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

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Manuscripts

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3 **Ectopic pregnancy – exploration of its global research architecture using**
4 **density-equalizing mapping and socioeconomic benchmarks**
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11 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.

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3 The method combines scientometric methods and “density equalizing
4 mapping projections in a reliable and standardized way.
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- 7 • The WoS focuses on English journals. It is a weakness that non-English
8 articles are underrepresented in our analysis.
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- 10 • We analysed citation-based parameters, which rather reflect the recognition of
11 the research in the scientific community than truly measure quality.
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INTRODUCTION

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Around 2% of zygotes implant outside the uterine lining and form an ectopic gestation¹. 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 mortality¹. During the last decades, transvaginal ultrasound and beta-human chorionic gonadotropin (beta-HCG) levels became part of the clinical routine²⁻⁶ leading to the timely detection of ectopic pregnancies and better patient outcomes⁷⁻⁹. 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 today¹³. 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 1990¹⁴. Although the mortality associated with ectopic gestations was halved in industrialized countries since the 1980s¹⁵, the condition constitutes a major cause of death continents like Asia and Africa¹⁶.

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

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

25 **NewQIS study protocol**

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28 We employed the 'New Quality and Quantity Indices in Science' (NewQIS) platform
29 to assess global ectopic pregnancy research in a standardized, reliable and objective
30 way^{17, 18}. This tool combines scientometric techniques to assess scientific
31 productivity and density equalizing mapping¹⁹ to generate global maps according to
32 analysed parameters²⁰⁻²³.
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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

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3 community, the number of citations, citation rates and the modified H-Indices (HI)
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5 were investigated, as previously described ²⁸. Therefore the citation numbers were
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7 retrieved for each publication and the average citations per item (citation rate) were
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9 calculated. Regression analysis was used to investigate the timely evolution of
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11 ectopic pregnancy research.
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15 After the transformation of the raw data to excel program charts and analysis, the
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17 findings were illustrated in numerous diagrams and visualized by the use of density-
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19 equalizing mapping projections (DEMP). The algorithm for this procedure was
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21 published by Gastner and Newman ¹⁹. In DEMPs, the territories of the different
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23 countries were resized in proportion to our selected variables such the distribution of
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25 country-specific numbers of published items, average citation rates and H-Indices.
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32 **Socioeconomic analysis**

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35 In order to assess research output with regard to the economic power of the most
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37 active countries, the publication activity was related to the Gross Domestic Product
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39 (GDP) and the GDP per capita in current USD, as described earlier ²⁹. According to
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41 the World Bank, the GDP at purchaser's prices is the sum of gross value added by all
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43 resident producers in the economy plus any product taxes and minus any subsidies
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45 not included in the value of the products. It is calculated without making deductions
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47 for depreciation of fabricated assets or for depletion and degradation of natural
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49 resources. Data are in current U.S. dollars. Dollar figures for GDP are converted from
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51 domestic currencies using single year official exchange rates. For a few countries
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53 where the official exchange rate does not reflect the rate effectively applied to actual
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3 foreign exchange transactions, an alternative conversion factor is used
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5 (<http://data.worldbank.org/indicator/NY.GDP.MKTP.CD>).
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8 The GDP per capita is defined as gross domestic product divided by midyear
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10 population. GDP is the sum of gross value added by all resident producers in the
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12 economy plus any product taxes and minus any subsidies not included in the value of
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14 the products. It is calculated without making deductions for depreciation of fabricated
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16 assets or for depletion and degradation of natural resources. Data are in current U.S.
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18 dollars (<http://data.worldbank.org/indicator/NY.GDP.PCAP.CD>).
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25 **Analysis of international ectopic pregnancy research collaborations**

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

49 **Global ectopic pregnancy research activity**

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52 We identified 8,040 ectopic pregnancy-related publications issued from 1900 to 2012;
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54 these were cited 86,680 times. 92.4% of these items were written in English and
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56 published by researchers from 76 different countries. US-American researchers
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3 authored 2612 publications accounting for 32% of all ectopic pregnancy-related
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5 publications. The US was identified as the country with the highest number of
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7 publications worldwide (Fig 1A). The United Kingdom (UK) was positioned second
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9 with 723 ectopic pregnancy publications, followed by Germany (370 publications),
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11 France (366 publications), Israel (248 publications), Canada (215 publications),
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13 Australia (203 publications), Italy (179 publications), Japan (169 publications), Turkey
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15 (162 publications), China (159 publications), Sweden (151 publications), the
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17 Netherlands (134 publications), Austria (124 publications) and Taiwan (122
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19 publications). Since North America, Western Europe and Australia were responsible
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21 for the majority of research output associated with “ectopic pregnancy”, their country
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23 sizes appear inflated in the DEMP-analysis (Fig 1A). Major parts of Asia (except
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25 China and Taiwan), Russia, Africa and South America occupied only small areas on
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27 the cartogram. The analysis of the timely evolution led to a regression coefficient of
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29 0.6793 for the period from 1900 until 2012 and of 0.8105 for the period from 1970
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31 until 2012 (Fig 1B). This indicated a strong increase of global research activity in the
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33 past 40 years.
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43 **Socioeconomic analysis of ectopic pregnancy research**

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

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3 past 20 years. A small but constant proportion of publications was attributed to the
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5 area of “Public, Environmental & Occupational Health”, which indicates that scientists
6
7 also focused upon Public Health issues related to ectopic pregnancy.
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10 We identified the leading, most impactful publication categories based on item and
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12 citation count (Fig 4B). The primary areas of ectopic pregnancy-research were
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14 “Obstetrics & Gynecology” and “Reproductive Biology”. The 5,100 publications
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16 assigned to “Obstetrics & Gynecology” were cited 57,879 times. “Reproductive
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18 Biology” with 1,496 publications was cited 22,545 times. When citation rates were
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20 analysed, the highest rate was present for the subject area “Infectious Diseases” with
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22 24.02 citations per ectopic pregnancy-related publication. The frequently assigned
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24 subject areas “Reproductive Biology” and “Obstetrics & Gynecology” were
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26 characterized by citation rates of 15.07 and 11.37 respectively.
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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 <i>Khan KS et al.</i> ³³	2006	Switzerland, United Kingdom, Argentina	534	LANCET
Comparative genomes of Chlamydia pneumoniae and C-trachomatis <i>Kalman S et al.</i> ³⁴	1999	United States	457	NAT GENET
Pelvic inflammatory disease and fertility <i>Westström L et al.</i> ³⁵	1992	United States	347	SEX TRANSM DIS
Genital chlamydial infections - epidemiology and reproductive sequelae <i>Cates W et al.</i> ³⁶	1991	United States	345	AM J OBSTET GYNECOL
Current methods of laboratory diagnosis of Chlamydia	1997	United States	293	CLIN MICROBIOL

1	trachomatis infections				REV
2	<i>Black CM et al.</i> ³⁷				
3	Prevalence of chlamydial and				
4	gonococcal infections among				
5	young adults in the				
6	United States				JAMA-J AM
7	<i>Miller WC et al.</i> ³⁸	2004	United States	270	MED ASSN
8	The epidemiology of smoking				
9	during pregnancy				
10	<i>Cnattingius S</i> ³⁹	2004	Sweden	250	NICOTINE TOB
11	Single-dose methotrexate - an				
12	expanded clinical-trial				
13	<i>Stovall TG and Ling FW</i> ⁴⁰	1993	United States	238	AM J OBSTET
14	A method of screening for				
15	ectopic pregnancy and its				
16	indications				
17	<i>Kadar N et al.</i> ⁴¹	1981	United States	235	OBSTET
18	Maternal age and fetal loss:				
19	population based register				
20	Linkage study				
21	<i>Nybo Andersen AM et al.</i> ⁴²	2000	Denmark	234	BRIT MED J
22	Treatment of interstitial ectopic				
23	pregnancy with methotrexate -				
24	report of a successful case				
25	<i>Tanaka T et al.</i> ⁴³	1982	Japan	233	FERTIL STERIL
26	Discriminatory HCG zone - its				
27	use in the sonographic				
28	evaluation for ectopic pregnancy				
29	<i>Kadar N et al.</i> ⁴⁴	1981	United States France	229	OBSTET
30	Conservative laparoscopic				
31	treatment of 321 ectopic				
32	pregnancies				
33	<i>Pouly JL et al.</i> ⁴⁵	1986	France	228	FERTIL STERIL
34	Incidence, trends, and risks of				
35	ectopic pregnancy in a				
36	population of woman				
37	<i>Westström L et al.</i> ⁴⁶	1981	Sweden	214	BRIT MED J
38	Early termination of pregnancy				
39	with mifepristone (RU-486) and				
40	the orally active prostaglandin				
41	misoprostol				
42	<i>Peyron R et al.</i> ⁴⁷	1993	France	216	N ENGL J MED

