Pregnancy Hypertension 18 (2019) 67–74

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

Quality of evidence on pre-eclampsia in the last three decades: An analysis of published literature

Hannah T.Y. Wang[a,1], Alston G.J. Ong[a,1], James M. Kemper[a], Ben W. Mol[a,b], Daniel L. Rolnik[a,b,*]

[a] Department of Obstetrics and Gynaecology, Monash University, Clayton, Victoria, Australia
[b] Monash Women's, Monash Health, Clayton, Victoria, Australia

ARTICLE INFO

Keywords:
Medical research
Pre-eclampsia
Randomized trials
Quality

ABSTRACT

Objectives: In recent years, there has been an increasing amount of information published on pre-eclampsia. We analyzed trends in pre-eclampsia literature between 1997 and 2016 and reported on the quality and utility of randomized controlled trials (RCTs) between 1987 and 2016.
Methods: We searched PubMed for all articles containing "pre-eclampsia" or "hypertensive disorders of pregnancy" in the title between 1997 and 2016 for the general literature and between 1987 and 2016 for RCTs. An analysis was performed based on study type, languages and publications from high-impact journals. Specific to RCTs, a quality and utility analysis based on the CONSORT guidelines and a usefulness checklist was adapted. An analysis by continents and proportion of RCTs published was also performed. Bibliometric network maps were created to determine trends in pre-eclampsia literature.
Results: In total, 9654 articles were identified, with a doubling in the number of annual average publications from 310 to 655 between 1997 and 2016. This increase occurred in both English and non-English publications. There was a decline in the proportion of publications from selected high-impact journals from 22% in 1997–2001 to 8% in 2012–2016. Out of the available 130 RCTs that we analyzed, the number of RCTs published in 5-yearly periods remained relatively stable between 1987 and 2016, with quality and utility scores increasing from 24.6 and 11.6 to 31.9 and 13.3, respectively. A geographical search by continents showed that North America produced the majority of RCTs, followed by Asia and Europe. For completed pre-eclampsia trials that were registered between 2005 and 2014, only 68% resulted in peer-reviewed publications.
Conclusion: The yearly number of publications on pre-eclampsia has substantially increased, with a stable number of high-level study types and publications from high-impact journals. The reporting quality and usefulness of RCTs relating to pre-eclampsia have improved over time.

1. Introduction

Pre-eclampsia, defined as new onset hypertension after 20 weeks of pregnancy with significant proteinuria [1], accounts for considerable maternal morbidity and mortality, more than 12% of small for gestational age infants, and one-fifth of all preterm births [2]. It also poses a financial burden to health systems, with disease-related costs estimated at US$ 2.2 billion annually in the United States of America [3].

Medical research aims to improve healthcare by providing new insights to areas of medicine. It can be encompassed by basic and clinical research, which targets clinical fields of screening, prevention, diagnosis and treatment. There has been an expansion in research over the past four decades; a mean of 442,756 articles were published annually between 1994 and 2001, a 46% increase from 1978 to 1985 [4]. This growth in literature corresponded with a tripling in the number of randomized controlled trials (RCTs) from 1.9% to 6.2% from 1978 to 2001 [4].

There is concern about waste in medical research. Research findings are at times unreproducible, with suboptimal study designs, small sample sizes and lack of transparency [5]. Approximately US$ 240 billion is spent annually on biomedical research worldwide, but about 85% of these research resources are estimated to be wasted [5,6]. Furthermore, low-quality studies may exacerbate uncertainties and cause pollution within the scientific literature, rather than adding value and ensuring progress [7]. Apart from the quality of the research, its utility has also been called into question; several key features that make clinical research useful have been identified, but many studies still fail to satisfy these features [8]. Unreliable clinical research has

* Corresponding author at: Department of Obstetrics and Gynaecology, Monash University, 246 Clayton Road, Clayton 3168, Victoria, Australia.
E-mail address: daniel.rolnik@monash.edu (D.L. Rolnik).
[1] HTYW and AGJO contributed equally to this article.

https://doi.org/10.1016/j.preghy.2019.09.005
Received 20 May 2019; Received in revised form 8 September 2019; Accepted 11 September 2019
Available online 20 September 2019

consequences for clinical decision making, with estimates that up to 50% of healthcare services delivered are inappropriate, wasting clinical resources and having negative impacts on patients' health [9,10].

The aim of this study is to evaluate research in pre-eclampsia, focusing on publications in the last two decades, and conducting an analysis of quality and utility of RCTs in the last three decades.

2. Materials and methods

2.1. Search terms

We conducted a search on PubMed with the aim of capturing all articles published between 1997 and 2016 about pre-eclampsia. This was performed using the search terms "Pre-eclampsia [Title] or pre eclampsia [Title] or preeclampsia [Title] or hypertensive disorders of pregnancy [Title]" and filtered to years 1997–2016.

2.2. Description of studies

To analyze the spread of literature, 13 'study type' filters in PubMed were applied to reflect four periods of five years each over two decades (1997–2001, 2002–2006, 2007–2011 and 2012–2016). Articles were filtered downwards from study type in a selected hierarchy, in the order of RCT and controlled clinical trial (CCT), meta-analysis, systematic review, clinical study and clinical trial, review, comparative and observational study, case reports, editorial, letter and multicenter study. RCT/CCT were subjectively designated as the highest-order study type by the authors, as it could be justified that a properly designed large scale RCT could be arguably better than a meta-analysis of small poor-quality studies. As PubMed articles could have multiple labels of study type attached, the highest label from the selected hierarchy was assigned to an article and excluded from the subsequent search, to ensure accurate allocation of study type.

The 'languages' filter was also applied to determine the trend of publications in English and other languages.

