Comparison of IVF cycles reported in a voluntary ART registry with a mandatory registry in Spain

F. Luceño 1, J.A. Castilla 2*, J.L. Gómez-Palomares 3, Y. Cabello 4, J. Hernández 5, J. Marqueta 6, J. Herrero 7, E. Vidal 8, S. Fernández-Shaw 9, and B. Coroleu 10

1Centro de Reproducción Humana, Granada 18012, Spain 2Unidad de Reproducción, HU Virgen de las Nieves, Granada 18014, Spain 3Clínica FIVMadrid, Madrid 28008, Spain 4Servicio de Ginecología y Obstetricia, Hospital San Pedro, Logroño 26001, Spain 5Servicio de Medicina reproductiva, Departamento de Obstetricia, Ginecología y Reproducción, Instituto Universitario Dexeus, Barcelona 08028, Spain

*Correspondence address. E-mail: josea.castilla.sspa@juntadeandalucia.es

Submitted on February 22, 2010; resubmitted on June 14, 2010; accepted on August 20, 2010

BACKGROUND: Monitoring assisted reproductive technology (ART) is essential to evaluate the performance of fertility treatment and its impact on birth rates. In Europe, there are two kinds of ART registers: voluntary and mandatory. The validity of register data is very important with respect to the quality of register-based observational studies. The aim of this paper is to determine the degree of agreement between voluntary and mandatory ART registers.

METHODS: The two sources for the data compared in this study (referring to 2005 and 2006) were FIVCAT.NET (an official compulsory Assisted Reproduction Registry within the Health Ministry of the Regional Government of Catalonia, from which all authorized clinics, both public and private, providing assisted reproduction in the region are obliged to report) and the register of the Spanish Fertility Society (SEF), to which data are provided on a voluntary basis. The SEF register data were divided into two groups: (i) data from clinics in Catalonia (SEF-CAT); (ii) data from the rest of Spain, excluding Catalonia (SEF-wCAT). The techniques compared were IVF cycle using patients’ own eggs (IVF cycle) versus donor egg cycles.

RESULTS: For IVF cycles, the voluntary ART register reflected 77.2% of those on the official one, but the corresponding figure was only 34.4% with respect to donated eggs. The variables analysed in the IVF cycle (insemination technique used, patients’ age, number of embryos transferred, pregnancy rates, multiple pregnancies and deliveries) were similar in the three groups studied. However, we observed significant differences in donor egg cycles with regard to the insemination technique used, pregnancy rates and multiple pregnancies between the voluntary and the official register.

CONCLUSIONS: Data from the voluntary ART register for IVF cycles are valid, but those for donor egg cycles are not. Further study is necessary to determine the reasons for this difference.

Key words: IVF / data registers / success rates / donor egg / Spain

Introduction

The principal aim of an assisted reproductive technology (ART) register is to describe the quantity and quality of ART. The validity of register data is very important, because register-based observational studies are usually the only feasible study type for assessing the performance and impact of fertility treatment on birth rates (Nyboe Andersen and Erb, 2006). Whether the focus of the study is the use (insemination technique, day of transfer, etc.), the quality (number of embryos transferred) or the safety (multiple pregnancy) of ART, the quality of study findings is entirely dependent on the quality of the original data.

The ART national register can be classified according to different criteria: (i) by organizers—a national health authority, a national health insurance agency, or a professional association. Some ART societies include an obligation to provide data to a national ART register. The data provided are usually mandatory. In a voluntary register, there is no obligation to the data providers to report data. Some professional associations are coordinating voluntary ART registers (see the list of voluntary ART registers in Table 1).

There are two main sources of voluntary ART data: (i) data published in the literature, and (ii) data from register-based observational studies. The principal aim of an ART register is to describe the quality and safety of ART. The effectiveness of fertility treatment is assessed by the number of children born (birth rate). Although the ART register is an important source of data, it is not the only feasible study type for assessing the performance and impact of fertility treatment on birth rates. Some ART societies are coordinating voluntary ART registers.