DISCUSSION

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3 Accounting for a percentage of 2% of all first-trimester pregnancies in the US,
4 ectopic gestation is a very common complication of pregnancy. It should therefore
5 merit a high degree of interest within the scientific community. Hence, this NewQIS
6 study^{17, 18} is focused on this condition and presents the first multifaceted analysis of
7 the related global research architecture using density equalizing mapping analysis
8 tools¹⁹. Additionally, we selected 15 publications that were defined as key articles in
9 the field based on 200 and more citations. These key publications provide relevant
10 background information for individual scholarship, practice and research endeavours.
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24 In total, we analysed 8,040 publications related to ectopic pregnancies. The US was
25 identified as the country dominating the field. With regard to total publishing activities,
26 it is important to compare ectopic pregnancy research to other disease entities or to
27 the field of OB/GYN in general: A recent study by Alexandre-Benavent et al. focused
28 on trends in reproductive medicine research over a period of 10 years⁴⁸. It was the
29 authors' objective to study the publication activity metrics from 2003 to 2012 and to
30 shed a light on the clinical, social, and epidemiologic implications of this relatively
31 new but rapidly emerging field. As outcome measures, they analysed most
32 productive and frequently cited investigators, institutions, and countries as well as
33 specific areas of research and scientific collaborations. The authors found that 90
34 investigators with more than 1,000 citations had jointly published 4,010 articles. The
35 most-cited study groups were located in the Netherlands, Belgium, Spain, the US,
36 and the UK, and collaborative studies have been increasing. It was concluded that
37 reproductive medicine research has attained scientific interest and importance. Also,
38 the increase in (inter)national collaborations seems to be the key to the field's
39 success. In contrast to Alexandre-Benavent et al., we focused on a single disease
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3 entity and encompassed more than one hundred years of research. Besides
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5 monitoring the scientific output we also related the numbers to the economic power
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7 of investigated countries in order to dissect the real interest of single nations in
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9 research related to a particular condition. Therefore, we related the ectopic
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11 pregnancy-related research activities to the total GDP and the GDP per capita. We
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13 found that the US still dominated when GDP per capita index was used. However,
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15 when related to the total GDP index, Israel exhibited the highest contribution of
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17 ectopic pregnancy research in relation to its overall economic power.
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21 We compared the present data to other OBGYN entities such as polycystic ovary
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23 syndrome (PCOS) or ovarian cancer ^{49, 50}: A published study on PCOS that covered
24
25 the years between 1900 and 2014 reported a total of 6261 PCOS-specific
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27 publications and 703 international research collaborations in the Web of Science. As
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29 in the present study, the USA was identified as the most active country in total and
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31 collaborative research activity ⁴⁹. In the socioeconomic analysis, the USA was also
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33 ranked first concerning PCOS-related publications per gross domestic product,
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35 followed by the UK, Italy and Greece ⁴⁹. For ovarian cancer research 23,378 reports
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37 were identified for the period 1900 - 2014. Denmark was positioned at the first place
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39 with a total of 1293.2 calculated ovarian cancer-specific articles per 1000 billion US-\$
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41 GDP ⁵⁰. Other gynecological topics, which have been screened for scientific
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43 productivity, were predominantly related to breast cancer ⁵¹⁻⁵⁴: Glynn et al. presented
44
45 an in-depth evaluation of breast cancer research. The authors screened publications
46
47 from 1945 to 2008 also using the NewQIS platform ⁵⁴. They identified 180,126 breast
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49 cancer-associated items; these had been cited 4,136,224 times. In comparison to our
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51 data on ectopic pregnancies encompassing a time span of 112 years, breast cancer
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53 research has produced a more than 20 times greater scientific output in a period of
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3 slightly over 60 years. One reason for this discrepancy is that breast cancer accounts
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5 for the most common malignancy among women, with an estimated 231,840 new
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7 cases diagnosed in the US in 2015 alone ⁵⁵. Hence, this disease receives large
8
9 amounts of public awareness. Also, significant volumes of scientific resources are
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11 allocated to support research in this area. In breast cancer, the US produced the
12
13 greatest publication output (n = 77,101; 42.8%), followed by the UK (n = 18,357;
14
15 10.2%) and Germany (n = 12,529, 7%) ⁵⁴. This ranking of the most productive
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17 nations was similar to ectopic pregnancy research with 32.5% ectopic pregnancy-
18
19 related publications originating from the US, around 9% from the UK and 4.6% from
20
21 Germany. The percentage of total global research activity exhibited by US-American
22
23 institutions is higher in breast cancer research than in ectopic pregnancy research.
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28 “Smoking in pregnancy” is another area of OB/GYN research that was studied ⁵⁶.
29
30 Here, 10,043 related publications were identified in a period from 1900 to 2012. As in
31
32 our investigation and the presented breast cancer study, the highest number of
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34 scientific works was published by the US (35.5%), followed by the UK (9.9%). For
35
36 both countries, we documented similar percentage values and the highest modified
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38 H-Indices of 128 (US) and 42 (UK) for ectopic pregnancy research activities. When
39
40 citation performance is compared, it is evident that research in “smoking and
41
42 pregnancy” receives a higher attention in the scientific community than scientific
43
44 endeavours related to “ectopic pregnancy” since the 10,043 publications in the field
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46 of “smoking and pregnancy” were cited 112,136 times (11.2 citations per publication)
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48 versus 8,040 ectopic pregnancy-related publications that received 86,680 citations
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50 (10.8 citations per publication).
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56 When the global research activity regarding ectopic pregnancy is compared to other
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58 biomedical fields, it can be stated that the observed dominance of the US is also
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3 common in other, non-OB/GYN medical specialties. In a study that analysed
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5 5,527,558 published items authored in all areas of medicine over the last 50 years,
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7 the following ranking of total research activity was found ⁵⁷: The US was the leading
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9 nation, followed by Japan, Germany, the UK, France, and Italy ⁵⁷. In our analysis, it
10
11 can be clearly stated that Japan does not exhibit comparable activities in the field of
12
13 ectopic pregnancy research with only 169 publications in the present set of data. This
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15 finding could be linked to a lower prevalence of ectopic pregnancies in Japan
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17 compared with other nations translating into disregard of the topic among local
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19 scientists and funding institutions. However, epidemiological data on the exact rates
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21 of ectopic pregnancies or pelvic inflammatory disease in Japan are lacking. Also,
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23 data on maternal mortality attributed to ectopic pregnancies are sparse. For the early
24
25 nineties, ectopic pregnancy-related maternal mortality was reported at 4% in Japan
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27 compared to 13% in the US (data collected until 1989) ^{58, 59}. Since this difference
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29 could indeed reflect a lower impact of ectopic pregnancies on the public health of
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31 Japanese women, this fact may explain a lacking interest of Japanese institutions to
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33 foster research on this topic.
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39 We identified a small number of international collaborations in the field of ectopic
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41 pregnancy research. The rate of 4.9% is substantially lower than in other fields.
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43 Additionally, we documented a very small number of ectopic pregnancy-related
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45 publications investigating Public Health aspects. These findings indicate a low
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47 awareness of this subject matter in terms of ectopic pregnancy research, which is
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49 contrasting the major disease burden this condition poses on women - especially in
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51 low-income countries with high rates of pelvic inflammatory diseases and only limited
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53 access to diagnostic and treatment procedures. Therefore, future research should
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55 pay attention to these problematic issues and focus on fostering collaborative efforts,
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3 involving developing countries in research networks and conducting projects in the
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5 field of Public Health.
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10 **CONCLUSIONS**

14 The present study is the first combined economic and scientometric study that
15 depicts a sketch of the global research activities on ectopic pregnancies. With regard
16 to other disease entities, it can be stated that a mere total of about 8000 related
17 publications highlights the need to foster research programs on this problematic
18 condition that endangers female health and human reproduction biology all around
19 the globe. The lack of research productivity in low-income countries and their missing
20 presence in international collaborations also exemplifies the need for Public Health
21 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.