2.3. High-impact journals

MEDLINE results were exported to Microsoft Excel for Windows 10 Version 2016. To assess the spread of articles published in high-impact journals, we determined a list of seven general high-impact journals including the British Medical Journal (BMJ), the Canadian Medical Association Journal (CMAJ), the Cochrane Database of Systematic Reviews, the Journal of the American Medical Association (JAMA), the Lancet, the New England Journal of Medicine (NEJM), and the Public Library of Science (PLOS) Medicine. Five journals from the field of Obstetrics and Gynecology, namely the American Journal of Obstetrics and Gynecology (AJOG), the British Journal of Obstetrics and Gynaecology (BJOG), Human Reproduction (Hum Rep), Ultrasound in Obstetrics and Gynecology (UOG), and Obstetrics and Gynecology were added to form a total of 12 high-impact journals. The number of articles published from each high-impact journal were analyzed to show the trend over time.

2.4. Bibliometric network maps

Bibliometric network maps were created for each five-year period utilizing VOSviewer Version 1.6.9 (Visualizing Scientific Landscapes, Centre for Science and Technology Studies, Leiden University, The Netherlands), a data visualization software. The size of the node indicated greater occurrence of a term in the literature, while shorter distances between nodes implied that terms were more closely related to each other. The authors manually assigned colors to each cluster highlighting their research fields, based on analysis of terms in a cluster.

2.5. Randomized controlled trials

A separate PubMed search using the following search terms was conducted: "Pre-eclampsia"[Title] OR "preeclampsia"[Title] OR "pre-eclampsia"[Title]. The in-built PubMed filter was used to restrict search results to RCTs only and the timeframe was set to 1987–2016, a decade longer than the original search to incorporate more RCTs into the analysis due to the limited number of RCTs available. The study authors manually excluded articles that were not true RCTs, secondary analyses of randomized trials and non-English language RCTs.

To assess for quality, articles were scored against the Consolidated Standards of Reporting Trials (CONSORT) 2010 checklist, a 25-item list with a maximum score of 37 that provides a standardized format for reporting trials, endorsed by many medical journals as part of a broader effort to improve quality of research in healthcare [11]. To assess for utility, the authors developed an eight-domain checklist with 20 subcategories based on a previously published list by Ioannidis [8] (Supplement A), allowing for a maximum score of 20. The eight domains include significant problem base, context placement, information gain, pragmatism, patient centeredness, value for money, feasibility, and transparency. A geographical analysis of RCTs was carried out by determining the country and continent of publication.

2.6. Trial registration and publications

To assess for possible publication bias, a search was performed to identify randomized trials on pre-eclampsia registered between 2005 (when trial registration was made a requirement) and 2014 (to allow for completion of such trials) on the World Health Organization (WHO) International Clinical Trials Registry Platform. This platform provides access to a central database containing several trial registration data sets. We used the in-built filter to include trials that have stopped recruiting, and filtered, using Microsoft Excel for Windows 10 Version 2016, trials having pre-eclampsia in the title or listed as a primary outcome. Trials were excluded manually if they were not yet completed, terminated prematurely, tagged as an observational study or non-randomized trial, or registered in a language other than English.

To further improve accuracy of the search, the following databases were also searched individually: ClinicalTrials.gov, International Standard Registered Clinical/Social Study Number (ISRCTN), and the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT). Overlaps were accounted for and removed. The scientific title and principal investigator name of selected trials were searched for in PubMed, to evaluate the proportion of trials that were published and peer-reviewed.

3. Results

The initial search returned 9654 articles. There was an increase in the number of articles published over time, with the average number of publications per year approximately doubling from 310 articles in the period 1997–2006 to 655 articles in the period 2007–2016.

The 'language' filter identified a total of 9517 articles in English or other languages; 137 articles did not have a PubMed language tag and thus were not incorporated. There was a steady rise in English articles published annually from 1997 to 2016, with a doubling of English articles between 2009 and 2016 (Fig. 1). The number of non-English language articles also increased over the decades; eight percent of all publications were published in 24 languages other than English, with the majority being Chinese (186/9517, 1.95%), followed by Spanish (130/9517, 1.37%) and French (117/9517, 1.23%). Spanish articles were the largest contributor to non-English publications up to 2011, when a 50% increase in Chinese publications from the previous year made the latter the main contributor.

An analysis by study type showed that higher level of evidence study types accounted for a minority of published literature and

