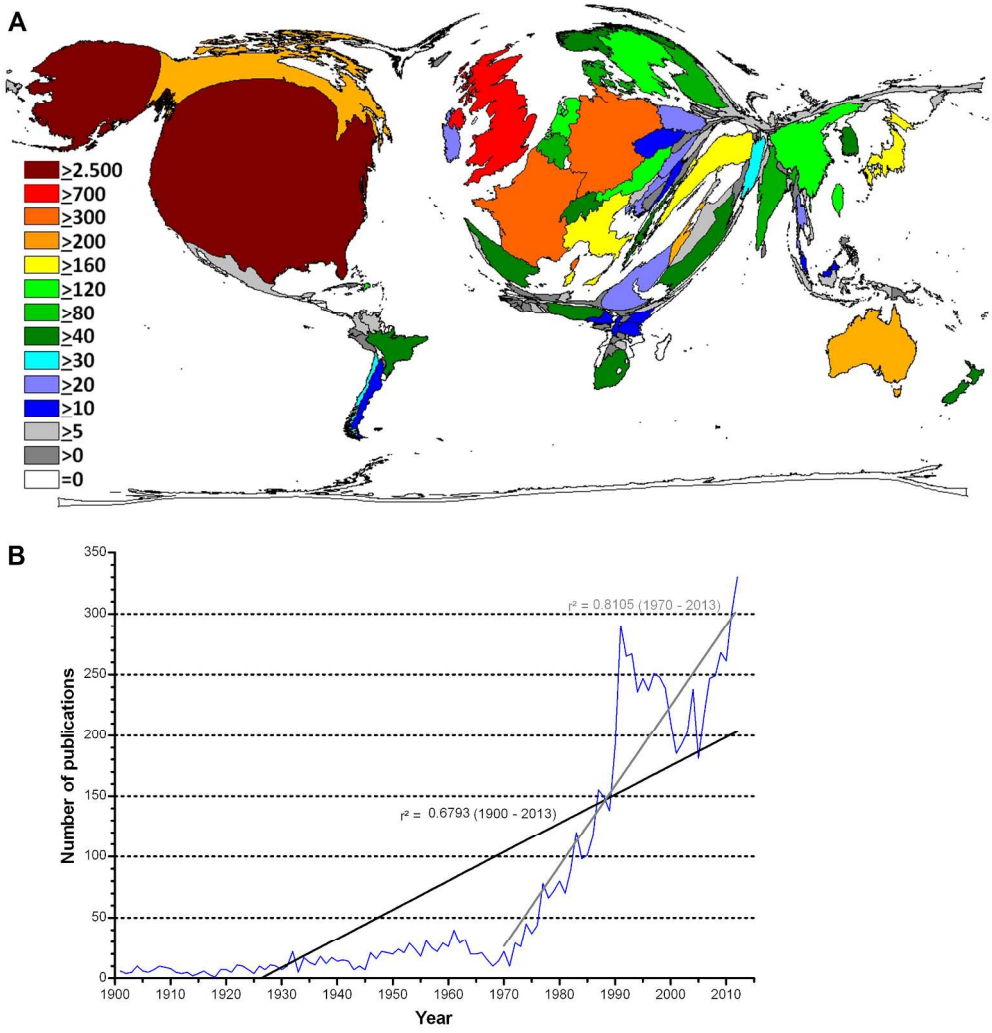
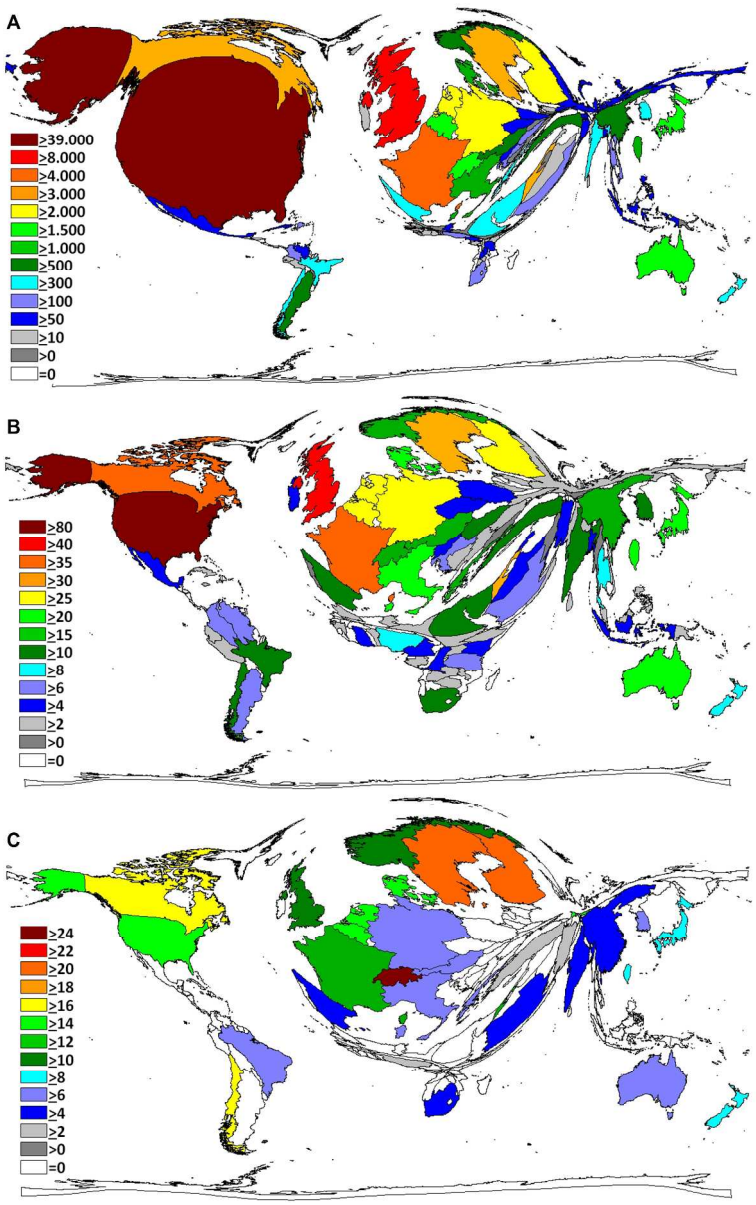


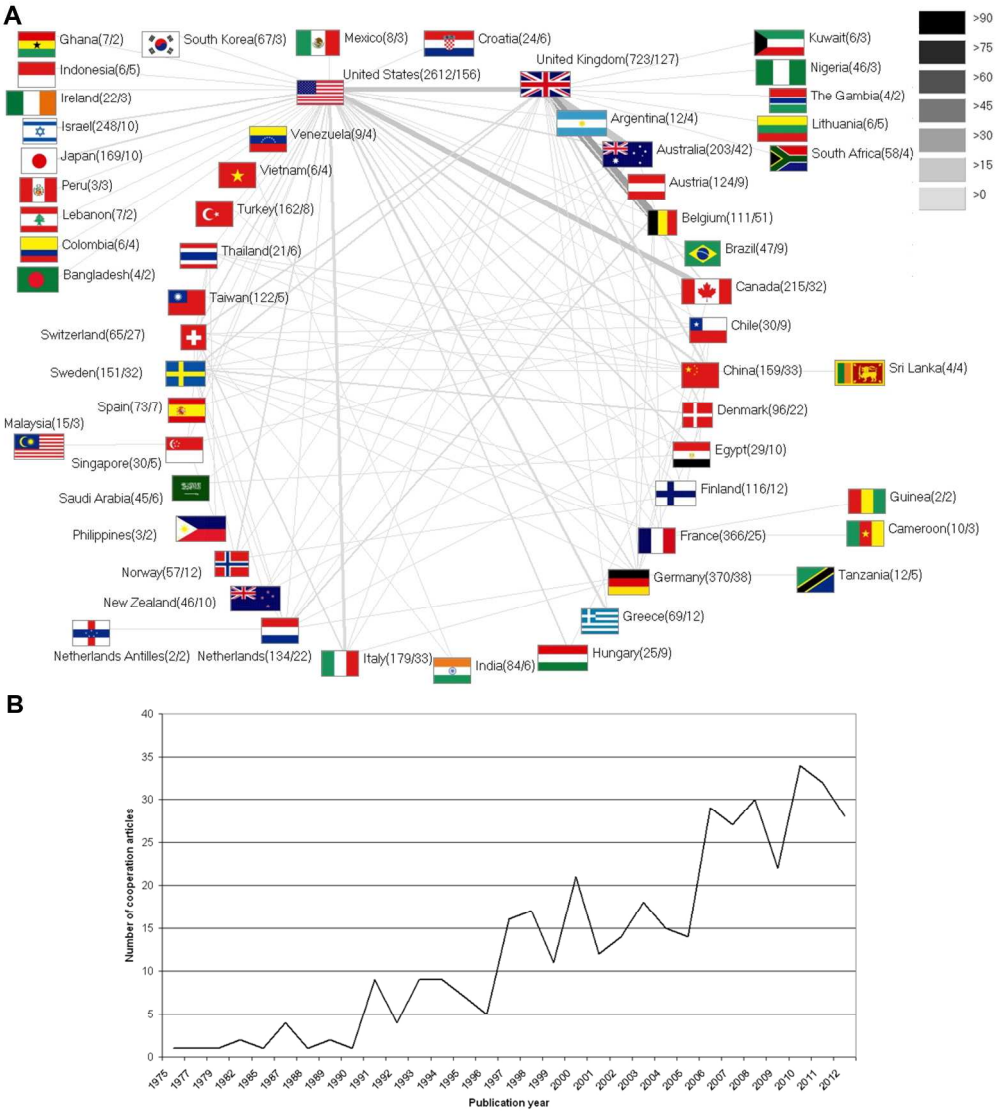
Publication output. A) Global Density-equalizing mapping of ectopic pregnancy publications. The area of each country is scaled in proportion to its total number of ectopic pregnancy-related publications. Colours encode numbers of ectopic pregnancy publications. B) Timely evolution of ectopic pregnancy-related publications.

