Reproductive BioMedicine Online (2015) **30**, 137–143

www.sciencedirect.com
www.rbmonline.com

ARTICLE

Reporting of embryo transfer methods in IVF research: a cross-sectional study

Pietro Gambadauro [a,b,*], **Ramesan Navaratnarajah** [c,d]

[a] *Karolinska Institutet, LIME/NASP - C7, 17 177 Stockholm, Sweden*; [b] *Res Medica Sweden, Gynaecology & Reproductive Medicine, 752 24 Uppsala, Sweden*; [c] *Bart's Health NHS Trust, Obstetrics and Gynaecology, The Royal London Hospital, E1 1BB London, UK*; [d] *Katherine Twining Network, Queen Mary University of London, E1 2AB London, UK*

* Corresponding author. *E-mail address:* gambadauro@gmail.com; pietro.gambadauro@ki.se (P Gambadauro).

Pietro Gambadauro, MD, PhD, is a gynaecologist and postdoctoral researcher affiliated to Karolinska Institutet, Stockholm. He specializes in reproductive medicine and gynaecological endoscopy, with a clinical and research focus on uterine factors, hysteroscopy, endometriosis and assisted reproduction techniques.Other interests include women's mental health, surgical education and innovation. He has authored several related peer-reviewed publications, and is referee of many international journals. He sits on ESHRE Committee of National Representatives, and represents the Swedish ObGyn Society on IFFS Board of Directors. Previous appointments held include Advisory Board Member, ESGE; Jr Deputy Coordinator, ESHRE SIG Reproductive Surgery; and Secretary, Swedish Reference Group on Infertility.

Abstract The reporting of embryo transfer methods in IVF research was assessed through a cross-sectional analysis of randomized controlled trials (RCTs) published between 2010 and 2011. A systematic search identified 325 abstracts; 122 RCTs were included in the study. Embryo transfer methods were described in 42 out of 122 articles (34%). Catheters (32/42 [76%]) or ultrasound guidance (31/42 [74%]) were most frequently mentioned. Performer 'blinding' (12%) or technique standardization (7%) were seldom reported. The description of embryo transfer methods was significantly more common in trials published by journals with lower impact factor (less than 3, 39.6%; 3 or greater, 21.5%; $P = 0.037$). Embryo transfer methods were reported more often in trials with pregnancy as the main end-point (33% versus 16%) or with positive outcomes (37.8% versus 25.0%), albeit not significantly. Multivariate logistic regression confirmed that RCTs published in higher impact factor journals are less likely to describe embryo transfer methods (OR 0.371; 95% CI 0.143 to 0.964). Registered trials, trials conducted in an academic setting, multi-centric studies or full-length articles were not positively associated with embryo transfer methods reporting rate. Recent reports of randomized IVF trials rarely describe embryo transfer methods. The under-reporting of research methods might compromise reproducibility and suitability for meta-analysis.

KEYWORDS: embryo transfer, in-vitro fertilization, randomized controlled trials, reproducibility of research, research methods, risk of bias

http://dx.doi.org/10.1016/j.rbmo.2014.10.013

Introduction

If we accept that reproducibility is one of the principles of the scientific method (Siegel, 2011), then reporting the methods of research is equally important as disseminating its results. A good description of a study's methodology allows others to replicate the experiment accurately and verify previous findings. Current research, however, shows that scientific reporting can often be inadequate, even in the case of high-quality studies such as randomized controlled trials (Péron et al., 2012; Turner et al., 2012; Wang et al., 2011).

In the context of IVF, embryo transfer is a crucial and integral part of the treatments, and evidence shows that different methods or performers of embryo transfer can influence the resulting pregnancy rates (Levi Setti et al., 2003; Mains and Van Voorhis, 2010). Nevertheless, no consensus exists on the best method of embryo transfer, and different techniques might be preferred by different clinics, and also by different physicians practising in the same clinic. We would, therefore, expect that relevant scientific literature would provide information on the embryo transfer procedure within the description of scientific methods, so that the risk of bias is reduced and reproducibility is permitted.

The aim of this study was to verify the frequency and quality of reporting of embryo transfer methods in scientific publications describing outcomes of IVF and embryo transfer.

Materials and methods

A cross-sectional study of randomized controlled trials (RCT) on IVF outcomes published in scientific research during the entire 2010–2011 biennium was conducted. Only RCTs on IVF, reporting pregnancy or live birth, either as the main or secondary outcome, were included. The analysis was restricted to articles published in English. As published data were used, the present study was exempt from institutional review board approval.