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3 **Fig 5. Country-specific analysis of assigned subject categories.** Analysis was
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5 performed of the 10 most active countries in ectopic pregnancy research in order to
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7 identify regional differences in ectopic pregnancy research.
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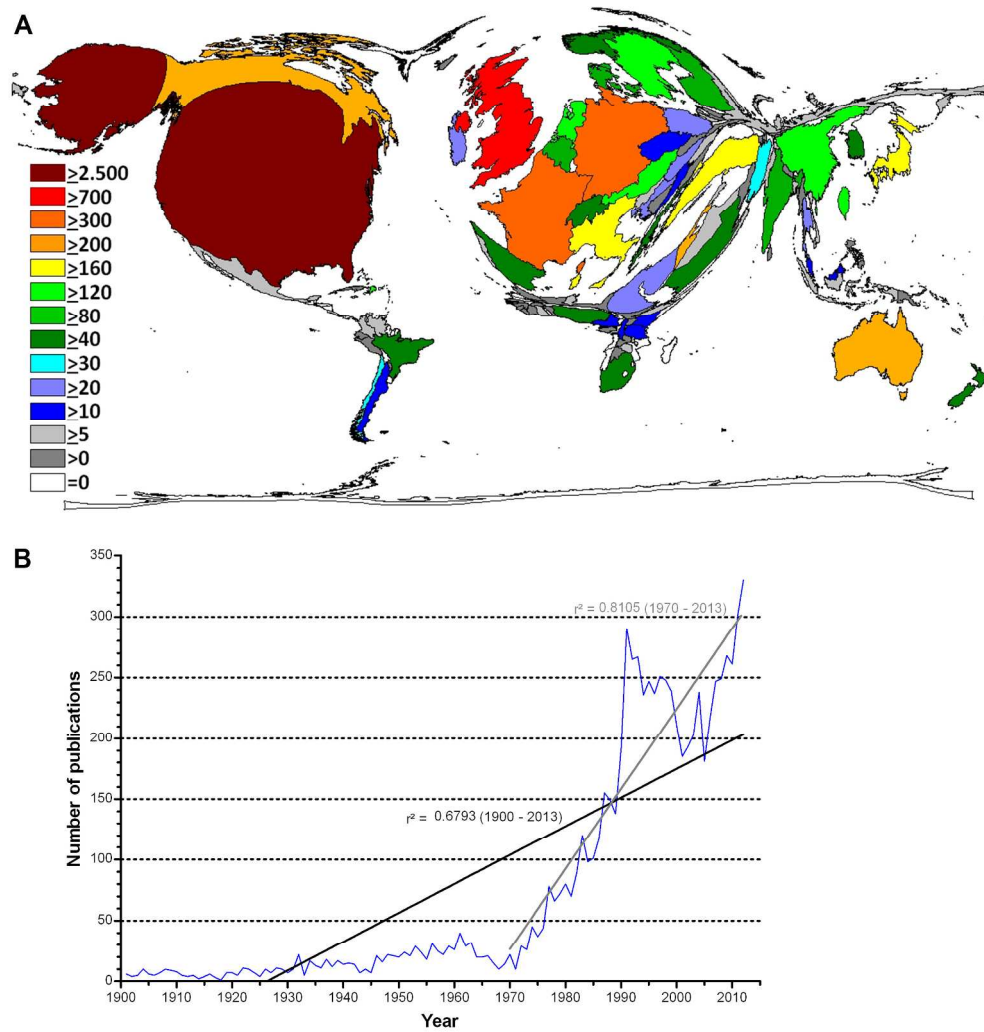
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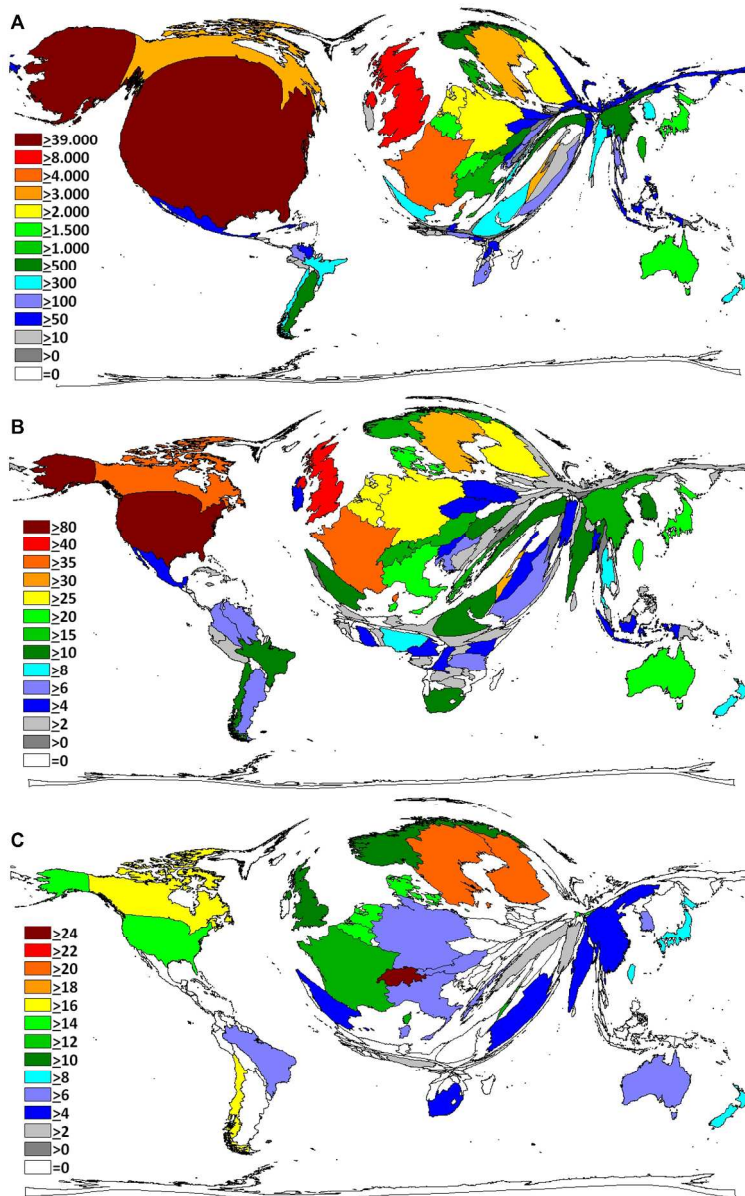
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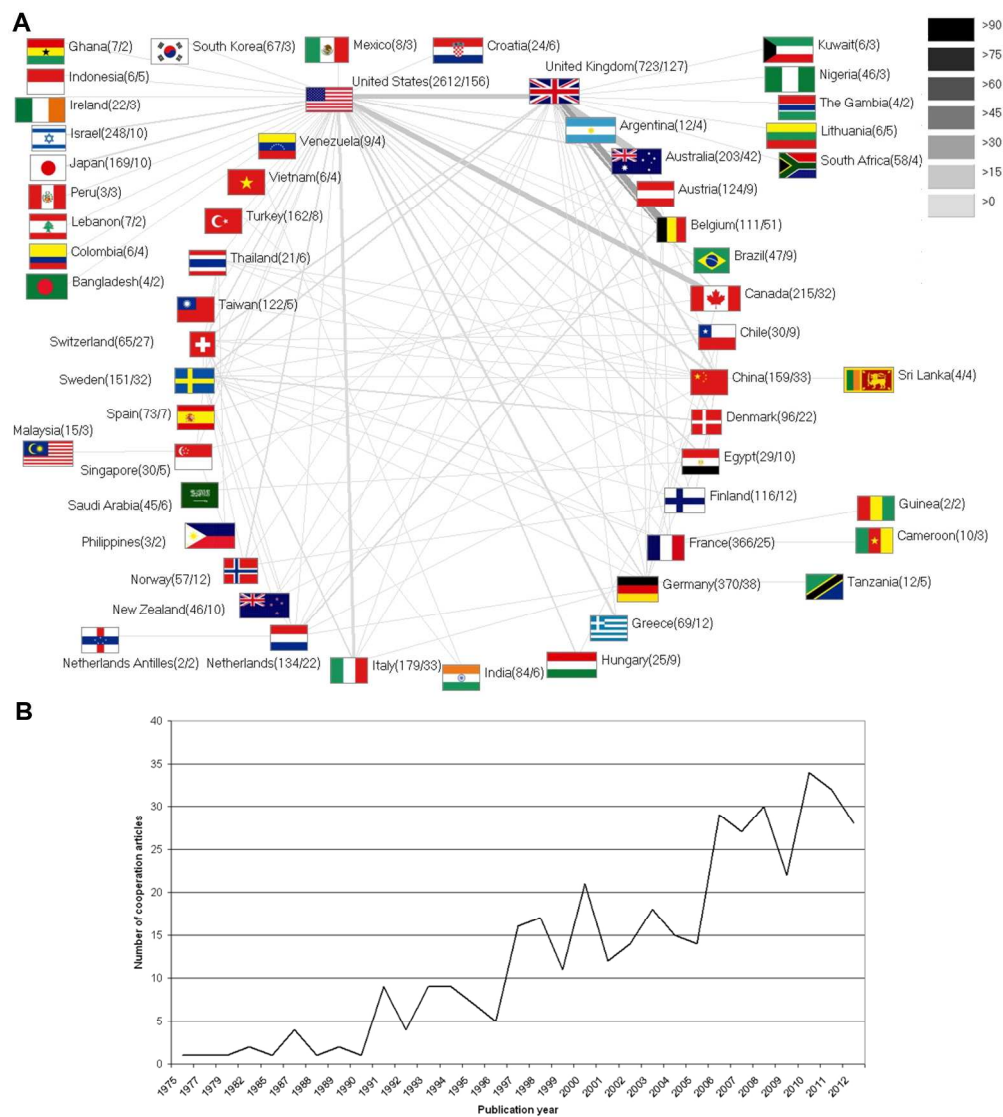
Publication output. A) Global Density-equalizing mapping of ectopic pregnancy publications. The area of each country is scaled in proportion to its total number of ectopic pregnancy-related publications. Colours encode numbers of ectopic pregnancy publications. B) Timely evolution of ectopic pregnancy-related publications.