250x260mm (300 x 300 DPI)



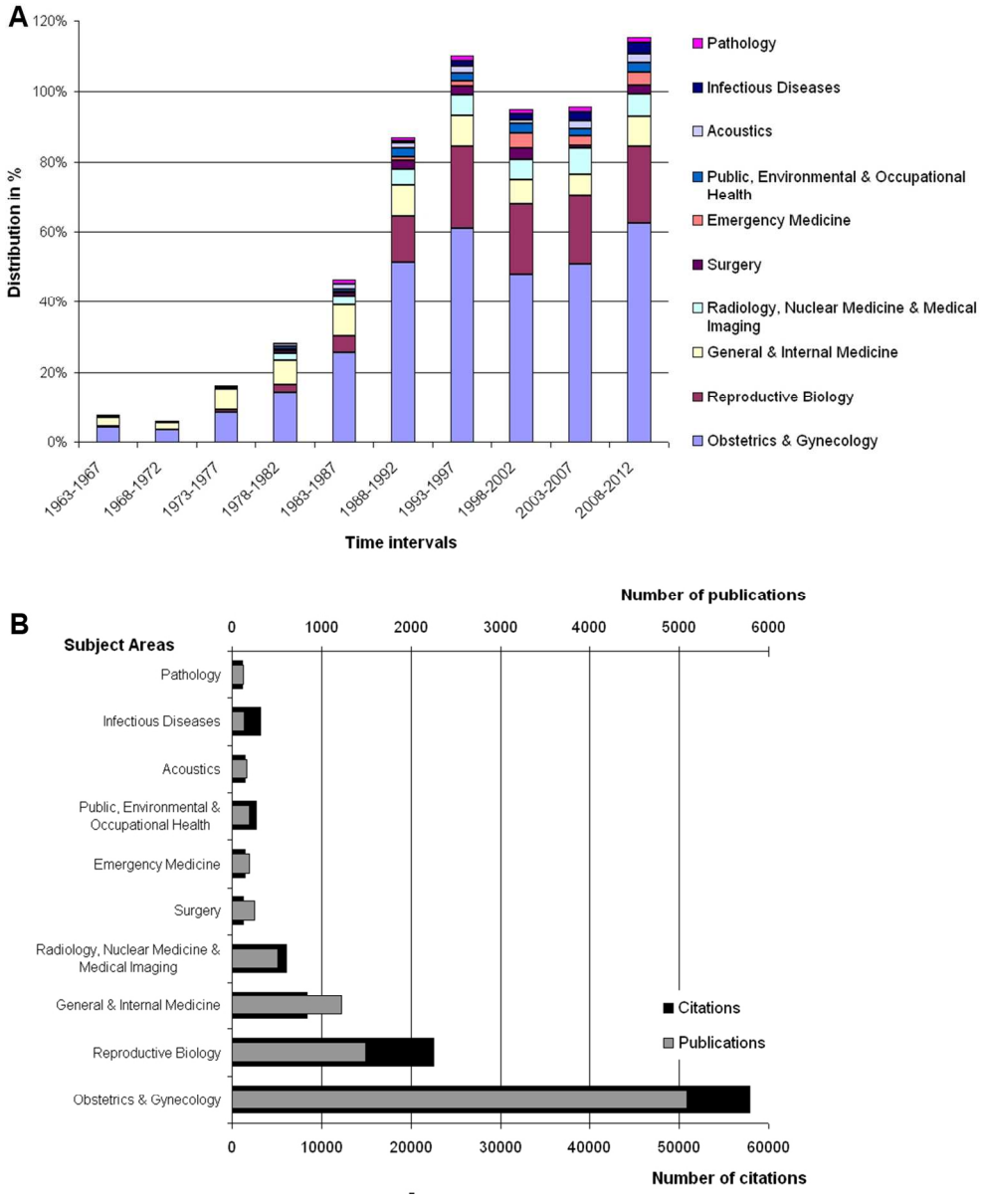
. Density-equalizing maps. A) Density-equalizing map of country total citations of ectopic pregnancy-related publications. The area of each country was scaled in proportion to its total number of ectopic pregnancy-related citations. Colours encode numbers of ectopic pregnancy-related citations. B) Density-equalizing map of country specific H-Index of ectopic pregnancy-related publications. The area of each country was scaled in proportion to the countries´ specific H-Index. C) Density-equalizing map of country specific citations per ectopic pregnancy-related publication. Colours encode ectopic pregnancy-related citation rate levels.

250x394mm (300 x 300 DPI)



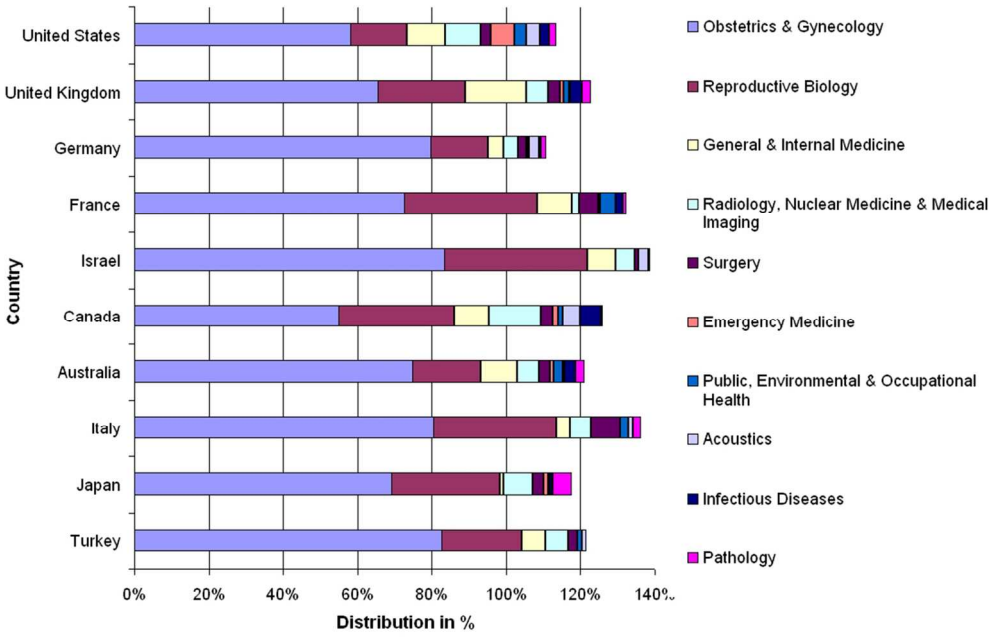
International collaboration. A) Net diagram of international ectopic pregnancy-related collaborations. Line width and grey scale encode numbers of ectopic pregnancy-related collaborations. Numbers in brackets indicate: (number of ectopic pregnancy-related publications of a specific country/number of ectopic pregnancy-related collaboration articles of a specific country). B) Timely evolution of number of ectopic pregnancy-related international collaborations per year.

