Outlook

Prevention of multiple pregnancy following IVF in Spain

Rosa Tur studied medicine at the University of Barcelona and completed her specialist training in obstetrics and gynaecology at the Institut Universitari Dexeus, where she continues to work in the Reproductive Medicine Service. Her doctoral thesis, for which she received a special award, concerned risk factors for multiple pregnancy following assisted reproduction. She has also published several papers about the prevention of multiple pregnancies. She takes an active part in the Embryo Health Special Interest Group of the Sociedad Española de Fertilidad, which is trying to reduce the multiple pregnancy rate in Spain.

Dr Rosa Tur

R Tur, B Coroleu, MJ Torelló, M Boada, A Veiga, PN Barri
Reproductive Medicine Service, Department of Obstetrics and Gynecology, Institut Universitari Dexeus, Paseo Bonanova 67, 08018 Barcelona, Spain
Correspondence: e-mail: rostur@dexeus.com

Abstract

Since the development of assisted reproduction techniques most countries have witnessed increased rates of multiple pregnancy. Despite the guidelines proposed by various scientific societies these rates continue to be abnormally high. In Spain, as in other Mediterranean countries, a greater number of embryos are transferred than in northern and central European countries and the incidence of multiple pregnancies is greater in comparison. Effective strategies must be established to prevent multiple pregnancy without reducing overall pregnancy rates. In the authors’ institute, taking into account the authors’ experience, the relevant literature, and despite the limitation of retrospective studies, it is recommended that a maximum of two embryos are transferred in young women with good quality embryos at the time of transfer. The transfer of three embryos is only recommended in women ≥38 years who have one or no good quality embryos available at the time of transfer. The responsibility for preventing multiple pregnancy lies with health professionals, who must be aware of the risks involved in twin and triplet pregnancy. Couples must be provided with objective information before starting an IVF cycle. Professional societies should highlight the problem and make suitable recommendations.

Keywords: embryo transfer, IVF, multiple pregnancy, prevention

Introduction

Spanish population registers show that between 1980 and 2004 a notable increase in the rate of multiple deliveries has taken place, particularly since 1990. According to data published by the Instituto Nacional de Estadística (INE, Spanish Institute of Statistics), in the last 20 years the rate of twin deliveries has doubled (75 in every 10,000 deliveries in 1980; 175 in 2004) and the rate of triplet deliveries has increased six times (11 in every 100,000 deliveries in 1980; 60 in 2004) (Figure 1).

In order to confirm the evidence of increased multiple pregnancy rates, supposedly due to assisted reproduction techniques, the same data sources (INE) have been used to calculate the incidence of twin and multiple gestations in the 1970s, when there were no assisted reproduction methods, and this has then been compared with the 1990s when assisted reproduction techniques were widely used. In the 1970s the rate of multiple deliveries was one set of twins per 120 deliveries, whilst in the case of triplets or more it was one in 11,967. However, in the 1990s twins accounted for one of every 89 deliveries, while the rate for triplets or more was one in 2,776 deliveries. This difference is substantial if we compare it with the theoretical progression that multiple deliveries should have had if the conditions of the 1970s had been maintained (Figure 2).

The causes should be sought, firstly, in the increase in maternal age and secondly, in the development of assisted reproduction techniques, namely IVF, in which more than one embryo is normally transferred; and ovarian induction/stimulation (whether or not associated with an insemination), in which more than one follicle can develop.
Figure 1. Multiple deliveries in Spain from 1980 to 2004. Source: Spanish Institute of Statistics (INE).

Figure 2. Incidence of multiple deliveries: expected and observed. Source: Spanish Institute of Statistics (INE).
Embryo Transfer Policy

According to data produced by the Sociedad Española de Fertilidad (SEF, Spanish Fertility Society) and recorded by the European Society for Human Reproduction and Embryology (ESHRE, 2002; 2004; 2005), in IVF/intracytoplasmic sperm injection (ICSI) cycles that took place during 1999, 2000 and 2001 three embryos were transferred in almost 50% of cycles during the 3 years (45.6%, 44.4% and 51.2%, respectively); in approximately 20% of cycles two embryos were transferred, with an increasing trend over the years (16.3%, 22.1% and 24.8%, respectively). In more than 20% of cycles four embryos were transferred during the years 1999 and 2000, while there is a decrease in 2001 (29.4%, 24.1% and 13.9%, respectively). Single embryo transfer only took place in 10% of cycles. The authors’ figures contrast notably with the overall European figures, which demonstrate that in 1999 the rate of two-embryo transfers was 39.2%, reaching 51.7% in 2001. In 2001 the European transfer rate for three embryos was 30.8%, while the four-embryo transfer rate was only 5.5%. Finally, in 12% of cycles only one embryo was transferred. In the USA, according to the American Society for Reproductive Medicine (ASRM) (SART/ASRM, 2002; 2004; 2005), the data are more similar to the authors’ own, although they show a bigger proportion of four or more embryo transfers (1999: 36.3%; 2000: 23.6%; and 2001: 31.9%) (Table 1).

