ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Economic evaluation of elective single-embryo transfer with subsequent single frozen embryo transfer in an in vitro fertilization/ intracytoplasmic sperm injection program

Elisa Hernandez Torres, M.Sc.,[a,b] José Luis Navarro-Espigares, Ph.D.,[a,b] Ana Clavero, M.D., Ph.D.,[c,d] M[a]Luisa López-Regalado, M.Sc.,[c] Jose Antonio Camacho-Ballesta, Ph.D.,[a] M[a]Ángeles Onieva-García, M.Sc.,[e] Luis Martínez, M.D., Ph.D.,[c] and Jose Antonio Castilla, M.D., Ph.D.[c,d,f,g]

[a] Department of International and Spanish Economics, University of Granada, Granada; [b] University Hospital Virgen de las Nieves, Granada; [c] U. Reproducción, UGC de Obstetricia y Ginecología, Hospital Universitario Virgen de las Nieves, Instituto de Investigación Biosanitaria de Granada, Granada; [d] UGC Laboratorio Clínico, Hospital Universitario Virgen de las Nieves, Granada; [e] UGC Medicina Preventiva, Vigilancia y Promoción de la Salud, Hospital Universitario Virgen de las Nieves, Granada; [f] Banco de Semen CEIFER, Granada; and [g] Centro Masvida Reproducción, Sevilla, Spain

Objective: To analyze the cost-effectiveness of IVF-ICSI cycles with elective single-embryo transfer (eSET), plus elective single frozen embryo transfer (eSFET) if pregnancy is not achieved, compared with double-embryo transfer (DET).
Design: Cost-effectiveness analysis.
Setting: Public hospital.
Patient(s): A population of 121 women (<38 years old), undergoing their first or second IVF cycles.
Intervention(s): We conducted a cost-effectiveness analysis using the results of a prospective clinical trial. The women in group 1 received eSET plus eSFET, and those in group 2 received DET. A probabilistic sensitivity analysis was performed.
Main Outcome Measure(s): Live birth delivery rate.
Result(s): The cumulative live birth delivery rate was 38.60% in the eSET+eSFET group versus 42.19% in the DET group. The mean costs per patient were €5,614.11 in the eSET+eSFET group and €5,562.29 in the DET group. These differences were not statistically significant. The rate of multiple gestation was significantly lower in the eSET group than in the DET group (0 vs. 25.9%).
Conclusion(s): This study does not show that eSET is superior to DET in terms of effectiveness or of costs. The lack of superiority of the results for the eSET+eSFET and the DET groups corroborates that the choice of strategy to be adopted should be determined by the context of the health care system and the individual prognosis. (Fertil Steril® 2015;■: ■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Economic evaluation, probabilistic sensitivity analysis, assisted reproduction, single-embryo transfer

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/torrese-economic-evaluation-single-embryo-transfer/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Received September 19, 2014; revised November 22, 2014; accepted November 26, 2014.
E.H.T. has nothing to disclose. J.L.N.-E. has nothing to disclose. A.C. has nothing to disclose. M.L.-R. has nothing to disclose. J.A.C.-B. has nothing to disclose. M.O.-G. has nothing to disclose. L.M. has nothing to disclose. J.A.C. has nothing to disclose.
Supported by a research grant from Instituto 371 de Salud Carlos III, code number PI09/90620.
Reprint requests: Ana Clavero, Ph.D. Human Reproduction Unit, Hospital Universitario Virgen de las Nieves. C / Dr. Azpitarte sn. 18013, Granada, Spain (E-mail: anaclaverogilabert@gmail.com).

Fertility and Sterility® Vol. ■, No. ■, ■ 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2014.11.032

Infertility is a disease of the reproductive system defined by the failure to achieve a pregnancy after ≥12 months of regular unprotected sexual intercourse. Medical treatments for infertility include assisted reproductive technologies (ART), which are treatments or procedures that include the in vitro handling of both human

oocytes and sperm, or of embryos, for the purpose of establishing a pregnancy (1). The rates of pregnancy and live birth following in vitro fertilization (IVF) have risen steadily over the past two decades (2), and since the first birth thus achieved in 1978 IVF has become a mainstay of infertility treatment the world over. To date, approximately one million babies have been conceived by means of the IVF procedure, and more than 50% of IVF patients aged <35 years now achieve pregnancy. With the consolidation of the results obtained by this technique, innovation in the field of assisted reproduction now focuses on quality issues, and special emphasis is placed on reducing the iatrogenic effects of the treatment. There is a general consensus that the main iatrogenic effect, and the one generating the highest costs, both short- and long-term, is that of multiple birth. Large-scale studies have highlighted the less favorable development of children born through assisted reproductive (AR) techniques compared with those who are naturally conceived, and in most cases the difference is attributable to the higher percentage of multiple pregnancies with IVF (3). It is accepted that restricting the number of embryos transferred is the most effective means of reducing the rate of multiple births.