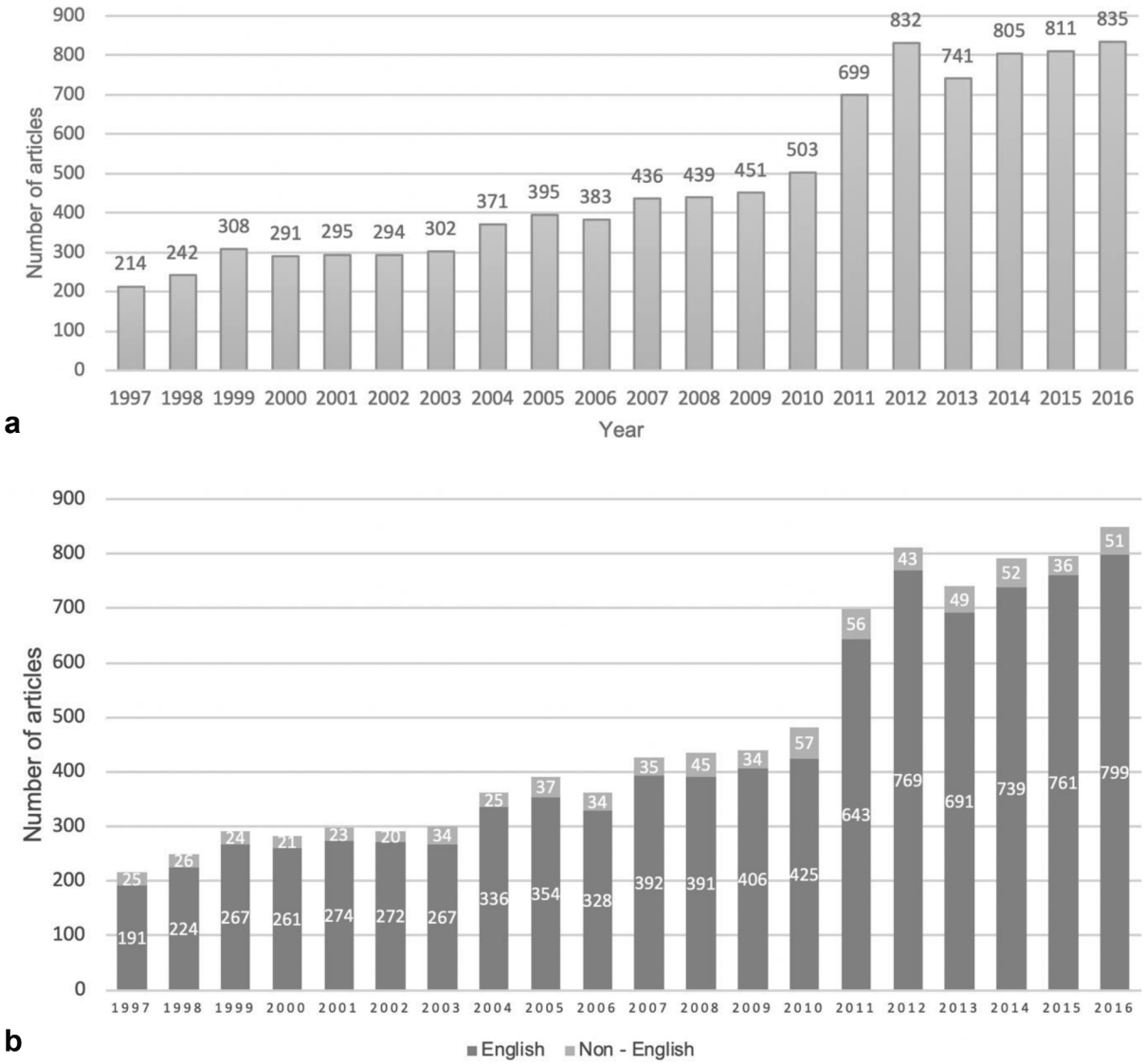


Fig. 1. a: Overall number of pre-eclampsia articles from 1997 to 2016; b: Number of English and non-English pre-eclampsia articles from 1997 to 2016.

remained relatively stable from 1997 to 2016. A combination of RCTs and CCTs comprised 3% (280/9656) of published literature, whilst meta-analyses comprised 2% (175/9656), as seen in Supplementary Fig. 1. The number of RCTs decreased from 1997 to 2011, before increasing between 2012 and 2016. Meta-analysis publications showed a steadily increasing trend over the decades, whilst the proportion of systematic reviews remained consistently low over time (92/9656, 1%). In contrast, lower levels of evidence, such as case reports (347/9656, 3.6%), contributed to a greater proportion of publications, despite showing a decreasing trend across the decades. The greatest proportion of the literature was tagged as 'review' (1096/9656, 11.4%).

Publications in high-impact journals remained constant over time, averaging 272 articles per five-year period from 1997 to 2016. The proportion of all pre-eclampsia articles published in high-impact journals declined from 22% (291/1344) in 1997–2001 to 8% (229/2593) in 2012–2016, indicating a rise of publications from non-high-impact journals. Among the selected high-impact journals, AJOG had the highest number of publications (525/1088, 48%), followed by UOG (125/1088, 11%) and BJOG (114/1088, 10%).

To gain a better understanding of the evolution of study types over time, VOSviewer was used to analyze terms in articles to create network maps. An overview of pre-eclampsia literature from 1997 to 2016 in Fig. 2 showed that most publications were interventional and pathophysiology studies, with a smaller proportion of cohort, genetic and screening studies. An analysis of literature in periods of five years showed that 2002–2006 first marked a significant proportion of interventional studies, before which the research focus was on cohort studies (Supplementary Fig. 2a and 2b). The popularity of interventional studies rose between 2007 and 2011 (Supplementary Fig. 2c), before replacing cohort studies as the only research study type for management of pre-eclampsia in 2012–2016 (Supplementary Fig. 2d). The prevalence of pathophysiology, genetic and screening studies remained constant over the decades.

The initial search for RCTs from PubMed yielded 262 results between 1987 and 2016; of these, 132 results were excluded on the basis that 84 were non-interventional studies, one was a non-RCT interventional study, 15 were RCTs not available in English, 29 were RCTs that could not be found online, and three were RCTs that were mislabeled and thus did not fall within the timeframe of our study (Fig. 3); therefore, 130 RCTs remained to be analyzed.

A sub-group analysis of RCTs from high-impact journals (52/130, 40%) was carried out. There was a rise in the proportion of RCTs from high-impact journals from 9% (1987–1996 = 12/130) to 21% (1997–2006 = 27/130) between the first and second decade, before approximately halving thereafter in the third decade (2007–2016 = 13/130, 10%). Obstetrics and Gynecology had the