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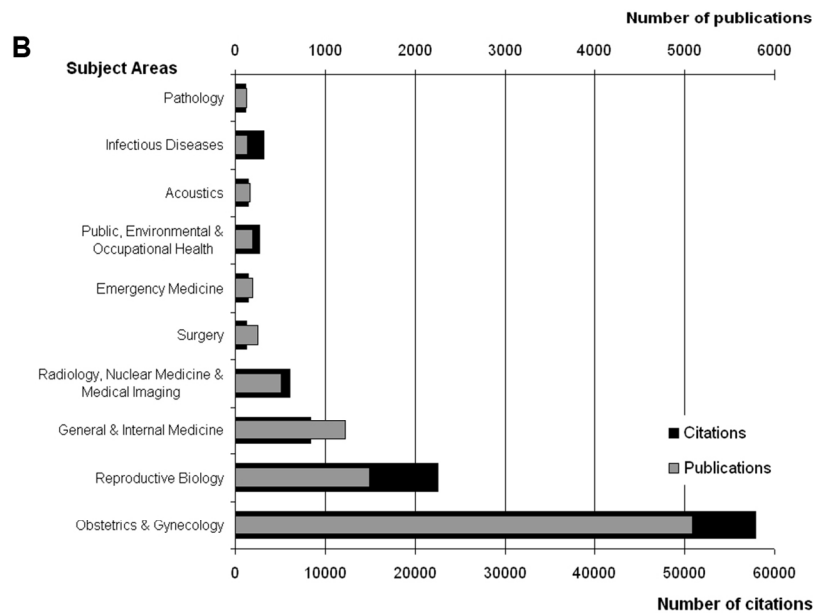
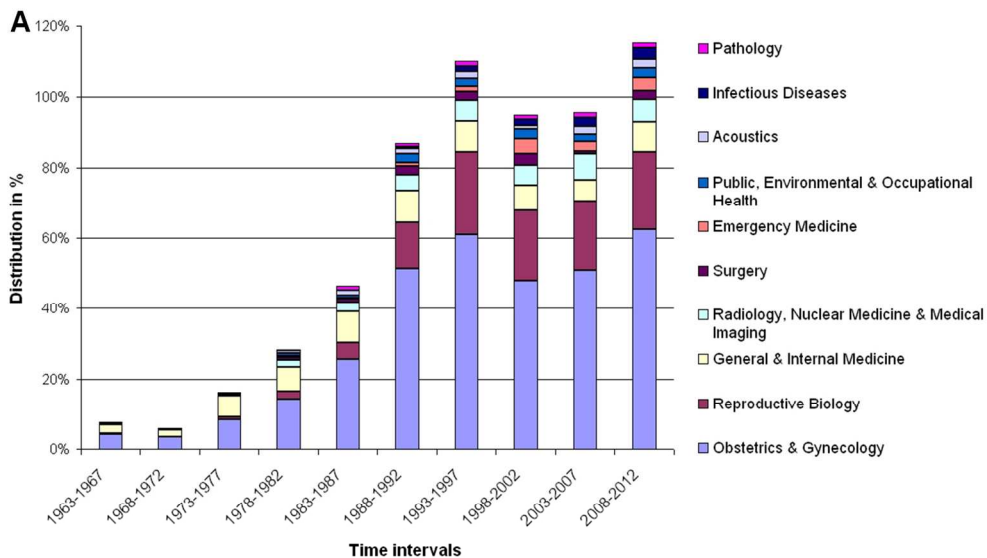
. Density-equalizing maps. A) Density-equalizing map of country total citations of ectopic pregnancy-related publications. The area of each country was scaled in proportion to its total number of ectopic pregnancy-related citations. Colours encode numbers of ectopic pregnancy-related citations. B) Density-equalizing 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.

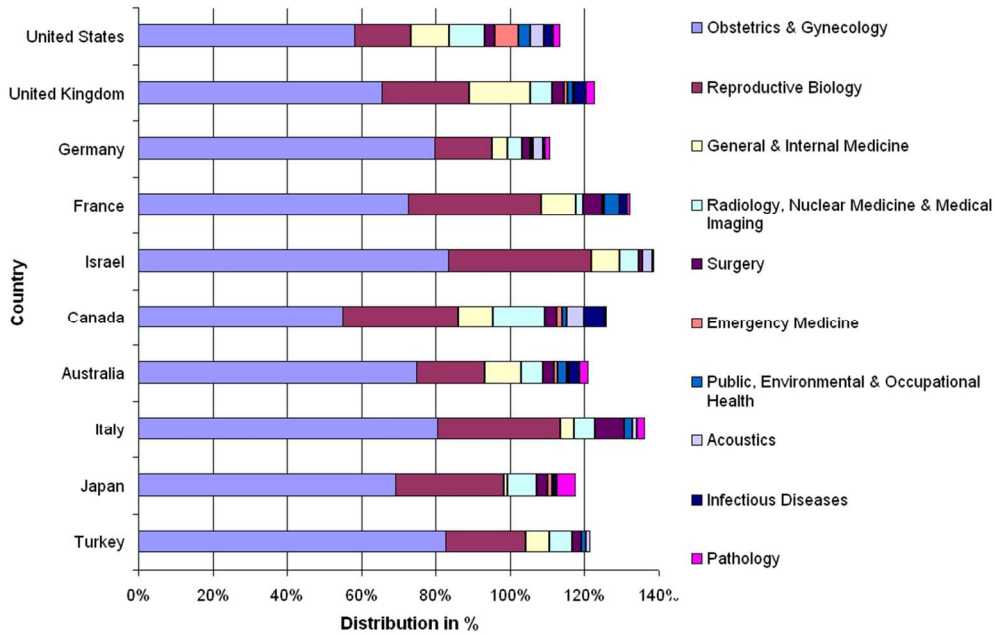
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Subject area analysis. A) Timely evolution of subject areas assigned to the ectopic pregnancy-related publications in 5-year periods. Proportion of the 10 most assigned subject areas in 5-year intervals in order to gain insights into the field activity.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

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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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View only

BMJ Open

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

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Keywords:	ectopic pregnancy, density equalizing mapping, female health, reproduction biology

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3 **Ectopic pregnancy – exploration of its global research architecture using**
4 **density-equalizing mapping and socioeconomic benchmarks**
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11 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

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Around 2% of zygotes implant outside the uterine lining and form an ectopic gestation¹. 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 mortality¹. During the last decades, transvaginal ultrasound and beta-human chorionic gonadotropin (beta-HCG) levels became part of the clinical routine²⁻⁶ leading to the timely detection of ectopic pregnancies and better patient outcomes⁷⁻⁹. 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 today¹³. 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 1990¹⁴. Although the mortality associated with ectopic gestations was halved in industrialized countries since the 1980s¹⁵, the condition constitutes a major cause of death continents like Asia and Africa¹⁶.