250x279mm (300 x 300 DPI)



Subject area analysis. A) Timely evolution of subject areas assigned to the ectopic pregnancy-related publications in 5-year periods. Proportion of the 10 most assigned subject areas in 5-year intervals in order to gain insights into the field activity. B) Citation analysis of the 10 most assigned subject areas of all ectopic pregnancy-related publications.

150x181mm (300 x 300 DPI)



Country-specific analysis of assigned subject categories. Analysis was performed of the 10 most active countries in ectopic pregnancy research in order to identify regional differences in ectopic pregnancy research.

150x95mm (300 x 300 DPI)

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Ectopic pregnancy – exploration of its global research architecture using density-equalizing mapping and socioeconomic benchmarks

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Ectopic pregnancy – exploration of its global research architecture using density-equalizing mapping and socioeconomic benchmarks

Short title: Global architecture of ectopic pregnancy research

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ABSTRACT

Objective: About 2% of all pregnancies are complicated by the implantation of the zygote outside the uterine cavity and termed ectopic pregnancy. Whereas a multitude of guidelines exists and related research is constantly growing, no thorough assessment of the global research architecture has been performed yet. Hence, we aim to assess the associated scientific activities in relation to geographical and chronological developments, existing research networks and socio-economic parameters.

Design: retrospective, descriptive study

Setting: On the basis of the NewQIS platform, scientometric methods were combined with novel visualizing techniques such as density equalizing mapping to assess the scientific output on ectopic pregnancy. Using the Web of Science, we identified all related entries from 1900 to 2012.

Results: 8,040 publications were analyzed. The United States (US) and the United Kingdom (UK) were dominating the field in regards to overall research activity (2,612 and 723 publications), overall citation numbers and country-specific H-Indices (US: 80, UK: 42). Comparison to economic power of the most productive countries demonstrated that Israel invested more resources in ectopic pregnancy-related research than other nations (853.41 ectopic pregnancy-specific publications per 1000 Bio USD GDP), followed by the UK (269.97). Relation to the GDP per capita index revealed 49.3 ectopic pregnancy-specific publications per 1000 USD GDP per capita for the US in contrast to 17.31 for the UK. Semi-qualitative indices such as country-specific citation rates ranked Switzerland first (24.7 citations per ectopic pregnancy-

specific publication), followed by the Scandinavian countries Finland and Sweden. Low-income countries did not exhibit significant research activities.

Conclusions: This is the first in-depth analysis of global ectopic pregnancy research since 1900. It offers unique insights into the global scientific landscape. Besides the US and the UK, Scandinavian countries and Switzerland can also be regarded as leading nations with regard to their relative socioeconomic input.

KEY WORDS

ectopic pregnancy; density equalizing mapping; female health; reproduction biology

STRENGTH AND LIMITATIONS

- We compiled the first concise depiction of the worldwide scientific productivity related to ectopic pregnancies.
- The NewQIS platform was used to evaluate the scientific output regarding quantitative and qualitative aspects, geographical and chronological developments, existing research networks and socio-economic benchmarks. The method combines scientometric methods and "density equalizing mapping projections in a reliable and standardized way.
- The WoS focuses on English journals. It is a weakness that non-English articles are underrepresented in our analysis.
- We analysed citation-based parameters, which rather reflect the recognition of the research in the scientific community than truly measure quality.

INTRODUCTION

Around 2% of zygotes implant outside the uterine lining and form an ectopic gestation [1]. Frequently, the products of conception grow in the fallopian tube. Other implantation sites are the ovaries or the cervix. Affected patients may face significant morbidity or even mortality [1]. During the last decades, transvaginal ultrasound and beta-human chorionic gonadotropin (beta-HCG) levels became part of the clinical routine[2-6] leading to the timely detection of ectopic pregnancies and better patient outcomes [7-9]. First scientific publications describing therapeutic measures for ectopic pregnancies date back to the 16th century. Since then, thousands of studies tackled the most pressing questions in the field [1, 10-12]. Numerous discoveries improved diagnosis and management, and shaped the clinical guidelines we are using today [13]. Despite these hallmark advances in clinical care, ectopic pregnancies pose a significant burden on million women around the globe: In the United States of America (US) alone, costs related to the condition were estimated at around $1 billion in 1990 [14]. Although the mortality associated with ectopic gestations was halved in industrialized countries since the 1980s [15], the condition constitutes a major cause of death continents like Asia and Africa [16].

A multitude of disciplines such as OB/GYN, Family Medicine, Internal Medicine and Surgery are involved in the management of ectopic pregnancies. Also, related research attracts the interest of scientists worldwide addressing the issue from a clinical, basic science and Public Health perspective. To carry out research according to identified shortcomings, establish global networks and allocate funds, scientists and funding institutions have to be aware of the global scientific landscape related to ectopic pregnancy research. Thus, this study provides a first comprehensive assessment of the research performance in the field and identifies trends in the

related literature by a scientometric approach [17, 18]. Therefore, we identified all ectopic pregnancy-related publications indexed in the Web of Science until 2012. These items were (1) analysed in reference to their content and citations describing geographical and historical developments, (2) research networks were identified and (3) the country-specific productivity was related to socioeconomic variables. Furthermore, we present the most cited publications related to ectopic pregnancies. These studies cover key discoveries in the field and provide the scientific fundament for many clinical decisions made daily around the globe.

MATERIALS AND METHODS

NewQIS study protocol

We employed the 'New Quality and Quantity Indices in Science' (NewQIS) platform to assess global ectopic pregnancy research in a standardized, reliable and objective way [17, 18]. This tool combines scientometric techniques to assess scientific productivity and density equalizing mapping [19] to generate global maps according to analysed parameters [20-23].

Data source

The database Web of Science (WoS, Thomson Scientific) was used to conduct this study. We selected this data source because it allows the assessment of publication activity similar to the PubMed database, but facilitates a thorough citation analysis for the research in focus [24, 25].

Search strategy

The following search term was used: *"ectopic pregnanc*" OR "ovarian pregnanc*" OR "cervical pregnanc*" OR "tubal pregnanc*" OR "abdominal pregnanc*" OR "extrauterine pregnanc*" OR "ectopic gestation*" OR "ovarian gestation*" OR "cervical gestation*" OR "tubal gestation*" OR "abdominal gestation*" OR "extrauterine gestation*"*. We performed a "Topic" search, and the term was inserted into the WoS search fields "title", "abstract" and "key words" to identify the total number of published items related to ectopic pregnancies.

Timeframe

The analysed timeframe for research on ectopic pregnancy encompassed the years between 1900 (01-01) and 2012 (31-12). Results from 2013 onwards were not considered due to incomplete data acquisition (i.e. citation rate) at the time the study was performed.

Data analysis and categorization

Metadata were retrieved in Plain Text Format (S1 File) as described in previously published NewQIS studies [26, 27]. Bibliometric details were analysed with respect to quantitative and semi-qualitative aspects such as originating countries, languages, journals, citations, cited references, year published and subject areas. Subject area categories are assigned to every journal and its publications by the Journal Citation Reports (provided by the Institute of Scientific Information) during the publication

process. These standard categories can be retrieved via WoS. For our analyses, these original WoS categories have been used.

As semi-qualitative items describing the recognition of publications by the scientific community, the number of citations, citation rates and the modified H-Indices (HI) were investigated, as previously described [28]. Therefore, the citation numbers were retrieved for each publication and the average citations per item (citation rate) were calculated. Regression analysis was used to investigate the timely evolution of ectopic pregnancy research.

After the transformation of the raw data to excel program charts and analysis, the findings were illustrated in numerous diagrams and visualized by the use of density-equalizing mapping projections (DEMP). The algorithm for this procedure was published by Gastner and Newman [19]. In DEMPs, the territories of the different countries were resized in proportion to our selected variables such the distribution of country-specific numbers of published items, average citation rates and H-Indices.