In a voluntary register, there is no obligation to the data providers to report data. Some professional associations are coordinating voluntary ART registers. The ART register can be classified according to different criteria: (i) by organizers—a national health authority, a national health insurance agency, or a professional association. Some ART societies include an obligation to provide data to a national ART register. The data provided are usually mandatory. Some professional associations are coordinating voluntary ART registers (see the list of voluntary ART registers in Table 1).
professional organization or health care insurance; (ii) by data collection systems—detailed, online, cycle-by-cycle, registration data or a summary by type of ART treatment on a yearly basis; (iii) by data validation—under a mandatory system, whether or not legally regulated—or without validation; (iv) by involvement: mandatory or voluntary. A voluntary register may present total coverage (e.g. Canada; Gunby et al., 2010), or partial coverage (e.g. Spain; Cabello et al., 2009b). The validity of the latter type of register has been called into question, because when data declaration is voluntary, there may be a trend towards an over-estimation of good outcomes, since clinics that declare their data are often those that have a better clinical practice. If this were so, they would be over-represented in the register (Bosser et al., 2009). One way to examine this possible bias is to compare data obtained from both voluntary and compulsory registers.

The Spanish region of Catalonia represents an unusual situation where the two kinds of registers can be compared. On the one hand, FIVCAT.NET is the official assisted reproduction register of the Health Ministry of the Regional Government of Catalonia, to which all clinics, both public and private, performing assisted reproduction in the region are obliged to report all their cycles (Bosser et al., 2009). On the other hand, the register of the Spanish Fertility Society (SEF) receives data from assisted reproduction clinics throughout Spain, including Catalonia, provided on a voluntary and anonymous basis (Cabello et al., 2009b).

Various aspects (financial, religious, cultural, legislative, demographic, etc.) must be taken into account in any analysis of the availability and outcome of ART in different countries (Navarro et al., 2008). One such aspect is the existence or otherwise of an official, compulsory ART register. However, analysing the impact on ART of this question is very difficult because national ART legislation varies considerably between countries (Ziebe and Devroey, 2008). A comparison of the results reported to FIVCAT.NET for Catalonia and to the SEF register for the rest of Spain (where no official register exists) would enable us to determine the influence on ART of the presence or absence of an official register under a common legal framework.

Accordingly, the aim of this study was to evaluate the accuracy of a voluntary register (SEF) and to analyse the relationship between an official register and ART treatments.

**Materials and Methods**

This study constitutes a retrospective data-exploratory analysis of activity registers concerning assisted reproduction clinics in Spain. The two sources for the data used in this study were the FIVCAT.NET (Bosser et al., 2009) and the SEF registers for the years 2005 and 2006 (Marqueta et al., 2008; Cabello et al., 2009a). The data from the SEF register were divided into two groups: (i) data from clinics in Catalonia (SEF-CAT); (ii) data from the rest of Spain (SEF-wCAT).

FIVCAT.NET collects data cycle-by-cycle, and is an administrative register for the purpose, among others, of determining patients’ medication costs and reimbursements. All cycles performed in Catalonia must be registered on FIVCAT.NET. Compliance with this obligation is ensured by a programme of inspections by the competent healthcare authorities. The costs of certain cycles are not reimbursed (those for the fourth and subsequent cycles for the same couple, and those provided to foreign patients).

The SEF register receives data from assisted reproduction clinics throughout Spain, provided on a voluntary and anonymous basis. Data are collected centre-by-centre. No class of inspection of the SEF register is made.

The techniques compared were IVF cycles using patients’ own eggs (hereafter referred to as ‘IVF cycle’) versus donor egg cycles. The definitions established by the International Committee Monitoring Assisted Reproductive Technologies (ICMART) are followed by both registers (Zegers-Hochschild et al., 2009). Comparison of frozen embryo cycles was not possible because the FIVCAT.NET and SEF registers have different recording systems, making them incompatible for a study of such cycles.

The variables analysed were grouped into the following categories: (i) characteristics of the clinic—the level of activity and range of services offered; (ii) clinical parameters—the age of the women treated and the treatment method adopted; (iii) effectiveness—pregnancy rates; (iv) quality—the number of embryos transferred; (5) safety and risks—multiple pregnancies and deliveries.

For the statistical analysis of the results, we carried out a bivariate analysis to determine the differences among the study groups, using the χ² test. In all cases, a level of significance of 5% was applied.