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

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3 related literature by a scientometric approach ^{17, 18}. Therefore, we identified all
4 ectopic pregnancy-related publications indexed in the Web of Science until 2012.
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6 These items were (1) analysed in reference to their content and citations describing
7 geographical and historical developments, (2) research networks were identified and
8
9 (3) the country-specific productivity was related to socioeconomic variables.
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11 Furthermore, we present the most cited publications related to ectopic pregnancies.
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13 These studies cover key discoveries in the field and provide the scientific fundament
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15 for many clinical decisions made daily around the globe.
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24 **MATERIALS AND METHODS**

25 **NewQIS study protocol**

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28 We employed the 'New Quality and Quantity Indices in Science' (NewQIS) platform
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30 to assess global ectopic pregnancy research in a standardized, reliable and objective
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32 way ^{17, 18}. This tool combines scientometric techniques to assess scientific
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34 productivity and density equalizing mapping ¹⁹ to generate global maps according to
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36 analysed parameters ²⁰⁻²³.
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46 **Data source**

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

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3 process. These standard categories can be retrieved via WoS. For our analyses,
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5 these original WoS categories have been used.
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8 As semi-qualitative items describing the recognition of publications by the scientific
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10 community, the number of citations, citation rates and the modified H-Indices (HI)
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12 were investigated, as previously described ²⁸. Therefore, the citation numbers were
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14 retrieved for each publication and the average citations per item (citation rate) were
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16 calculated. Regression analysis was used to investigate the timely evolution of
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18 ectopic pregnancy research.
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22 After the transformation of the raw data to excel program charts and analysis, the
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24 findings were illustrated in numerous diagrams and visualized by the use of density-
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26 equalizing mapping projections (DEMP). The algorithm for this procedure was
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28 published by Gastner and Newman ¹⁹. In DEMPs, the territories of the different
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30 countries were resized in proportion to our selected variables such the distribution of
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32 country-specific numbers of published items, average citation rates and H-Indices.
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40 **Socioeconomic analysis**

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42 In order to assess research output with regard to the economic power of the most
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44 active countries, the publication activity was related to the Gross Domestic Product
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46 (GDP) and the GDP per capita in current USD, as described earlier ²⁹. According to
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48 the World Bank, the GDP at purchaser's prices is the sum of gross value added by all
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50 resident producers in the economy plus any product taxes and minus any subsidies
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52 not included in the value of the products. It is calculated without making deductions
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54 for depreciation of fabricated assets or for depletion and degradation of natural
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56 resources. Data are in current U.S. dollars. Dollar figures for GDP are converted from
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3 domestic currencies using single year official exchange rates. For a few countries
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5 where the official exchange rate does not reflect the rate effectively applied to actual
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7 foreign exchange transactions, an alternative conversion factor is used
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10 (<http://data.worldbank.org/indicator/NY.GDP.MKTP.CD>).

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

30 **Analysis of international ectopic pregnancy research collaborations**

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

52 **RESULTS**

55 **Global ectopic pregnancy research activity**

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3 We identified 8,040 ectopic pregnancy-related publications issued from 1900 to 2012;
4 these were cited 86,680 times. 92.4% of these items were written in English and
5 published by researchers from 76 different countries. US-American researchers
6 authored 2612 publications accounting for 32% of all ectopic pregnancy-related
7 publications. The US was identified as the country with the highest number of
8 publications worldwide (Fig 1A). The United Kingdom (UK) was positioned second
9 with 723 ectopic pregnancy publications, followed by Germany (370 publications),
10 France (366 publications), Israel (248 publications), Canada (215 publications),
11 Australia (203 publications), Italy (179 publications), Japan (169 publications), Turkey
12 (162 publications), China (159 publications), Sweden (151 publications), the
13 Netherlands (134 publications), Austria (124 publications) and Taiwan (122
14 publications). Since North America, Western Europe and Australia were responsible
15 for the majority of research output associated with “ectopic pregnancy”, their country
16 sizes appear inflated in the DEMP-analysis (Fig 1A). Major parts of Asia (except
17 China and Taiwan), Russia, Africa and South America occupied only small areas on
18 the cartogram. The analysis of the timely evolution led to a regression coefficient of
19 0.6793 for the period from 1900 until 2012 and of 0.8105 for the period from 1970
20 until 2012 (Fig 1B). This indicated a strong increase of global research activity in the
21 past 40 years.
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49 **Socioeconomic analysis of ectopic pregnancy research**

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

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3 remained relatively constant with no rapid increase of one particular area within the
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5 past 20 years. A small but constant proportion of publications was attributed to the
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7 area of “Public, Environmental & Occupational Health”, which indicates that scientists
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9 also focused upon Public Health issues related to ectopic pregnancy.
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12 We identified the leading, most impactful publication categories based on item and
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14 citation count (Fig 4B). The primary areas of ectopic pregnancy-research were
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16 “Obstetrics & Gynecology” and “Reproductive Biology”. The 5,100 publications
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18 assigned to “Obstetrics & Gynecology” were cited 57,879 times. “Reproductive
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20 Biology” with 1,496 publications was cited 22,545 times. When citation rates were
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22 analysed, the highest rate was present for the subject area “Infectious Diseases” with
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24 24.02 citations per ectopic pregnancy-related publication. The frequently assigned
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26 subject areas “Reproductive Biology” and “Obstetrics & Gynecology” were
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28 characterized by citation rates of 15.07 and 11.37 respectively.
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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 <i>Khan KS et al.</i> ³³	2006	Switzerland, United Kingdom, Argentina	534	LANCET
Comparative genomes of Chlamydia pneumoniae and C-trachomatis <i>Kalman S et al.</i> ³⁴	1999	United States	457	NAT GENET
Pelvic inflammatory disease and fertility <i>Westström L et al.</i> ³⁵	1992	United States	347	SEX TRANSM DIS
Genital chlamydial infections - epidemiology and reproductive sequelae <i>Cates W et al.</i> ³⁶	1991	United States	345	AM J OBSTET GYNECOL
Current methods of laboratory diagnosis of Chlamydia	1997	United States	293	CLIN MICROBIOL

1	trachomatis infections				REV
2	<i>Black CM et al.</i> ³⁷				
3	Prevalence of chlamydial and				
4	gonococcal infections among				
5	young adults in the				
6	United States				JAMA-J AM
7	<i>Miller WC et al.</i> ³⁸	2004	United States	270	MED ASSN
8	The epidemiology of smoking				
9	during pregnancy				
10	<i>Cnattingius S</i> ³⁹	2004	Sweden	250	NICOTINE TOB
11	Single-dose methotrexate - an				
12	expanded clinical-trial				
13	<i>Stovall TG and Ling FW</i> ⁴⁰	1993	United States	238	AM J OBSTET
14	A method of screening for				
15	ectopic pregnancy and its				
16	indications				
17	<i>Kadar N et al.</i> ⁴¹	1981	United States	235	OBSTET
18	Maternal age and fetal loss:				
19	population based register				
20	Linkage study				
21	<i>Nybo Andersen AM et al.</i> ⁴²	2000	Denmark	234	BRIT MED J
22	Treatment of interstitial ectopic				
23	pregnancy with methotrexate -				
24	report of a successful case				
25	<i>Tanaka T et al.</i> ⁴³	1982	Japan	233	FERTIL STERIL
26	Discriminatory HCG zone - its				
27	use in the sonographic				
28	evaluation for ectopic pregnancy				
29	<i>Kadar N et al.</i> ⁴⁴	1981	United States France	229	OBSTET
30	Conservative laparoscopic				
31	treatment of 321 ectopic				
32	pregnancies				
33	<i>Pouly JL et al.</i> ⁴⁵	1986	France	228	FERTIL STERIL
34	Incidence, trends, and risks of				
35	ectopic pregnancy in a				
36	population of woman				
37	<i>Westström L et al.</i> ⁴⁶	1981	Sweden	214	BRIT MED J
38	Early termination of pregnancy				
39	with mifepristone (RU-486) and				
40	the orally active prostaglandin				
41	misoprostol				
42	<i>Peyron R et al.</i> ⁴⁷	1993	France	216	N ENGL J MED
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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 tools¹⁹. 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 years⁴⁸. 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,