Limiting to two the number of embryos per transfer has significantly reduced the incidence of high-order pregnancies (three or more fetuses) without reducing treatment effectiveness, i.e., pregnancy and birth rates after IVF remain unchanged (4–6). Strategies aimed at reducing twin births, such as elective single-embryo transfer (eSET), are becoming increasingly popular (7), although their consolidation remains an issue of some controversy (8–10). Even though eSET does indeed reduce the rate of twin births, it is less clear whether it maintains effectiveness, because more cycles are required to obtain similar results.

Cost-effectiveness studies, in which a fresh eSET cycle is compared with a fresh double-embryo transfer (DET) cycle, have shown eSET to be less effective but also less costly, primarily owing to lower neonatal costs because of the lower rate of twin births (2, 11–13). This lower cost would offset the need to carry out more cycles to increase pregnancy rates. Similarly, studies comparing the performance of two fresh cycles of eSET (14) or one cycle of fresh eSET plus one frozen SET (eSFET) (2, 15) versus DET have obtained mixed results, largely owing to methodologic differences in calculating costs.

The aim of the present paper was to analyze the efficiency, in terms of cost-effectiveness, of IVF-ICSI cycles in which eSET is performed, followed, if this does not result in a pregnancy, by the transfer of cryopreserved embryos (eSET+eSFET), versus DET.

MATERIALS AND METHODS

We conducted a cost-effectiveness analysis of the results of a prospective clinical trial (FIS 09/01968; ClinTrial.gov no. NCT01909570). The study subjects were patients at Virgen de las Nieves University Hospital (Granada, Spain) undergoing a first or second cycle of IVF/ICSI, during the period of January 2010 to December 2012. The details of the trial can be found in López-Regalado et al. (16). In brief, patients fulfilling the following inclusion criteria were considered eligible to participate in the trial: 1) women aged <38 years; 2) body mass index 19–29 kg/m^2; 3) FSH <15 mUI/mL on the 3rd day of the cycle; 4) first cycle of IVF/ICSI or second cycle after an earlier attempt with a positive pregnancy test result. Patients were excluded from the study if they had been infertile for >5 years or had previous uterine surgery (fibroids, endometriosis, hydrosalpinx), uterine malformations, or repeated spontaneous abortions (two or more). Information on the AR treatment was compiled in a database specifically designed for this study. After the estimated delivery date, the patients were telephoned to obtain information about the birth and any complications occurring during pregnancy, childbirth, and the postnatal period.

The study was approved by the Clinical Research Ethics Committee of the Virgen de las Nieves University Hospital (Granada, Spain), on April 20, 2009, and met the eligibility requirements of the protocol in relation to the study goals and current legislation on data protection. Written informed consents were obtained from all of the couples.

Measure of Effectiveness

Live birth delivery rate (LBDR).

Cost Analysis

The cost analysis was performed from the perspective of the health care system, including the direct medical costs associated with AR treatment, pregnancy, childbirth, and neonatal care. Direct medical costs include the hospital costs of the AR treatment (test diagnostics, controls, monitoring, puncture, embryo transfer, AR laboratory, and embryo vitrification, conservation, and devitrification) and the medication required during the period of ovarian stimulation. Pregnancy follow-up was evaluated in accordance with the Integrated Healthcare Process stipulated by the Government of Andalusia (17).

Vaginal or cesarean deliveries, regardless of the number of children born in each case, were assessed by means of the corresponding diagnostic related group (DRG): no. 373, "uncomplicated vaginal delivery"; and no. 371, "uncomplicated cesarean section." Resource consumption by the neonate was assessed according to the following DRGs, taking into account the weight at birth: no. 604, "neonate, birth weight 750–999 g, live birth"; no. 607, "neonate, birth weight 1.0–1.5 kg, without significant intervention, live birth"; no. 614, "neonate, birth weight 1.5–2.0 kg, without significant intervention, presenting other problems"; and no. 621, "neonate, birth weight 2.0–2.5 kg, without significant intervention, presenting other problems." If the infant had a weight at birth >2.5 kg, there was assumed to be no additional associated cost. Additionally, note was taken of the presence of complications at any time during treatment follow-up, the most important of which were ovarian hyperstimulation syndrome, emergencies arising from the danger of miscarriage, and the risk of preterm birth.

The cost information for the economic evaluation of the resources consumed was obtained from the Integrated Logistics Management System of the Andalusian Health Service,

the Analytical Accounting System of the Andalusian Health Service, and the purchase prices of the medication acquired by the hospital.

