Publication bias in the field of subfertility

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ABSTRACT

Publication bias, the selective publication of studies reporting statistically significant outcomes, can affect the total evidence available and may eventually compromise patient care. This study aims to assess whether the statistical significance of Randomised Controlled Trials (RCTs) abstracts in the field of subfertility correlates with their subsequent publication as full-text articles.

Abstracts presented at conferences from 2007 to 2009 captured by the Cochrane Menstrual Disorders and Subfertility Group Specialised Register (MDSGSR) were screened. Eligible abstracts included RCTs that investigated a fertility intervention and reported at least one reproductive outcome. Articles were searched on electronic databases including Embase, Pubmed, MEDLINE and CINAHL. Data were then extracted from the articles using a structured form. Authors were contacted if the articles were not found in the search.

Overall, 229 out of 337 RCTs retrieved were eligible, with 48% of 229 abstracts subsequently published. Preliminary analysis indicates that 38% were oral presentations, 1% were registered, and 3% were interim or preliminary analyses, 10% of studies acknowledged industry funding while the source of funding was not reported in 69%.

There was a statistically significant difference between the probability of abstracts reporting statistically significant outcomes and those reporting non-statistically significant outcomes being published (59% versus 43%, p=0.03). Of studies reporting non-significant results, 13% made a positive statement about their findings. This study suggests the presence of publication bias in the field of subfertility.

INTRODUCTION

Well designed Randomised Controlled Trials (RCTs) are the cornerstone of evidence-based medicine.[1,2] However, it has been suggested that many RCTs are either not submitted or not accepted for publication.

Publication bias is a phenomenon in which the probability of publication is influenced by the study result. The selective publication of articles that show statistically significant outcomes, or beneficial treatment effects, can affect the body of evidence available for physicians and policymakers to base their decisions. If the RCT fails to show any treatment difference, the researchers may be influenced by the results and lose interest in completing the study.

If the researchers produce a manuscript showcasing their negative findings, journal editors may fail to publish it as they consider such information less appealing to readers. Even when an RCT with non-statistically significant results gets published, it is unlikely to be in a high profile journal.[3] Hence, publication bias can arise due to the overexposure of positive result trials in leading journals. This in turn may lead to overestimation of treatment effects.

Meta-analysis is a method for combining the results of similar studies to give an overall indication of whether a specific intervention is beneficial or harmful for a specific health condition. Evidence based medicine relies increasingly on meta-analyses which are considered the top tier of evidence used by policy makers and physicians to make clinical decisions. As meta-analyses can be distorted by publication bias, the extent and consequence of this bias warrants investigation.

The problem of publication bias may be particularly likely to occur when the research is sponsored by entities with a vested financial interest in achieving positive results, such as pharmaceutical companies, as was highlighted in the recent Tamiflu controversy.[4] This highlights the need to examine the presence of publication bias in RCTs, especially those sponsored by pharmaceutical companies.

Ultimately, publication bias may contribute to inappropriate treatment decisions for patients that compromise their quality of care, and lead to the emergence of suboptimal healthcare policies and thwarted planning of future research that further deteriorates patient care standards.

AIM

This study aims to investigate if there is an association between the statistical significance of results reported in RCT abstracts and their subsequent publication as full-text articles from a cohort of abstracts from the Cochrane Menstrual Disorders and Subfertility Group Specialised Register (MDSGSR).

METHODS

Search strategy

The study started with a search for abstracts of RCTs from years 2007 to 2010 in the MDSGSR.

Selection criteria

Two authors independently screened all the abstracts to identify those that meet the eligibility criteria. Eligible studies had to be RCTs that investigated a fertility intervention, such as In-vitro fertilisation (IVF) or intrauterine insemination (IUI), and reported at least one reproductive outcome, such as pregnancy rates or implantation rate. Studies that solely reported endocrine or biochemical outcomes were excluded. After the screening process, any discrepancies in the list of included abstracts were resolved by consensus or consultation with a third author.

Data collection

Data was extracted from eligible abstracts. Information collected from the abstracts included title of abstract, list of authors involved, type of presentation (oral or poster), funding source, whether the study was registered, type of outcome (statistically significant or non-statistically significant), stage of study and country of origin. If a study was not stated to be in an interim stage, it was assumed to be completed.

Article publications were identified. A search for article versions of all included abstracts in the databases Embase, Pubmed, MEDLINE and CINAHL was carried out using the following match criteria: matching trial registry numbers and/or matching some of the same authors, and having an identical or very similar title, methodology and research question to the initial abstract.