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3 the increase in (inter)national collaborations seems to be the key to the field's
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5 success. In contrast to Aleixandre-Benavent et al., we focused on a single disease
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7 entity and encompassed more than one hundred years of research. Besides
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9 monitoring the scientific output, we also related the numbers to the economic power
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11 of investigated countries in order to dissect the real interest of single nations in
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13 research related to a particular condition. Therefore, we related the ectopic
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15 pregnancy-related research activities to the total GDP and the GDP per capita. We
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17 found that the US still dominated when GDP per capita index was used. However,
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19 when related to the total GDP index, Israel exhibited the highest contribution of
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21 ectopic pregnancy research in relation to its overall economic power.
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26 We compared the present data to other OBGYN entities such as polycystic ovary
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28 syndrome (PCOS) or ovarian cancer^{49, 50}: A published study on PCOS that covered
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30 the years between 1900 and 2014 reported a total of 6261 PCOS-specific
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32 publications and 703 international research collaborations in the Web of Science. As
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34 in the present study, the USA was identified as the most active country in total and
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36 collaborative research activity⁴⁹. In the socioeconomic analysis, the USA was also
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38 ranked first concerning PCOS-related publications per gross domestic product,
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40 followed by the UK, Italy and Greece⁴⁹. For ovarian cancer research 23,378 reports
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42 were identified for the period 1900 - 2014. Denmark was positioned at the first place
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44 with a total of 1293.2 calculated ovarian cancer-specific articles per 1000 billion US-\$
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46 GDP⁵⁰. Other gynecological topics, which have been screened for scientific
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48 productivity, were predominantly related to breast cancer⁵¹⁻⁵⁴: Glynn et al. presented
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50 an in-depth evaluation of breast cancer research. The authors screened publications
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52 from 1945 to 2008 also using the NewQIS platform⁵⁴. They identified 180,126 breast
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54 cancer-associated items; these had been cited 4,136,224 times. In comparison to our
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3 data on ectopic pregnancies encompassing a time span of 112 years, breast cancer
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5 research has produced a more than 20 times greater scientific output in a period of
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7 slightly over 60 years. One reason for this discrepancy is that breast cancer accounts
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9 for the most common malignancy among women, with an estimated 231,840 new
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11 cases diagnosed in the US in 2015 alone ⁵⁵. Hence, this disease receives large
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13 amounts of public awareness. Also, significant volumes of scientific resources are
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15 allocated to support research in this area. In breast cancer, the US produced the
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17 greatest publication output (n = 77,101; 42.8%), followed by the UK (n = 18,357;
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19 10.2%) and Germany (n = 12,529, 7%) ⁵⁴. This ranking of the most productive
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21 nations was similar to ectopic pregnancy research with 32.5% ectopic pregnancy-
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23 related publications originating from the US, around 9% from the UK and 4.6% from
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25 Germany. The percentage of total global research activity exhibited by US-American
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27 institutions is higher in breast cancer research than in ectopic pregnancy research.
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32 “Smoking in pregnancy” is another area of OB/GYN research that was studied ⁵⁶.
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34 Here, 10,043 related publications were identified in a period from 1900 to 2012. As in
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36 our investigation and the presented breast cancer study, the highest number of
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38 scientific works was published by the US (35.5%), followed by the UK (9.9%). For
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40 both countries, we documented similar percentage values and the highest modified
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42 H-Indices of 128 (US) and 42 (UK) for ectopic pregnancy research activities. When
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44 citation performance is compared, it is evident that research in “smoking and
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46 pregnancy” receives a higher attention in the scientific community than scientific
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48 endeavours related to “ectopic pregnancy” since the 10,043 publications in the field
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50 of “smoking and pregnancy” were cited 112,136 times (11.2 citations per publication)
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52 versus 8,040 ectopic pregnancy-related publications that received 86,680 citations
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54 (10.8 citations per publication).
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3 In our study, the US occupied the top position among all countries in regards to
4 overall publication and citation numbers as well as the H-index. We explain this
5 finding with the outstanding research environment and funding provided for scientists
6 in the US. Further, we hypothesize that the prominent position of the US might also
7 be linked to a possible bias: Four of the most prolific journals in the field are based in
8 the US; they provide an impactful publishing platform for ectopic pregnancy research
9 (as shown in our journal analysis). US-American reviewers are known for their
10 favourable evaluation of publications submitted by local researchers leading to a
11 predominance of US-American works among the accepted manuscripts^{57, 58}. But we
12 regard this “reviewer bias” overall as limited since it can be stated that the observed
13 dominance of the US is also common in other, non-OB/GYN medical specialties. In a
14 study that analysed 5,527,558 published items authored in all areas of medicine over
15 the last 50 years, the following ranking of total research activity was found⁵⁹: The US
16 was the leading nation, followed by Japan, Germany, the UK, France, and Italy⁵⁹.
17 Furthermore, it can be clearly stated that Japan does not exhibit comparable
18 activities in the field of ectopic pregnancy research with only 169 publications in the
19 present set of data. This finding could be linked to a lower prevalence of ectopic
20 pregnancies in Japan compared with other nations translating into disregard of the
21 topic among local scientists and funding institutions. However, epidemiological data
22 on the exact rates of ectopic pregnancies or pelvic inflammatory disease in Japan are
23 lacking. Also, data on maternal mortality attributed to ectopic pregnancies are sparse.
24 For the early nineties, ectopic pregnancy-related maternal mortality was reported at
25 4% in Japan compared to 13% in the US (data collected until 1989)^{60, 61}. Since this
26 difference could indeed reflect a lower impact of ectopic pregnancies on the public
27 health of Japanese women, this fact may explain a lacking interest of Japanese
28 institutions to foster research on this topic.

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

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34 The present study is the first combined economic and scientometric study that
35 depicts a sketch of the global research activities on ectopic pregnancies. With regard
36 to other disease entities, it can be stated that a mere total of about 8000 related
37 publications highlights the need to foster research programs on this problematic
38 condition that endangers female health and human reproduction biology all around
39 the globe. The lack of research productivity in low-income countries and their missing
40 presence in international collaborations also exemplifies the need for Public Health
41 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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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.