Socioeconomic analysis

In order to assess research output with regard to the economic power of the most active countries, the publication activity was related to the Gross Domestic Product (GDP) and the GDP per capita in current USD, as described earlier [29]. According to the World Bank, the GDP at purchaser's prices is the sum of gross value added by all resident producers in the economy plus any product taxes and minus any subsidies not included in the value of the products. It is calculated without making deductions for depreciation of fabricated assets or for depletion and degradation of natural resources. Data are in current U.S. dollars. Dollar figures for GDP are converted from

domestic currencies using single year official exchange rates. For a few countries where the official exchange rate does not reflect the rate effectively applied to actual foreign exchange transactions, an alternative conversion factor is used (http://data.worldbank.org/indicator/NY.GDP.MKTP.CD).

The GDP per capita is defined as gross domestic product divided by midyear population. GDP is the sum of gross value added by all resident producers in the economy plus any product taxes and minus any subsidies not included in the value of the products. It is calculated without making deductions for depreciation of fabricated assets or for depletion and degradation of natural resources. Data are in current U.S. dollars (http://data.worldbank.org/indicator/NY.GDP.PCAP.CD).

Analysis of international ectopic pregnancy research collaborations

To investigate international research collaborations, the affiliations of all identified ectopic pregnancy-related publications were screened as described earlier [30, 31]. In brief, if at least two authors, who were working in different countries, contributed to one ectopic pregnancy-related publication, this relationship was defined as a collaborative publication. To visualize the productivity of collaborations for each pair of countries, a vector was calculated. Its line width and shade of grey is proportional to the number of depicted collaborations [24, 32].

RESULTS

Global ectopic pregnancy research activity

We identified 8,040 ectopic pregnancy-related publications issued from 1900 to 2012; these were cited 86,680 times. 92.4% of these items were written in English and published by researchers from 76 different countries. US-American researchers authored 2612 publications accounting for 32% of all ectopic pregnancy-related publications. The US was identified as the country with the highest number of publications worldwide (Fig 1A). The United Kingdom (UK) was positioned second with 723 ectopic pregnancy publications, followed by Germany (370 publications), France (366 publications), Israel (248 publications), Canada (215 publications), Australia (203 publications), Italy (179 publications), Japan (169 publications), Turkey (162 publications), China (159 publications), Sweden (151 publications), the Netherlands (134 publications), Austria (124 publications) and Taiwan (122 publications). Since North America, Western Europe and Australia were responsible for the majority of research output associated with “ectopic pregnancy”, their country sizes appear inflated in the DEMP-analysis (Fig 1A). Major parts of Asia (except China and Taiwan), Russia, Africa and South America occupied only small areas on the cartogram. The analysis of the timely evolution led to a regression coefficient of 0.6793 for the period from 1900 until 2012 and of 0.8105 for the period from 1970 until 2012 (Fig 1B). This indicated a strong increase of global research activity in the past 40 years.

Socioeconomic analysis of ectopic pregnancy research

In order to assess the relative magnitude of the countries research activities in relation to their economic wealth, the two indicators GDP and GDP per capita were used for our evaluation. The analysis of publication activity in relation to the most productive countries´ GDP demonstrated that Israel published the highest amount of

ectopic pregnancy-specific research relative to its GDP: 853.41 publications per 1000 bn USD GDP. It was followed by the UK with 269.97 ectopic pregnancy-specific publications per 1000 bn USD GDP, Turkey (196.79 publications per 1000 bn USD GDP) and the US (155.77 publications per 1000 bn USD GDP) (Table 1).

When the ectopic pregnancy publication activity was related to the GDP per capita, the US again gained the leading position with a level of 49.3 ectopic pregnancy specific publications per 1000 USD GDP per capita. This benchmarking largely resembled the total publication activity analysis with the exception of Turkey, which climbed from tenth to third position due to its extremely low GDP per capita (Table 1).

Table 1. Socio-economic analysis of ectopic pregnancy research of the ten most active countries. Sources for GDP and GDP per capita in 2013: http://data.worldbank.org/indicator/NY.GDP.PCAP.CD

Country	Number of publications	GDP in 1000 bn US-$	Publications / GDP in 1000 bn US-$	GDP per capita in 1000 US-$	Publ. / GDP per Capita in 1000 US-$
Israel	248 (5)	0.2906 (10)	853.41 (1)	36.05 (8)	6.88 (6)
United Kingdom	723 (2)	2.6781 (5)	269.97 (2)	41.78 (6)	17.31 (2)
Turkey	162 (10)	0.8232 (9)	196.79 (3)	10.99 (10)	14.75 (3)
United States	2612 (1)	16.7681 (1)	155.77 (4)	52.98 (2)	49.30 (1)
France	366 (4)	2.8102 (4)	130.24 (5)	42.63 (5)	8.59 (4)
Australia	203 (7)	1.5604 (8)	130.09 (6)	67.47 (1)	3.01 (10)
Canada	215 (6)	1.8389 (7)	116.92 (7)	52.31 (3)	4.11 (9)
Germany	370 (3)	3.7303 (3)	99.19 (8)	46.26 (4)	8.00 (5)

Italy	179 (8)	2.1369 (6)	83.77 (9)	35.48 (9)	5.05 (7)
Japan	169 (9)	4.9195 (2)	34.35 (10)	38.63 (7)	4.37 (8)

Global citation analysis

Citation analysis of all country-specific publications demonstrated a leading position of the US. US-American publications dedicated to ectopic pregnancy research received a total of 39,404 citations (Fig. 2A). It was followed by the UK with over 8,000 citations, France (4,423 citations), Canada (3,578 citations), Israel (3,057 citations) and Sweden (3,349 citations). DEMP analysis regarding the citation activity was similar to the cartogram reflecting absolute publication numbers: The map represents nearly no citations for African, South American or Asian countries leading to a minimized appearance of these areas whereas North America and Europe are depicted increased in size (Fig 2A).

The calculation of the country-specific H-Index (Fig 2B) showed a leading position of the US with 80 ectopic pregnancy-related publications being cited at least 80 times. The US was followed by the UK with a country-specific H-Index of 42, Canada (H-Index: 36), France (H-Index: 35), Israel (H-Index: 31), Sweden (H-Index: 30), Finland (H-Index: 29), the Netherlands (H-Index: 29), Belgium (H-Index: 25) and Germany (H-Index: 25). Again, countries from Africa, Eastern Europe, Latin America or Russia exhibited very low rates.

The results of the country-specific citation rate (Fig 2C) contrasted all other benchmarks since Switzerland ranked first with a citation rate (CR) of 24.7, followed by the Scandinavian countries Finland and Sweden with CR of 20.9 and 20.2, respectively.

Cooperation articles

Out of the 8,040 ectopic pregnancy-related publications, only 397 were published within international collaborations. This equates a relatively small percentage of 4.9%. With 82.1% (326 publications), bilateral collaborations were the most common type of established collaborative efforts, followed by trilateral (51) co-operations. The US was the leading country with 156 collaborations followed by the UK with 127 international relationships. The most frequent bilateral collaboration was set up between the UK and Belgium with 37 joint studies. Interestingly, 51 out of the 111 total studies from Belgium arose from international collaborations, which equals a percentage of 45.9% (Fig 3A). In comparison, the US was characterized by a ratio of 156 collaborative publications out of 2,612 (6%), the UK by 17.6% and Germany by 10.3%. A continuous increase in the numbers of collaborations was present until 2010 with 34 collaborative publications in this year (Fig 3B).

Subject area analysis

The timely evolution in subject categories of ectopic pregnancy-related publications was analysed since 1973 and the proportion of the different subject areas was investigated (Fig 4A). Articles can be assigned to more than one category, hence percentages of more than 100 were possible. From the beginning until 2012, “Obstetrics & Gynecology“ remained the most prominent category. “Reproductive Biology” gained importance after 1988. The field diversified in 1978 when research was also published in the categories of “Emergency Medicine” (since 1978) and “Pathology” (since 1983). Overall, the percentages of all assigned subject categories

remained relatively constant with no rapid increase of one particular area within the past 20 years. A small but constant proportion of publications was attributed to the area of “Public, Environmental & Occupational Health”, which indicates that scientists also focused upon Public Health issues related to ectopic pregnancy.

We identified the leading, most impactful publication categories based on item and citation count (Fig 4B). The primary areas of ectopic pregnancy-research were “Obstetrics & Gynecology” and “Reproductive Biology”. The 5,100 publications assigned to “Obstetrics & Gynecology” were cited 57,879 times. “Reproductive Biology” with 1,496 publications was cited 22,545 times. When citation rates were analysed, the highest rate was present for the subject area “Infectious Diseases” with 24.02 citations per ectopic pregnancy-related publication. The frequently assigned subject areas “Reproductive Biology” and “Obstetrics & Gynecology” were characterized by citation rates of 15.07 and 11.37 respectively.

