Review

Identification and description of controlled clinical trials published in Spanish Gynaecology and Obstetrics journals and risk of bias assessment of trials on assisted reproductive techniques

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ABSTRACT

Objectives: To identify and describe controlled clinical trials (CCTs) published in Spanish Gynaecology and Obstetrics journals. In addition, to assess the quality of the CCTs on Assisted Reproduction Techniques (ART) identified in this project.

Study design: In order to identify eligible CCTs, all Spanish Gynaecology and Obstetrics journals were handsearched. Handsearching was conducted following the guidelines provided by the Cochrane Collaboration, which state that each journal article must be carefully reviewed, including original articles and other types of studies, letters to the editor, abstracts, and conference presentations. The results of the handsearching process were compared with an electronic search conducted in MEDLINE (PubMed). A descriptive analysis of the main characteristics of the identified CCTs was performed, as well as a methodological assessment of CCTs on ART.

Results: Sixteen Gynaecology and Obstetrics journals were identified, four of which have been indexed in MEDLINE at some point, although not currently. The journal with the most CCTs was "Progresos de Obstetricia y Ginecología". A total of 235 CCTs were published in these journals, of which 29 were on ART. Most CCTs (216, 91.9%) were carried out in a hospital setting; 201 (89.4%) were unicentric. Obstetrics was the most studied subspecialty (46.4%). Among CCTs on ART, the risk of bias was predominantly high.

Conclusions: The number of CCTs published in Spanish Gynaecology and Obstetrics journals is limited. CCTs on ART present deficiencies in the report of results and low methodological quality. It is advised that authors and journals adhere to the CONSORT statement and to the Cochrane Collaboration recommendations to reduce risk of bias when designing and disseminating research projects.

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Introduction

Well-designed and properly executed controlled clinical trials (CCTs) provide the best evidence on the impact of health interventions. Nevertheless, these might result in exaggerated estimates of this effect, if carried out using an inappropriate methodology [1–3]. Therefore, CCTs ought to be properly evaluated before being used in clinical practice. Evidence-Based Medicine (EBM) is defined as “conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” [4]. EBM depends largely on the methodological quality of the CCTs and its exhaustive identification. These features are equally indispensable for conducting systematic reviews (SR) [4,5] and Clinical Practice Guidelines (CPG) [6,7]. Given these prerequisites, identifying the highest number of CCTs is critical to have SR and CPGs with no publication bias.

It is known that the best strategy to identify clinical trials is to combine electronic and manual (handsearch) search strategies [8,9]. Electronic search strategies, widely used and based on filters and keywords applied to databases, are limited for different reasons [10–12]. First, because only since 2004 the World Health Organization (WHO) recorded CCTs of different languages, which means that many CCTs published in previous years may not have been included in this platform [12]. Second, because even though there are other bibliographic databases accessible online that allow identifying CCTs through electronic searching, the sensitivity of these searches is limited due to issues with classification (indexing) of the CCTs. In addition, the term “controlled clinical trial” was only indexed as such in 1990, and introduced in MEDLINE and EMBASE in 1991 and 1994, respectively. For this reason, it is considerably more difficult to identify older CCTs publications using algorithms and search filters [10,1].

Given this problem, the Cochrane Collaboration proposed to complement electronic search strategies with a handsearching strategy. Handsearching involves the progressive review of all articles (conference proceedings, theses, letters, editorials, etc.) published in a journal [8–13]. It requires a rigorous inspection, which allows the identification of CCTs that are not included in electronic databases, as well as CCTs that have not been properly indexed or that simply cannot be retrieved through an electronic search. Handsearching allows identifying 92% to 100% of CCTs available, whereas electronic searches of the main databases, MEDLINE and EMBASE, contribute only 55% and 49% of these, respectively [13]. This difference is due to the fact that the handsearching allows the identification of CCTs published before 1991, those published as abstracts or letters, and those published in languages other than English [8,13].