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3 **Fig 5. Country-specific analysis of assigned subject categories.** Analysis was
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5 performed of the 10 most active countries in ectopic pregnancy research in order to
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7 identify regional differences in ectopic pregnancy research.
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12 **Fig 6.** Number of articles and average citation rate of the most publishing journals on
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14 ectopic pregnancy.
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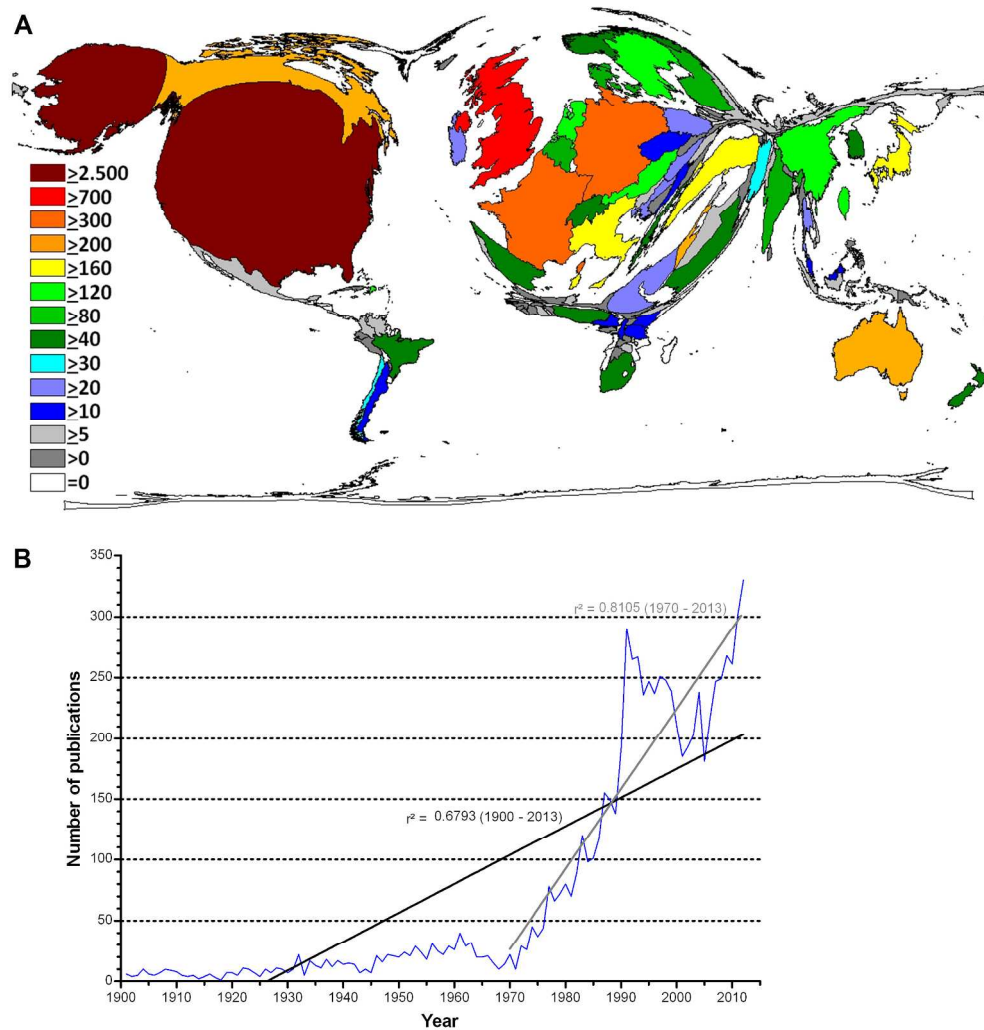
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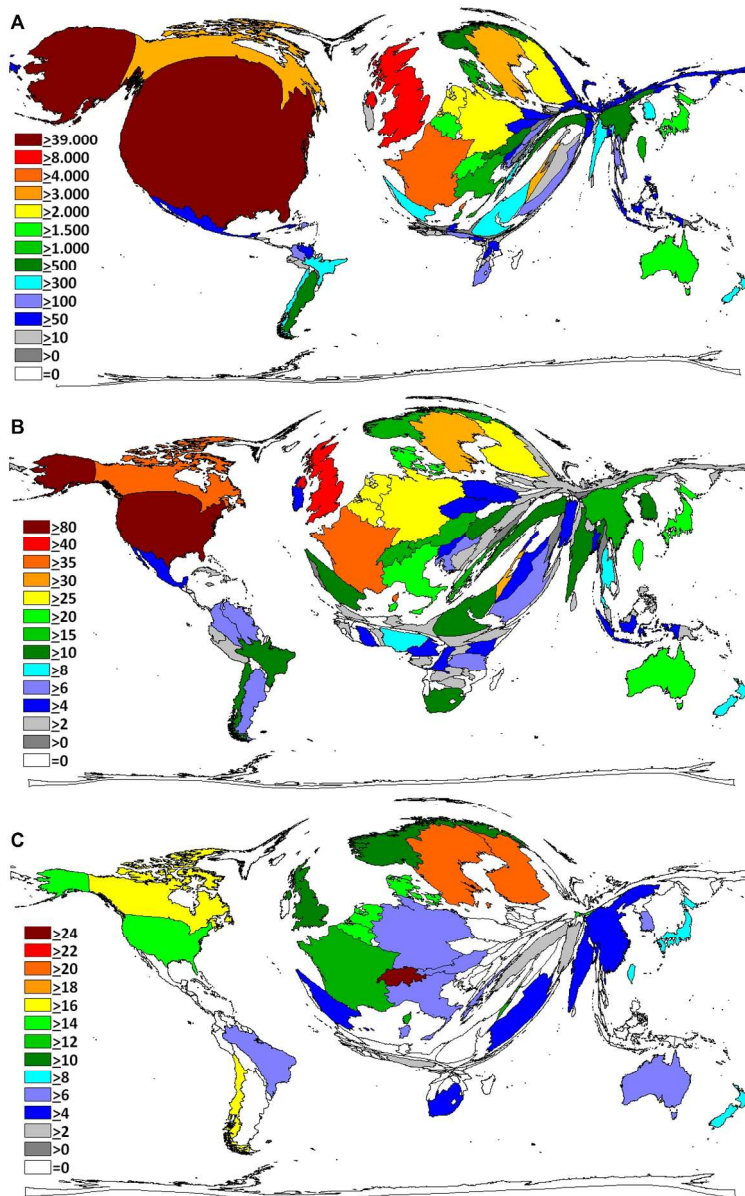
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Publication output. A) Global Density-equalizing mapping of ectopic pregnancy publications. The area of each country is scaled in proportion to its total number of ectopic pregnancy-related publications. Colours encode numbers of ectopic pregnancy publications. B) Timely evolution of ectopic pregnancy-related publications.

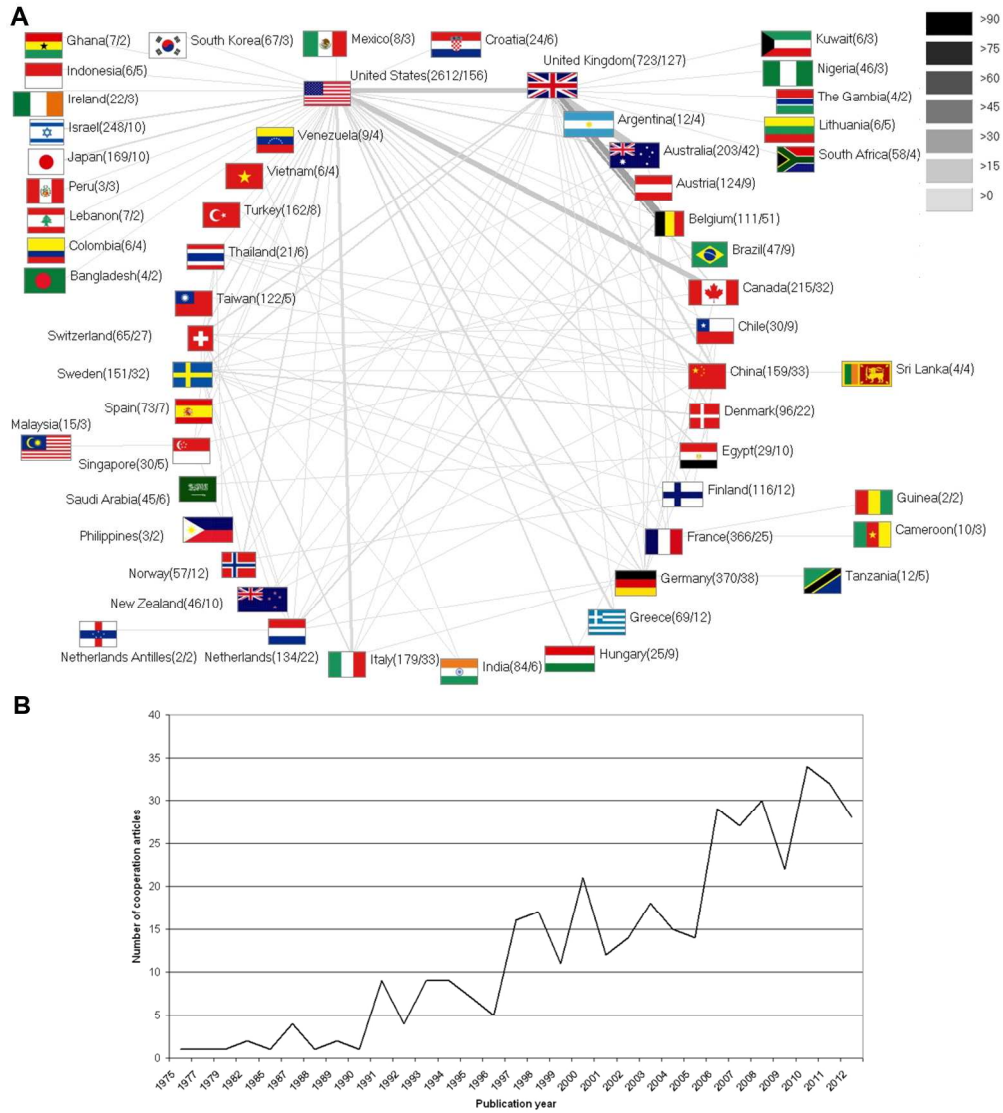
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. Density-equalizing maps. A) Density-equalizing map of country total citations of ectopic pregnancy-related publications. The area of each country was scaled in proportion to its total number of ectopic pregnancy-related citations. Colours encode 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.

