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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 (RCT) 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 RCT 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 (RCT). In case of equipoise, RCT 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, RCT 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 RCT published in the past decade, and assessed whether a multiple cycle approach was used in these RCT, and which trial characteristics were associated with reporting multiple cycles.

Materials and methods

To create a representative database with RCT on MAR, a systematic Medline search of RCT 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 RCT 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 RCT 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; Higgins 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 RCT

The RCT were selected by first screening title and abstract for eligibility and then by reading the full text of the remaining RCT. 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 RCT, 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.

Statistical analysis

Numbers and percentages of trials were described using single and multiple cycles per type of MAR. A linear-by-linear association was conducted to test for trend in the duration of treatment in the 5-year intervals. Chi-squared test for trend was used to test differences between the use of multiple cycles for the studied trial characteristics. When a significant difference was found in a characteristic, in-depth analysis with chi-squared test using dummy variables was carried out to identify which characteristic caused the difference. Calculations were conducted with IBM SPSS statistics 22® (SPSS Inc., Chicago, IL).

Results

By combining a broad search filter for RCT and for studies on MAR, 1194 records were found in the selected publication years in the 11 pre-selected peer reviewed journals. After screening for eligibility on title and abstract, 417 articles were judged full text, of which 253 full-text articles were identified that met the inclusion criteria (Figure 1). A total of 243 of the 253 studies (96%) were published in *Human Reproduction*, *Fertility and Sterility* and *Reproductive BioMedicine Online*.

Data on the number of cycles reported per type of MAR are summarized in Table 1. Of the 253 trials included, 196 studied IVF (77%), 37 studied IUI (15%) and 20 (8%) studied ovulation induction. Multiple cycles were used in 19% of all RCT and was significantly more common in trials on IUI (n = 21 [57%]) and ovulation induction (n = 13 [65%]) than in those on IVF (n = 14 [7%]) ($P < 0.01$). A trend over time in reporting multiple cycle follow-up could not be identified.

The trial characteristics and their association with single or multiple cycles of treatment are listed in Table 2. Trials on IVF that were carried out in a multicentre setting reported more often on multiple cycles (OR 3.7 CI 1.1 to 12.5). Furthermore, IVF trials using live birth as primary outcome reported more often on multiple cycles of treatment compared with trials with another primary outcome (OR 8.7 CI 1.8 to 40.3). Trials on IVF comparing protocol variations reported less often on multiple cycles as trials studying other comparisons (OR 0.07 CI 0.01 to 0.74). Year of publication, sample size and the type of funding were not significantly as-