We performed a subject area analysis for the most productive countries aiming to pinpoint the particular focus researchers are working on in these nations: In France, a high volume of “Public Health”-related work was published. This finding underlines the nation’s interest to allocate considerable resources to Public Health issues in context with ectopic pregnancies. A relatively high percentage of Public Health-related ectopic pregnancy research originated from the US when compared to other countries, e.g. Japan. Also, US-American scientists focused more on emergency medicine aspects of ectopic pregnancy research than researchers from all other countries. This is reflected by a high percentage of allocated publications originating from the US to that category (Fig 5). Also, we identified the key publications in the field of ectopic pregnancy research, which were cited 200 times or more (Table 2).

Table 2. Key publications in the field of ectopic pregnancy research. These articles were published since 1900 and cited 200 times or more.

Title	Publication Year	Country	Citations	Journal
WHO analysis of causes of maternal death: a systematic review *Khan KS et al.* [33]	2006	Switzerland, United Kingdom, Argentina	534	LANCET
Comparative genomes of Chlamydia pneumoniae and C-trachomatis *Kalman S et al.* [34]	1999	United States	457	NAT GENET
Pelvic inflammatory disease and fertility *Weström L et al.* [35]	1992	United States	347	SEX TRANSM DIS
Genital chlamydial infections - epidemiology and reproductive sequelae *Cates W et al.* [36]	1991	United States	345	AM J OBSTET GYNECOL
Current methods of laboratory diagnosis of Chlamydia	1997	United States	293	CLIN MICROBIOL

trachomatis infections *Black CM et al.* [37]				REV
Prevalence of chlamydial and gonococcal infections among young adults in the United States *Miller WC et al.* [38]	2004	United States	270	JAMA-J AM MED ASSN
The epidemiology of smoking during pregnancy *Cnattingius S* [39]	2004	Sweden	250	NICOTINE TOB RES
Single-dose methotrexate - an expanded clinical-trial *Stovall TG and Ling FW* [40]	1993	United States	238	AM J OBSTET GYNECOL
A method of screening for ectopic pregnancy and its indications *Kadar N et al.* [41]	1981	United States	235	OBSTET GYNECOL
Maternal age and fetal loss: population based register Linkage study *Nybo Andersen AM et al.* [42]	2000	Denmark	234	BRIT MED J
Treatment of interstitial ectopic pregnancy with methotrexate - report of a successful case *Tanaka T et al.* [43]	1982	Japan	233	FERTIL STERIL
Discriminatory HCG zone - its use in the sonographic evaluation for ectopic pregnancy *Kadar N et al.* [44]	1981	United States France	229	OBSTET GYNECOL
Conservative laparoscopic treatment of 321 ectopic pregnancies *Pouly JL et al.* [45]	1986	France	228	FERTIL STERIL
Incidence, trends, and risks of ectopic pregnancy in a population of woman *Westström L et al.* [46]	1981	Sweden	214	BRIT MED J
Early termination of pregnancy with mifepristone (RU-486) and the orally active prostaglandin misoprostol *Peyron R et al.* [47]	1993	France	216	N ENGL J MED

Journal analysis

We carried out an analysis of the most publishing journals in the field of ectopic pregnancy research (Fig. 6). Here, “Fertility and Sterility” published the most articles on ectopic pregnancy (689 publications), followed by the “American Journal of Obstetrics and Gynecology” (653 publications), “Obstetrics and Gynecology” (466 publications), and “Human Reproduction” (396 publications). These four journals belong to the top ranked journals in Gynecology and Obstetrics with impact factors more than 4.5. Regarding the average citation rate among the 15 most publishing journals, “Obstetrics and Gynecology” received the highest rate with 20.5 citations per article (CR = 20.5). We found the “British Journal of Obstetrics and Gynecology” (CR = 17.3) in second position. It was ranked 14th regarding the total number of publications (95 publications). It existed until 2012 and was continued as “International Journal of Gynecology and Obstetrics” that ranked 8th regarding total publication numbers (166 publications) and reached an average citation rate of 5.93. Actually, the publication performance of both journals should be summed up, resulting in 261 publications and a CR = 10.05.

Regarding the CR, “Human Reproduction” was positioned third (CR = 16.9) and was ranked before the “Lancet” (CR = 14.4 and 129 publications). Among the 15 most publishing was only one non-English journal – the German journal “Geburtshilfe und Frauenheilkunde” (ranked 9th with 156 publications on ectopic pregnancy and a CR = 3.1). It is the official publication platform of the German Society of Gynecology and Obstetrics. Among the 15 most publishing journals, 7 are published in the UK, 4 in the US, 2 in Germany and 1 in Australia and Scandinavia, respectively.

DISCUSSION

Accounting for a percentage of 2% of all first-trimester pregnancies in the US, ectopic gestation is a very common complication of pregnancy. It should therefore merit a high degree of interest within the scientific community. Hence, this NewQIS study [17, 18] is focused on this condition and presents the first multifaceted analysis of the related global research architecture using density equalizing mapping analysis tools [19]. Additionally, we selected 15 “publication classics” that were defined as key articles in the field based on 200 and more citations. These key publications provide relevant background information for individual scholarship, practice and research endeavours.

In total, we analysed 8,040 publications related to ectopic pregnancies. The US was identified as the country dominating the field. With regard to total publishing activities, it is important to compare ectopic pregnancy research to other disease entities or to the field of OB/GYN in general: A recent study by Aleixandre-Benavent et al. focused on trends in reproductive medicine research over a period of 10 years [48]. It was the authors’ objective to study the publication activity metrics from 2003 to 2012 and to shed a light on the clinical, social, and epidemiologic implications of this relatively new but rapidly emerging field. As outcome measures, they analysed most productive and frequently cited investigators, institutions, and countries as well as specific areas of research and scientific collaborations. The authors found that 90 investigators with more than 1,000 citations had jointly published 4,010 articles. The most-cited study groups were located in the Netherlands, Belgium, Spain, the US, and the UK, and collaborative studies have been increasing. It was concluded that reproductive medicine research has attained scientific interest and importance. Also,

the increase in (inter)national collaborations seems to be the key to the field's success. In contrast to Aleixandre-Benavent et al., we focused on a single disease entity and encompassed more than one hundred years of research. Besides monitoring the scientific output, we also related the numbers to the economic power of investigated countries in order to dissect the real interest of single nations in research related to a particular condition. Therefore, we related the ectopic pregnancy-related research activities to the total GDP and the GDP per capita. We found that the US still dominated when GDP per capita index was used. However, when related to the total GDP index, Israel exhibited the highest contribution of ectopic pregnancy research in relation to its overall economic power.

We compared the present data to other OBGYN entities such as polycystic ovary syndrome (PCOS) or ovarian cancer [49, 50]: A published study on PCOS that covered the years between 1900 and 2014 reported a total of 6261 PCOS-specific publications and 703 international research collaborations in the Web of Science. As in the present study, the USA was identified as the most active country in total and collaborative research activity [49]. In the socioeconomic analysis, the USA was also ranked first concerning PCOS-related publications per gross domestic product, followed by the UK, Italy and Greece [49]. For ovarian cancer research 23,378 reports were identified for the period 1900 - 2014. Denmark was positioned at the first place with a total of 1293.2 calculated ovarian cancer-specific articles per 1000 billion US-$ GDP [50]. Other gynecological topics, which have been screened for scientific productivity, were predominantly related to breast cancer [51-54]: Glynn et al. presented an in-depth evaluation of breast cancer research. The authors screened publications from 1945 to 2008 also using the NewQIS platform [54]. They identified 180,126 breast cancer-associated items; these had been cited 4,136,224 times. In comparison to our

data on ectopic pregnancies encompassing a time span of 112 years, breast cancer research has produced a more than 20 times greater scientific output in a period of slightly over 60 years. One reason for this discrepancy is that breast cancer accounts for the most common malignancy among women, with an estimated 231,840 new cases diagnosed in the US in 2015 alone [55]. Hence, this disease receives large amounts of public awareness. Also, significant volumes of scientific resources are allocated to support research in this area. In breast cancer, the US produced the greatest publication output (n = 77,101; 42.8%), followed by the UK (n = 18,357; 10.2%) and Germany (n = 12,529, 7%) [54]. This ranking of the most productive nations was similar to ectopic pregnancy research with 32.5% ectopic pregnancy-related publications originating from the US, around 9% from the UK and 4.6% from Germany. The percentage of total global research activity exhibited by US-American institutions is higher in breast cancer research than in ectopic pregnancy research.