**Results**

The voluntary SEF register registered 61.7% of the cycles recorded by the official FIVCAT.NET register. The distribution of clinics according to the number of cycles provided was similar in FIVCAT.NET and SEF-wCAT. Regarding their level of activity, the ART clinics that did not provide voluntary reports to the SEF register in Catalonia mainly performed 50–500 transfers per year (Table I).

**IVF cycles**

For IVF cycles, the SEF-CAT register accounted for 77.2% of all the cycles included in the FIVCAT.NET register. The use of IVF, ICSI and IVF + ICSI, together with the age distribution of the patients reported by FIVCAT.NET, SEF-CAT and SEF-wCAT were all similar (Table I).

The number of embryos transferred in IVF cycles is similar in the FIVCAT.NET and SEF-CAT registers, and in turn, this value coincides with that corresponding to the rest of Spain (Table III).

The rate of pregnancies per transfer is similar in the different registers analysed: 37.3% in FIVCAT.NET, 38.1% in SEF-CAT and 38.5% in SEF-wCAT. Moreover, the rate of multiple pregnancy is also similar in

<table>
<thead>
<tr>
<th>Table I</th>
<th>Size of the ART clinics reporting to the FIVCAT.NET and SEF registers in 2005 and 2006.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FIVCAT.NET</td>
</tr>
<tr>
<td>≤50 transfers, n (%)</td>
<td>11 (18.9)</td>
</tr>
<tr>
<td>50–500 transfers, n (%)</td>
<td>36 (62.1)</td>
</tr>
<tr>
<td>&gt;500 transfers, n (%)</td>
<td>11 (19)</td>
</tr>
<tr>
<td>All</td>
<td>58</td>
</tr>
</tbody>
</table>

FIVCAT.NET, official compulsory Assisted Reproduction Registry within the Health Ministry of the Regional Government of Catalonia; Spanish Fertility Society (SEF), data from clinics in Catalonia (SEF-CAT); data from the rest of Spain, excluding Catalonia (SEF-wCAT).
the three registers examined (20% in FIVCAT.NET, 23% in SEF-CAT and 25.9% in SEF-wCAT). Nor are there significant differences with respect to the rate of twin and triplet pregnancies, or in the percentage of multiple births reported in each register (Table III).

### Egg donor cycles

For cycles with donated eggs, the SEF-CAT register contained 34.4% of the number of cycles reported on the FIVCAT.NET register. The use of IVF, ICSI and IVF + ICSI in Catalonia varies between the two corresponding registers (FIVCAT.NET and SEF-CAT), and the difference is statistically significant (15.1 versus 30.6%; $P < 0.05$ for IVF cycles; 78.8 versus 55.8%; $P < 0.05$ for ICSI cycles; and 6.1 versus 13.6%; $P < 0.05$ for IVF + ICSI cycles). Furthermore, the differences are also significant on comparison of the FIVCAT.NET cycles with those for the rest of Spain (30.6 versus 19%; $P < 0.001$ in IVF cycles; 55.8 versus 73.2%; $P < 0.001$ in ICSI cycles; and 13.6 versus 7.7%; $P < 0.001$ in IVF + ICSI cycles; Table II).

The age distribution of the patients registered in FIVCAT.NET is similar to that for SEF-CAT, and to that found for the rest of Spain. The rate of single-embryo transfers in cycles with donated eggs, as reported to FIVCAT.NET, was different from that of the SEF-CAT register and also from that for the rest of Spain, although this difference was not significant (8.6 versus 3.4 versus 6.2%, respectively; Table III).

The rates of pregnancy per transfer also varied among the different registers analysed. Thus, for FIVCAT.NET and SEF-CAT, the respective values were 44.1 versus 55.3%; $P < 0.001$; and for FIVCAT.NET