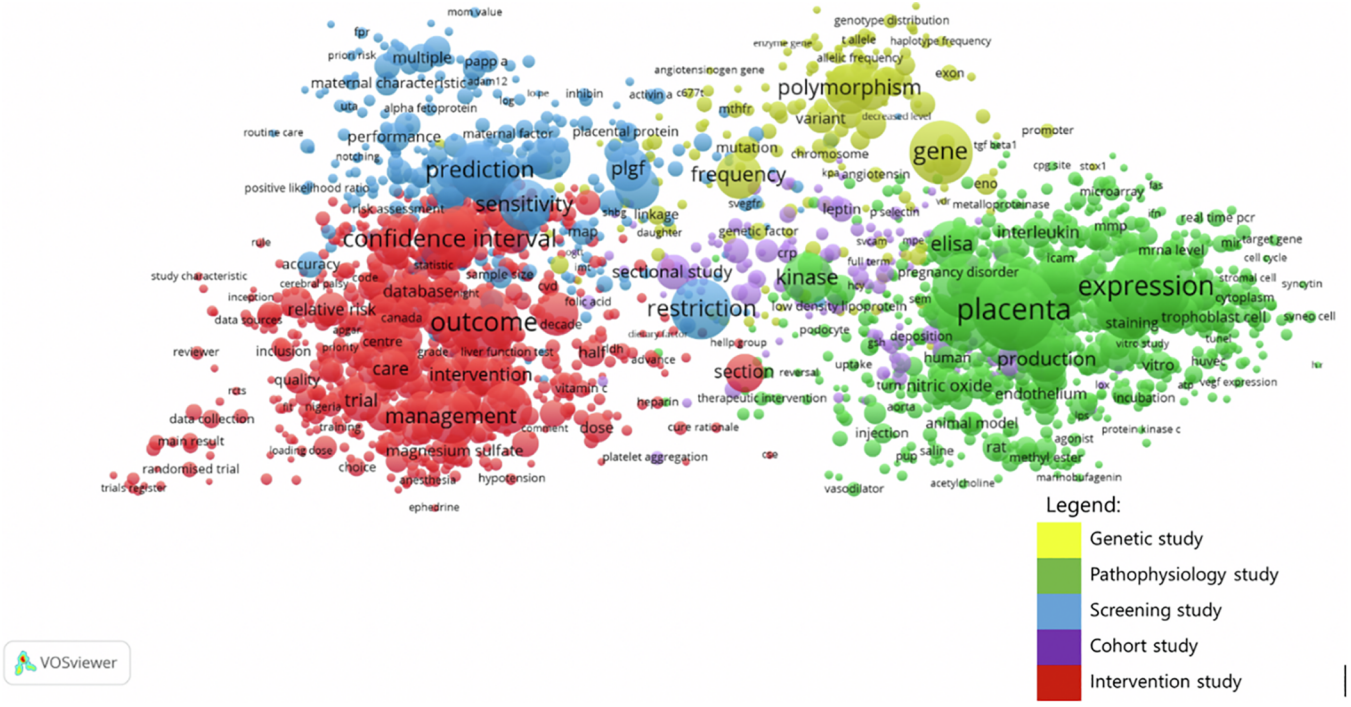


Fig. 2. Network map of pre-eclampsia articles from 1997 to 2016 (legend also applies to all other network maps in Supplementary Fig. 2).

highest proportion of publications (18/130, 14%), followed by AJOG (14/130, 11%), Lancet (7/130, 5%) and BJOG (5/130, 4%). The average usefulness scores of the RCTs from high-impact journals increased across the decades, improving from 59% (11.8/20, n = 12) in 1987–1996 to 65% (13/20, n = 27) in 1997–2006 and 74% (14.8/20, n = 13) between 2007 and 2016. All RCTs from high-impact journals exceeded the average RCT usefulness score of 12.4, with the highest scoring journals being BMJ (17/20, 85%, n = 1), followed by Lancet (14.9/20, 75%, n = 7), NEJM (14.3/20, 71%, n = 4) and BJOG (14/20, 70%, n = 5).

When including all 130 RCTs, an overall positive trend with increasing quality and utility of RCTs published over the years was noted (Table 1), however with great variation of individual scores within both quality and utility checklists. The poorest-performing CONSORT quality criterion was “availability of trial protocol”, with only eight percent of the articles fulfilling this criterion (Fig. 4a). The best-performing CONSORT quality criterion was “revealing the reason behind early trial cessation”; all articles either stated the reason for early trial cessation or were able to complete the trial. During the three-decade timeframe, the average CONSORT score was 78%.

In terms of utility assessment, none of the articles satisfied the criterion of having patient input prior to the trial and indicating the amount of funding received (Fig. 4b). The best-performing utility criterion was “sufficient follow-up period”, with 99% of the articles fulfilling this criterion. On average, articles scored approximately 62% of the total possible score for the utility checklist.

A geographical analysis by continents showed that North America produced the majority of RCTs (41/130, 32%), followed by Asia (36/130, 28%), Europe (29/130, 22%), South America (11/130, 8%), Africa (10/130, 8%) and lastly Australia (3/130, 2%). When analyzing the average usefulness scores of subcontinents, Africa produced the highest scoring RCTs (13.8/20, 69%, n = 10), followed by Australia (12.7/20, 64%, n = 3), Europe (12.3/20, 61%, n = 29), South America (12.1/20, 61%, n = 11), North America (12/20, 60%, n = 41) and Asia (12/20, 60%, n = 28).

The search in the WHO database identified 161 registered trials on pre-eclampsia that were no longer recruiting. 89 trials were excluded as they were not completed, were terminated prematurely, were not RCTs or were registered in languages other than English. Of the remaining 72 RCTs, 49 (68%) had at least one peer-reviewed publication, and 32% (23/72, n = 23) appear to not have been published (Table 2).

4. Discussion

4.1. Main findings

The overview of research showed an increase in the number of publications and lower evidence studies related to pre-eclampsia, while the number of studies from high-impact journals remained stable. To our knowledge, this is the first study to date evaluating quantity, quality and utility of evidence on pre-eclampsia.

Recent studies have found an increasing presence of Chinese articles in medical literature [12]. The rise of Chinese language articles from 2011 onwards in the results suggests that China and Asia play an increasing role in the expansion of pre-eclampsia literature. Reasons behind the increase in Asia’s scientific output could be attributed to its growing economy and increased government funding of research and development industry [12], which is also supported by our analysis by continent. Given that most medical journals publish in English, the most accepted language for communication between scientists around the world, our results may underestimate the number of articles in languages other than English since often these articles are not indexed in PubMed.