If the 2001 European figures published in 2005 (ESHRE, 2005) are analysed and compared with data from Scandinavian countries (Finland, Sweden and Denmark), central European countries (France, UK, Belgium) and Mediterranean countries (Spain, Italy and Portugal) the following can be observed: in Scandinavian countries there is a clear trend towards single and two-embryo transfers, and there are practically no transfers of three or more embryos; their data reveal that triple pregnancies are almost non-existent. In central European countries, two embryos are transferred in more than 50% of cases, while in approximately 20% of cycles three embryos are transferred; rates of triple pregnancy are about 1%. Finally, in Mediterranean countries three embryos are transferred in 50% of cycles and triplets result from 3–4% of pregnancies, this figure being notably higher than the European average (in 2001 the registry’s European average was 1.5%). In the case of Spain it is important to point out that the data given to ESHRE represents only a small percentage of the total cycles performed. For the 2001 registry, only 47 of the 182 recognized centres contributed data, and therefore it is probable that the published figures do not accurately reflect the real ones; the rates of multiples could thus be higher than those recorded.

Number of embryos to be transferred: legislation and recommendations

An increasing number of countries now legislate for the number of embryos that can be transferred in an IVF/ICSI cycle. The most restrictive among them is Sweden, which limits transfer to only one embryo. In the UK, the Netherlands and Denmark the limit is two embryos (with the possibility of three in special cases). Most countries have set a limit at three embryos (Spain, Switzerland, Italy and India), while Hungary and Saudi Arabia include exceptions for four. However, other countries simply give recommendations, ranging from one to two and even up to six embryos. Belgium recommends from one to two, Finland from one to three, Austria and Poland two, the USA from two to five, France, Ireland, Portugal and Japan three, China and Venezuela from three to four, Hong Kong from three to five, the Czech Republic four and Canada fewer than six (IFFS, 2004).

In Spain, the 1988 law made the number of embryos to be transferred conditional on the criteria of each clinic or centre. Article four of the 35/1988 law stated that: ‘The number of pre-embryos transferred to the uterus will be that which is scientifically considered to be the most adequate to reasonably ensure pregnancy’. However, since the modification of the 45/2003 law it is not possible to transfer more than three embryos per cycle: ‘Authorisation is given for the transfer of a maximum of three pre-embryos per woman in each cycle’.

In addition to legislation, scientific societies also establish recommendations on the number of embryos to be transferred. In the UK, the Royal College of Obstetricians and Gynaecology makes general recommendations (such as inform couples of the risks implied in multiple pregnancies, evaluate the risks and consequences of multiple pregnancies, etc.) and does not recommend the transfer of more than two embryos in a first cycle.

Table 1. Percentage of number of embryos transferred according to IVF/ICSI registers.

<table>
<thead>
<tr>
<th>Register</th>
<th>Year</th>
<th>1 embryo (%)</th>
<th>2 embryos (%)</th>
<th>3 embryos (%)</th>
<th>&gt;3 embryos (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESHRE</td>
<td>1999</td>
<td>11.9</td>
<td>39.2</td>
<td>39.6</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>12.1</td>
<td>46.7</td>
<td>33.3</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
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<td>12.0</td>
<td>51.7</td>
<td>30.8</td>
<td>5.5</td>
</tr>
<tr>
<td>SEF</td>
<td>1999</td>
<td>8.6</td>
<td>16.3</td>
<td>45.6</td>
<td>29.4</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>9.4</td>
<td>22.1</td>
<td>44.4</td>
<td>24.1</td>
</tr>
<tr>
<td></td>
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<td>10.1</td>
<td>24.8</td>
<td>51.2</td>
<td>13.9</td>
</tr>
<tr>
<td>ASRM</td>
<td>1999</td>
<td>6.2</td>
<td>23.3</td>
<td>34.2</td>
<td>36.3</td>
</tr>
<tr>
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<td>2000</td>
<td>5.7</td>
<td>25.8</td>
<td>34.9</td>
<td>23.6</td>
</tr>
<tr>
<td></td>
<td>2001</td>
<td>6.2</td>
<td>27.3</td>
<td>34.5</td>
<td>31.9</td>
</tr>
</tbody>
</table>
Multiple pregnancy prevention strategies