### Table II Comparison between FIVCAT.NET, SEF-CAT and SEF-wCAT in IVF and donor egg cycles in 2005 and 2006.

<table>
<thead>
<tr>
<th></th>
<th>IVF cycles</th>
<th>Donor egg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FIVCAT.NET</td>
<td>SEF-CAT</td>
</tr>
<tr>
<td>No. of cycles</td>
<td>10 398</td>
<td>8026</td>
</tr>
<tr>
<td>IVF, n (%)</td>
<td>1507(14.5)</td>
<td>1464(18.2)</td>
</tr>
<tr>
<td>ICSI, n (%)</td>
<td>7120(68.5)</td>
<td>5162(64.3)</td>
</tr>
<tr>
<td>IVF + ICSI, n (%)</td>
<td>1771(17.0)</td>
<td>1400(17.4)</td>
</tr>
<tr>
<td>Patient age (yrs)</td>
<td>10 398</td>
<td>8495</td>
</tr>
<tr>
<td>&lt;30, n (%)</td>
<td>1058(10.2)</td>
<td>707(8.3)</td>
</tr>
<tr>
<td>30–34, n (%)</td>
<td>3882(37.3)</td>
<td>3057(36.0)</td>
</tr>
<tr>
<td>35–39, n (%)</td>
<td>4004(38.5)</td>
<td>3351(39.4)</td>
</tr>
<tr>
<td>&gt;44, n (%)</td>
<td>87(0.8)</td>
<td>83(1.0)</td>
</tr>
</tbody>
</table>

*P < 0.001 for insemination technique in donor egg cycles.

### Table III Transfers, pregnancies and deliveries in FIVCAT.NET, SEF-CAT and SEF-wCAT in IVF and donor egg cycles in 2005 and 2006.

<table>
<thead>
<tr>
<th></th>
<th>IVF cycles</th>
<th>Donor egg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FIVCAT.NET</td>
<td>SEF-CAT</td>
</tr>
<tr>
<td>No. of transfers</td>
<td>9969</td>
<td>7647</td>
</tr>
<tr>
<td>1 embryo, n (%)</td>
<td>1460(14.6)</td>
<td>1090(14.3)</td>
</tr>
<tr>
<td>2 embryos, n (%)</td>
<td>5369(53.9)</td>
<td>4341(56.8)</td>
</tr>
<tr>
<td>3 embryos, n (%)</td>
<td>3140(31.5)</td>
<td>2216(29.0)</td>
</tr>
<tr>
<td>No. of pregnancies, n (per transfer)</td>
<td>3281(37.3)</td>
<td>2773(38.1)</td>
</tr>
<tr>
<td>Singleton, n (%)</td>
<td>2625(80.0)</td>
<td>2135(77.0)</td>
</tr>
<tr>
<td>Multiple, n (%)</td>
<td>656(20.0)</td>
<td>638(23.0)</td>
</tr>
<tr>
<td>T / n (%)</td>
<td>614(18.7)</td>
<td>601(21.7)</td>
</tr>
<tr>
<td>Triplets, n (%)</td>
<td>42(1.3)</td>
<td>37(1.3)</td>
</tr>
<tr>
<td>No. of deliveries</td>
<td>2517</td>
<td>1688</td>
</tr>
<tr>
<td>Singleton, n (%)</td>
<td>1919(76.2)</td>
<td>1318(78.1)</td>
</tr>
<tr>
<td>Multiple, n (%)</td>
<td>598(23.8)</td>
<td>370(21.9)</td>
</tr>
<tr>
<td>T / n (%)</td>
<td>571(22.7)</td>
<td>350(20.7)</td>
</tr>
<tr>
<td>Triplets, n (%)</td>
<td>27(1.1)</td>
<td>20(1.2)</td>
</tr>
</tbody>
</table>

*P < 0.001 for % pregnancies per transfer in donor egg cycles; $P < 0.001$ for type of pregnancies in donor egg cycles.
and SEF-wCAT, they were 44.1 versus 49.9%; \( P < 0.001 \). The difference between SEF-CAT and SEF-wCAT was not statistically significant.

The rate of multiple pregnancy, too, was different among the three registers. For FIVCAT.NET and SEF-CAT, the respective values were 20.6 versus 33.3%; \( P < 0.001 \). For the rest of Spain, the rate of multiple pregnancy reported was 29.7%, and so this, too, differed significantly from the other two registers.

The rates of multiple birth reported by the three registers were different, but the difference was not significant (24.1% in FIVCAT.NET, 27.9% in SEF-CAT and 28.1% in SEF-wCAT).