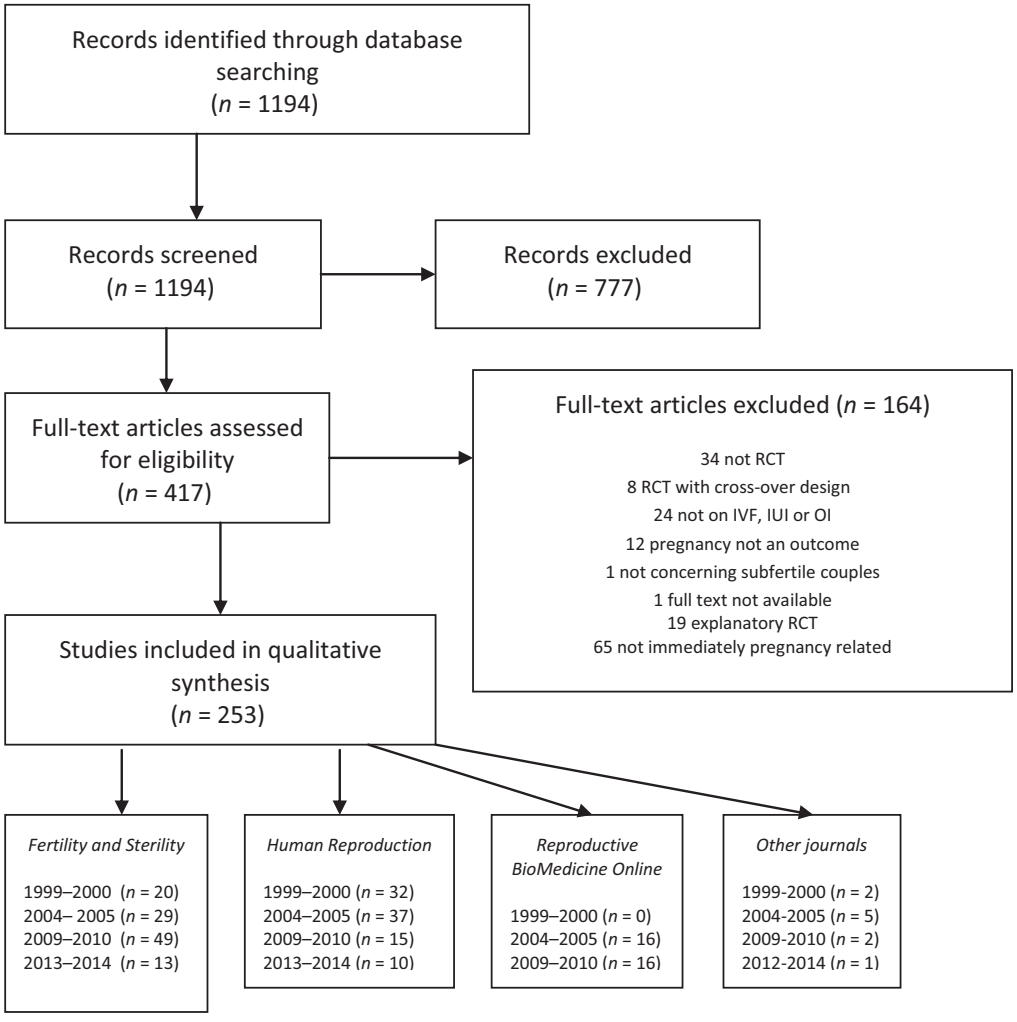

Figure 1 Selection of randomized controlled trials included in the analysis.

Table 1 Studies reporting single- and multiple-cycle follow-up in randomized controlled trials on medically assisted reproduction.

	Number of cycles included in analysis			
	1	*2–6*	*7–12*	*>12*
	(n = 205)	*(n = 37)*	*(n = 6)*	*(n = 5)*
IVF/ICSI ($n = 196$)	182 (93)	11 (6)	1 (1)	2 (1)
Intrauterine insemination ($n = 37$)	16 (43)	18 (49)	0	3 (8)
Ovulation induction ($n = 20$)	7 (35)	8 (40)	5 (25)	0

Values expressed as number (percentage) within treatment module. Percentages do not add up to 100 due to rounding.
ICSI, intracytoplasmic sperm injection.

sociated with the use of either single or multiple cycles of treatment in IVF studies. For trials on IUI and ovulation induction, no significant associations with any of the trial characteristics could be identified.

Discussion

This systematic analysis of RCT on MAR shows that most trials do not report multiple treatment cycles. This is especially true for trials on IVF, where only 7% of trials studied multiple cycles. In IUI and ovulation induction trials, multiple cycles were significantly more common, in 57% and 65%, respectively. In IVF trials, studies on protocol variations were identified as studies that were associated with not reporting multiple cycles, whereas live birth as primary outcome was associated with reporting multiple cycles as well as trial performed in a multiple cycle setting. In IUI and ovulation induction trials, such characteristics could not be identified, presumably because of the small number of trials on these treatments. Most RCT in MAR, especially those on IVF, do not report on cumulative pregnancy chances, and therefore do no capture the full chance of a live birth. Generalizability of the data generated by these studies is therefore problematic.

As far as is known, the present study is the first to assess the extent to which multiple cycles are studied in trials on MAR. Although not all published RCT on the selected treatments were included, a representative overview is provided as a systematic sample of RCT published in high-impact journals in general and reproductive medicine was collected. The number of trials on IUI and ovulation induction was quite small in the selected journals, which makes it difficult to draw firm conclusions for these treatments. The trials included in the present study all aimed to study the effectiveness of MAR. For these pragmatic trials, it is imperative to report multiple cycles of treatment. The funding of fertility treatments, especially IVF, differs widely between countries (Chambers et al., 2009). In non-funded countries, couples may not have the money for multiple cycles, and, therefore, for them the pregnancy rate per cycle might be more relevant. Yet, in other countries IVF is fully funded, in which case the multiple pregnancy rate is valuable.

In the past decade, frozen embryo transfer (FET) cycles have contributed greatly to the cumulative pregnancy rate after a started IVF cycle. In the present study, we have focused on reporting single or multiple cycles. Most RCT included in the present study included fresh embryo transfers and not the FET cycles from the same fresh cycles. Obviously, the better way to measure pregnancy rate is the cumulative pregnancy rate from fresh and FET transfers. Between 2013 and 2014, we see an increase in reporting the cumulative pregnancy rate of fresh and FET transfer. Yet, this still often concerns a single started cycle.

It has already been acknowledged 10 years ago that randomization should be carried out at the first cycle and the allocation should be continued thereafter, since a per cycle analysis or a cross-over design in RCT on MAR may lead to an overestimation of treatment success (Daya, 2005). Multiple cycle analysis reflects how a treatment works in daily practice. Couples might switch treatments between cycles, natural conception can occur or couples can drop out of treatment as shown in cohort studies on patient flow over a certain treatment period (Custers et al., 2012).