Cost-effectiveness Analysis

The cost-effectiveness analysis performed in this study compared the LBDR after IVF and the unit cost per patient for the eSET+eSFET option versus the DET option. The analysis result is summarized as the incremental cost-effectiveness ratio, which is obtained by applying the following formula: (mean DET cost − mean SET cost)/(% live births DET − % live births SET) (18). The results of the clinical study, known as the baseline case, were subjected to a sensitivity analysis in accordance with the guidelines issued for economic evaluations of healthcare interventions (19, 20). Probabilistic sensitivity analysis was performed by the repeated sampling (bootstrap) method and by plotting a cost-effectiveness acceptability curve.

Repeated sampling consists in constructing an empirical estimate of a sample distribution by resampling without replacement from the original data. In the case described, 1,000 resamplings were performed. The result obtained from each resampling is summarized as an incremental cost-effectiveness ratio. From these results, the cost-effectiveness plane and the acceptability curve are obtained. The former is a representation in a plane of the incremental cost and effectiveness of each simulation. The cost-effectiveness acceptability curve is derived from a calculation of the percentage of simulations in which the alternative considered has an incremental cost-effectiveness ratio that is below the threshold for different values of this ratio, and it summarizes the evidence of a cost-effective (acceptable) intervention for different potential values of the decision rule (21, 22).

Because the time in the study was less than 1 year, discounting was not used.

RESULTS

A total of 194 patients were initially included in the study. Finally, 175 were randomized into each group, and 27 patients dropped out of each. Thus, 121 patients were finally analyzed, with 57 in the eSET+eSFET group and 64 in the DET group.

The pregnancy rate achieved per cycle was 49.12% (28/57) in the eSET+eSFET group and 46.88% (30/64) in the DET group. Of the 28 pregnancies in the eSET+eSFET group, 19 were obtained from the fresh SET cycle and nine from the eSFET cycle. Nine miscarriages took place, six in the eSET+eSFET group (6/28, 21.43%), of which five were after eSET and one after eSFET, and three in the DET group (3/30, 10%). The LBDRs were 38.60% (22/57) and 42.19% (27/64) in the eSET+eSFET and DET groups, respectively. These differences were not of statistical significance. The rate of multiple births was 25.93% (7/27) in the DET group, and there were no twin births in the eSET+eSFET group. Of the 39 thaws in the eSET+eSFET group, 37 embryo transfers were performed. The mean waiting time from the eSET to eSFET was 98 days.

Table 1 lists the unit costs used in the cost-effectiveness analysis, distinguishing the costs strictly attributable to AR from those related to the pregnancy, miscarriage (if any), and delivery, neonatal costs (according to birth weight), and costs arising from complications occurring at any stage of treatment. The average cost per patient was €5,832.34 (95% confidence interval [CI] €3,227.24–€9,934.60) in the eSET+eSFET group and €5,562.29 (95% CI €2,877.45–€14,766.11) in the DET group. This difference was not statistically significant.

Figure 1 shows a cost-effectiveness plane of the clinical study results (deterministic result) and 1,000 bootstrap replications, comparing eSET+eSFET and DET. The deterministic result is located in quadrant 2, near the horizontal axis. Regarding the probabilistic results, 32.20% of the replications are located in quadrant 3, which suggests that the eSET+eSFET strategy is less effective, but also less costly, than DET; 41% of the replications are located in quadrant 2, which indicates a higher cost and lower effectiveness for eSET+eSFET compared with DET. Finally, 21.10% and 5.70% of cases are located in quadrant 1 (greater effectiveness and higher cost of eSET+eSFET vs. DET) and quadrant 4 (greater effectiveness and lower cost of eSET+eSFET vs. DET), respectively.

Figure 2 shows the incremental cost-effectiveness acceptability curve. It can be seen that the chance of an eSET+eSFET being cost-effective is <50% for all of the threshold values, reaching the minimum value at ~€5,000, with a 20% probability of achieving cost-effectiveness.

Figure 3 presents the results of this study compared with those reported in similar earlier research, in terms of effectiveness, costs, and cost-effectiveness.

DISCUSSION

This study, comparing a strategy of eSET+eSFET versus one of DET, confirms the absence of clinically significant differences between the two treatment groups. Finally, the outcome is not presented in terms of an incremental cost-effectiveness ratio, because the study results do not indicate either alternative to be more effective at a higher cost than the other, so it makes no sense to calculate this ratio. The probabilistic sensitivity analysis performed with the use of bootstrapping shows that the results are homogeneous in most of the replicas. The cost-effectiveness acceptability curve summarizes the results of the cost-effectiveness plane and shows that for any threshold value the probability of eSET being cost-effective does not reach 50% and is always below the probability of DET being cost-effective.