**Discussion**

At an EU-wide level, the European IVF-monitoring (EIM) consortium compiles information that clinics declare, voluntarily or otherwise, on ART cycles (Nyboe Andersen et al., 2009). In Spain, although calls have been made for the implementation of an official ART register, this has only been put into practice in the region of Catalonia, and the only national one is the voluntary SEF register. We compare these two sources of information, voluntary and official, to shed light on the validity of ART register-based data. To the best of our knowledge, this is one of the first such studies performed. A striking result is that only 61.7% of the ART cycles reported to the official FIVCAT.NET register are reflected in SEF-CAT. Several factors could account for this low percentage. Firstly, clinics might not be interested in sending data to a voluntary register because they have already transmitted them to the official one. Secondly, clinics that decline to participate voluntarily might take this attitude in the belief that the SEF register lacks validity, because it compiles summarized data centre-by-centre instead of detailed data cycle-by-cycle as is done by FIVCAT.NET. In our opinion, if this were the case, the percentage of non-SEF-registered cycles would be similar for both types of procedure (IVF and donor egg cycles). However, we found differences in the percentages of cycles registered: for IVF cycles, the SEF rate was 77.2%, while for donor egg cycles, it was 34.4%.

Our results show that the clinics which do not voluntarily contribute to an ART register are those which carry out a high number of donor egg cycles. Therefore, there must be reasons other than those described above to account for our data. Firstly, there might be some difference in the characteristics of the patients treated at these clinics that would persuade the clinics not to supply the data voluntarily; for example, their nationality. In Catalonia, in 2005, 26.2% of the patients treated were residents of other countries (Bosser et al., 2009). In countries with a similar proportion of cross-border reproductive care, most patients travel in order to receive egg donation (Pennings et al., 2008). Secondly, there could be differences in clinical practice among the clinics that lead them not to participate voluntarily. In this sense, our data show that the number of embryos transferred, and the rates of pregnancy and multiple pregnancy are similar for IVF cycles in SEF-CAT and FIVCAT.NET. However, the data reported to FIVCAT.NET regarding donor egg cycles reflect a tendency to transfer fewer embryos (single embryo transfer 8.6 versus 3.4%, respectively), and therefore a significantly lower percentage of pregnancies per transfer (44.1 versus 53.3%) and of multiple pregnancies (20.6 versus 33.3%) is achieved. A possible explanation for these findings is that the clinics which do not participate voluntarily in the SEF-CAT register may have pro-active policies for single embryo transfer; alternatively, these clinics may assign a certain number of donor eggs per recipient, and so there would be fewer embryos available for transfer, and thus a lower rate of pregnancies per transfer and of multiple pregnancies. As noted previously (Materials and Methods), the systems for registering cryotransfers are different in the SEF and FIVCAT.NET registers, and mutually incompatible; accordingly, these hypotheses cannot be analysed by comparing the cryotransfer cycles on each register.

After adjusting the 2005 SEF data reported to the EIM (Nyboe Andersen et al., 2009) for the percentage of non-registered cycles observed in the present study, we calculate that in Spain, in 2005, a total of 37 279 IVF cycles and 17 279 donor egg cycles were performed, which would make Spain the third-ranking country in Europe (after France and Germany) for IVF cycles, and first for donor egg cycles, at 11.2 and 75.5% of the IVF and donor egg cycles, respectively, performed in Europe (Nyboe Andersen et al., 2009). Moreover, if we apply the percentage of foreign residents using assisted reproduction services in Catalonia (commented above) to this figure and take into account that in countries with a similar percentage when egg donation is considered separately, 60% of all recipients are foreigners (College of Physicians ‘Reproductive Medicine’ and the Belgian Register for Assisted Procreation, 2001), this might constitute the first serious estimation of cross-border reproductive care in Spain, showing that around 4000 IVF and 10 000 donor egg cycles for this population are carried out in Spain each year. This would place Spain as the leading country in Europe with respect to the absolute number of cycles carried out for foreign residents (Pennings, 2004).