Several CCTs identification studies that combine electronic and handsearching strategies conducted in Pharmacology journals [14], General and Internal Medicine [15], Ophthalmology [16] and patient safety [17], confirm the limitations of electronic search strategies. Through these projects, it has been found that the sensitivity of electronic searches is about 77%, whereas the accuracy or specificity hovers around 50%, with cases in which it does not exceed 5% [15,17].

During recent years, there is a marked increase in scientific production published on Gynaecology and Obstetrics in Spanish language. To our knowledge, no handsearching project has been conducted so far in order to identify these CCTs. In reference to Assisted Reproduction Techniques (ART), and the importance of gathering all available evidence on this field, it is essential to evaluate the quality of work carried out [18,19], considering that since 1978, when the first baby conceived through Fertilization In vitro was born, ART techniques have evolved considerably without this being reflected in higher pregnancy rates [20–23].

This study was conducted in order to identify and describe the main features of CCTs published in Spanish Gynaecology and Obstetrics journals. Additionally, in order to obtain a clearer picture of the strengths and challenges of research in ART, a description of the methodological aspects and potential risk of bias of CCTs identified in this area was made. The studies identified in this article will be incorporated into CRS, the global CCTs registry of the Cochrane Collaboration.

Materials and methods

Identification of eligible journals and handsearching of clinical trials

The first step of this study consisted of determining which journals should be handsearched, considering eligible those that publish original research in the field of Gynaecology and Obstetrics. Eligible journals were identified through the Spanish Medical Index (SMI), the National Catalogue of Spanish Publications in Health Sciences Libraries C-17, Latindex, Periodic, LILACS, Scielo, and MEDLINE (PubMed). This search was carried out by a trained investigator who followed a protocol that established the order in which the sources had to be consulted. All relevant information for each journal was collected and their full texts were identified on the Internet, libraries, publishers, corporations, and other sources.

The handsearching of each journal was systematic and performed according to the guidelines of the Cochrane Collaboration, which establish that each journal must be carefully reviewed, not only original articles but also letters to the editor, abstracts and conference presentations. Handsearching consists of four stages: first, reading table of contents; second, location of keywords in the title of each article (randomized, random, fortuitous, blind, etc.); third, reading of the summary (abstract) of each article; and fourth, reading of the materials and methods section. The process must be completed retrospectively, i.e. backwards from the last year of publication. If no CCTs are found in a period of five years, handsearching for the corresponding journal must be stopped.

The process of handsearching involved 12 reviewers. Following the recommendations of the Cochrane Collaboration, each reviewer conducted a pilot test which involved handsearching of a volume journal that had been previously reviewed by personnel with expertise in this field.

Electronic identification of clinical trials

Additionally, an electronic search was conducted on MEDLINE (PubMed access) in order to identify CCTs amongst the eligible journals for this study and compare results with those of the handsearch. The search strategy used can be found in Annex 1.
Subsequently, we calculated the sensitivity and specificity of this search with the following definitions:

- **Sensitivity**: Proportion of all studies identified by the electronic search over those identified by handsearching.
- **Specificity**: Proportion of truly eligible studies among all those recovered by the electronic search strategy.

**Inclusion criteria**

To be considered a CCT, a study had to fulfil the eligibility criteria of clinical trials proposed by the Cochrane Collaboration:

(a) The study compares treatments in humans.
(b) The study is prospective (interventions are planned before the study takes place, and assignment of subjects to intervention is decided by the researchers).
(c) Two or more treatments or interventions are compared (one can be a control with no treatment or placebo group). Interventions can be of any type: drugs, surgery, diagnostic, educational, rehabilitative, organizational, etc.
(d) The allocation to treatments should be randomized or quasi-randomized:
   - Random: the authors explained that the compared groups were formed by random assignment, usually describing the allocation method.
   - Quasi-randomized: it attempts to produce similar groups to assign each participant intervention. The methods used include allocation according to date of birth of the subject, day or month of the year, even and odd numbers, or medical record number.