A minor proportion of articles were high-level evidence studies including RCTs, meta-analyses and systematic reviews. Moreover, an even smaller amount of these publications may be clinically relevant; a recent evaluation estimated that only 3% of published meta-analyses were reliable and useful [13]; and with regard to the rising number of meta-analyses produced in China, the majority of those related to candidate gene associations were unreliable [7].

There is also a concern that outcomes of some RCTs may have misleading conclusions; Flacco et al. revealed that 96.5% of non-inferiority trials reached conclusions that supported the use of a new intervention [14], an ongoing concern with industry-sponsored RCTs. The declining proportion of research from higher levels of evidence may not be entirely negative as, although it points to an increase in

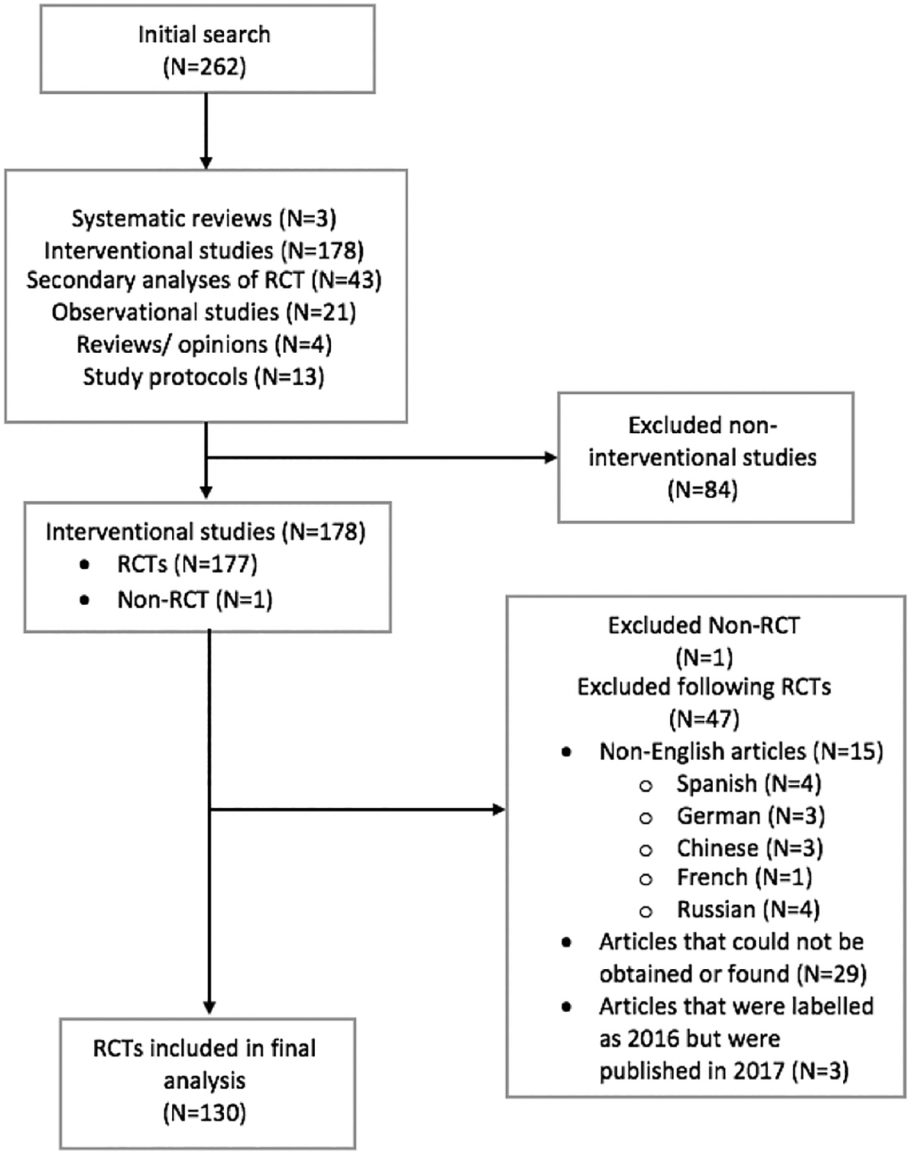


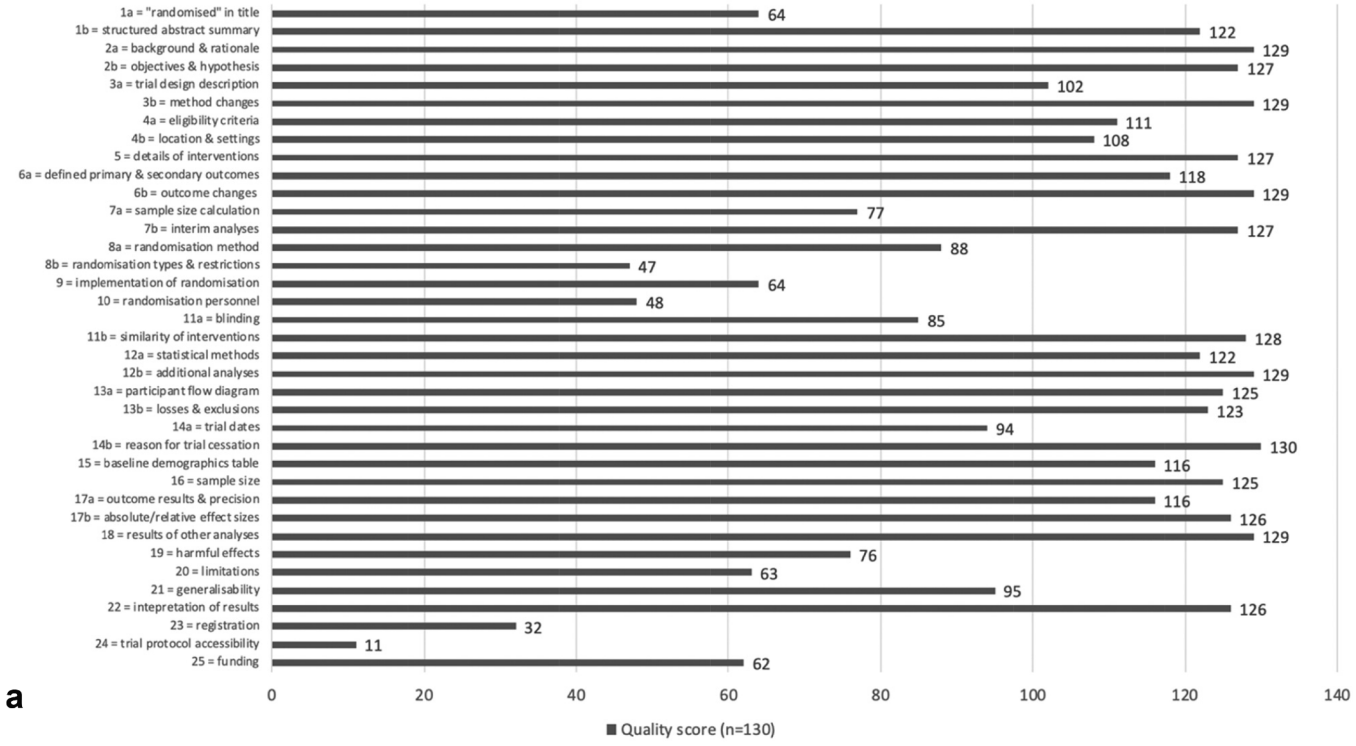
Fig. 3. Pre-eclampsia randomized controlled trials search results between 1987 and 2016.

