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ARTICLE

Impact of the Spanish Fertility Society guidelines on the number of embryos to transfer

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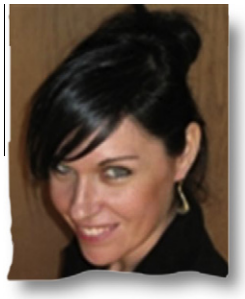

Yolanda Cabello's first degree in Biology (1999) was obtained from the University of Balearic Islands. She has been responsible of several IVF laboratories in Spain and was Associated Professor in the University of Balearic Islands. At present, she is working in Madrid. She has been a member of the Spanish Fertility Society's Assisted Reproductive Technology Register Committee since the National Register started in year 2000.

Abstract The multiple pregnancy rate in assisted reproduction treatment cycles depends, fundamentally, on the number of embryos transferred. It is essential that patients and professionals should have good practical guidelines on the best number of embryos to be transferred in each cycle in order to obtain high pregnancy rates with minimal risk of multiple pregnancies. This study analysed the impact made by the Spanish Fertility Society (SEF) guidelines on the number of embryos to be transferred, as regards the policies adopted at clinics in Spain and the resulting financial repercussions. Data were collected from the assisted reproduction treatment register of the SEF and compared over three periods of time: 2002—2003, with no legal regulation and no SEF guidelines; 2004, with only legal regulation; and 2005—2006, with legal regulation and SEF guidelines. The acceptance of SEF guidelines varies according to the IVF technique. The guidelines have led to a reduction in multiple pregnancy rates, especially concerning triplets, in patients' own-egg and with donor-egg cycles. Even without full implantation, these results validate the clinical utility of the SEF guidelines. They constitute a useful tool to reduce the incidence of the principal adverse effect of treatment cycles: multiple pregnancies.

KEYWORDS: economic impact, ICSI, IVF, multiple pregnancy, number of embryos

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Introduction

The number of multiple pregnancies occurring has increased in parallel with the rise in pregnancy rates achieved by assisted reproductive treatment. In many cases, due to the difficulty in choosing the best embryos in each cycle and the desire to obtain a successful cycle, many patients (and doctors) choose to transfer more than two embryos, and so the percentage of multiple deliveries in assisted reproduction treatment cycles remains high (Nyboe Andersen et al., 2008, 2009).

A twin pregnancy (and more so one of a higher order) is an at-risk pregnancy, even when the vanishing twin syndrome occurs (Shebl et al., 2008): 57% of assisted reproduction twins and 95% of assisted reproduction triplets or higher-order multiples are low birthweight (Wright et al., 2008). Women with multifetal pregnancies have a significantly higher risk of pregnancy-related death than their counterparts with singleton pregnancies (MacKay et al., 2006). Triplet and quadruplet pregnancies have significantly higher risks than twin pregnancies for most maternal and neonatal complications (Luke and Brown, 2008). Furthermore, assisted reproduction treatment-conceived twin pregnancies are at greater risk than naturally conceived ones for pregnancy complications and adverse perinatal outcome (Daniel et al., 2000).

The European Society for Human Reproduction and Embryology (ESHRE) encourages the single-embryo transfer policy (SET). The implementation of elective SET is possible in combination with high-quality laboratories and good cryopreservation programmes. Some studies have shown a decrease in the live birth rate in fresh IVF/intracytoplasmic sperm injection (ICSI) cycles after elective SET in comparison with double-embryo transfer. However, the combination of SET with a good quality freezing programme and subsequent replacement of a single frozen–thawed embryo achieves a live birth rate comparable with that of double-embryo transfer (Pandian et al., 2005). Moreover, ESHRE discourages the transfer of three and four embryos (http://www.eshre.com).

In 2003, under Spanish decree 45/2003, the maximum number of embryos that can be transferred was limited to three. The law currently in force (14/2006) repealed the previous one but maintained the same limitations related to the number of embryos to be transferred (Ricciarelli, 2007).