A significant finding of this clinical study is the very low incidence of extremely-low-birth-weight infants. The birth weight is one of the main determinants of the costs associated with AR, and in the present study only one infant weighed <1.5 kg at birth. This birth was in the eSET+eSFET group and had a strong impact on the costs calculated for this group, which were transferred to the sensitivity analysis by bootstrapping. Many studies have noted the higher incidence of delivery complications following pregnancies achieved by IVF, compared with those achieved by natural conception, with evidence of increased risks in the IVF pregnancies, for

TABLE 1

Unit and average costs (2012 €) and according to embryo transfer protocol.

		eSET (n = 57)		DET (n = 64)	
Procedure	**Unit cost**	**Units**	**Costs**	**Units**	**Costs**
Average procedure cost			5,832.34		5,562.29
Assisted reproduction costs			3,471.36		3,175.75
Diagnostic tests	347.50	57		64	
Monitoring of controlled ovarian stimulation	146.32	114		128	
Drugs for controlled ovarian stimulation	962.49	57		64	
Egg retrieval	146.32	57		64	
Laboratory costs of IVF/ICSI	1,243.15	57		64	
Embryo transfer	146.32	95		64	
Laboratory costs of cryobiology	124	57		0	
Drugs for cryotransfer cycle	230	57		0	
Pregnancy			464.23		618.77
Single	1,202.78	22		20	
Twins	2,220.76	0		7	
Miscarriage	2,158.84	5	189.37	3	101.20
Delivery			1,038.00		981.33
Vaginal	732.00	11		16	
Cesarean	1,344.00	11		11	
Neonatal costs (according to neonatal weight), g			1,279.69		1,161
<1,000	132,467.10	0		0	
1,000–1,500	58,523.27	1		0	
1,500–2,000	10,355.62	0		3	
2,000–2,500	4,806.43	3		9	
>2,500	0.00	18		22	
Complications			27.06		91.26
Ovarian hyperstimulation syndrome	1,755.16	0		2	
Threatened miscarriage	1,542.34	1		0	
Threatened preterm labor	679.42	0		3	

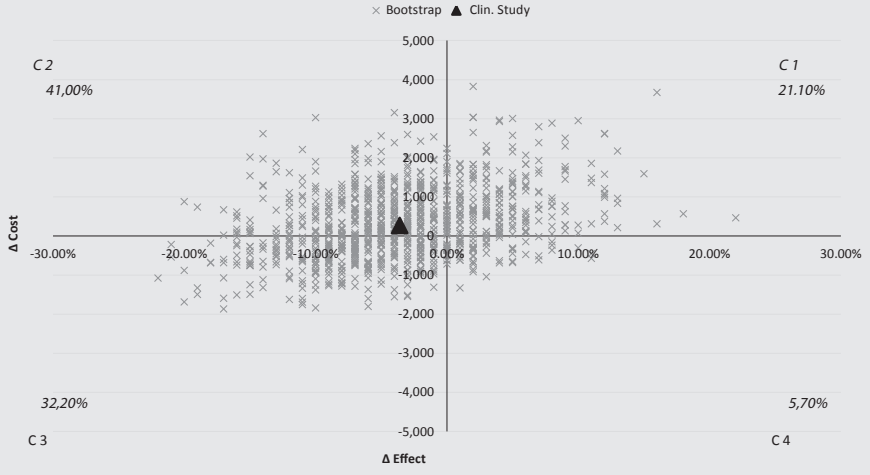
Note: DET = double-embryo transfer; eSET = elective single-embryo transfer.

Hernandez Torres. Economics of single-embryo transfer in IVF. Fertil Steril 2015.

both twin and singleton births. The characteristics of the couple regarding fertility or the fertility treatment received also seem to influence pregnancy and birth (23–29).

The present study's findings of clinical similarity and a lower incidence of multiple births are in accordance with two recent meta-analyses (30, 31) and Kjellberg et al. (15), with LBDRs of ~38% and ~42% for eSET and DET, respectively. Lukasssen et al. (14) also reported similar overall values, although eSET was found to be more effective than DET. Dixon et al. (2), on the other hand,