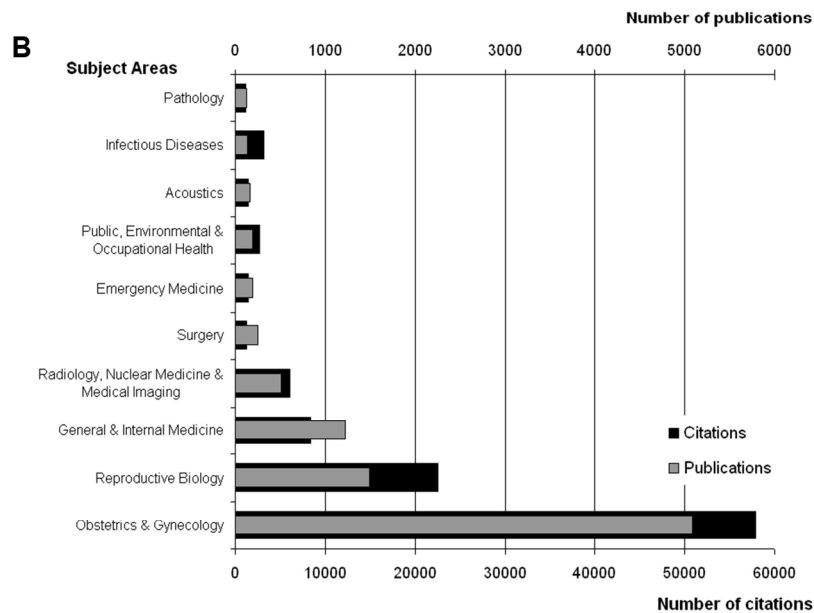
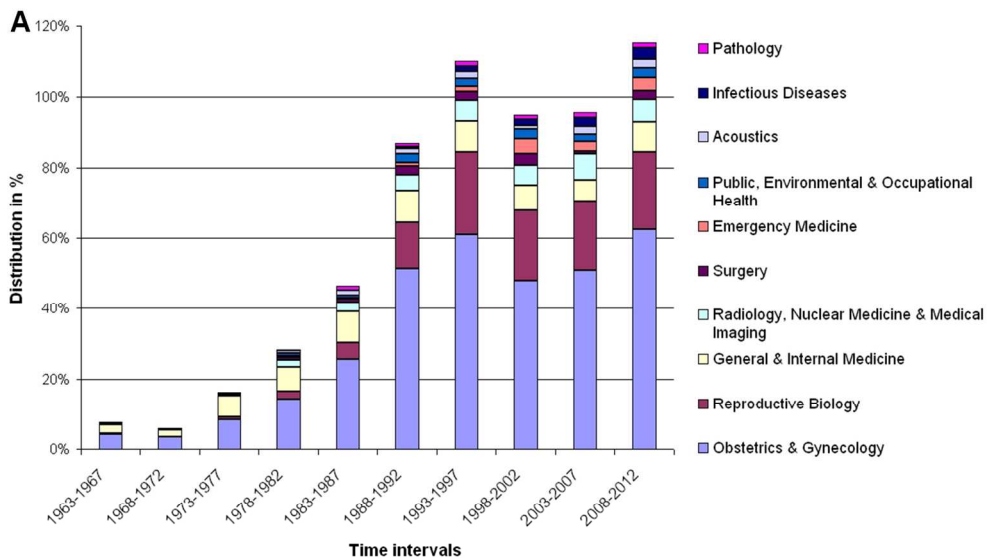
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International collaboration. A) Net diagram of international ectopic pregnancy-related collaborations. Line width and grey scale encode numbers of ectopic pregnancy-related collaborations. Numbers in brackets indicate: (number of ectopic pregnancy-related 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.

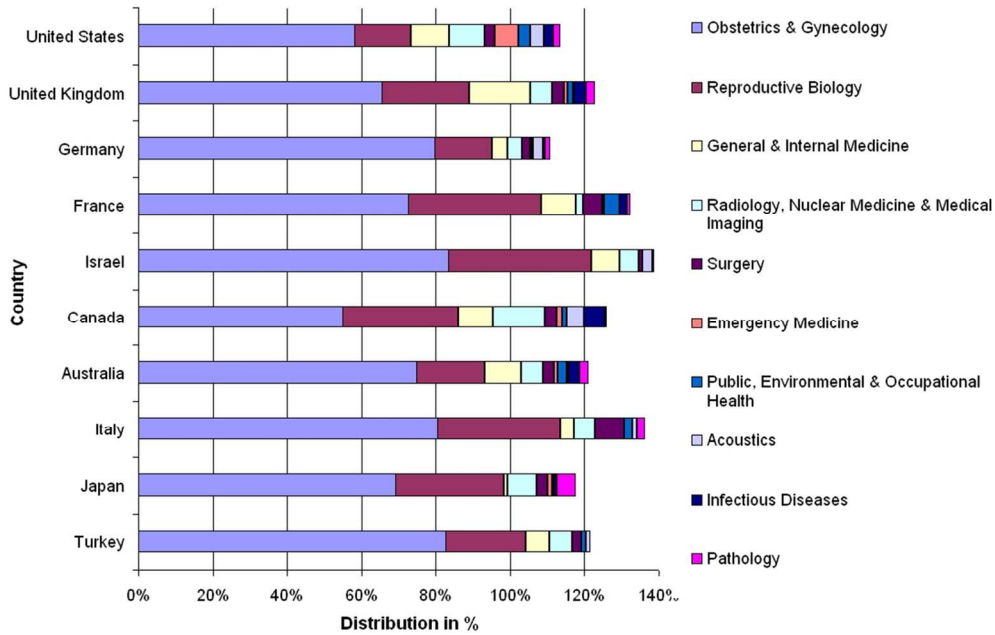
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Subject area analysis. A) Timely evolution of subject areas assigned to the ectopic pregnancy-related publications in 5-year periods. Proportion of the 10 most assigned subject areas in 5-year intervals in order to gain insights into the field activity.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

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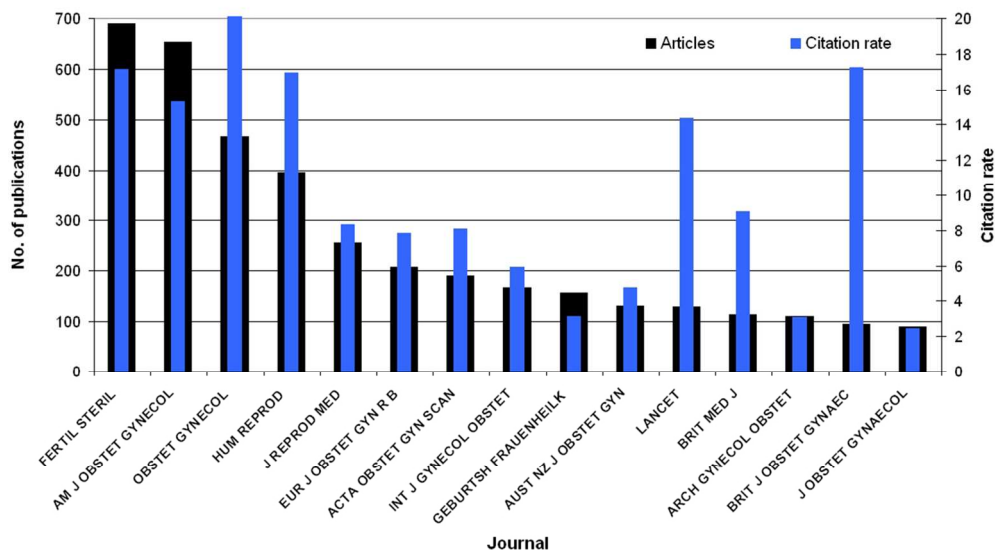
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Country-specific analysis of assigned subject categories. Analysis was performed of the 10 most active countries in ectopic pregnancy research in order to identify regional differences in ectopic pregnancy research.

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View only



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

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review only

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