In 2004, the Spanish Fertility Society (SEF) formed a special interest group (the Embryo Health Group, *Grupo de Salud Embrionaria*) to draw up guidelines for the number of embryos to transfer (SEF guidelines), referring to maternal age, embryo quality, previous cycles, year and type of technique (own or donor egg). Frozen–thawed embryo cycles were not considered. These SEF guidelines are not mandatory and every centre decides for itself how many embryos are to be transferred in each case.

The purpose of this study is to review the impact made by the SEF guidelines, the policies implemented at Spanish assisted reproduction treatment clinics and the resulting financial repercussions.

Materials and methods

This retrospective data exploratory study summarizes assisted reproduction treatment treatments performed in Spain related to IVF/ ICSI with own-egg, donor-egg and frozen–thawed cycles, focusing on the number of embryos transferred and the number of single, twin, triplet or higher-order pregnancies and deliveries obtained. The source for the data used in this study was the Register of the Spanish Fertility Society (SEF) for the years 2002, 2003, 2004, 2005 and 2006 (Hernández et al., 2006; Marqueta et al., 2006, 2007a,b, 2008). The SEF register receives data from assisted reproduction clinics, provided on a voluntary and anonymous basis. Between 50% and 60% of authorized assisted reproduction treatment clinics in Spain participate in the SEF register, accounting for 60–80% of treatment cycles performed in Spain.

In order to evaluate the effect of the legislative changes made in late 2003, which limited the number of embryos to be transferred to three (Royal Decree 45/2003), and the effect of the publication of the SEF guidelines in 2004 (Tur et al., 2005, 2006) (**Table 1**), three periods were considered. First, a period when there were no legal indications or SEF guidelines, the years 2002 and 2003. Second, a period with only legal requirements, the year 2004. Third, a final period in which both legal requirements and SEF guidelines were established, years 2005 and 2006. Frozen–thawed cycles were used as a control group, as this technique was not included in the SEF guidelines. Preimplantation genetic diagnosis, preimplantation genetic screening, in-vitro maturation and intrauterine insemination cycles were not included in this study.

To disseminate the SEF guidelines among professionals in Spain, the recommendations were published in the following: (i) SEF web page: http://nuevo.sefertilidad.com/quienessomos/saludembrionaria/Folletoinformativo.pdf; (ii) SEF Bulletin, spring 2005; (iii) SEF National Congress, La Coruña, 2004; and (iv) scientific journals (Tur et al., 2005, 2006). To publicise the SEF guidelines among patients, 10,000 fliers were distributed among all the registered centres (of which there were 182 in 2004) (Nyboe Andersen et al., 2009) (http://nuevo.sefertilidad.com/socios/grupo-salud-embrionaria.php). They were also published on the SEF web page http://nuevo.sefertilidad.com/quienessomos/saludembrionaria/Folletoinformativo.pdf.

Estimation of financial impact

As the SEF register only included assisted reproduction clinics, the data on deliveries represented approximately 50% of

Table 1 Spanish Fertility Society guideline (2004).

Age (years)	*No. of embryos to transfer*	*Exceptions*
<30	1–2	None
30–37	1–2	After the third cycle, consider transfer of three embryos if there are no embryos of top or good quality
≥38	2	After the first cycle, consider transfer of three embryos if there are no embryos of top or good quality
Egg donation	1–2	None

the pregnancies obtained and so, for the cost calculation, it was necessary to estimate the number of deliveries on the basis of the percentage of each type of delivery registered during each of the study periods and the total number of pregnancies registered in 2005–2006, adjusted by an estimated 18% loss of pregnancies due to abortions, miscarriages and ectopic pregnancies (Marqueta et al., 2008). In addition, unit costs were calculated taking into account the type of delivery, according to a study carried out in Spain using data for 2004 (Prieto, 2005). In brief, the costs taken into account for this study were exclusively neonatal costs, amounting to €882.60 in the case of a single delivery, €16,181 for a twin delivery and €39,717 for triplet or higher-order deliveries.