Since multiple pregnancies are the most frequent complication in assisted reproduction, measures are required to reduce their incidence. However, the prevention of multiple pregnancies depends on limiting the number of embryos transferred and the question thus arises of how it should be done without significantly affecting overall pregnancy rates.

Over the years, different strategies to prevent multiple pregnancies have been established:

Two- or three-embryo transfers

In 1991, Waterstone et al. proposed an elective double embryo transfer (DET). Since then, most studies (Nijs et al., 1993; Staessen et al., 1993; Tasdemir et al., 1998; Dean et al., 2000) have demonstrated that in young women with good quality embryos it is possible to reduce the rate of triplets without altering overall pregnancy rates by using DET; thus, in these cases two-embryo transfers are advisable. However, conditions are not always optimum and other authors (Qasim et al., 1995; Svendsen et al., 1996; Geva et al., 1998; Salha et al., 2000) suggest transferring more embryos in cases of poor prognosis (such as advanced age, repeated failure of IVF, poor embryo quality, etc.). The question is whether in these circumstances three-embryo transfers justify the risk involved or if the transfer of more embryos in cases of poor prognosis simply increases the possibility of pregnancy.

In the authors’ institute a retrospective study was carried out in which two-embryo and three-embryo transfers were compared (2 ET versus 3 ET), the objective being to determine whether the transfer of more embryos in cases of a worse prognosis increases pregnancy rates and what the repercussions are for the rate of triple pregnancies.

As previously reported (Coroleu et al., 2000), in the authors’ IVF programme ovarian stimulation is routinely accomplished using a long protocol (under pituitary suppression with gonadotrophin-releasing hormone agonist [GnRHa] starting in the mid-luteal phase, and stimulation with 225 IU of recombinant FSH). In those patients with a previous poor response and/or baseline FSH serum concentrations >10.5 IU/l (cycle day 2–4), a flare-up protocol was used (GnRHa starting on day 2 of the menstrual cycle and follicular stimulation beginning on day 3 with 225 IU of recombinant FSH plus three ampoules of human menopausal gonadotrophin) (Barri et al., 2000).

Embryo transfer was carried out 2 days after oocyte retrieval and embryo quality was assessed according to the number and size of the blastomeres and the degree of cytoplasmic fragmentation. Embryos with at least four blastomeres of similar size and less than 20% fragmentation were considered good quality embryos (Coroleu et al., 2002).

Pregnancy was diagnosed by positive urine and/or blood human chorionic gonadotrophin (HCG) tests and the subsequent demonstration of at least one intrauterine gestational sac by transvaginal ultrasonography at 6 weeks’ gestation. The subsequent outcome of pregnancy was not considered for the specific purpose of this study.

A total of 1508 two-embryo transfer cycles (elective 1248, 82.8%; non-elective 260, 17.2%) were analysed and compared with 880 three-embryo transfer cycles (elective 684, 77.7%; non-elective 196, 22.3%), all of which were performed between January 2001 and December 2004. Three embryos were transferred in women with a worse prognosis (older, greater number of previous IVF cycles, etc.). Similar pregnancy rates were obtained for the transfer of two (692/1508, 45.9%) or three embryos (386/880, 43.9%), the latter having the additional factor of 7.5% triple pregnancies. The results are in agreement with those of Elizur et al. (2005), who report no differences in delivery rates when comparing three-embryo versus two-embryo transfers; moreover, the rate of triplet pregnancies following three-embryo transfer was 5.3%.

When analysed by age group, the pregnancy rates were similar in two- and three-embryo transfers, except in women older than 40 in whom three-embryo transfers produced a significantly higher rate (57/214, 26.6%) than two-embryo transfers (33/202, 16.3%) ($P < 0.05$). Triplets were observed in all age groups, but the incidence was higher in younger patients (<30 years = 16.7%; 30–32 years = 12.5%) than in patients older than 33 years (5–6%).