Initially, 325 potentially eligible abstracts were identified through a prospective, systematic search conducted on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/; mid-2012). The search was based on the following query:('in-vitro fertilisation'[All Fields] OR 'fertilization in-vitro'[MeSH Terms] OR ('fertilization'[All Fields] AND 'vitro'[All Fields]) OR 'fertilization in-vitro'[All Fields] OR ('vitro'[All Fields] AND 'fertilization'[All Fields]) OR 'in-vitro fertilization'[All Fields] OR 'embryo transfer'[All Fields]) AND ('humans'[MeSH Terms] AND (Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp]) AND ('2010/01/01'[PDAT]: '2011/12/31'[PDAT])).

Once the titles and abstracts had been screened, 150 articles were selected for full-text download and further assessment of eligibility. Finally, 122 RCTs were identified and included in the study (**Figure 1**). Most of the excluded articles were not RCTs, did not report pregnancy as outcome, or were written in a language other than English. References and articles were managed using free online (MyNCBI; http://www.ncbi.nlm.nih.gov/myncbi/) and offline (Zotero; http://www.zotero.org/) tools (Hull et al., 2008). All articles were searched for data by hand and with the assistance of desktop-search software to guarantee accuracy (Magos and Gambadauro, 2005).

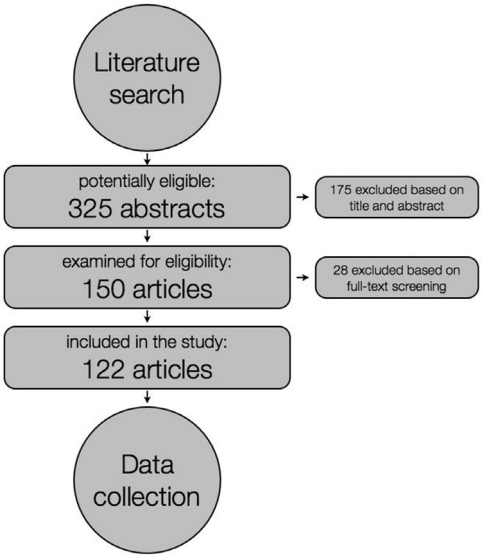

Figure 1 Article selection. The selection of articles was in accordance with criteria described in the Material and Methods section.

Data were collected on the reporting of the following aspects of embryo transfer procedures: methods, blinding, standardization, ease of embryo transfer and performer. It was recorded whether the study's main subject was related to embryo transfer technique or not. The following data on the kind of publication and study characteristics were collected and treated as categorical variables: article length (full/short), patient population (general/specific, e.g. whether the patient had polycystic ovary syndrome or were low responders), pregnancy as main outcome (yes/no), positive outcomes (yes/no), multi-centric study (yes/no), trial registration (yes/no) and academic setting (yes/no). The journal's impact factor (Journal Citation Reports ®, Thomson Reuters, 2011) was also treated as a categorical variable, dividing the articles into two groups (impact factor less than 3, and impact factor 3 or over). All data were collected by means of a dedicated digital form and temporarily stored on an online database created through the free Google Drive platform (Gambadauro and Magos, 2008).

Descriptive statistics were used to calculate the frequencies of different embryo transfer methods reporting. Comparative analyses by bivariate and multivariate statistics were performed after excluding articles whose subject was the embryo transfer procedure itself. Fisher's exact or chi-squared tests were carried out as appropriate to measure the association between different variables and the description of embryo transfer methods. A multivariate analysis with logistic regression was used to control for confounding and identify the odds ratio (OR) and 95% confidence interval (CI) for factors independently related to embryo transfer methods reporting. The same calculations were also repeated with the blinding of the embryo transfer performer as dependent variable. $P < 0.05$ (two-tailed) was considered statistically significant. The Statistical Package for Social Sciences (SPSS, IBM Corp., USA) for Mac OSX was used for statistical calculations.

Table 1 Source journals for articles included in the present study.