Table 1
Average quality and utility scores in 5-year periods among randomized controlled trials.

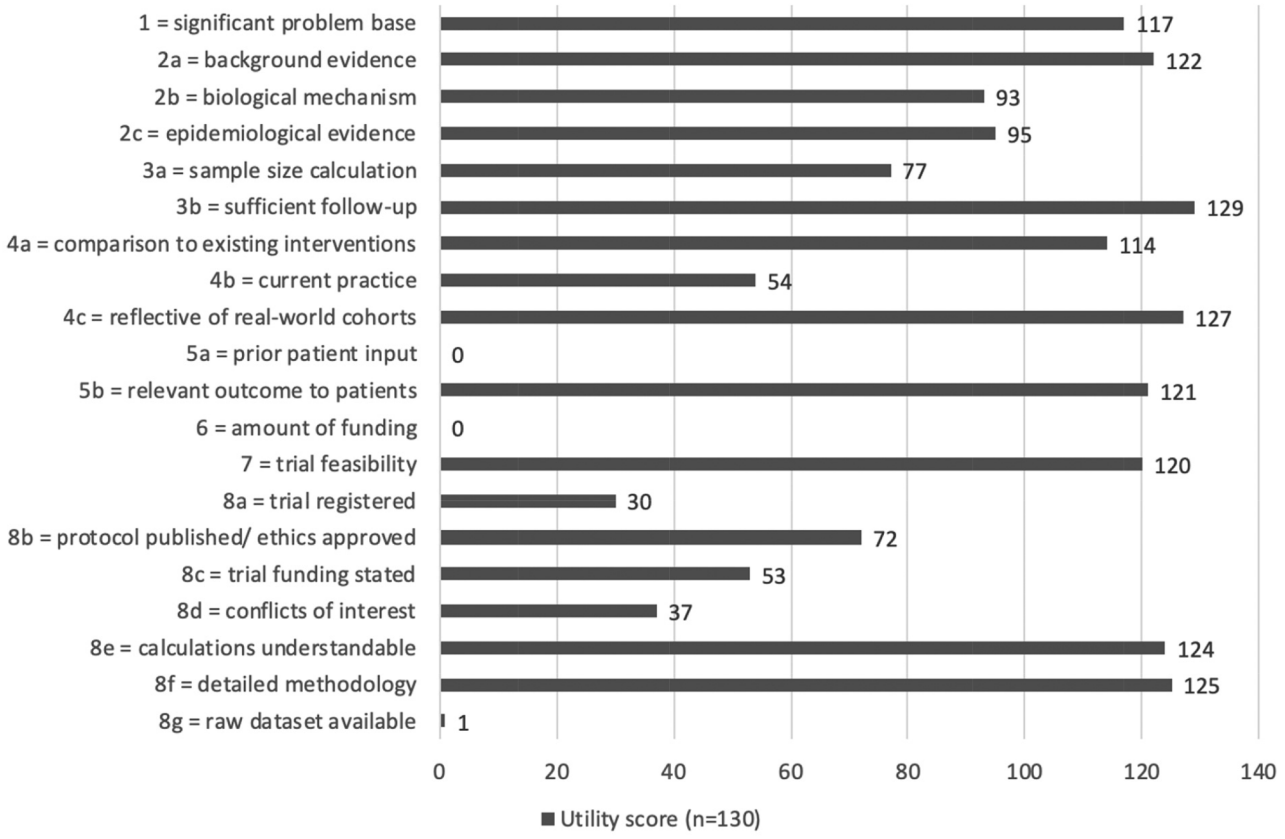
Time period	Quality score (out of 37)	Utility score (out of 20)
1987–1991 (n = 5)	24.6	11.6
1992–1996 (n = 18)	24.9	11.3
1997–2001 (n = 26)	27.1	12.0
2002–2006 (n = 30)	28.1	12.2
2007–2011 (n = 22)	31.3	13.0
2012–2016 (n = 29)	31.9	13.3

number of publications from non-high-impact journals that may publish lower levels of evidence, the absolute numbers of high-impact journals' publications remained stable. Previous studies have similarly identified that overall scientific literature has expanded; our study provides novel insights in assessing the quality of evidence through indirect and direct means. We indirectly evaluated quality through the analysis of publications from high-impact journals and spread of study themes through bibliometric network maps; the scoring of RCTs allowed direct judgement of study quality. Our findings showed a constant publication rate from each high-impact journal per annum, accounting for the diminishing proportion of publications from high-impact journals as the number of overall publications has increased. This does not directly indicate a decline in quality, as high-impact journals may have a regular publication schedule and a fixed number of publications per year, and thus cannot meet the demands of the growing number of articles with potential to be published. Indeed, a direct analysis of RCTs from high-impact journals further showed an overall increase in quality, with these RCTs scoring higher than average on the usefulness index. Approximately a third of the registered randomized trials on pre-eclampsia did not result in a peer-reviewed publication, suggesting the possibility of publication bias, which represents a higher likelihood of publishing trials with positive findings as compared to those with negative results, potentially overestimating treatment effects.