Data was extracted from the article publications and the following information were collected: title of publication, list of authors, publication status, month and year of publication, name of journal and funding source.

Data analysis

Finally, data collected from this study was analysed. Characteristics of included abstracts were presented in a table format. The odds ratios were generated to evaluate whether there was a statistically significant difference between publication rates of studies with significant versus non-significant outcomes. All results were presented with 95% confidence intervals and associated p values, as appropriate. Tests were performed using a two-sided P-value of less than 0.05 for statistical significance.

Results

Of 327 abstracts screened from the MDSGSR, 229 abstracts were selected based on the eligibility criteria (Figure 1). Article publications were found for 111 article publications, representing a publication rate of 48%.

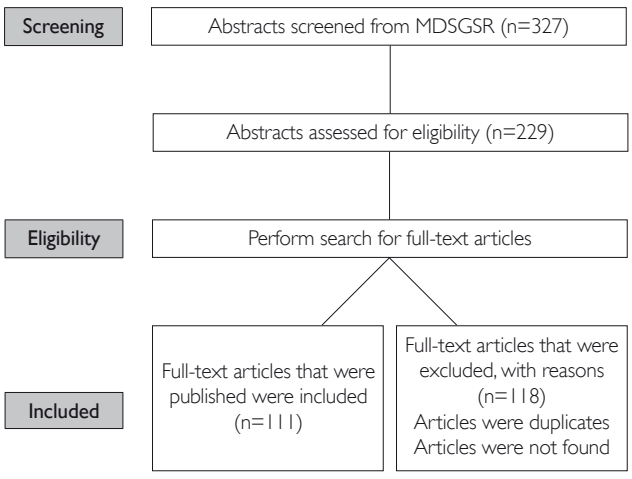

Figure 1. Flow of studies

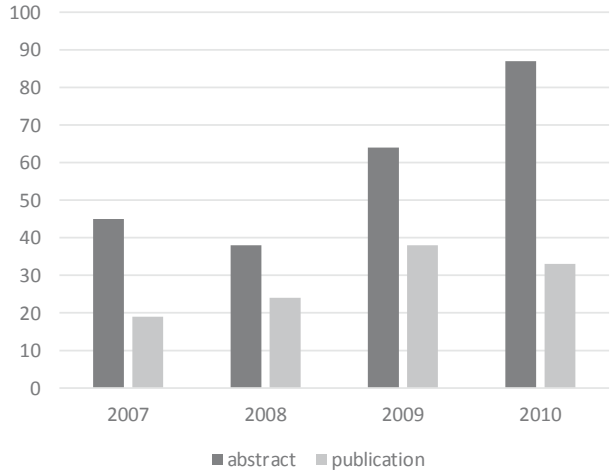

Figure 2. Comparison between number of abstracts versus article publications from 2007- 2010

Table 1 demonstrates a summary of the characteristics of the eligible abstracts, which also includes the percentage of trials in each category that were subsequently published. 38% of abstracts were oral presentations, the majority of abstracts originated from Europe and Asia, 1% were stated as registered, and 3% were stated as interim analyses. 10% acknowledged industry funding while the source of funding was not reported in 69% of studies.

A higher proportion of abstracts presented orally were found to be published than those presented in the form of a poster, with the difference being statistically significant (p=0.002). Abstracts originating from the UK and Australia/New Zealand also had a higher publication rate 71% & 65%. There was also a statistically significant (p=0.03) higher rate of publication for abstracts reporting significant versus non-significant outcomes. However, when the definition of statistically significant outcomes widened to encompass abstracts reporting non-significant outcomes yet positive findings , the difference in publication rate became non-statistically significant (p=0.23). Also, no differences were found when comparing the publication rates of articles with a difference in registration status and stage of study.

Figure 2 illustrates a comparison of the proportion of abstracts that were eventually published as articles over time. There is an overall increasing trend in the proportion of abstracts published as articles with the progression of time from 2007 to 2010. A statistically significant difference was found with regards to the proportion of abstracts published in subsequent years (p= 0.009).

DISCUSSION

It remains unknown how many RCTs on subfertility are never submitted to a scientific meeting. This discussion aims to explore and explain the different statistical findings derived from the current study, reflect on challenges faced in this study and comment on various methods that could be used to manage the problem of publication bias in medical research.