Journal	*2010*	*2011*	*Total*	*%*
Fertility and Sterililty	28	28	56	45,90
Human Reproduction	5	6	11	9,02
Reproductive BioMedicine Online	6	4	10	8,20
Journal of Assisted Reproduction and Genetics	4	4	8	6,56
Gynecological Endocrinology	2	3	5	4,10
Archives of Gynecology and Obstetrics	2	2	4	3,28
European Journal of Obstetrics & Gynecology and Reproductive Biology	0	3	3	2,46
European Review for Medical and Pharmacological Sciences	2	1	3	2,46
The Journal of Reproductive Medicine	2	1	3	2,46
Others[a]	11	8	19	15,57
Total	62	60	122	100

[a]Journals contributing two articles or less to this study.

Table 2 Frequency of articles reporting different aspects of the embryo transfer procedure during the study period (2010–2011).

	n	%	*Details reported (% of articles)*
Embryo transfer methods	42	34	Catheter (76) Ultrasound (74) Site (17) Mucus removal (14) Straightening of cervix (14) Dummy transfer (14) Bed rest (12) Mechanical closure of cervix (12) Afterloading (10)
Embryo transfer performer	11	9	Physician or other (91) No. of performers (55) Experience (36) Individual success rates (9) Performer as a variable/ cofactor (0)
Ease of embryo transfer	6	5	Difficult transfers (100) Repeat transfers (33) Blood on catheter (17)
Blinding	15	12	
Standard embryo transfer	8	7	

Results

A similar number of RCTs, out of the 122 considered in this study, were published in 2010 and 2011 (62 and 60, respectively). *Fertility and Sterility* published most trials (56 [45.9%]), followed by *Human Reproduction* (11 [9.0%]) and *Reproductive Biomedicine Online* (10 [8.2%]). Interestingly, the distribution of published trials between 2010 and 2011 was even for most of the journals (**Table 1**).

The main descriptive findings are summarized in **Table 2**. Nine out of 122 studies included methods of embryo transfer as a main subject (7.4%). A description of embryo transfer methods was present in 42 out of 122 trials (4.4%). Unsurprisingly, 100% of the trials studying embryo transfer techniques reported transfer methods (9/9), compared with the 29.2% of those studying other interventions, such as drugs or laboratory techniques (33/113).

When available, the description of embryo transfer methods mainly consisted of information on the catheter (32/42 [76.2%]) or the use of ultrasound guidance (31/42 [73.8%]). A minority of trials reported blinding of the embryo transfer performer (15/122) or standardization of the embryo transfer routines (8/122). In 11 of the 122 articles (9%), any of the following information about the person performing embryo transfer was available: whether it was a physician or not; number of different performers; performers' experience or common success rates. In no case was the embryo transfer performer treated as a variable. Only 4.9% (6/122) of the articles referred to the ease of embryo transfer (e.g. difficult procedures, repeat embryo transfer or blood on the catheter).

Comparative analyses were performed on 113 articles, having excluded the nine studies about embryo transfer techniques or methods. At bivariate analysis, the description of embryo transfer methods was significantly more common in trials published by journals with lower impact factor (impact factor less than 3, 39.6%; impact factor 3 or over, 21.5%; $P = 0.037$) (**Table 3**).

Embryo transfer methods were reported more often in trials with pregnancy as one of the main end-points (29/88 versus 4/25) or with positive outcomes (14/37 versus 19/76), albeit not significantly (**Table 3**).

The multivariate analysis with logistic regression confirmed that RCTs published in higher impact factor journals are less likely to describe the methods of embryo transfer (OR 0.371; 95% CI 0.143 to 0.964) (**Table 4**).

An association was also found between multi-centric studies and blinding of the embryo transfer performer, both at bivariate analysis (multi-centric 33.3%; single centre 9.5%; $P = 0.006$) (**Table 5**) and logistic regression (OR 3.979; 95% CI 1.058 to 14.972).

Discussion

To the best of our knowledge, this is the first study focusing on the frequency and quality of reporting of embryo transfer methods among published trials on IVF. Its results show that current research papers rarely include information about the methods and circumstances of execution of embryo transfer, as if these were not relevant to the outcomes.

The sample of RCTs included in this study was obtained by conducting a systematic search on *PubMed* (Wilczynski et al., 2013). Our query included the term 'randomized

Table 3 Frequency with which embryo transfer methods are described.