The use of VOSviewer provides a new insight to publication trends over time; findings revealed sizable proportions of genetic and pathophysiology studies that remained constant over the decades, aligning with research areas of concern highlighted in a clinical review by Steegers et al., who suggested priority should be given to genetic studies that elucidate the pathogenesis of pre-eclampsia [15]. Approximately ten percent of article types from 1997 to 2016 were



a



b

Fig. 4. a: Number of RCTs fulfilling each CONSORT criterion; b: Number of RCTs fulfilling each utility criterion.

Table 2
Search results from registration databases.

Registry	Registrations	Registrations excluded	RCTs post-exclusion	Publications	Publication rate (%)
ACTRN	10	4 observational 2 non-randomized trial 1 terminated prematurely	3	2	66.7
ChiCTR	3	2 observational 1 ongoing	0	–	–
CTRI	2	0	2	2	100
DRKS	3	3 observational	0	–	–
EuCTR	4	3 not in English	1	1	100
IRCT	8	1 non-randomized trial	7	7	100
ISRCTN	14	2 observational 1 non-randomized trial	11	8	72.7
JPRN	3	1 observational 1 non-randomized trial	1	0	–
NCT	109	47 observational 9 non-randomized trial 1 ongoing 7 terminated prematurely	45	27	60.0
NTR	2	2 observational	0	–	–
PACTR	3	1 ongoing	2	2	100
Total	161	89	72	49	68.1

ACTRN: Australian New Zealand Clinical Trials Registry; ChiCTR: Chinese Clinical Trial Registry; CTRI: Clinical Trials Registry – India; DRKS: German Clinical Trials Register; EuCTR: European Union Clinical Trials Register; IRCT: Iranian Registry of Clinical Trials; ISRCTN: International Standard Randomized Controlled Trials Number; JPRN: Japan Primary Registries Network; NCT: National Clinical Trial; NTR: Netherlands Trial Registry; PACTR: Pan African Clinical Trial Registry.

observational studies or case reports possibly correlating with genetic research.

4.2. Limitations

Our findings are solely from MEDLINE, PubMed's main database; while MEDLINE remains one of the biggest indexes of biomedical literature, other databases exist that were not utilized for this study due to the sheer amount of results. The true estimate of articles published over the years may be impossible to obtain. Given the overwhelming amount of publications on the subject, we focused on grading RCTs, a high study type on the research hierarchy, to make a global assessment on literature. Quality of non-RCT research was not directly measured. Additionally, a weakness in using VOSviewer to map research findings is that although trends can be visualized over time, it is impossible to obtain an exact value for the number of articles in each cluster. There was also difficulty obtaining 44 full articles of all 174 the RCTs identified in the search, leading to a possible under-representation in our results.

4.3. Implications

In keeping with the marked increase in annual number of pre-eclampsia articles, a recent study demonstrated that more than 9000 researchers can be considered hyper-prolific [16], and yet it is known that a significant proportion of research funding is wasted [17]. A series of five articles was published in The Lancet in 2014 addressing the reduction of research waste and improvement of research values, recommending improved transparency as a key factor in raising the value of research [6,18–20]. This recommendation is supported by our proposed utility criterion and our results in assessing transparency via domains such as trial registration, declaring conflicts of interests and availability of raw dataset. Our findings on prior patient input for RCTs also agree with the recommendation for adopting more efficient practices such as involvement of patients in designing the trial [21]. Patients and stakeholders should play a greater role in the design of research and its implementation to ensure woman-centered research that improves clinical outcomes [22]. Although the value of research appears to be improving, a significant proportion of the published research is of low or moderate utility and much more could be done to improve research efficiency. Recommendations for improvement include a list of research priorities co-driven by patients, use of core outcome sets for randomized controlled trials, and collaboration to give them sufficient power. At the same time, redundant meta-analyses, smaller retrospective and other low-quality studies should be avoided, while non-preregistered RCTs should not be published.

5. Conclusions

Although clinical research on pre-eclampsia is increasing, caveats exist that compromise the quality and usefulness of research results. Given the vast amount of information published that is not necessarily of high-quality, clinicians should critically appraise research articles, to avoid making misguided medical decisions at the patients' expense. There is concern as to whether recent clinical research has contributed to new findings that improve pregnancy and long-term health outcomes; future research goals should aim to enhance the quality of published literature by having women-centered and well-conducted, pragmatic studies.

Authors' roles

BWJM and DLR conceived of the idea for this paper. HWTY conducted the overview analysis of literature with review from BWJM and DLR. AGJO conducted the quality and utility analysis for the RCTs. AGJO and HWTY wrote the initial draft manuscript, with subsequent editing and input from BWJM, DLR, JMK. All authors reviewed and agreed upon the final manuscript prior to submission.

Funding

No specific funding was received for this project.

Declaration of Competing Interest

BWM is supported by a NHMRC Practitioner Fellowship [GNT1082548] and reports consultancy for ObsEva, Merck Merck KGaA and Guerbet.

The other authors report no conflicts of interest.

Acknowledgements

Nil.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.09.005.