Under these premises, a budgetary impact analysis was carried out, with the aim of extrapolating the unit cost results to the entire population to whom the recommendations were made, in this case regarding the number of deliveries obtained. The results of the budgetary impact analysis are presented in the form of a bivariate sensitivity analysis concerning the variables with greatest impact on total costs: the occurrence rates for each type of delivery. Thus, the total incremental cost for each percentage point of multiple delivery avoided was calculated.

In addition, extreme scenarios were analysed, using the limits of the 95% confidence intervals (CI) per type of delivery for each of the periods in question. For example, for own-egg cycles in the period 2002–2003, the study observed 70.2 ± 0.74% single deliveries, 27.1 ± 0.72% twin deliveries, 2.4 ± 0.25% triplet deliveries and 0.3 ± 0.09% higher-order deliveries. As 17,897 pregnancies were reported in the period 2005–2006 and assuming a miscarriage rate of 18%, it is estimated that in this period there were 14,675 deliveries. Therefore, if the distribution of types of delivery had been as reported for the period 2002–2003, during the period 2005–2006, single-delivery costs would have been $14{,}675 \times 0.702 \times €882.60$, amounting to a total of €9,092,412.81 (95% CI €8,996,566.80–9,188,258.70). Subsequently, the cost of multiple deliveries was estimated. The same exercise was repeated for donor-egg cycles, applying the percentage of deliveries recorded for the period 2002–2003 to the number of deliveries estimated to have taken place in 2005–2006. The same procedure was then applied to compare the period 2004 with 2005–2006 for own-egg and donor-egg cycles.

Statistical analysis

The following variables were analysed: number of transfers, average number of embryos transferred, type of transfer according to the number of embryos transferred (one, two, three or more than three embryos), number of pregnancies, pregnancy rate per transfer, type of pregnancy (single, twin, triplet or higher-order pregnancy), implantation rate, number of deliveries, type of deliveries (single, twin, triplet or higher-order delivery).

The chi-squared test was used for the qualitative variables. The confidence intervals of the percentages were calculated using the exact method based on the *F*-Snedecor distribution. $P < 0.05$ was considered significant.

Results

Table 2 provides a summary of results using fresh own eggs according to the number of embryos transferred. Both IVF and ICSI cycles are included in the summary. Legislative changes at the end of 2003 led to a decrease in the number of embryos transferred. Consequently, the rate of multiple pregnancies fell (from 31.5% to 27.4%, $P < 0.05$) as did that of multiple deliveries (from 29.8% to 26.9%, $P < 0.05$). Since then, no pregnancies or deliveries of more than three fetuses have been reported. The SEF 2004 recommendations produced another decrease in the average number of embryos transferred, which led to a further decrease in the percentage of multiple pregnancies (from 27.4% to 25.4%, $P < 0.05$) and multiple deliveries (from 26.9% to 25.4%) (**Table 2**).

Table 3 summarizes fresh donor-egg cycles. The decrease observed after the publication of the 45/2003 decree in the number of embryos transferred was not followed by a significant decrease in the percentage of multiple pregnancies (36.7% versus 36.5%) or multiple deliveries (32.5% versus 34.0%). The number of triplets or higher-order pregnancies did fall but the number of twin pregnancies rose. According to the SEF guidelines, only one or two embryos should be transferred in donor-egg cycles. Despite this, 19.0% of transfers in the period 2005–2006 were of three embryos. Nevertheless, the number of multiple pregnancies decreased significantly from 2004 to the 2005–2006 period (36.5% versus 30.3%, $P < 0.001$). A similar pattern was observed for multiple deliveries (34.0% versus 28.0%, $P < 0.001$).