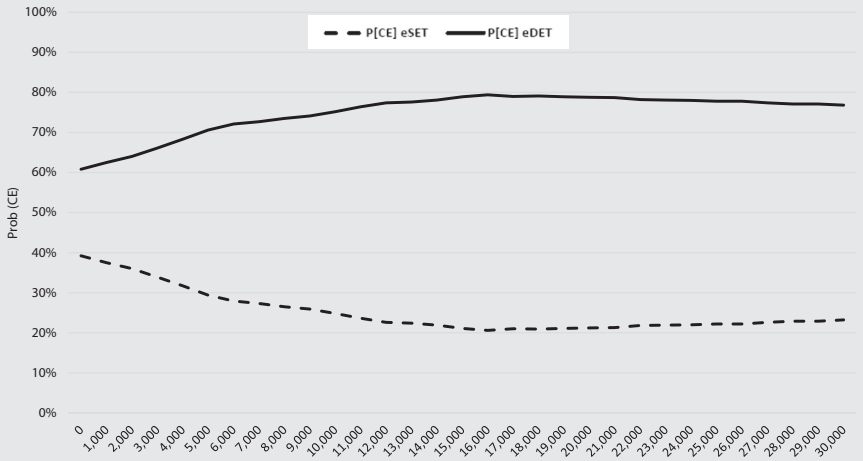
FIGURE 1



Cost-effectiveness plane.

Hernandez Torres. Economics of single-embryo transfer in IVF. Fertil Steril 2015.

FIGURE 2



Cost-effectiveness acceptability curve. CE = cost-effectiveness; eDET = elective double-embryo transfer; eSET = elective single-embryo transfer.

Hernandez Torres. Economics of single-embryo transfer in IVF. Fertil Steril 2015.

reported lower levels of effectiveness in both treatment groups, for all age groups. This difference could have arisen because the latter study did not select patients with a good prognosis.

Cost comparison among different studies is a complex issue owing to differences of context (countries), monetary units, and time scales, but we can compare the differences and similarities observed between the two treatment groups in the different analyses made. In all cases, except in our own study, eSET is found to present a lower cost than DET, although this difference is slight except in the case of Kjellberg et al. (15), where DET was found to be >€3,000 more costly than eSET (Fig. 3). That study, unlike the others, includes the productivity costs associated with maternity leave taken after childbirth.

Regarding the cost-effectiveness results, earlier studies agree that this criterion does not determine the strategy of choice, with small differences found in this respect (2, 14). However, Kjellberg et al. (15) does refer to eSET as a preferable strategy to DET, owing to the above-mentioned differences in costs between the two strategies due to losses in productivity. A review by Fiddelers et al. (32) of economic evaluations of SET versus DET concluded that, in terms of cost-effectiveness, SET combined with frozen-thawed cycles is preferred in good-prognosis patients. However, that review included different eSET strategies, whereas in our study the protocol analyzed is exclusively eSET+eSFET. The neutrality of the arguments based on the cost-effectiveness of eSET versus DET, derived from the relatively insignificant differences found, shifts the debate toward other issues. Proponents of eSET argue that SET avoids the very high long-term costs resulting from the increased morbidity of twins after birth, while not experiencing any significant reduction in pregnancy rates (15, 33). Meanwhile, opponents of this approach argue that the lower pregnancy rates achieved make it necessary to increase the number of cycles performed (8).

The applicability of the above studies to standard IVF practice has been questioned on the basis of the lack of representativeness of the clinical protocols evaluated (34). So far, research on long-term outcomes of twins and singletons after IVF is considered to be scant and inconclusive, with little analysis performed according to specific age groups, with the use of the LBDR as an outcome measure, and with a limited time horizon for the analysis of complications and of costs (35). Nevertheless, these protocols can be considered as part of the overall treatment plan for IVF patients, and they do provide useful information for a possible redesign of treatment programs.

Moreover, the difficulty of conducting clinical studies capable of responding satisfactorily to the above-mentioned design issues has spurred the application of analytic decision making models (2, 36–38) to allow the comparison of results with a broad time horizon and numerous treatment alternatives. Another factor to take into account regarding the applicability of the results is their robustness, such that even if some conditions change, the result should be the same. Nonparametric bootstrapping is commonly used to characterize this uncertainty when patient-level data (on costs and effects) are available, adding confidence in estimates of cost-effectiveness (34, 39).

The embryo transfer strategy varies greatly among different countries and is influenced by various factors, such as the type of health system, whether IVF coverage is mandated, patient populations, legislation, guideline recommendations and culture (10, 40). For example, in the Nordic countries SET is performed in 56% of fresh embryo treatment cycles compared with 13% in the USA (41). To date, the most representative experiences of SET promotion programs at the international level are those of Sweden (42) and Belgium (43–45), which have yielded very positive results.

In Sweden, the live birth rate has been maintained despite successive reductions in the number of embryos replaced,

FIGURE 3

Comparison of different studies regarding effectiveness, costs, and cost-effectiveness. DET = double-embryo transfer; SET = single-embryo transfer.