If, instead of age, the number of good quality embryos at the time of transfer is taken as a reference (there being at least one good quality embryo), the pregnancy rates were similar for two- and three-embryo transfers. However, the rates were...
significantly higher in three-embryo transfers when there were no good quality embryos (33.5% versus 22.9%; \( P < 0.05 \)). The number of triplet pregnancies remained unchanged in all circumstances (4.6–11.6%), even in cases of three-embryo transfers with no good quality embryos (4.6%).

When analysing both variables (age and embryo quality) under equivalent conditions and with the same number of good quality embryos for women under the age of 38, there were no significant differences in the rates for two- and three-embryo transfers. What is important is that when transferring three embryos the incidence of triple gestations was 6–10% of gestations (Figure 3). When the same variables were analysed in women older than 38, pregnancy rates increased significantly when three embryos were transferred instead of two, both when there were no good quality embryos (24.2% versus 4.1%; \( P < 0.001 \)) and when there were more than two good quality embryos (45.9% versus 31.5%; \( P < 0.05 \)); however, there were 12.8% triple pregnancies in the latter case.

Given this and taking into account the results, three-embryo transfers should not be recommended under any circumstance in women under the age of 38; here it would simply influence the rate of triplets. However, in women older than 38, three-embryo transfers could be justified in cases where there is just one or no good quality embryos (Figure 4), although prospective and randomized studies are necessary to confirm these recommendations.

### Single-or two-embryo transfers

In 1999, Vilska and colleagues proposed an elective single embryo transfer (SET) in cases of good prognosis (Vilska et al., 1999). Later, in the ESHRE consensus meeting held in Maastricht in May 2002 (Land and Evers, 2003), it was concluded that twin pregnancy is a complication of assisted reproduction techniques and SET was thus suggested for cases of good prognosis (young women in their first or second cycle and with good quality embryos).

A recently published review of SET (Bergh, 2005) has shown, after evaluating the data published in randomized prospective studies, that the overall pregnancy rates are higher in two-embryo transfers (48%) compared with single-embryo transfers (32%), but with a twin birth rate of 35% when transferring two embryos. However, proper evaluation of SET results implies evaluating not only the fresh pregnancy and cumulative pregnancy rates post embryo cryotransfer but also the final outcome of the process: ‘born alive, healthy baby’. Other studies have concluded that in countries that have systematically incorporated SET in recent years, there have been no repercussions on their overall pregnancy rates (De Neubourg and Gerris, 2003; Tiitinen and Gissler, 2004; Debrock et al., 2005).

In the author’s institute a multiple pregnancy reduction policy was introduced a few years ago (Barri, 2005). In 2002, SET was included among the different strategies proposed, and is suggested for women under the age of 38 provided they have at least two good quality embryos. The results obtained from October 2002 to September 2004 are as follows: SET was proposed to 297 couples, of whom 191 (64.5%) accepted and 105 (35.5%) requested a double embryo transfer (DET). The two groups were similar, except that those requesting DET had undergone more cycles (1.6 ± 0.9) than those who chose SET (1.1 ± 0.4) (\( P < 0.0001 \)). The pregnancy rates were significantly higher in the DET (61%) compared with the SET group (48%) (\( P < 0.05 \)), the twinning rate being 34.4% with DET. However, when analysing this information by age groups, the differences in pregnancy rates were not significant in women <33 (SET, 54.9% versus DET, 64.8%), although they were so in older women (SET, 38.5% versus DET, 56.9%) (\( P < 0.05 \)). Thus, SET is an option to be considered in young women in their first cycles as long as they have good quality embryos.

### Blastocyst transfer

Transfer at the blastocyst stage allows selection of the embryo with the highest developmental potential and, at the same time, enables synchronization of the transfer with the ideal moment for implantation. Both factors will contribute to achieving the best implantation rate, and this could be a good way to reduce multiple pregnancies. Several authors recommend limiting the number of transferred blastocysts in order not to increase multiple pregnancies and some even suggest it as an option to reduce them (Toledo et al., 2000; Vidaeff et al., 2000; García-Velasco and Simon, 2001; Schoolcraft et al., 2001; Karaki et al., 2002).