Cryopreservation cycles are summarized in **Table 4**. There was observed to be a decrease in the number of embryos transferred, but this had no impact on the number of multiple pregnancies (22.2% versus 22.0%) or multiple deliveries (20.2% versus 19.9%). Due to legal considerations, there were no cycles with more than three embryos transferred after 2003. This technique was not addressed in the SEF guidelines, but nevertheless there was a slight downward trend in the average number of embryos transferred and the number of multiple pregnancies produced, but this was not enough to significantly diminish the number of multiple deliveries (19.9% versus 19.4%).

Over the three periods, and considering both own and donor-egg cycles, the rate of single pregnancies observed was 67.3% in the 2002–2003 period, 70.6% in 2004 and 73.3% in the 2005–2006 period. With respect to twin pregnancies, the corresponding values were 28.0% in 2002–2003, 26.6% in 2004 and 25.1% in 2005–2006. Those for triplet pregnancies were 4.5% in 2002–2003, 2.9% in 2004 and 1.6% in 2005–2006.

The budgetary impact analysis (**Table 5**) concludes that SEF guidelines produced a saving of between €890,187 and €18,593,242. The average cost saving was €9,741,715. The cost saving for each percentage point of multiple pregnancy avoided was €2,989,613. This saving was obtained without a reduction in the pregnancy rate per transfer (**Tables 2** and **3**). **Figure 1** shows the reduction in total delivery costs (Y-axis) according to the percentage of single deliveries (X-axis) at three levels of triplet delivery (0%, 1% and 2%).

Table 2 Assisted reproduction treatment results in fresh own-egg cycles.

Results	*2002–2003* *No legislation and no SEF guidelines*	*2004* *Legislation and no SEF guidelines*	*2005–2006* *Legislation and SEF guidelines*
No. of cycles	37,823	27,481	57,758
No. of transfers	31,487	21,085	46,617
1 embryo	3720 (11.8)	2798 (13.3)[b]	6781(14.5)[b]
2 embryos	12,698 (40.3)	10,500 (49.8)[a]	26,486 (56.8)[b]
3 embryos	12,303 (39.1)	7787 (36.9)[a]	13,350 (28.6)[b]
>3 embryos	2766 (8.8)	ND	ND
Mean no. of embryos/transfer	2.4	2.2	2.1
No. of pregnancies (% per transfer)[c]	11,532 (36.6)	7866 (37.3)	17,897 (38.4)
Singleton	7096 (68.5)	5331 (72.6)	12,704 (74.6)
Multiple	3268 (31.5)	2014(27.4)[a]	4336 (25.4)[b]
Twin	2770 (26.7)	1793 (24.4)	4059 (23.8)
Triplets	474 (4.6)	221 (3.0)	277 (1.6)
Higher	24 (0.2)	ND	ND
Rate of embryo implantation (%)	18.3	20.3	21.7
No. of deliveries	7089	3818	8655
Single	4973 (70.2)	2790 (73.1)	6459 (74.6)
Multiple	2116 (29.8)	1028 (26.9)[a]	2196 (25.4)
Twin	1921 (27.1)	959 (25.1)	2074 (24.0)
Triplets	168 (2.4)	69 (1.8)	122 (1.4)
Higher	27 (0.4)	ND	ND

Values are *n* (%) unless otherwise stated.
ND = no data; SEF = Spanish Fertility Society.
From the end of 2003, no more than three embryos could be transferred in accordance with Spanish Law.
[a] $P < 0.05$, 2002–2003 versus 2004.
[b] $P < 0.05$, 2004 versus 2005–2006.
[c] The total number of pregnancies is greater than the sum of singleton and multiple pregnancies as some centres only provide the number of pregnancies without data on singleton/multiple pregnancies.

Discussion

In recent years, various strategies have been implemented to prevent multiple pregnancies, such as less aggressive stimulation protocols, increased echographic and blood tests during stimulation and fewer embryos transferred. This latter measure has been achieved through legislative changes and thanks to the intervention of relevant scientific societies.