Hernandez Torres. Economics of single-embryo transfer in IVF. Fertil Steril 2015.

which have resulted in a dramatic decrease in the multiple birth rate (42). According to the latest data available, Sweden has the largest rate of implementation of SET in Europe, at 73.3% of all transfers, and a low overall multiple delivery rate of 5.8% together with a cumulative LBDR in a range of 22.8%–31.9% (46). In Belgium, current legislation combines the reimbursement of six ART cycles with a legally enforced reduction in the number of embryos transferred. This policy has enabled pregnancy rates to be maintained while limiting the number of ART cycles to six and the duration of ART treatment to 36 months, and at the same time it has produced a 50% reduction in the multiple pregnancy rate, from 24% to 12%, as well as a reduction in the associated costs (43–45). In Andalusia, Spain, the number of cycles is being increased from two to three, provided that an eSET has been performed during the first cycles (47).

In the USA, and in accordance with American Society for Reproductive Medicine recommendations, eSET rates among

patients <35 years old have increased by ~1%–2% each year since 2002, accounting for ~10% of all transfers to patients aged <35 years in 2009. These trends have resulted in an increased number of DETs, leading to a reduction in the number of triplet gestations but an unchanged rate of twin gestations (10).

Another important issue to consider when assessing eSET is the perception of the couples involved regarding twin pregnancy. According to a survey conducted in Denmark of 588 couples, 58.7% preferred twins, compared to 37.9% who preferred a singleton pregnancy. The reason given for this was that most respondents wished to determine in a single cycle the definitive number of children to be born, thus minimizing the stress of AR techniques (48). Another very important factor to consider is that patients' preferences for one or two embryos do not remain stable during treatment. According to Fiddelers et al. (49), patients who receive eSET and become pregnant continue to prefer eSET, whereas those who do not become pregnant prefer DET in the next cycle. It is important to note that, in addition to clinical reasons, social and economic factors are relevant to this phenomenon (50); moreover, the national regulatory and economic scenario is important, because in countries where legislation limits the number of embryos transferred, both patients and clinicians are more receptive to eSET (50, 51). Nevertheless, these preferences can be influenced by informing and educating patients about the risks of multiple births (52, 53).

As part of the discussion of these results, some limitations of this study should be acknowledged. Although the data were collected prospectively for each patient, once the patients left the area of attention of the AR unit, the data were collected according to the information provided by the patients themselves, because pregnancy monitoring and childbirth were performed at various health centers unrelated to University Hospital the Virgen de las Nieves. However, this circumstance applied to all patients, and so any potential bias would have affected the two study groups in the same way. Another factor to be taken into account is the lack of power due to restricted sample size, as determined by the time horizon established for this study, which limits the validity of any extrapolation of these results, especially regarding the incidences of very-low-birth-weight infants and miscarriages.

In summary, this study does not show that eSET is superior to DET in terms of cost or effectiveness. The choice ultimately made should be determined by the context in question, which is defined by the health system (the coverage for AR treatment) and the prognosis of the women seeking treatment and the preferences of the patients.

Acknowledgments: The authors thank the doctors, embryologists, nurses, and staff at the Virgen de las Nieves University Hospital in Granada for their enthusiastic help during all phases of this study, especially to Maria Josefa Aldana Espinal and Mercedes Rodriguez Molina for their comments on this manuscript. They also thank the infertile couples for their participation to improve the results obtained in the future by infertile couples receiving assisted reproduction.