The lower percentage of deliveries per clinical pregnancy observed in the SEF register (58.2%) versus FIVCAT.NET (76.8%) suggests that losses to follow-up are higher in the voluntary than in the official ART register. We reject the hypothesis that the clinics participating in a voluntary register have less strict respect for the definitions of clinical pregnancy, and in some cases may have included chemical pregnancies as clinical ones, because the rate of pregnancies per transfer was similar in IVF cycles in both registers. In agreement with Nygren (2004), we believe that pregnancy rates are more reliable and more valid than delivery rates because each clinic has direct information on pregnancies, whereas the deliveries corresponding to some clinics may suffer a high proportion of losses to follow-up. Therefore, before using data on delivery outcomes obtained from ART registers (official or voluntary), whenever possible these should be cross-linked to other national registers (deliveries, malformations, etc.), which are available.

The results obtained by the SEF register for the rest of Spain (i.e. excluding Catalonia) for IVF cycles are similar to those found for Catalonia by both FIVCAT.NET and SEF-CAT, and so we consider the evidence of the SEF register for this type of cycle to be valid. Therefore, we reject the hypothesis of Bosser et al. (2009) that when data declaration is voluntary, there may be a tendency to over-estimate good outcomes. The voluntary involvement of Spanish clinics in the SEF register is a reflection of the honest commitment to the SEF register by members of the IVF Directors group and of the dedication of their staff.

Different strategies may be employed to increase the participation rate in a voluntary register. Firstly, its successful implementation requires more intervention than simple distribution or (electronic)
publication, and may involve methods such as educational meetings, local consensus processes and the employment of local opinion leaders. Secondly, financial compensation or advantage may be given to participating clinics, as is the case with the official FIVAT.NET register in Catalonia, whereby the costs of most cycles registered are reimbursed. Nevertheless, this particular action is not possible for a professionally controlled observational register such as SEF. Thirdly, in the specific situation of Spain, the official and voluntary data may be processed jointly. However, this measure would oblige analysts to combine data obtained from different sources (compulsory, detailed data cycle-by-cycle together with voluntary, summarized data centre-by-centre). In other registers where such a situation occurs, data from different origins are not mixed (Gunby et al., 2009).

Finally, the usefulness of the register for both clinics and patients could be increased by publishing the data and results received from participating clinics. This measure has been the subject of considerable discussion (Nygren, 2004; Belaisch-Allart, 2006; Pouly, 2006; Bouyer and Olivennes, 2006), and is currently applied in some countries, including the USA (http://www.cdc.gov/ART/ART2006/index.htm) and the UK (http://guide.hfea.gov.uk/guide). Together with other authors (Haan et al., 1991; Marshall and Spiegelhalter, 1998; Castilla et al., 2008) we have suggested previously that IVF clinic ranking should be avoided, because differences between IVF clinics are dependent on the classification methods used and may not reflect the real performance achieved. Lintsen et al. (2010) showed that only 17% of the differences in pregnancy rates among IVF centres are explained by patient mix, suggesting that other factors, such as lifestyles, should also be taken into account. In this respect, in an earlier study, we highlighted the importance of healthcare coverage for infertility treatment (Castilla et al., 2009). The above-mentioned strategies for increasing the usefulness of registers should be accompanied by some kind of validation of the data reported by clinics, for example in the form of auditing and feedback response. Such a measure has been adopted by the SEF register to be applied in forthcoming years (http://registrosef.wordpress.com).

Although several sources of uncertainty remain, such as data on donor egg cycles, it can be concluded that voluntary ART register-based information is, at the least, a satisfactory source for estimating the use of IVF cycles and clinical practice in this respect. The generalization of our results to include other aspects of ART (cryopreserved embryos, preimplantation genetic diagnosis, in vitro maturation, etc.) is an open question. With respect to validation of the register, it is important to achieve and maintain excellent quality regarding the data recorded.

**Authors’ roles**
All authors contributed to the study design. F.L. led the study, together with J.L.G., P.Y.C. and J.A.C.; B.C., J.H. and J.M contributed to analysis and interpretation of data. J.H., E.V. and S.F.-S. supervised the study. All authors contributed to the drafting, revision and final approval of the manuscript.

**Acknowledgements**
We thank Schering-Plough for their technical support to the Assisted Reproductive Technology Register of the Spanish Fertility Society. We would also like to thank the Spanish ART clinics whose efforts made the work possible (list in supplementary data section of the European IVF-Monitoring report at http://humrep.oxfordjournals.org).

**Funding**
The SEF register is supported by SEF foundation and by the Spanish Health Ministry (010020090353).

**References**