In Spain, the first attempt to control the rate of multiple pregnancies was in 2003, with Law 45/2003 of 21 November, which limited the number of embryos transferred to a maximum of three per stimulation cycle. The present study shows that this law produced a reduction in the number of higher-order multiple pregnancies, but that the number of twin pregnancies remained high.

In some European countries, there exists legislation similar to that applying in Spain. For example, in the UK, the Human Fertilisation and Embryology Authority (HFEA) published stipulations based on consensus between legislators and IVF clinics (www.hfea.gov.uk). The assisted reproduction clinics, themselves, proposed that a multicentre study should be carried out, to determine the lowest number of embryos that could be transferred without prejudice or reducing the pregnancy rates achieved. The results of and the conclusions drawn from this study were received by the HFEA, which on 1 March 2004 ruled that assisted reproduction centres must transfer no more than two embryos per stimulation cycle. Exceptions were allowed in cases of transfers to women aged over 40 years, provided that no egg donation was involved (HFEA, 2004).

In Sweden, the initiative was also taken by IVF centres, which began to transfer just one embryo or, only in exceptional cases, two. This decision was taken, too, by the Swedish National Medical Board Authority (Hovatta, 2002; Karlström and Bergh, 2007).

In Italy, a legislative change in 2004 brought about changes; the Italian Parliament passed a law in March 2004 by which no more than three oocytes per cycle could be fertilized and all embryos thus created had to be transferred. A study carried out by Ragni et al. (2005) concluded that although the pregnancy rate per transfer had fallen (from 30.5% to 27.2%), the difference was not significant. At the same time, the rate of multiple pregnancies fell (from 20.8% to 18.1% for twins and from 5% to 2.8% for triplets), although this difference was not statistically significant, either.

In Spain, the above-mentioned reduction in multiple pregnancies that followed the legislative changes of late 2003 was accompanied by a further reduction with the publication of the SEF guidelines. This decrease did not affect the rate of pregnancies per transfer and indeed in some

Table 3 Assisted reproductive technology results in fresh donor-egg cycles.

Results	*2002–2003* *No legislation and no SEF guidelines*	*2004* *Legislation and no SEF guidelines*	*2005–2006* *Legislation and SEF guidelines*
No. of cycles	7564	4801	12,313
No. of transfers	6607	4219	11,864
1 embryo	226 (3.4)	221 (5.2)[a]	685 (5.8)
2 embryos	3516 (53.2)	2924 (69.3)[a]	8929 (75.3)
3 embryos	2513 (38.0)	1074 (25.6)[a]	2250 (19.0)
>3 embryos	352 (5.3)	ND	ND
Mean no. of embryos/transfer	2.5	2.2	2.1
No. of pregnancies (% per transfer)[b]	3409 (51.6)	2190 (51.9)	5934 (50.0)
Singleton	1980 (63.3)	1323 (63.5)	3988 (69.7)
Multiple	1150 (36.7)	760 (36.5)	1733 (30.3)[c]
Twin	1011 (32.3)	712 (34.2)	1649 (28.8)
Triplets	132 (4.2)	48 (2.3)	84 (1.5)
Higher	7 (0.2)	ND	ND
Rate of embryo implantation (%)	27.3	31.1	29.8
No. of deliveries	2424	1151	3131
Single	1636 (67.5)	760 (66.0)	2253 (72.0)
Multiple	788 (32.5)	391 (34.0)	878 (28.0)[c]
Twin	747 (30.8)	381 (33.1)	864 (27.6)
Triplets	40 (1.7)	10 (0.9)	14 (0.4)
Higher	1 (0.04)	ND	ND

Values are *n* (%) unless otherwise stated.
ND = no data; SEF = Spanish Fertility Society.
From the end of 2003, no more than three embryos may be transferred in accordance with Spanish Law.
[a] $P < 0.001$, 2002–2003 versus 2004.
[b] The total number of pregnancies is greater than the sum of singleton and multiple pregnancies as some centres only provide the number of pregnancies without data on singleton/multiple pregnancies.
[c] $P < 0.001$, 2004 versus 2005–2006.

cases it has even increased (from 36.6% in 2004 to 38.4% in 2005–2006 for own-egg cycles; **Table 2**). This is accounted for by the fact that during the periods analysed, the rate of embryo implantation increased steadily in the case of embryo transfers derived from own-egg cycles (**Table 2**). This is probably the consequence of the evident improvement in treatment indications, ovarian stimulation protocols and conditions in which gametes and embryos are cultivated in embryology laboratories, as well as the better selection being made of embryos when the transfer is effected.