The only prospective randomized trial (Gardner et al., 2004) compares transfers of one and two embryos at the blastocyst stage. The implantation rates (56% and 60.9%, respectively) and pregnancy rates (76% and 60.9%, respectively) are excellent in both groups and show no significant differences, although the twin rate reached 47.4% in two-embryo transfers. Although these results are encouraging they remain controversial, as in terms of efficiency the superiority of a blastocyst stage transfer over a cell stage transfer has yet to be demonstrated. In the future, cultivation and freezing/thawing techniques will probably have to be improved in order for this model to become a realistic option.

### Prevention of multiple pregnancy

– Sociedad Española de Fertilidad (SEF, Spanish Fertility Society)

One of SEF’s greatest challenges is reducing the multiple pregnancy rate and thus it set up the Embryo Health Special Interest Group in 2003. This group has developed several projects of which the main objective is the reduction of multiple pregnancies, the greatest challenge being to eliminate triple and higher multiple pregnancies but also, as far as possible, to decrease the rate of twin births.

The starting point was a survey sent out to all assisted reproduction centres, the results of which were presented at the SEF congress in La Coruña (Bruna et al., 2005). A total of 41 centres contributed data from 13,316 IVF/ICSI cycles performed in 2002 to the SEF analysis. In 47.4% of cycles three embryos were transferred (6325 cycles), in 32% two embryos were transferred (4266), in 10.2% (1359 cycles) only one embryo was transferred, in 9.7% (1294) four, and in 0.42% (56 cycles) more than four embryos were transferred. If these figures are compared with those for 1999, 2000 and 2001 a slight reduction can be observed from three-embryo to two-
Figure 3. Transfer of two versus three embryos: percentage of pregnancies, twins and triplets in women under 38 years of age.

Figure 4. Transfer of two versus three embryos: percentage of pregnancies, twins and triplets in women over 38 years of age.
embryo transfers (three embryos: 2001 = 51.2%, 2002 = 47.4%; two embryos: 2001 = 13.9%, 2002 = 32%). Even though the pregnancy rates were excellent (38.89%), there was still a high rate of multiple pregnancies (28.7% of twins, 6.1% of triplets and 0.32% of quadruplets).

Of particular importance among the conclusions of this survey is the fact that of the great number of embryos transferred, only a small percentage (1%) are single embryo transfer; furthermore, multiple pregnancy rates are high (35%), especially for triplets or more (6.4%). The different centres used similar but not universal criteria in evaluating embryo quality and the number of embryos to be transferred. Most centres do not use algorithms when deciding how many embryos should be transferred; 90% of centres accept embryo reduction but half of them refer such cases to other centres; 83% of centres do the obstetric follow-up of pregnancies achieved through assisted reproductive techniques. Considering these data, the SEF Embryo Health Special Interest Group considered a series of objectives: (i) the creation of an information brochure for patients; (ii) recommendations on the number of embryos to be transferred; (iii) unification of the optimum embryo criteria; (iv) embryo selective transfer project; and (v) conducting a survey of ovarian stimulation cycles in insemination processes.

All these projects are ongoing and are available to all members and/or reproduction centres through the SEF, and they will surely help to reduce the excessive rates of multiple pregnancies that occur in Spain.

**Number of embryos to be transferred: SEF recommendations**

The consensus recommendations regarding the number of embryos to be transferred in IVF are as follows: (i) in women under the age of 30, transfer a maximum of two embryos without exception; (ii) between the ages of 30 and 37, transfer a maximum of two embryos; from the third cycle onwards evaluate the possibility of transferring three embryos if there are no good quality embryos; (iii) in women older than 37, it is recommended to transfer two embryos but if there are no good quality embryos, a transfer of three should be evaluated; (iv) if there is an oocyte donation, it is recommended to transfer one or two without exception (Table 2).

Finally, the responsibility for preventing multiple pregnancy lies with various individuals and bodies: health professionals must be aware of the risks of multiple pregnancies, not only of triplets but also of twins. Couples must be informed of these risks and given objective information before starting an IVF cycle. Scientific societies must raise awareness of the problem, facilitate the necessary means to rectify it, where appropriate, and make suitable recommendations. The pharmaceutical industry should collaborate in reducing the costs of IVF cycles and the price of gonadotrophins. The government has a dual responsibility: on the one hand, to develop mechanisms that oblige recognized centres to contribute data to the SEF and, on the other, to evaluate the possibility of greater investment in order to cover the costs of IVF cycles, which could help to reduce the pressure to transfer more embryos in order to achieve pregnancy. The incidence of multiple pregnancies could thus be reduced and the costs to the public health system would decrease.

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