REFERENCES

1. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary on ART terminology, 2009. Hum Reprod 2009;24:2683–7.
2. Dixon S, Faghih Nasiri F, Ledger WL, Lenton EA, Duenas A, Sutcliffe P, et al. Cost-effectiveness analysis of different embryo transfer strategies in England. BJOG 2008;115:758–66.
3. Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. BMJ 2004;328:261.
4. Templeton A, Morris JK. Reducing the risk of multiple births by transfer of two embryos after in vitro fertilization. N Engl J Med 1998;339:573–7.
5. Dowling-Lacey D, Jones E, Mayer J, Bocca S, Stadtmauer L, Oehninger S. Elective transfer of two embryos: reduction of multiple gestations while maintaining high pregnancy rates. J Assist Reprod Genet 2007;24:11–5.
6. Luceño F, Vidal E, Castilla JA. Registro FIV-ICSI de la Sociedad Española de Fertilidad. Año 2008. Rev Iberoam Fertil Reprod Hum 2010;27:9–34.
7. Vilska S, Tiitinen A, Hydén-Granskog C, Hovatta O. Elective transfer of one embryo results in an acceptable pregnancy rate and eliminates the risk of multiple birth. Hum Reprod 1999;14:2392–5.
8. Gleicher N, Barad D. The relative myth of elective single embryo transfer. Hum Reprod 2006;21:1337–44.
9. Gleicher N. The irrational attraction of elective single-embryo transfer (eSET). Hum Reprod 2013;28:294–7.
10. American Society for Reproductive Medicine. Elective single-embryo transfer. Fertil Steril 2012;97:835–42.
11. Wølner-Hanssen P, Rydhstroem H. Cost-effectiveness analysis of in-vitro fertilization: estimated costs per successful pregnancy after transfer of one or two embryos. Hum Reprod 1998;13:88.
12. Gerris J, De Sutter P, De Neubourg D, Van Royen E, Vander Elst J, Mangelschots K, et al. A real-life prospective health economic study of elective single embryo transfer versus two-embryo transfer in first IVF/ICSI cycles. Hum Reprod 2004;19:917–23.
13. Fiddelers AA, van Montfoort AP, Dirksen CD, Dumoulin JC, Land JA, Dunselman GA, et al. Single versus double embryo transfer: cost-effectiveness analysis alongside a randomized clinical trial. Hum Reprod 2006;21:2090–7.
14. Lukassen HG, Braat DD, Wetzels AM, Zielhuis GA, Adang EM, Scheenjes E, et al. Two cycles with single embryo transfer versus one cycle with double embryo transfer: a randomized controlled trial. Hum Reprod 2005;20:702–8.
15. Kjellberg AT, Carlsson P, Bergh C. Randomized single versus double embryo transfer: obstetric and paediatric outcome and a cost-effectiveness analysis. Hum Reprod 2006;21:210–6.
16. López-Regalado ML, Clavero A, Gonzalvo MC, Serrano M, Martínez L, Mozas J, et al. Randomised clinical trial comparing elective single-embryo transfer followed by single-embryo cryotransfer versus double embryo transfer. Eur J Obstet Gynecol Reprod Biol 2014;178:192–8.
17. Dueñas JL, Bailón E, Gracia MI, Granados C, Rodríguez RM, Rufo A. Embarazo, parto y puerperio. Proceso asistencial integrado. 2nd ed. Sevilla: Consejería de Salud; 2005.
18. Drummond MF, McGuire A. Economic evaluation in health care. Merging theory with practice. Int J Epidemiol 2002;31:877–8.
19. López J, Oliva J, Antoñanzas F, García-Altés A, Gisbert R, Mar J, et al. A proposed guideline for economic evaluation of health technologies. Gac Sanit 2010;24:154–70.
20. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health 2013;162:231–50.
21. van Hout B, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. Health Econ 1994;3:309–19.
22. O'Brien BJ, Drummond MF, Labelle RJ, Willian A. In search of power and significance issues in the design and analysis of stochastic cost-effectiveness studies in health care. Med Care 1994;32:150–63.