The impact of the SEF guidelines is apparent from an analysis of the results of cryotransfer cycles, a technique that is not included in these guidelines; this shows that here, on the contrary to the case of the techniques that are included, the rate of multiple deliveries did not change significantly following publication of the guidelines.

The acceptance of any guideline for good clinical practice is a gradual process. Although not specifically analysed in the present study, the differences between 2005 and 2006 (www.registrosef.com) were not sufficiently important to lead us to believe that current strategies will lead to the achievement of 100% implementation within the next few years. Among the factors favouring the mixed acceptance of the SEF guidelines among assisted reproduction clinics in Spain are defects in the guidelines themselves, difficulties in communicating them to patients and problems of acceptance among professionals (Franssen et al., 2007).

As regards the factors related to the directives, it is not the case that they are outdated or difficult to apply. A key element to the successful implantation of any guideline is that it should be distributed specifically, in the form of publications or meetings or via local opinion-leaders (Grimshaw et al., 2006). For this reason, and as remarked above, the SEF guidelines were widely disseminated among professionals and patients.

Relevant factors concerning the medical practitioner might include a lack of awareness or disagreement with the guidelines. In Spain, 80% of treatment cycles are performed in the private sector and, as in any other activity, there exists competition among different suppliers. This competition, and the need to maintain a high rate of pregnancies per cycle, might lead the professionals involved to reject any measure that could affect this rate. Public centres, on the other hand, limit the range of services provided (for example, regarding egg donation) (GICRHA, 2002) and the limitations could induce them to seek to maximize the possibility of achieving pregnancies with the treatments available by increasing the number of embryos transferred (Castilla et al., 2009).

Table 4 Assisted reproductive technology results in cycles using cryopreserved embryos.

Results	*2002–2003*	*2004*	*2005–2006*
	No legislation and no SEF guidelines	*Legislation and no SEF guidelines*	*Legislation and SEF guidelines*
No. of cycles	7225	5242	14,926
No. of transfers	5926	4475	12,267
1 embryo	1019 (17.2)	926 (20.7)[a]	3055 (24.9)[b]
2 embryos	2347 (39.6)	2131 (47.6)[a]	6347 (51.7)[b]
3 embryos	2010 (33.9)	1418 (31.7)[a]	2865 (23.4)[b]
>3 embryos	550 (9.3)	ND	ND
Mean no. of embryos/transfer	2.4	2.1	2
No. of pregnancies (% per transfer)[c]	1533 (25.9)	1229 (27.5)	3217 (26.2)
Singleton	1180 (77.8)	934 (78.0)	2529 (81.6)
Multiple	337 (22.2)	264 (22.0)	571 (18.4)
Twin	291 (19.2)	239 (19.9)	538 (17.4)
Triplets	43 (2.8)	25 (2.1)	33 (1.1)
Higher	3 (0.2)	ND	ND
Rate of embryo implantation (%)	13.6	15.7	15.2
No. of deliveries	1046	537	1299
Single	835 (79.8)	430 (80.1)	1047 (80.6)
Multiple	211 (20.2)	107 (19.9)	252 (19.4)
Twin	198 (18.0)	101 (18.8)	246 (18.9)
Triplets	13 (1.2)	6 (1.1)	6 (0.5)
Higher	0	ND	ND

Values are *n* (%) unless otherwise stated.
ND = no data; SEF = Spanish Fertility Society.
[a] $P < 0.001$, 2002–2003 versus 2004.
[b] $P < 0.001$, 2004 versus 2005–2006.
[c] From the end of 2003, no more than three embryos may be transferred in accordance with Spanish Law.