"Smoking in pregnancy" is another area of OB/GYN research that was studied [56]. Here, 10,043 related publications were identified in a period from 1900 to 2012. As in our investigation and the presented breast cancer study, the highest number of scientific works was published by the US (35.5%), followed by the UK (9.9%). For both countries, we documented similar percentage values and the highest modified H-Indices of 128 (US) and 42 (UK) for ectopic pregnancy research activities. When citation performance is compared, it is evident that research in "smoking and pregnancy" receives a higher attention in the scientific community than scientific endeavours related to "ectopic pregnancy" since the 10,043 publications in the field of "smoking and pregnancy" were cited 112,136 times (11.2 citations per publication) versus 8,040 ectopic pregnancy-related publications that received 86,680 citations (10.8 citations per publication).

In our study, the US occupied the top position among all countries in regards to overall publication and citation numbers as well as the H-index. We explain this finding with the outstanding research environment and funding provided for scientists in the US. Further, we hypothesize that the prominent position of the US might also be linked to a possible bias: Four of the most prolific journals in the field are based in the US; they provide an impactful publishing platform for ectopic pregnancy research (as shown in our journal analysis). US-American reviewers are known for their favourable evaluation of publications submitted by local researchers leading to a predominance of US-American works among the accepted manuscripts [57, 58]. But we regard this "reviewer bias" overall as limited since it can be stated that the observed dominance of the US is also common in other, non-OB/GYN medical specialties. In a study that analysed 5,527,558 published items authored in all areas of medicine over the last 50 years, the following ranking of total research activity was found [59]: The US was the leading nation, followed by Japan, Germany, the UK, France, and Italy [59]. Furthermore, it can be clearly stated that Japan does not exhibit comparable activities in the field of ectopic pregnancy research with only 169 publications in the present set of data. This finding could be linked to a lower prevalence of ectopic pregnancies in Japan compared with other nations translating into disregard of the topic among local scientists and funding institutions. However, epidemiological data on the exact rates of ectopic pregnancies or pelvic inflammatory disease in Japan are lacking. Also, data on maternal mortality attributed to ectopic pregnancies are sparse. For the early nineties, ectopic pregnancy-related maternal mortality was reported at 4% in Japan compared to 13% in the US (data collected until 1989) [60, 61]. Since this difference could indeed reflect a lower impact of ectopic pregnancies on the public health of Japanese women, this fact may explain a lacking interest of Japanese institutions to foster research on this topic.

We identified a small number of international collaborations in the field of ectopic pregnancy research. The rate of 4.9% is substantially lower than in other fields. Additionally, we documented a very small number of ectopic pregnancy-related publications investigating Public Health aspects. These findings indicate a low awareness of this subject matter in terms of ectopic pregnancy research, which is contrasting the major disease burden this condition poses on women - especially in low-income countries with high rates of pelvic inflammatory diseases and only limited access to diagnostic and treatment procedures. Therefore, future research should pay attention to these problematic issues and focus on fostering collaborative efforts, involving developing countries in research networks and conducting projects in the field of Public Health.

CONCLUSIONS

The present study is the first combined economic and scientometric study that depicts a sketch of the global research activities on ectopic pregnancies. With regard to other disease entities, it can be stated that a mere total of about 8000 related publications highlights the need to foster research programs on this problematic condition that endangers female health and human reproduction biology all around the globe. The lack of research productivity in low-income countries and their missing presence in international collaborations also exemplifies the need for Public Health approaches to help women in these parts of the world.

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AUTHORS' CONTRIBUTIONS

DB, JK, DQ, MHB, DK, FL, JJ, and DAG have made substantial contributions to the conception and design of the study, acquisition of the data and interpretation. They have been involved in drafting and revising the manuscript. All authors have read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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SUPPORTING INFORMATAION

S1 File. **Raw data used in analysis**. For our study, metadata were retrieved in Plain Text Format to establish an interim database, which was used to sort and analyse bibliometric data in regards to variables of interest.

FIGURE LEGENDS

Fig 1. Publication output. A) Global Density-equalizing mapping of ectopic pregnancy publications. The area of each country is scaled in proportion to its total number of ectopic pregnancy-related publications. Colours encode numbers of ectopic pregnancy publications. B) Timely evolution of ectopic pregnancy-related publications.

Fig 2. Density-equalizing maps. A) Density-equalizing map of country total citations of ectopic pregnancy-related publications. The area of each country was scaled in proportion to its total number of ectopic pregnancy-related citations. Colours encode numbers of ectopic pregnancy-related citations. B) Density-equalizing map of country specific H-Index of ectopic pregnancy-related publications. The area of each country was scaled in proportion to the countries´ specific H-Index. C) Density-equalizing map of country specific citations per ectopic pregnancy-related publication. Colours encode ectopic pregnancy-related citation rate levels.

Fig 3. International collaboration. A) Net diagram of international ectopic pregnancy-related collaborations. Line width and grey scale encode numbers of ectopic pregnancy-related collaborations. Numbers in brackets indicate: (number of ectopic pregnancy-related publications of a specific country/number of ectopic pregnancy-related collaboration articles of a specific country). B) Timely evolution of number of ectopic pregnancy-related international collaborations per year.

Fig 4. Subject area analysis. A) Timely evolution of subject areas assigned to the ectopic pregnancy-related publications in 5-year periods. Proportion of the 10 most assigned subject areas in 5-year intervals in order to gain insights into the field activity. B) Citation analysis of the 10 most assigned subject areas of all ectopic pregnancy-related publications.

Fig 5. Country-specific analysis of assigned subject categories. Analysis was performed of the 10 most active countries in ectopic pregnancy research in order to identify regional differences in ectopic pregnancy research.

Fig 6. Number of articles and average citation rate of the most publishing journals on ectopic pregnancy.