23. Koudstaal J, Bruinse HW, Helmerhorst FM, Vermeiden JP, Willemsen WN, Visser GH. Obstetric outcome of twin pregnancies after in-vitro fertilization: a matched control study in four Dutch university hospitals. Hum Reprod 2000;15:935–40.
24. Koudstaal J, Braat DD, Bruinse HW, Naaktgeboren N, Vermeiden JP, Visser GH. Obstetric outcome of singleton pregnancies after IVF: a matched control study in four Dutch university hospitals. Hum Reprod 2000;15:1819–25.
25. Klemetti R, Gissler M, Hemminki E. Comparison of perinatal health of children born from IVF in Finland in the early and late 1990s. Hum Reprod 2002;17:2192–8.
26. Koivurova S, Hartikainen AL, Karinen L, Gissler M, Hemminki E, Martikainen H, et al. The course of pregnancy and delivery and the use of maternal healthcare services after standard IVF in northern Finland 1990–1995. Hum Reprod 2002;17:2897–903.
27. De Geyter C, De Geyter M, Steimann S, Zhang H, Holzgreve W. Comparative birth weights of singletons born after assisted reproduction and natural conception in previously infertile women. Hum Reprod 2006; 21:705–12.
28. Allen VM, Wilson RD, Cheung A. Pregnancy outcomes after assisted reproductive technology. J Obstet Gynaecol Can 2006;28:220–50.
29. Tomic V, Tomic J. Neonatal outcome of IVF singletons versus naturally conceived in women aged 35 years and over. Arch Gynecol Obstet 2011; 284:1411–6.
30. McLernon DJ, Harrild K, Bergh C, Davies MJ, de Neubourg D, Dumoilin JC, et al. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. BMJ 2010; 341:c6945.
31. Pandian Z, Bhattacharya S, Ozturk O, Serour G, Templeton A. Number of embryos for transfer following in-vitro fertilization or intra-cytoplasmic sperm injection. Cochrane Database Syst Rev 2013:CD003416.
32. Fiddelers A, Severens J, Dirksen C, Dumoulin J, Land J, Evers J. Economic evaluations of single versus double-embryo transfer in IVF. Hum Reprod 2007;13:5–13.
33. Bergh C. Single embryo transfer: a mini-review. Hum Reprod 2005;20: 323–7.
34. Scotland GS, McNamee P, Bhattacharyab S. Is elective single embryo transfer a cost-effective alternative to double embryo transfer? BJOG 2007;114:5–7.
35. van Heesch MM, Bonsel GJ, Dumoulin JC, Evers JL, van der Hoeven MA, Severens JL, et al. Long term costs and effects of reducing the number of twin pregnancies in IVF by single embryo transfer: the Twinsing study. BMC Pediatr 2010;10:75.
36. de Sutter P, Gerris JM, Dhont M. A health-economic decision-analytic model comparing double with single embryo transfer in IVF/ICSI. Hum Reprod 2002;17:2891–6.
37. Fiddelers AA, Dirksen CD, Dumoulin JC, van Montfoort PA, Land JA, Janssen JM, et al. Cost-effectiveness of seven IVF strategies: results of a Markov decision-analytic model. Hum Reprod 2009;24:1648–55.
38. Polinder S, Heijnen EM, Macklon NS, Habbema JD, Fauser BJ, Eijkemans MJ. Cost-effectiveness of a mild compared with a standard strategy for IVF: a randomized comparison using cumulative term live birth as the primary endpoint. Hum Reprod 2008;23:316–23.
39. Drummond MF, Sculpher MJ, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2005.
40. Navarro JL, Castilla JA, Martínez L, Hernández E, Fontes J. Coverage and current practice patterns regarding assisted reproduction techniques. Eur J Obstet Gynecol Reprod Biol 2008;138:3–9.
41. Chambers GM, Hoang VP, Sullivan EA, Chapman MG, Ishihara O, Zegers-Hochschild F, et al. The impact of consumer affordability on access to assisted reproductive technologies and embryo transfer practices: an international analysis. Fertil Steril 2014;101:191–8.e4.
42. Karlstrom PO, Bergh C. Reducing the number of embryos transferred in Sweden—impact on delivery and multiple birth rates. Hum Reprod 2007; 22:2202–7.
43. Gerris JM. The near elimination of triplets in IVF. Reprod Biomed Online 2009;15:40–4.
44. Gerris JM. IVF and ICSI reimbursed in Belgium. J Assist Reprod Genet 2004; 21:135.
45. Peeraer K, Debrock S, Laenen A, De Loecker P, Spiessens C, De Neubourg D, et al. The impact of legally restricted embryo transfer and reimbursement policy on cumulative delivery rate after treatment with assisted reproduction technology. Hum Reprod 2014;29:267–75.
46. Kupka MS, Ferraretti AP, de Mouzon J, Erb K, D'Hooghe T, Castilla JA, et al, European IVF-Monitoring (EIM) Consortium, for the European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2010: results generated from European registers by ESHRE. Hum Reprod 2014;(29):2099–113.
47. Consejería de IgualdadSalud y Políticas sociales de Andalucía. Guía de reproducción humana asistida en el Sistema Sanitario Público de Andalucía. Available at: www.juntadeandalucia.es/servicioandaluzdesalud; 2013. Accessed December 23, 2013.
48. Hojgaard A, Ottosen LD, Kesmodel U, Ingerslev HJ. Patient attitudes toward twin pregnancies and single embryo transfer—a questionnaire study. Hum Reprod 2007;22:2673–8.
49. Fiddelers AA, Nieman FH, Dumoulin JC, van Montfoort AP, Land JA, Evers JL, et al. During IVF treatment patient preference shifts from singletons toward twins but only a few patients show an actual reversal of preference. Hum Reprod 2011;26:2092–100.
50. Maheshwari A, Griffiths S, Bhattacharya S. Global variations in the uptake of single embryo transfer. Hum Reprod Update 2011;17:107–20.
51. van Peperstraten AM, Nelen WL, Hermens RP, Jansen L, Scheenjes E, Braat DD, et al. Why don't we perform elective single embryo transfer? A qualitative study among IVF patients and professionals. Hum Reprod 2008;23:2036–42.
52. van den Akker OB, Purewal S. Elective single-embryo transfer: persuasive communication strategies can affect choice in a young British population. Reprod Biomed Online 2011;23:838–50.
53. Griffin D, Brown L, Feinn R, Jacob MC, Scranton V, Egan J, et al. Impact of an educational intervention and insurance coverage on patients' preferences to transfer multiple embryos. Reprod Biomed Online 2012;25:204–8.