Table 5 Total costs of deliveries estimated for the period 2005–2006, under different scenarios, based on the confidence intervals obtained per type of delivery in each period.

Type of delivery	*Measure*	*Estimated cost (€)*		
		No legislation and no SEF guidelines	*Legislation and no SEF guidelines*	*Legislation and SEF guidelines (real scenario)*
Own eggs	Mean	90,027,929	79,566,192	74,816,745
	95% CI	85,987,877–94,067,981	76,528,273–82,604,111	71,980,030–77,653,460
Donated eggs	Mean	28,582,441	30,643,196	25,650,929
	95% CI	24,694,850–32,470,032	29,024,941–32,261,451	24,292,290–27,009,567
Total	Mean	118,610,370,00	110,209,389	100,467,674
	95% CI	110,682,727–126,538,013	105,553,214–114,865,562	96,272,320–104,663,027

Patient-related factors could include resistance to following the guidelines, perhaps due to limitations imposed on the number of cycles offered to users at public centres which would make couples more reluctant to accept any reduction in the number of embryos transferable. Moreover, couples at the upper age limit or those subjected to a long waiting list might be more inclined to take risks regarding embryo transfer. It should also be taken into account that at private clinics embryo freezing involves extra expense and so some patients would be willing to have a transfer with a greater number of embryos in order to avoid this added cost. A further factor to bear in mind is that couples' perceptions regarding multiple pregnancy are not always negative (Højgaard et al., 2007).

The results suggest that there has been an unequal compliance with the SEF guidelines between own-egg and donor-egg cycles. Although the SEF guidelines advise against the transfer of three embryos in egg donation, during the 2 years following publication of the guidelines, 19.0% of embryo transfers in egg donation were of three embryos (**Table 3**). The difference in compliance with the guidelines between the two techniques (own egg versus donor egg)

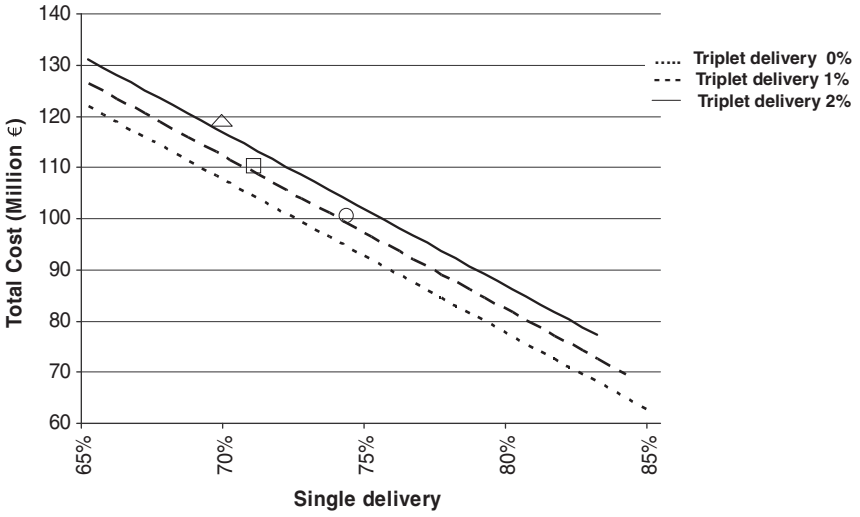

Figure 1 Sensitivity analysis of the total costs for different percentages of type of delivery following the transfer of own-egg or donated-egg embryos for the period 2005—2006 under the three scenarios analysed: no legislation (triangle), with legislation (square), and with both legislation and Spanish Fertility Society guidelines (circle).

could occur because the donor-egg technique is normally offered to patients who are unable to achieve pregnancy with the other available methods (because of advanced age of the woman, lack of response to ovarian stimulation or to IVF/ICSI failures) and thus egg donation would be a last resort and patients and/or medical practitioners would be prepared to take more risks in embryo transfer. Another factor would be the financial aspect, as this technique is more costly than IVF/ICSI with fresh own eggs.