References

[1] M.A. Brown, M.D. Lindheimer, M. de Swiet, A. Van Assche, J.M. Moutquin, The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP), Hypertens. Pregnancy 20 (1) (2001) IX–XIV, https://doi.org/10.1081/PRG-100104165.

[2] L. Duley, The global impact of pre-eclampsia and eclampsia, Semin. Perinatol. 33 (3) (2009) 130–137, https://doi.org/10.1053/j.semperi.2009.02.010.

[3] W. Stevens, T. Shih, D. Incerti, T.G.N. Ton, H.C. Lee, D. Peneva, G.A. Macones, B.M. Sibai, A.B. Jena, Short-term costs of preeclampsia to the United States health care system, Am. J. Obstet. Gynecol. 217 (3) (2017), https://doi.org/10.1016/j.ajog.2017.04.032 237-248 e16.

[4] B.G. Druss, S.C. Marcus, Growth and decentralization of the medical literature: implications for evidence-based medicine, J. Med. Libr. Assoc. 93 (4) (2005) 499–501.

[5] J.P. Ioannidis, Why most published research findings are false, PLoS Med. 2 (8) (2005) e124, , https://doi.org/10.1371/journal.pmed.0020124.

[6] I. Chalmers, M.B. Bracken, B. Djulbegovic, S. Garattini, J. Grant, A.M. Gulmezoglu, D.W. Howells, J.P. Ioannidis, S. Oliver, How to increase value and reduce waste when research priorities are set, Lancet 383 (9912) (2014) 156–165, https://doi.org/10.1016/S0140-6736(13)62229-1.

[7] E.C.W. Group, Protect us from poor-quality medical research, Hum. Reprod. 33 (5) (2018) 770–776, https://doi.org/10.1093/humrep/dey056.

[8] J.P.A. Ioannidis, Why most clinical research is not useful, PLoS Med. 13 (6) (2016) e1002049, , https://doi.org/10.1371/journal.pmed.1002049.

[9] J.S. Garrow, What to do about CAM: how much of orthodox medicine is evidence based? BMJ 335 (7627) (2007) 951, https://doi.org/10.1136/bmj.39388.393970.1F.

[10] J.P.A. Ioannidis, M.E. Stuart, S. Brownlee, S.A. Strite, How to survive the medical misinformation mess, Eur. J. Clin. Invest. 47 (11) (2017) 795–802, https://doi.org/10.1111/eci.12834.

[11] K.F. Schulz, D.G. Altman, D. Moher, C. Group, CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials, BMJ 340 (2010) c332, , https://doi.org/10.1136/bmj.c332.

[12] W. Quan, B. Chen, F. Shu, Publish or impoverish: An investigation of the monetary reward system of science in China (1999-2016), 2017. https://arxiv.org/pdf/1707.01162.pdf. (Accessed 20/02/2019). Doi: 10.1108/AJIM-01-2017-0014.

[13] J.P. Ioannidis, The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses, Milbank Q. 94 (3) (2016) 485–514, https://doi.org/10.1111/1468-0009.12210.

[14] M.E. Flacco, L. Manzoli, S. Boccia, L. Capasso, K. Aleksovska, A. Rosso, G. Scaioli, C. De Vito, R. Siliquini, P. Villari, J.P. Ioannidis, Head-to-head randomized trials are mostly industry sponsored and almost always favor the industry sponsor, J. Clin. Epidemiol. 68 (7) (2015) 811–820, https://doi.org/10.1016/j.jclinepi.2014.12.016.

[15] E.A. Steegers, P. von Dadelszen, J.J. Duvekot, R. Pijnenborg, Pre-eclampsia, Lancet 376 (9741) (2010) 631–644, https://doi.org/10.1016/S0140-6736(10)60279-6.

[16] J.P.A. Ioannidis, R. Klavans, K.W. Boyack, Thousands of scientists publish a paper every five days, Nature 561 (7722) (2018) 167–169, https://doi.org/10.1038/d41586-018-06185-8.

[17] I. Chalmers, P. Glasziou, Avoidable waste in the production and reporting of research evidence, Lancet 374 (9683) (2009) 86–89, https://doi.org/10.1016/S0140-6736(09)60329-9.

[18] J.P. Ioannidis, S. Greenland, M.A. Hlatky, M.J. Khoury, M.R. Macleod, D. Moher, K.F. Schulz, R. Tibshirani, Increasing value and reducing waste in research design, conduct, and analysis, Lancet 383 (9912) (2014) 166–175, https://doi.org/10.1016/S0140-6736(13)62227-8.

[19] A.W. Chan, F. Song, A. Vickers, T. Jefferson, K. Dickersin, P.C. Gotzsche, H.M. Krumholz, D. Ghersi, H.B. van der Worp, Increasing value and reducing waste: addressing inaccessible research, Lancet 383 (9913) (2014) 257–266, https://doi.org/10.1016/S0140-6736(13)62296-5.

[20] P. Glasziou, D.G. Altman, P. Bossuyt, I. Boutron, M. Clarke, S. Julious, S. Michie, D. Moher, E. Wager, Reducing waste from incomplete or unusable reports of biomedical research, Lancet 383 (9913) (2014) 267–276, https://doi.org/10.1016/S0140-6736(13)62228-X.

[21] R. Al-Shahi Salman, E. Beller, J. Kagan, E. Hemminki, R.S. Phillips, J. Savulescu, M. Macleod, J. Wisely, I. Chalmers, Increasing value and reducing waste in biomedical research regulation and management, Lancet 383 (9912) (2014) 176–185, https://doi.org/10.1016/S0140-6736(13)62297-7.

[22] R. Townsend, J.M.N. Duffy, A. Khalil, Increasing value and reducing research waste in obstetrics: towards woman-centred research, Ultrasound Obstet. Gynecol. (2019), https://doi.org/10.1002/uog.20294.