The review of journals was conducted individually. Two authors (RG and IA or DB) verified the eligibility of each possible CCT identified. Discrepancies were resolved by consensus or consultation with a third author (HP, XB).

**Data extraction**

Once the CCTs are identified and classified according to the previous criteria, in order to make a descriptive analysis of trials, the variables collected were evaluated in a data sheet specifically designed for this study.

Also, an assessment of risk of bias (high/medium/low) of the identified CCTs in ART was conducted using the Cochrane Collaboration tool recommended for this objective [9]. This tool values several aspects of the methodology of CCTs, including method of generating the allocation sequence, concealing of this sequence, blinding of patients or investigators, intention-to-treat analysis, reasons for missing data (where applicable) and other likely sources of bias.

**Analysis**

A descriptive analysis of the variables of interest was performed using SPSS version 17 (SPSS, Inc., Chicago, IL, USA). Central measures and dispersion measures were calculated and the features of quantitative variables were described. In addition, the absolute and relative frequencies of qualitative variables were calculated.

**Results**

Sixteen Gynaecology and Obstetrics journals were identified, of which 11 published CCTs. A total of 235 CCTs on different subspecialties were retrieved from these publications. The most active journal was *Progresos de Obstetricia y Ginecológica* with 54 CCTs (23%), followed by *Clínica e Investigación en Ginecología y Obstetricia* with 46 CCTs (19.6%) and *Acta Ginecológica* with 35 CCTs (14.9%) (Table 1). Of all the CCTs, 29 (12.3%) were of ART.

The first CCT was published in 1967 in *Acta Ginecológica* (Víctor Ruiz Velasco y Gonzalo Río de la Rosa. La pentazaicina en la alteración de la sed). The latest was published in 1990 in *Gynaecology Obstetrics and Fertility*. The year with the highest number of CCTs was 1982 with a total of 14 (6%), followed by 1990 with 12 (5.1%). The decade with the most identified CCTs was the 90s (Fig. 1).

A total of 187 (79.6%) of the CCTs identified were classified as randomized clinical trials (RCTs), whereas 48 (20.4%) were quasi-randomized. The most studied subspecialty was Obstetrics with 109 CCTs (46.4%), followed by Gynaecology with 72 (30.6%). The main researched topics were pregnancy and any associated conditions, including premature rupture of membranes, intrauterine growth restriction, preterm labour, gestational diabetes,
anaemia, and others (24.7%). Infertility treated with RMA was studied in 12.1% of the studies (Fig. 2).

The average age of participants in the identified CCTs was 34.04 years (DS 9.318), with a minimum age of 20 and a maximum of 60. However, age was reported only in 126 CCTs, representing 54.2% of the identified studies. Most studies were conducted among subjects with pathology, and the most common comparison was treatment versus treatment (156, 66.4%). Most CCTs were conducted in hospitals (216, 91.9%), followed by primary care centres (9, 3.8%). A total of 210 (89.4%) of the CCTs were single centre, compared to 9 (3.8%) multicentre (Table 2).

In 224 (95.3%) of the cases, the authors did not specify the sponsor(s) of the study, while nine (3.8%) reported receiving private funds and two (0.9%) public funds. 234 CCTs (99.6%) did not report whether there was a conflict of interest, compared to one (0.4%) that did report it (Table 2).

29 ART studies were identified in six of the eligible journals (Revista Iberoamericana de Fertilidad y Reproducción Humana, Revista Española Obstétrica Ginecológica, Acta Ginecológica, Progresos de Obstetricia y Ginecología, Tokoginecología Práctica and Actualidad Obstétrica Ginecológica). Regarding their methodological quality, we found that risk of bias was high in 20 CCTs (69%). In most (18, 62.1%), randomization sequence generation features were unidentifiable, while in nine (31%) randomization was performed properly. Only one CCT (3.4%) implemented a proper strategy to conceal allocation of patients to treatments or interventions. Double-blind assessment of results was adopted in five CCTs (17.2%). Intention-to-treat analysis was implemented in 21 studies (72.2%); in 24 (82.8%) all relevant data was reported, and groups were comparable at baseline in 22 (75.9%) studies (Table 3).