Investigators continue to design and execute single cycle trials for several reasons. First, investigators might consider multiple cycles not relevant to their topic and assume, erroneously, that data derived from a single cycle provide enough information to implement a treatment. This is especially the case for IVF trials comparing variations of a protocol within a treatment regimen. Indeed, our study showed that single cycles are significantly more common in this type of trial. In an explanatory trial in which the effect of an intervention should be tested under ideal circumstances, studying the first IVF cycle is quite appropriate to minimize the effect of possible confounders. As this was not the topic of our study, we excluded explanatory trials. Yet, after an explanatory trial, a pragmatic trial, assessing the effect in daily practice should follow, regardless of the specifics of the intervention. Second, single-cycle studies might conclude faster, thus facilitating swift completion of trials for a low price. Recruitment for clinical trials often takes longer than expected and, therefore, trials are at risk of not reaching the required sample size, thus lacking precision in estimating the magnitude of the effect of a treatment (Oude Rengerink et al., 2010). Third, as overestimation of treatment success may lead to carrying out more treatments, companies making money on these treatments might benefit from single cycle trials, and therefore may be prone to conduct these. Finally, patients may be more willing to participate in a single cycle trial, as they are only bound to the trials' rules for one cycle.

The solution is to conduct multicentre trials, in which a high number of participants can be gathered and followed for

Table 2 Trial characteristics and the association with single- and multiple-cycle follow-up.

	IVF–ICSI			IUI			Ovulation induction		
	Single	*Multiple*	*P-value*	*Single*	*Multiple*	*P-value*	*Single*	*Multiple*	*P-value*
	n = *182*	n = *14*		n = *16*	n = *21*		n = *7*	n = *13*	
Year of publication			NS			NS			NS
1999–2000	41	4		3	5		0	1	
2004–2005	62	6		5	7		3	4	
2009–2010	58	1		6	6		4	7	
2013–2014	21	3		2	3		0	1	
Journal of publication			<0.01[a]			NS			NS
New England Journal of Medicine	0	1		0	1		0	1	
The Lancet	0	0		0	1		0	0	
BMJ	0	0		0	1		0	1	
Human Reproduction	69	8		8	4		1	4	
Fertility and Sterility	81	4		7	10		4	5	
Reproductive BioMedicine Online	30	1		1	3		1	2	
American Journal ofr Obstetrics and Gynecology	0	0		0	1		1	0	
British Journal of Obstetrics and Gynaecology	2	0		0	0		0	0	
Multicenter study			0.02[b]			NS			NS
Yes	39	7		5	7		4	5	
No	143	7		11	14		3	8	
Sample size			ns			NS			NS
<100	53	3		5	5		1	6	
100–500	108	8		10	15		6	6	
500–1000	14	3		0	1		0	1	
>1000	7	0		1	0		0	0	
Type of comparison under study			<0.01[c]			NS			NS
Protocol variations	180	12		14	17		7	9	
Comparison of two separate treatments	2	1		2	4		0	1	
Comparison with no treatment	0	1		0	0		0	0	
Other	0	0		0	0		0	3	
Primary outcome under study			0.02[d]			NS			NS
Number of oocytes and follicles	33	2		3	0		0	0	
Fertilization	13	0		NA	NA		NA	NA	
Biochemical pregnancy	6	0		1	2		1	1	
Clinical pregnancy	74	4		7	13		0	4	
Ongoing pregnancy	23	1		2	3		0	1	
Livebirth	8	4		2	1		0	1	
Other, e.g. not direct pregnancy related	25	3		1	2		6	6	
Funding			ns			NS			NS
Yes, commercial	33	2		1	0		1	0	
Yes, non-commercial	17	2		1	3		0	3	
Yes, both commercial and non-commercial	3	1		0	1		0	1	
No	18	2		2	3		1	1	
Not reported	111	7		12	14		5	8	

ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; NA, not available; NS, not significant.

[a]In-depth analysis: multiple cycle analysis is significantly more seen in IVF–ICSI studies published in *New England Journal of Medicine* (OR 26.1 CI 1.7 to 781).

[b]In-depth analysis: multiple cycle analysis is significantly more seen in IVF–ICSI studies that were multicenter trials (OR 3.7 CI 1.1 to 12.5).

[c]In-depth analysis: multiple cycle analysis is significantly less seen in IVF–ICSI studies that study protocol variations (OR 0.07 CI 0.01 to 0.74).

[d]In-depth analysis: multiple cycle analysis is significantly more seen in IVF–ICSI studies with livebirth as primary outcome (OR 8.7 CI 1.8 to 40.3).

a longer time per participant, thereby providing more useful information within the same time span as that needed to conduct a single-centre trial. Participation in multicentre trials is also associated with a better knowledge of trial results and an improvement in the implementation of the results (Litjens et al., 2013). Indeed, a multicentre trial with multiple cycles of treatment might be more difficult to conduct, but a single centre trial, the results of which cannot be implemented in daily practice is a waste of effort and resources.

In conclusion, although acknowledged as an important feature for RCT on MAR treatments, multiple cycle treatment is reported in a minority of pragmatic trials on IVF and one-half of all pragmatic trials on IUI and ovulation induction that were designed to improve patient care. This is important information for clinicians, as the results of the single cycle trials they implement in daily practice might not represent the best estimate of the truth.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.rbmo.2016.08.006.

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