	Embryo transfer methods described	
	Yes	*No*
Total articles (122)	42 (34%)	80 (66%)
Articles with embryo transfer methods as main subject (9)	9	0
Articles included in the analysis (113)	33 (29.2%)	80 (70.8%)
Article length[a]		
Full-length (100)	30	70
Short (13)	3	10
Patients[b]		
General population (71)	22	49
Specific group (42)	11	31
Pregnancy as main outcome[a]		
Yes (88)	29	59
No (25)	4	21
Positive outcomes[b]		
Yes (37)	14	23
No (76)	19	57
Multi-centric study[a]		
Yes (18)	3	15
No (95)	30	65
Trial registration[b]		
Yes (38)	8	30
No (75)	25	50
Academic setting[b]		
Yes (93)	28	65
No (20)	5	15
Journal's Impact Factor[bc]		
< 3 (48)	19	29
≥ 3 (65)	14	51

P values calculated according to [a]Fisher's exact test or [b]chi-squared test, all non-significant apart from [c]$P = 0.037$.

Table 4 Factors associated with the reporting of embryo transfer methods.

	Odds ratio	*95% Confidence interval*
Full-length article	0.917	0.211 to 3.991
Specific patient group	0.760	0.297 to 1.947
Pregnancy as main outcome	1.818	0.507 to 6.520
Positive outcomes	1.756	0.680 to 4.537
Multi-centric	0.430	0.104 to 1.782
Trial registration	0.884	0.319 to 2.450
Academic setting	1.318	0.391 to 4.440
Higher impact factor (≥3)[a]	0.371	0.143 to 0.964

Logistic regression based on 113 articles, having excluded nine studies about embryo transfer techniques or methods (methods yes 33; no 80).
[a]$P = 0.042$.

controlled trial [ptype]', which identified randomized studies as publication type. McKibbon et al. (2009) previously showed that this query alone works well for retrieving RCTs from PubMed, in terms of sensitivity (93.7%; 95% CI 92.5 to 94.9) and specificity (97.6%; 95% CI 97.4 to 97.7). In an effort to increase sensitivity, the term 'clinical trial[ptype]' was also included, leading to the retrieval of 325 abstracts, from which the 122 trials were identified. We therefore believe that our search strategy guarantees a consistently representative sample of all the IVF RCTs published during the study period.

Embryo transfer is often described by reproductive medicine specialists as a critical step in IVF treatment. In fact, the embryo transfer procedure should be considered one of the plausible causes of IVF failure, together with embryo quality

Table 5 Frequency of reporting blinding of the embryo transfer performer.

	Blinding reported	
	Yes	*No*
Total articles (122)	15 (12.3%)	107(87.7%)
Articles with embryo transfer methods as main subject (9)	0	9
Articles included in analysis (113)	15 (13.3%)	98(86.7%)
Article length[a]		
Full-length (100)	13	87
Short (13)	2	11
Patients[b]		
General population (71)	10	61
Specific group (42)	5	37
Pregnancy as main outcome[b]		
Yes (88)	9	79
No (25)	6	19
Positive outcomes[a]		
Yes (37)	3	34
No (76)	12	64
Multi-centric[bc]		
Yes (18)	6	12
No (95)	9	86
Trial registration[b]		
Yes (38)	8	30
No (75)	7	68
Academic setting[a]		
Yes (93)	14	79
No (20)	1	19
Journal's Impact Factor[a]		
<3 (48)	4	44
≥3 (65)	11	54

P-values calculated according to [a]Fisher's exact test or [b]chi-squared test, all non-significant apart from [c]$P = 0.006$.

and uterine and endometrial factors (Das and Holzer, 2012; Penzias, 2012; Revel, 2012).

The lack of reporting of embryo transfer methods documented by this study may be seen as a potential source of bias, in a way that is similar to that which occurs in surgical research (Paradis, 2008). Surgical interventions are more difficult to standardize than, for instance, medical treatments or laboratory procedures. Performance bias is therefore more common and more difficult to tackle in surgical research, possibly leading to lack of internal validity (Paradis, 2008). Being an operative, albeit minimal, procedure, embryo transfer shares similarities with surgery, and evidence exists that specific techniques or tools increase the chances of embryo implantation and pregnancy. Among several routines that have been associated with better outcomes of embryo transfer, ultrasound guidance and the use of soft catheters seem to be the most important ones. Both have been shown to increase significantly the success rates of embryo transfer at meta-analysis (Brown et al., 2010; Buckett, 2006), and this knowledge is partially reflected in the findings of our study. Most commonly, the description of embryo transfer methods consists of information on ultrasound guidance or type of catheter.