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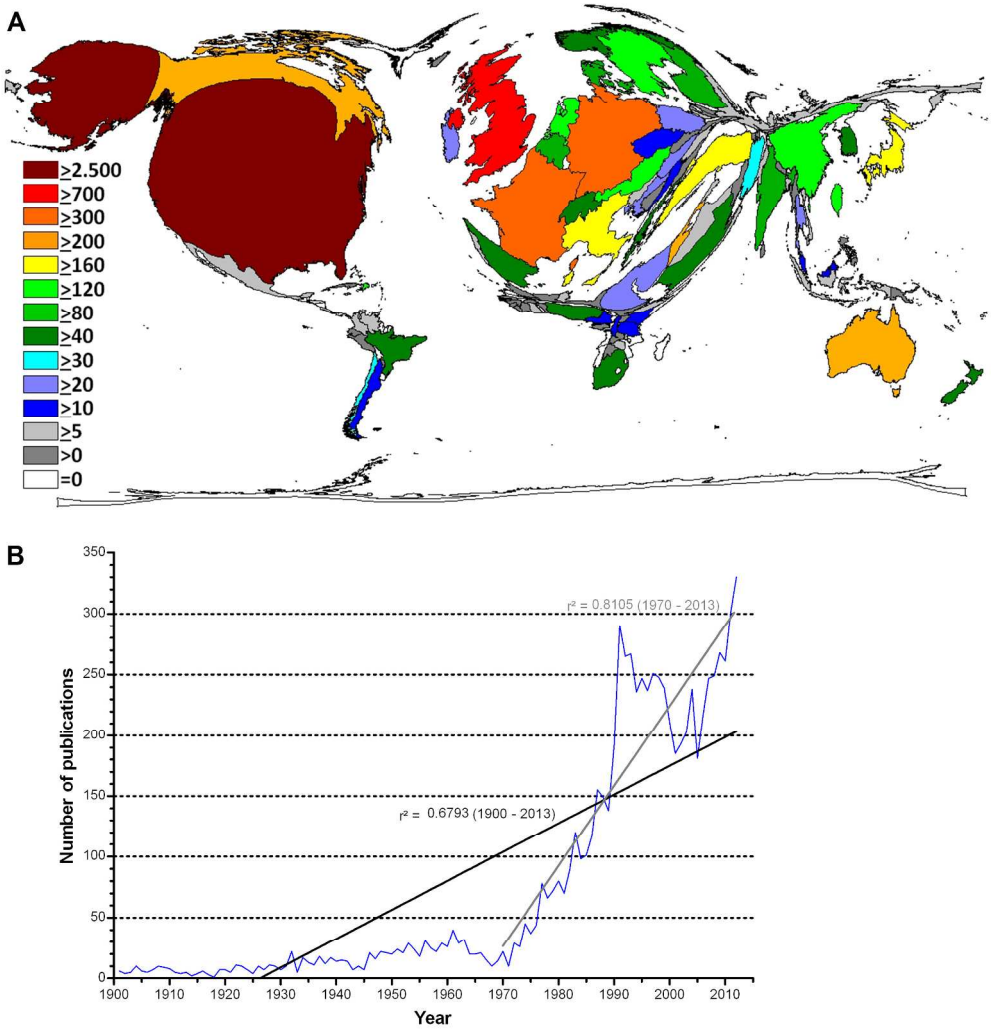
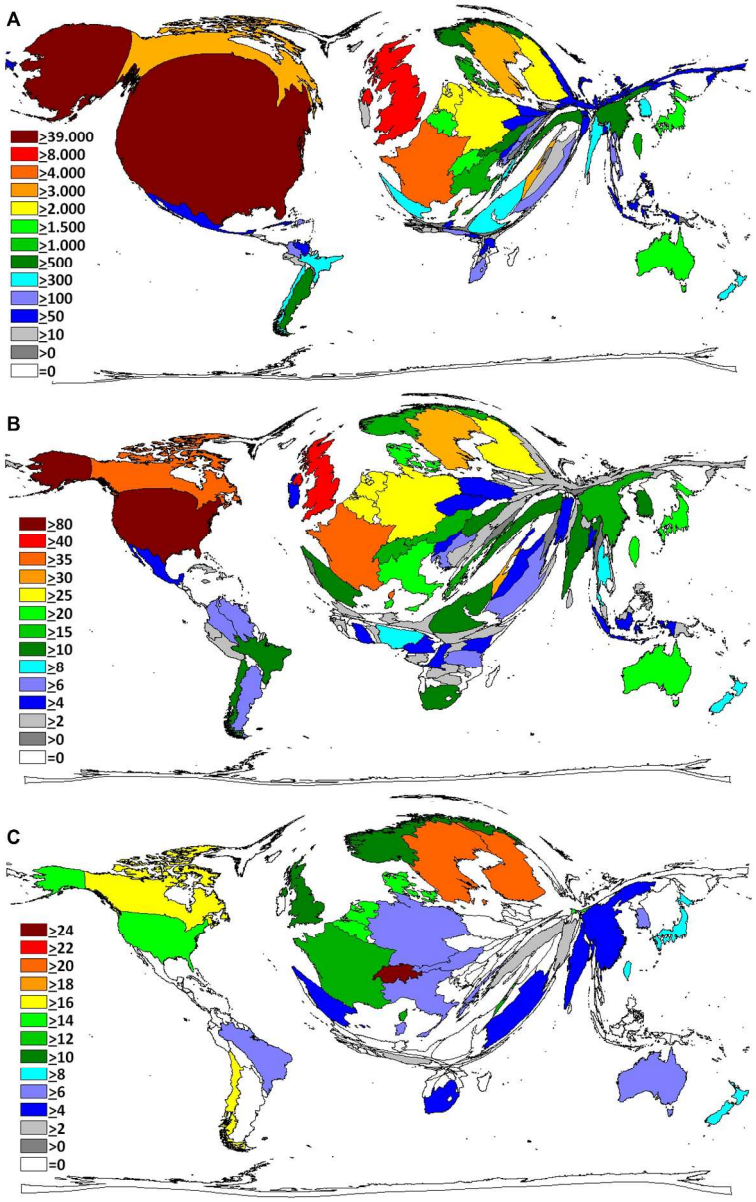


Publication output. A) Global Density-equalizing mapping of ectopic pregnancy publications. The area of each country is scaled in proportion to its total number of ectopic pregnancy-related publications. Colours encode numbers of ectopic pregnancy publications. B) Timely evolution of ectopic pregnancy-related publications.

250x260mm (300 x 300 DPI)



. Density-equalizing maps. A) Density-equalizing map of country total citations of ectopic pregnancy-related publications. The area of each country was scaled in proportion to its total number of ectopic pregnancy-related citations. Colours encode numbers of ectopic pregnancy-related citations. B) Density-equalizing map of country specific H-Index of ectopic pregnancy-related publications. The area of each country was scaled in proportion to the countries´ specific H-Index. C) Density-equalizing map of country specific citations per ectopic pregnancy-related publication. Colours encode ectopic pregnancy-related citation rate levels.

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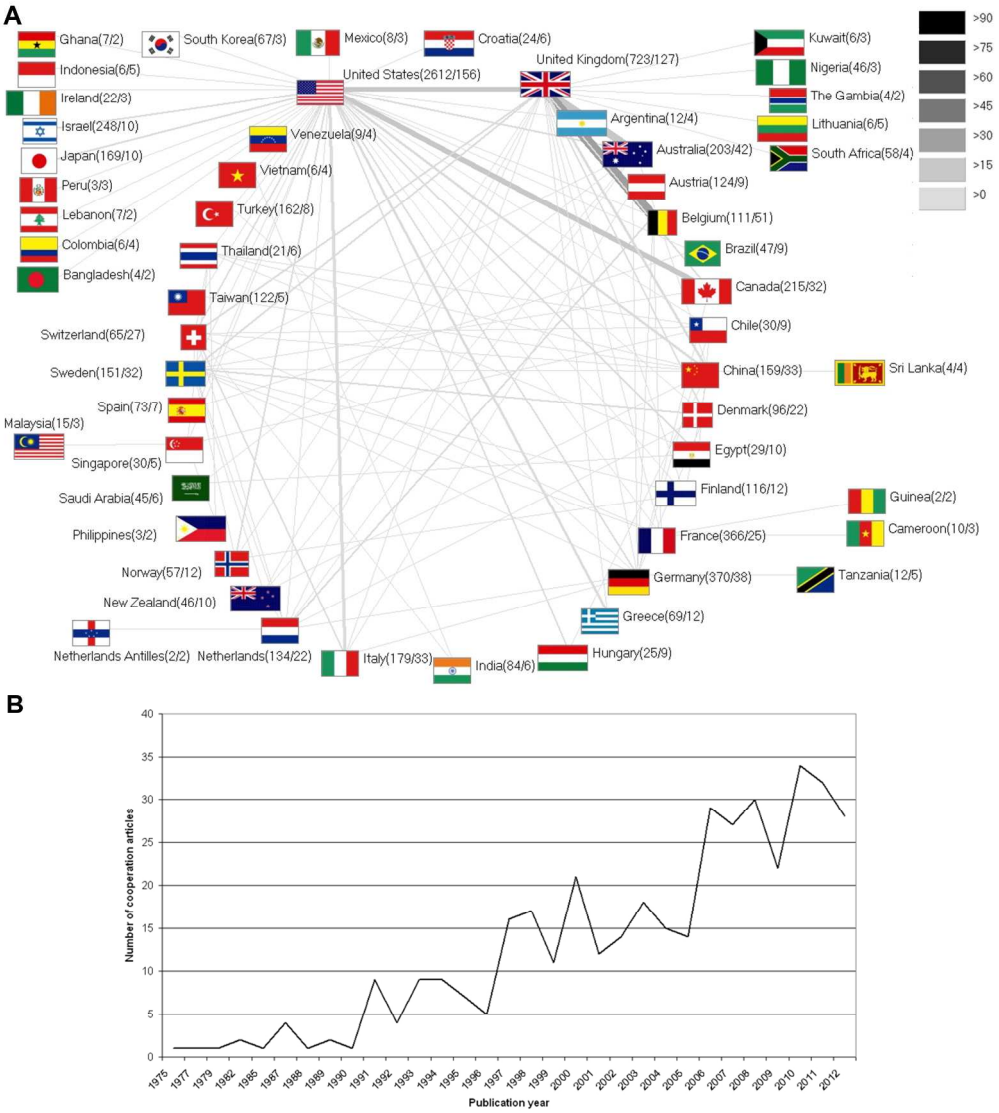

International collaboration. A) Net diagram of international ectopic pregnancy-related collaborations. Line width and grey scale encode numbers of ectopic pregnancy-related collaborations. Numbers in brackets indicate: (number of ectopic pregnancy-related publications of a specific country/number of ectopic pregnancy-related collaboration articles of a specific country). B) Timely evolution of number of ectopic pregnancy-related international collaborations per year.

