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ARTICLE

Reporting multiple cycles in trials on medically assisted reproduction

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Irma Scholten obtained her MSc in Medicine at the University of Groningen, the Netherlands. She recently obtained her PhD, in which she studied medically assisted reproduction in the context of time. The present study is part of this thesis and was conducted at the Centre for Reproductive Medicine of the Academic Medical Centre, Amsterdam, the Netherlands. Furthermore, she is in training to become a gynaecologist.

Abstract Trials assessing effectiveness in medically assisted reproduction (MAR) should aim to study the desired effect over multiple cycles, as this reflects clinical practice and captures the relevant perspective for the couple. The aim of this study was to assess the extent to which multiple cycles are reported in MAR trials. A sample of randomized controlled trials (RCTs) was collected on MAR, published in four time periods, in 11 pre-specified peer-reviewed journals; 253 trials were included: 196 on IVF, 37 on intrauterine insemination and 20 on ovulation induction. Forty-eight (19%) reported on multiple cycles, which was significantly more common in trials on intrauterine insemination and ovulation induction compared with trials on IVF ($P < 0.01$). Both trials on IVF were multicentre trials, and those using live birth as primary outcome, reported significantly more often on multiple cycles (OR 3.7 CI 1.1 to 12.5) and (OR 8.7 CI 1.8 to 40.3), respectively. Trials designed to compare protocol variations reported multiple cycles less often (OR 0.07 CI 0.01 to 0.74). Most RCTs on MAR, especially those on IVF, do not report cumulative pregnancy rates. As not all women become pregnant in their first cycle, the clinical significance of these trials is limited.

KEYWORDS: multiple cycles, cumulative pregnancy rate, randomized clinical trials

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Introduction

About 10% of couples who wish to conceive fail to do so within 1 year of unprotected intercourse (Gnoth et al., 2003). These couples may choose to enter fertility care and, if indicated, receive medically assisted reproduction (MAR). Decisions on adequate treatment for subfertile couples should be based on sound knowledge, which is ideally generated by randomized controlled trials (RCTs). In case of equipoise, RCTs are widely accepted as the most robust method to evaluate effectiveness of an intervention (Glasziou et al., 2007; Guyatt et al., 2000).

Just as for natural conception, in MAR, cumulative pregnancy rates rise with additional cycles (Gnoth et al., 2003; Malizia et al., 2009; Smith et al., 2015). One treatment cycle can therefore not be seen as independent, and effectiveness can only be assessed when multiple cycles, and in some instances, even multiple treatments are reported (Daya, 2003). Therefore, the cumulative live birth rate over a given period of time instead of per cycle success has been proposed as the primary outcome of trials (Eijkemans et al., 2006). To capture overall chances of a live birth, RCTs on MAR should reflect this (Gnoth et al., 2003; Malizia et al., 2009; Smith et al., 2015).

This issue has been emphasized by a recent editorial published in the *BMJ* that advised studies on MAR with pregnancy or live birth rates as the outcome of interest to report cumulative rates with a follow-up period of at least 1 year (Romundstad et al., 2015). This would greatly enhance the clinical significance of trials.

It is unclear to what extent this approach is actually used in studies on MAR. Therefore, we systematically analysed a representative sample of RCTs published in the past decade, and assessed whether a multiple cycle approach was used in these RCTs, and which trial characteristics were associated with reporting multiple cycles.

Materials and methods

To create a representative database with RCTs on MAR, a systematic Medline search of RCTs published in the years 1999–2000, 2004–2005, 2009–2010 or 2013–2014 was conducted. By choosing 5-year intervals, changes over time could be described. The last interval is a 4-year interval, as not all data during 2015 were available. Six journals in reproductive medicine and obstetrics and gynaecology with a high impact factor were selected (*Human Reproduction*, *Fertility and Sterility*, *Reproductive BioMedicine Online*, *British Journal of Obstetrics and Gynaecology*, *American Journal of Obstetrics and Gynecology*, *Obstetrics and Gynecology*), as well as five high ranked general journals (*New England Journal of Medicine*, *the Lancet*, *Journal of the American Medical Association*, *British Medical Journal and Plos Medicine*).

Search methods

An information specialist (JL) identified RCTs on MAR by electronically searching *OVID MEDLINE* for the selected journals and the chosen publication years in combination with two broad search filters: one for RCTs and one for fertility treatments. In the filter fertility, treatment MAR was included, as well as the separate treatments IVF, intrauterine insemination (IUI), ovulation induction and their synonyms. The RCT filter was adapted from the sensitivity- and precision-maximizing version of the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE (Glanville et al., 2006; Higgings and Green, 2013). The search filter for fertility treatments was subjectively derived, using a reference set of six random publication years of the above-mentioned reproductive medicine journals combined with the broad RCT-filter (**Appendix 1**).

Selection of RCTs

The RCTs were selected by first screening title and abstract for eligibility and then by reading the full text of the remaining RCTs. Studies were included if they conducted an RCT on effectiveness of MAR with pregnancy as an outcome. For this study, IVF, IUI and ovulation induction were considered as MAR (Zegers-Hochschild et al., 2009). Pragmatic trials, which are designed to evaluate the effectiveness of interventions in real-world settings, were included. Explanatory trials, which aim to test whether an intervention works under optimal situations were excluded (Gaglio et al., 2014).

Studies with a cross-over design were also excluded, as empirical evidence shows that they produce biased results (Khan et al., 1996). For the present study, two researchers (IS and MB) selected the appropriate studies (**Appendix 2**).

Data extraction

For all included RCTs, general data were extracted on journal and year of publication. Single cycle was defined as reporting one treatment cycle. Multiple cycles were defined as reporting two or more consecutive treatment cycles. In addition to our main outcome, i.e. reporting multiple cycles, data were extracted on whether the study was single- or multicentre, on sample size, type of funding, type of comparison and primary outcome. We hypothesized that these characteristics were associated with the reporting of multiple cycles. For type of comparison, comparisons were distinguished between various treatment regimens. These were defined as trials in which different treatment protocols within one treatment modality were tested; different forms of stimulation or different types of progesterone in the luteal phase in trials on IVF; comparisons between two separate treatments, defined as trials in which two different treatment modalities were tested, e.g. IVF versus IUI within a certain patient category; and comparisons with no treatment. For primary outcome, number of oocytes and follicles, fertilization, biochemical pregnancies, clinical pregnancies, ongoing pregnancies, live birth and other outcomes, not directly related to pregnancy, were distinguished. All data were analysed separately for IVF, IUI and ovulation induction studies. For type of funding, commercial funding, non-commercial funding, both commercial and non-commercial funding and funding not reported were distinguished.

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