Another common evidence-based recommendation is to avoid difficult transfers, as they are associated with poorer outcomes (Mains and Van Voorhis, 2010). In spite of such knowledge, only 5% of the randomized trials in our study reported information about difficult transfers. This fact can raise concerns on the homogeneity of groups in a controlled study, since the variable 'difficult transfer' could be distributed unevenly in spite of the randomization.

Apart from being influenced by tools and techniques, embryo transfer reasonably seems to be operator-dependent (Yao et al., 2009). Proper education is therefore required, but less than 50% of fellows in reproductive endocrinology and infertility have reported specific training in embryo transfer during their fellowship (Wittenberger et al., 2007). Interestingly, the number of procedures needed to achieve competence is individual. Dessolle et al. (2010) studied the learning curve of five trainees performing their first transfers by means of a cumulative summation test. The number of transfers needed to reach proficiency showed high variation, from 11 to 99, therefore showing the need for individualized training. In spite of the available evidence, only 9% of the trials included in the present study provided information about the embryo transfer performer, and only one-third of those (3%)

described the performers as 'experienced'. These figures are not satisfactory, considering that more than 80% of trials were conducted in academic or academic-affiliated centres, where part of the personnel is, by definition, under training.

Despite our findings, our study does not necessarily undermine the internal validity of the quality and integrity of the analysed research. All the trials were randomized, and we cannot exclude that the embryo transfers were performed in the same standardized fashion and conditions, or by similarly experienced and blinded physicians, across the groups under comparison. The lack of reporting, however, generates doubts, as well as it is potentially affecting external validity and generalizability (Paradis, 2008). The description of materials and methods is an essential part of scientific reporting. Also in the case of randomized trials, the proper description of sound methodology ensures the minimization of potential bias and allows for reproducibility. The latter is of paramount relevance, since the replication of experiments is the foundation to the highest possible level of scientific evidence, represented by systematic reviews and meta-analysis of homogeneous trials.

The quality of a research article is primarily relevant to the mission of scientific literature as a tool to spread new knowledge. Therefore, not only does original research need to be properly conducted, but equally the reports conveying the results should be adequate.

The quality of research articles is also relevant to the authors, whose scientific output is essential for funding and career progression. No adequate tools are available, however, to assess the quality of single scientific papers. Hence, misleading and misinterpreted bibliometric parameters, such as the journal impact factor, are often used (Gambadauro and Torrejón, 2007). The impact factor, originally created to compare journals, is a quantitative measure of the overall citations of a journal but does not reflect the quality of individual articles, even less that of their authors (Opthof, 1997). Only a minor proportion of published articles contributes to the impact factor of a journal (Kurmis, 2003), and articles are more likely to be cited because of the journal's impact factor rather than their intrinsic value (Callaham et al., 2002). In the present study, we studied whether the description of embryo transfer methods was associated with the impact factor or other variables that might be considered to be realited to quality, such as full-length reports, academic setting, trial registration, or multi-centric study. Moreover, only RCTs were included. None of the mentioned 'quality' variables increased the odds of reporting of embryo transfer methods. On the contrary, the papers in the journals with higher impact factors were less likely to report embryo transfer methods. A possible explanation might be that more prestigious journals might have stricter policies on the word count limit. Authors would, therefore, be induced to dedicate space to the description of their novel experimental interventions, hence neglecting to report the 'established' procedures. This hypothesis, however, is not directly supported by our results, which show no difference in embryo transfer methods reporting rate between short and full-length articles.

In conclusion, recent reports of randomized trials on IVF rarely include a description of embryo transfer methods, particularly when published in higher impact factor journals. This may be indicative of opinions held by scholars, such as diminished confidence in the embryo transfer procedure as a determinant of IVF results, despite available evidence and common IVF practice view points. This explanation, however, contrasts with our finding that multi-centric studies are more likely to report the person performing the embryo transfer to be blinded.

Irrespective of the reasons, the lack of reporting of embryo transfer methods is evident. This expresses the distinct possibility that the reproducibility of published IVF trials and their suitability for meta-analysis may be compromised.

References

Brown, J., Buckingham, K., Abou-Setta, A.M., Buckett, W., 2010. Ultrasound versus 'clinical touch' for catheter guidance during embryo transfer in women. Cochrane Database Syst. Rev. (1), CD006107. doi:10.1002/14651858.CD006107.pub3.

Buckett, W., 2006. A review and meta-analysis of prospective trials comparing different catheters used for embryo transfer. Fertil. Steril. 85, 728–734.