The electronic search conducted in MEDLINE allowed identifying five potential CCTs with no summaries (abstracts) available. These articles were identified in four journals: Acta Obstétrica Ginecológica Hispana Lusitana, Acta Ginecológica, Toko Ginecología Práctica, and Revista Española de Obstetricia y Ginecología. These journals are indexed in MEDLINE in different periods of time, although not currently. The full-text of the potential CCTs was

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**Table 2**

<table>
<thead>
<tr>
<th>Features</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speciality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynaecology</td>
<td>72</td>
<td>30.6%</td>
</tr>
<tr>
<td>Obstetrics</td>
<td>109</td>
<td>46.4%</td>
</tr>
<tr>
<td>Assisted Reproduction Techniques</td>
<td>29</td>
<td>12.3%</td>
</tr>
<tr>
<td>Gynaecologic Oncology</td>
<td>7</td>
<td>3.0%</td>
</tr>
<tr>
<td>Mastology</td>
<td>3</td>
<td>1.3%</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>15</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

**Key issues investigated in CCT**

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**Fig. 1.** Number of published CCT by decade.

**Fig. 2.** Key issues investigated in CCT.
was expected that the most studied problem would be ART, since Spain is one of the countries in the European Union with the lowest fertility rates (1.48 per female), along with Greece, Italy and Germany [24].

Most CCTs were single-centre (210, 89.4%) and were developed in hospital care (216, 91.9%), which is consistent with the fact that these studies were conducted mainly among patients with pathologies. The average age of participants was 34.04 years (DS9.318), but this variable was not reported in 104 CCTs, which represents 45.8% of the identified studies. These deficiencies coincide with similar studies in other specialties, with slight deviations [14,15]. It was detected that only 11 CCTs (4.9%) reported who was the promoter of the study, compared with 224 (95.8%) who did not. In the same line, 99.6% of CCTs did not report whether there were conflicts of interest, which is consistent with the results of other similar studies [15,17].

A total of 29 studies were on ART, equivalent to less than one per year. The leading journal in publishing on this subject was Revista Iberoamericana de Fertilidad y Reproducción Humana, with 85.2% of the total. In relation to the methodological quality of these studies, the majority present a high risk of bias. Randomization sequence generation characteristics are unknown in 62.1% of the cases, and frequently the sequence of allocation was not concealed. Furthermore, only 17.2% reported a method for blinding the interventions. These biases may overstate results of the corresponding studies [24]. On the other hand, over 70% of the CCTs completed an intention-to-treat analysis, 82.8% reported all clinical variables, and 75% had groups comparable at baseline groups. These data is encouraging because it contributes to reduce reporting and attrition biases [9].

This study emphasizes that the CCTs identified through handsearching would not have been identified via an electronic search in MEDLINE (PubMed). This is proof of the limitations of exclusively electronic searches and the invaluable role of handsearch in identifying CCTs, especially those reported as abstracts or letters to the editor, or reported in languages other than English [15–17]. Moreover, it is worth-mentioning the large number of publications reviewed: a total of 15 journals. Handsearching, in accordance with the criteria of the Cochrane Collaboration, was systematic and exhaustive for all volumes and supplements.

A possible limitation of this study is that the electronic and handsearching strategies were limited to Spanish journals. This may have left out CCTs published in foreign journals, or in journals that are not specifically on Gynaecology and Obstetrics. In addition, this paper focuses exclusively on studies in Spain: a study on journals from Latin American countries is being carried out at present. Another limitation is that the handsearching of journals were conducted individually, which could have left out some eligible CCTs. However, the possibility of false positives was minimized since the 235 CCTs identified were verified by at least two of the authors. Likewise, the possibilities of false negatives were minimized since each researcher conducted a pilot test to standardize the handsearching process.