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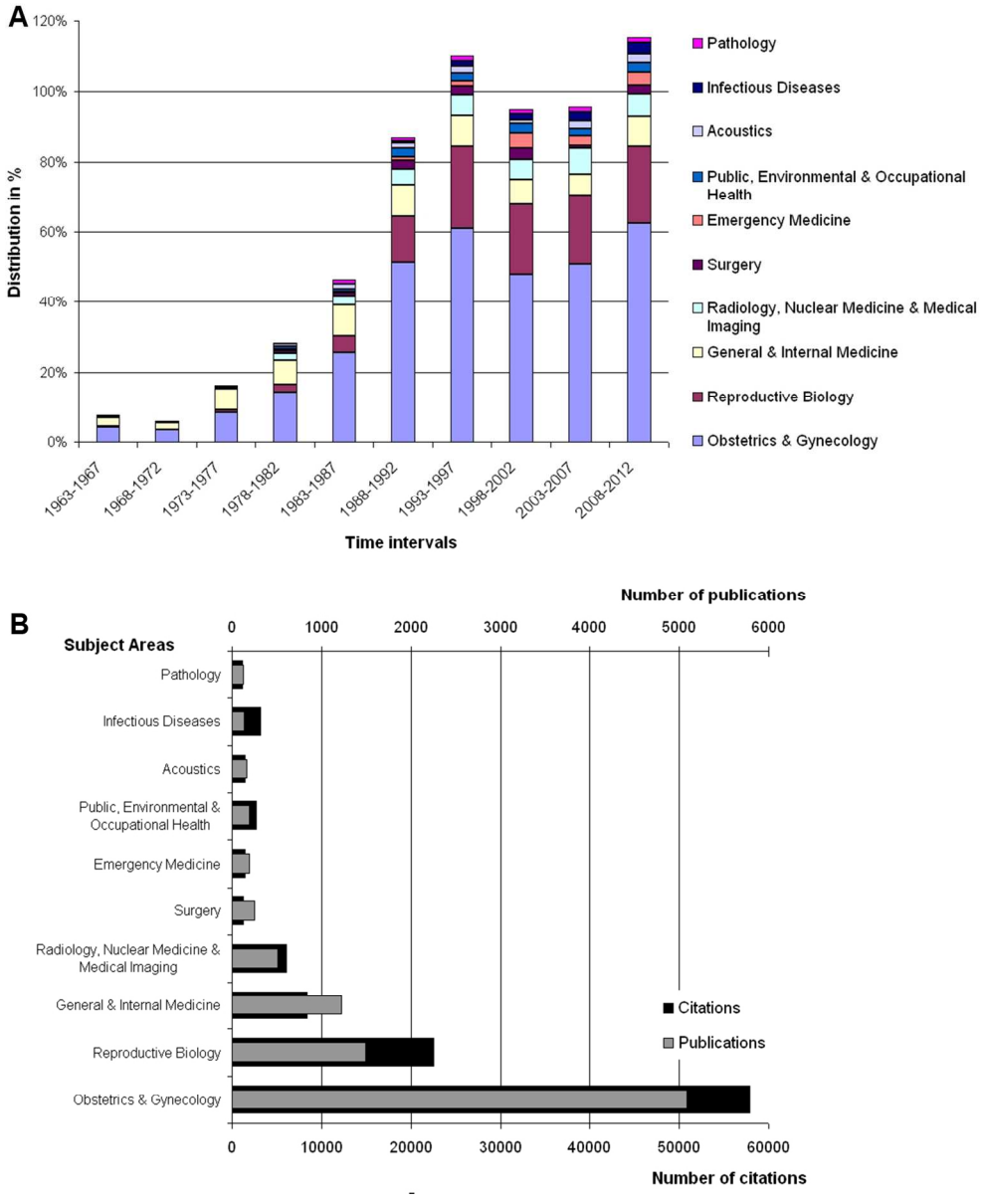
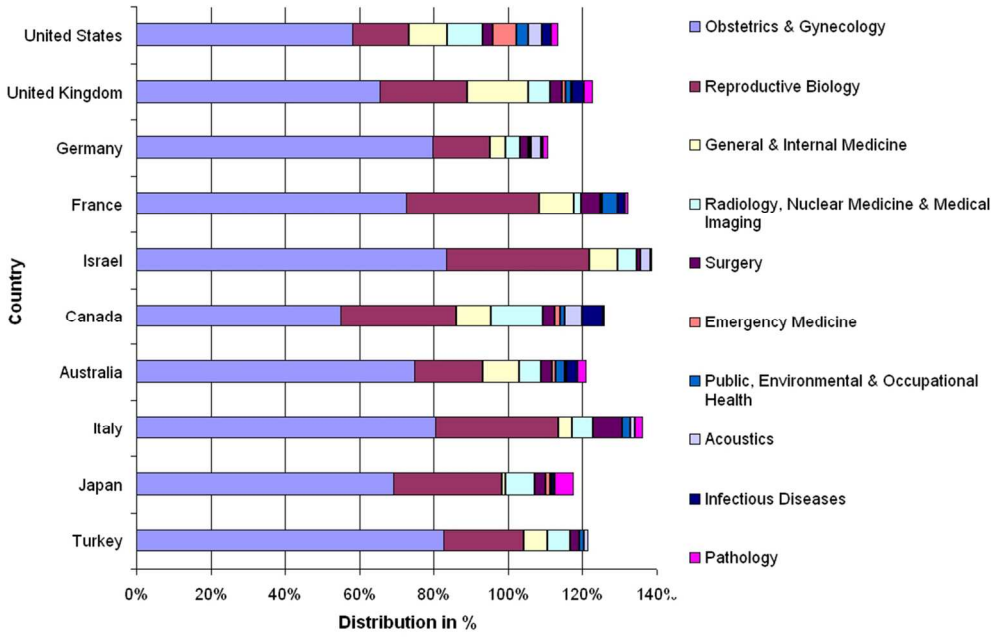


Subject area analysis. A) Timely evolution of subject areas assigned to the ectopic pregnancy-related publications in 5-year periods. Proportion of the 10 most assigned subject areas in 5-year intervals in order to gain insights into the field activity. B) Citation analysis of the 10 most assigned subject areas of all ectopic pregnancy-related publications.

150x181mm (300 x 300 DPI)



Country-specific analysis of assigned subject categories. Analysis was performed of the 10 most active countries in ectopic pregnancy research in order to identify regional differences in ectopic pregnancy research.

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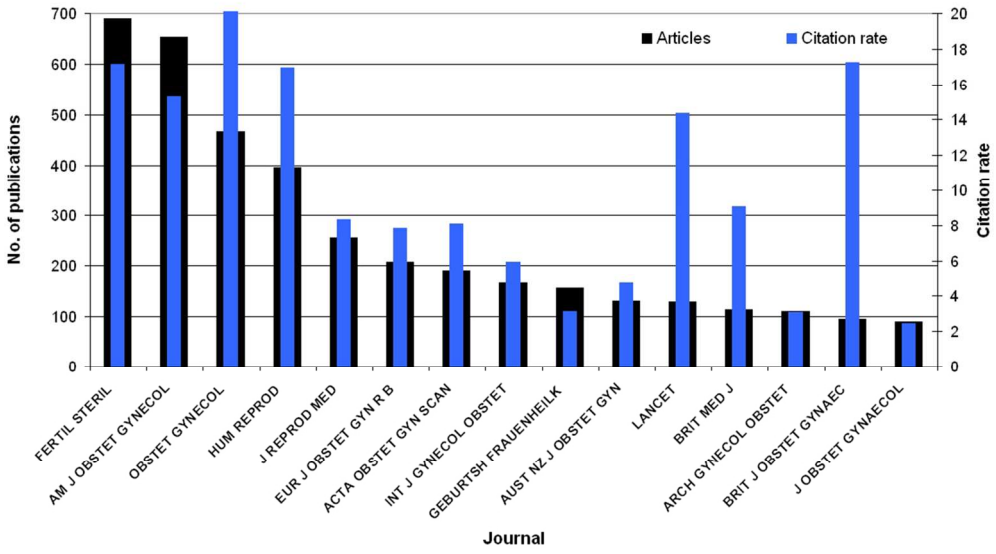

Number of articles and average citation rate of the most publishing journals on ectopic pregnancy.

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