Of all abstracts of RCTs presented in the European Society of Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) annual meetings (2007-2010), 48% were found to eventually reach article publication status in scientific journals.[5, 6] Based on the current study conducted, the outcome of RCTs (statistically significant versus non-significant results) and country of origin affected the rate of publication. RCTs reporting statistically significant results, or positive outcomes favouring a new therapy, had a greater likelihood of being published, thus confirming the presence of publication bias in the field of subfertility. This may lead to an overestimation of the effects of subfertility therapy in the study.[5] These findings highlight that by using only published literature to examine the effectiveness of a new treatment, one could get a biased and inflated perspective of the treatment. It would be unethical

Table 1. Characteristics of subfertility abstracts screened from MDSGSR and publication rate

characteristics of MDSGSR subfertility abstracts	total number of abstracts (%)	number of published abstracts (%)	p-value
Type of presentation			
oral	88 (38)	56 (64)	0.002
poster	141 (62)	60 (43)	
Location of country			
UK	7 (3)	5 (71)	
South America	16 (7)	6 (38)	
Europe	74 (33)	39 (53)	
North America	44 (19)	19 (43)	
Asia	71 (32)	30 (42)	
Other (Pacific)	17 (6)	11 (65)	
Funding source			
Industry	24 (10)	12 (50)	
Government/Institution	11 (5)	7 (64)	
Charity	3 (1)	2 (67)	
None	33 (15)	12 (34)	
Not reported	158 (69)	77 (49)	
Any outcome			
Statistically significant	73 (32)	43 (59)	0.03
Non-significant			
Where definition of statistically significant outcome includes non-significant outcome with positive statement			
Statistically significant	94 (41)	50 (53)	0.23
Non-significant	135 (59)	61 (45)	
Registered			
Yes	3 (1)	2 (67)	0.56
No	226 (99)	112 (50)	
Stage of study			
Interim	6 (3)	5 (83)	0.12
Complete	223 (97)	106 (48)	

to falsely claim a treatment as effective based on a lacking in totality of evidence identified (both published and unpublished).

These results are in agreement with the findings of a meta-analysis, which found a publication rate of 51% for abstracts presented at 11 surgical, cardiology, anaesthesiology, paediatric, oncological, perinatology and ophthalmological meetings.[6] Another finding in agreement with this study is that RCTs accepted for oral presentation had a significantly higher chance of eventually getting published than poster presentations (p=0.002). This could be explained by higher quality research being reflected in better written abstracts which then qualified preferentially for oral presentations at the annual conference meetings, and by the same token for publication in the more prestigious journals.

Previous reports have shown that the lack of subsequent publication is often due to the lack of submission rather than rejection of manuscripts.[7, 8] This was usually due to lack of resources such as time, or loss of interest of authors in the study due to negative results produced not favouring a particular therapy.[9, 10] The survey of authors of unpublished RCTs will be conducted in the later phase of this study.

The influence of sponsorship has been explored in a limited number of studies. External funding was associated with a higher rate of full publication in two studies.[11, 12] The role of pharmaceutical industrial funding has been addressed in two studies, both of which found pharmaceutically sponsored trials to be less likely to be published.[13, 14] The data suggested that sponsorship by pharmaceutical industries acted as a moderate predictor of publication, with such studies producing the third highest rate of publication, after studies sponsored by charities and governmental institutions. The discrepancies between these study findings and those of previous studies might be due to a change in trends with time and inclusion of only RCTs, whereas previous reports included observational and case control studies.

Potential limitations of this study included the use of abstracts to identify trials, the limited range of abstracts screened in the MDSGSR and insufficient time to contact authors of unpublished studies. The disadvantage of using conference abstracts to screen for trials was that authors might be less inclined to submit abstracts reporting non-significant outcomes.[15] This may underestimate the effects of publication bias, as there may be many trials out there that were never presented at conferences or subsequently published.[16,17] The limited number of abstracts screened, and the specialized field of subfertility resulted in a smaller sample size for this study. This makes it challenging to reflect the true extent of publication bias in the general medical literature for this field solely based on these study results.

CONCLUSION

Although the collection of RCTs presented at scientific meetings in this study did not capture the entirety of RCTs performed in the field of subfertility, it still provided a useful filter to examine the presence of publication bias. By investigating all subfertility studies captured in the MDSGR we confirmed that publication bias does exist. We strongly urge funding agencies, governmental Institutions, health policymakers, researchers, and clinicians to work together to eliminate this important and increasingly serious problem.[18, 19] Possible methods that could be used to manage publication bias include an improved research standard that mandates the pre-registration of protocols for RCTs, performing higher powered RCTs by increasing size of study and increasing the use of online open access journals which may actively encourage the publication of negative results.[20 21]

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