In conclusion, the number of CCTs published in Spanish Gynaecology and Obstetrics journals is low. The CCTs identified in this study would not have been retrieved through an electronic search, which highlights the importance of handsearching of journals. Regarding CCTs on ART, the number of articles published is similarly low; they carry a high risk of bias in their methodology. Authors are advised to carefully consider the design and completion of CCTs, in order to minimize potential bias and ensure their methodological quality. They are advised to adhere to the Consolidated Standards of Reporting Trials (CONSORT) statement [25] when publishing the results of their studies.

Table 3
Risk of bias assessment of CCTs on ART.

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1</td>
<td>3.4%</td>
</tr>
<tr>
<td>Moderate</td>
<td>8</td>
<td>27.6%</td>
</tr>
<tr>
<td>High</td>
<td>20</td>
<td>69.0%</td>
</tr>
</tbody>
</table>

1. Selection bias Sequence generation
   - Adequate                      | 9      | 31.0%      |
   - Unclear                       | 18     | 62.1%      |
   - Inadequate                    | 2      | 6.9%       |

Allocation concealment
   - Adequate                      | 1      | 3.4%       |
   - Unclear                       | 26     | 89.7%      |
   - Inadequate                    | 2      | 6.9%       |

2. Performance bias Double blind
   - Adequate                      | 5      | 17.2%      |
   - Unclear                       | 0      | 0%         |
   - Inadequate                    | 24     | 82.8%      |

3. Detection bias
Blinding of outcome assessors
   - Yes                            | 0      | 0%         |
   - No                             | 5      | 17.2%      |
   - Not reported/Unclear           | 24     | 82.8%      |

4. Attrition bias (incomplete outcome data)
Analysis by intention to treat
   - Yes                            | 21     | 72.4%      |
   - No                             | 2      | 6.9%       |
   - Not reported/Unclear           | 6      | 20.7%      |

5. Selective reporting of results
   - Clinical                       | 24     | 82.8%      |
   - Intermediate                   | 2      | 6.9%       |
   - Not reported/Unclear           | 3      | 10.3%      |

6. Other sources of bias
Comparable at baseline groups
   - Yes                            | 22     | 75.9%      |
   - No                             | 1      | 3.4%       |
   - Not reported/Unclear           | 6      | 20.7%      |

Table 4
Items identified by both searches.

<table>
<thead>
<tr>
<th>Items identified</th>
<th>Identified</th>
<th>Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Identified by handsearching</td>
<td>257</td>
<td>98.69%</td>
</tr>
<tr>
<td>Identified by electronic search</td>
<td>5</td>
<td>3.91%</td>
</tr>
<tr>
<td>Total</td>
<td>262</td>
<td>100%</td>
</tr>
</tbody>
</table>

retrieved; it was then determined that none were CCTs. Therefore, the sensitivity and specificity of the electronic search was 0% (Table 4).

Comments

The main objective of this study was to identify and describe the CCTs published in Spanish Gynaecology and Obstetrics journals until December 31, 2013. The number of CCTs identified in these publications is low, specifically 224 published between 1967 and 2013, an average of 4.82 CCTs per year. The journal that published the most CCTs was Progresos de Obstetricia y Ginecologia, with 24.1% of CCTs.

The most researched health problems were conditions associated with pregnancies, including premature rupture of membranes, intrauterine growth restriction, preterm labour, gestational diabetes, and anaemia, among others. However, it
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Conflicts of interest

The authors have no conflicts of interest to declare.

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Annex I. Strategy search in PubMed


References

controlled handsearching interventions
www.cochrane-handbook.org
identifying
Lefebvre
searching reviews.
Barajas-Nava
Dickersin
Marti
Garcia-Alamino
Hopewell
OMS.
Lefebvre 2002.
Bonfill
C.
X.
Description
et al.
Lusher
A,
C.
X,
S.
R.
B.
et
al.
X.
Kupka
Montag


OMS. Plataforma de registros internacionales de ensayos clínicos; 2015, Accesible en http://www.who.int/ictrp/about/es/.