Callaham, M., Wears, R.L., Weber, E., 2002. Journal prestige, publication bias, and other characteristics associated with citation of published studies in peer-reviewed journals. JAMA 287, 2847–2850.

Das, M., Holzer, H.E., 2012. Recurrent implantation failure: gamete and embryo factors. Fertil. Steril. 97, 1021–1027.

Dessolle, L., Fréour, T., Barrière, P., Jean, M., Ravel, C., Daraï, E., Biau, D.J., 2010. How soon can I be proficient in embryo transfer? Lessons from the cumulative summation test for learning curve (LC-CUSUM). Hum. Reprod. 25, 380–386.

Gambadauro, P., Torrejón, R., 2007. Impact factor and the quality of research: what is a rose defined by, its name or its scent? Eur. J. Obstet. Gynecol. Reprod. Biol. 134, 269–270.

Gambadauro, P., Magos, A., 2008. Office 2.0: a web 2.0 tool for international collaborative research. Lancet 371, 1837–1838.

Hull, D., Pettifer, S.R., Kell, D.B., 2008. Defrosting the digital library: bibliographic tools for the next generation web. PLoS Comput. Biol. 4, e1000204. doi:10.1371/journal.pcbi.1000204.

Kurmis, A.P., 2003. Understanding the limitations of the journal impact factor. J. Bone Joint Surg. 85-A, 2449–2454.

Levi Setti, P.E., Albani, E., Cavagna, M., Bulletti, C., Colombo, G.V., Negri, L., 2003. The impact of embryo transfer on implantation – a review. Placenta 24 (Suppl. B), S20–S26.

Magos, A., Gambadauro, P., 2005. Desktop search engines: a modern way to hand search in full text. Lancet 366, 203–204.

Mains, L., Van Voorhis, B.J., 2010. Optimizing the technique of embryo transfer. Fertil. Steril. 94, 785–790.

McKibbon, K.A., Wilczynski, N.L., Haynes, R.B., Hedges Team, 2009. Retrieving randomized controlled trials from medline: a comparison of 38 published search filters. Health Info. Libr. J. 26, 187–202.

Opthof, T., 1997. Sense and nonsense about the impact factor. Cardiovasc. Res. 33, 1–7.

Paradis, C., 2008. Bias in surgical research. Ann. Surg. 248, 180–188.

Péron, J., Pond, G.R., Gan, H.K., Chen, E.X., Almufti, R., Maillet, D., You, B., 2012. Quality of reporting of modern randomized controlled trials in medical oncology: a systematic review. J. Natl. Cancer Inst. 104, 982–989.

Penzias, A.S., 2012. Recurrent IVF failure: other factors. Fertil. Steril. 97, 1033–1038.

Revel, A., 2012. Defective endometrial receptivity. Fertil. Steril. 97, 1028–1032.

Siegel, V., 2011. Reproducibility in research. Dis. Model. Mech. 4, 279–280.

Turner, L., Shamseer, L., Altman, D.G., Weeks, L., Peters, J., Kober, T., Dias, S., Schulz, K.F., Plint, A.C., Moher, D., 2012. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. Cochrane Database Syst. Rev. (11), MR000030. doi:10.1002/14651858.MR000030.pub2.

Wang, J.L., Sun, T.T., Lin, Y.W., Lu, R., Fang, J.Y., 2011. Methodological reporting of randomized controlled trials in major hepatogastroenterology journals in 2008 and 1998: a comparative study. BMC Med. Res. Methodol. 11, 110.

Wilczynski, N.L., McKibbon, K.A., Walter, S.D., Garg, A.X., Haynes, R.B., 2013. MEDLINE clinical queries are robust when searching in recent publishing years. J. Am. Med. Inform. Assoc. 20, 363–368.

Wittenberger, M.D., Catherino, W.H., Armstrong, A.Y., 2007. Role of embryo transfer in fellowship training. Fertil. Steril. 88, 1014–1015.

Yao, Z., Vansteelandt, S., Van der Elst, J., Coetsier, T., Dhont, M., De Sutter, P., 2009. The efficacy of the embryo transfer catheter in IVF and ICSI is operator-dependent: a randomized clinical trial. Hum. Reprod. 24, 880–887.

Declaration: The authors report no financial or commercial conflicts of interest.

Received 1 April 2014; refereed 23 October 2014; accepted 23 October 2014.

A list of the PMID (PubMed IDs) of the articles included in this cross-sectional study can be provided to other members of the scientific community on motivated request directed to the corresponding author.