The present study has shown that decreasing the number of embryos transferred brings about a significant reduction in the costs of deliveries (between €890,187 and €18,593,242). Under the Belgian refunding policy, embryo transfers have been reduced from two to one in most cases, which has decreased the costs associated with multiple deliveries by some €7 million. This sum was reinvested in assisted reproduction treatment by increasing the offer to sux IVF cycles per couple in the Belgian health system (Gerris, 2007). If this model were applied in Spain, assigning the money saved from changing the embryo transfer policy to carrying out more assisted reproduction treatments, under the assumption that each ICSI treatment has a cost of €1,300 (Navarro et al., 2006) and the average saving per delivery as estimated in this study, the total saving would be €9,741,715 (**Table 5**), which would be sufficient to pay for almost 7500 ICSI transfers at public clinics.

Although the reduction achieved in the rate of multiple pregnancies following the legislative changes and the publication of the SEF guidelines, has been very significant, it is still insufficient and remains well above that recorded in other European countries: 21.8% for the year 2005 versus 26.1% for the period 2005—2006 in Spain (Nyboe Andersen et al., 2009). If Spain had matched the above European rate, this would have represented an additional saving of €13 million in delivery costs according to the sensitivity analysis carried out here (Figure 1).

This study does present certain limitations. Although a relationship between legislative changes was found, the publication of the SEF guidelines and the multiple pregnancies rate, this relationship is not proof of direct causality. Other reasons, such as the result of improvements over time in methodology such as embryo cryopreservation techniques could also lead clinicians to reduce their embryo transfer numbers over succeeding years. All the calculations made are based on the SEF register, which accounts for 60—80% of activity in Spain and so the cost reduction described here could probably be even greater. For an accurate valuation of these costs, it would be necessary to develop an official register.

As most of the centres that are included in the SEF register are exclusively assisted reproduction clinics, the SEF register of deliveries is incomplete (approximately 50% of all pregnancies) and so the cost calculations were performed on the basis of assumptions that may be slightly inaccurate regarding, for example, the rate of lost pregnancies due to miscarriage or ectopic pregnancy. Nevertheless, the rate used in this paper (18%) is similar to that described in other records of assisted reproduction pregnancies achieved (Gunby et al., 2010).

The costs by type of delivery were based on a study carried out in Spain using data for 2004 (Prieto, 2005): although these data are similar to those described in studies of other countries (Ledger et al., 2006), to obtain a more precise calculation, these estimates would need to be updated. Moreover, the present study does not include the medium or long-term costs arising from the morbidity of premature infants. In studies in which this type of cost has been included, the final cost estimates obtained are more than double those employed in this paper (Dixon et al., 2008). Other costs not taken into account in the present study are those arising from the increased use of frozen embryo transfer as a result of the decreasing numbers of embryos transferred. Nevertheless, although cycles with fresh plus frozen embryo transfers are more costly in terms of IVF costs, in terms of total costs, this strategy is less costly than cycles performed in which more embryos are transferred

(Dixon et al., 2008; Veleva et al., 2009). To determine the added IVF cost of embryo freezing, it would be necessary to use cycle-specific information, which unfortunately the SEF register does not possess.

In conclusion, although total acceptance has not been attained, the impact of the SEF guidelines has been significant in terms of cost savings in deliveries. Analysis of the causes of the unequal compliance with these guidelines is fundamental if the take-up rate is to be increased. These results validate the clinical utility of the SEF guidelines, which have proved to be a useful tool to decrease the incidence of the principal adverse effect of assisted reproduction treatment cycles, namely multiple pregnancies.

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