Impact of assisted reproduction treatments on Spanish newborns: report of 14,119 pregnancies

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Abstract

Purpose To investigate neonatal malformation, prematurity, and stillbirth in singleton and multiple pregnancies derived from different Assisted Reproductive Techniques (ART).

Methods In this prospective cohort study data were collected, from private and public Spanish IVF units, during the years 2008 and 2009. During this period, 8,682 pregnancies were analysed from the initial 14,119 pregnancies reported. Pregnancies included in the study derived from IUI ($n=1,065$), IVF ($n=838$), ICSI ($n=5,080$), FET ($n=1,404$) and PGD ($n=295$). This first analysis focuses primarily on neonatal malformation, prematurity, and stillbirth both in singleton and multiple pregnancies derived from different ART. Malformations were classified according to the WHO ICD 10 code.

Results Malformations were found in 0.83 % of our newborns. No differences in malformations were observed between

singletons or multiples independently of the ART used. There was a significant difference in prematurity rate among singletons depending on treatment but this association was not observed in multiple pregnancies. Stillbirth was significantly lower in singleton (0.72 %) than in multiple pregnancies (1.82 %).

Conclusions The percentage of malformations observed in ART newborns was similar to the rate observed in the normally-conceived Spanish population. Multiplicity seems to be the most important factor associated with an increased incidence of newborn complications such as prematurity or stillbirth.

Keywords ART · Pregnancy outcome · Perinatal outcome · Malformations · Prematurity · Stillbirth

Capsule This report examines the impact of Assisted Reproductive Techniques (ART) on malformation in Spain. Malformations were found in 0.83 % of newborns, similar to levels in the general Spanish birth population.

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Introduction

Many couples seek fertility enhancement via assisted human reproduction procedures. Concerns about health issues in infants born as a result of these treatments have been attributed to the multiple births and preterm deliveries, and their sequelae. However, since 1987, it has been suggested that birth defects in children could be associated with the assisted reproductive treatments (ART) used [21]. The studies that have investigated the prevalence of birth defects in ART since then offer conflicting results, primarily due to methodological factors including the limitations of the inclusion criteria, the use of suboptimal sample sizes, the heterogeneity of both control groups and definitions of congenital anomalies [24, 26, 29, 30]. We know about the French (FIVNAT), British (HFEA), Danish [37, 40] and Swedish Registries [3] of Assisted Conceptions and, more recently, those from the Australian and New Zealand [6], all of which contain information about reported congenital malformations and other neonatal results. Aware of its importance and with the aim of collecting such information in Spain, the Embryo Health Interest Group (GISE) of the Spanish Fertility Society (SEF) has, since 2007, been collecting voluntary results from public and private clinics in order to develop a Spanish Registry for obstetrical and neonatal results after ART.

Here we report results from the years 2008 and 2009, including 14 119 pregnancies and 10 653 newborns from Intrauterine Insemination (IUI), In Vitro Fertilisation (IVF), Intracytoplasmic Sperm Injection (ICSI), Frozen Embryo Transfer (FET) and Preimplantation Genetic Diagnosis (PGD) in Spain.

The main objective of this analysis was to determine if any of the treatments was related to an increase in the rate of malformations in the newborns. Furthermore, since multiparity has been associated with an increase in malformations, prematurity and stillbirth [9, 36], we studied these parameters independently in singleton and multiple pregnancies, in order to evaluate the validity of these correlations.

Materials and methods

On recommendation from the GISE, after confirmation of pregnancy, each of the 29 participating centers gave the patient a questionnaire (Fig. 1) that included data about the gestation (prenatal diagnosis, miscarriage, gestational age at the time of delivery and type of delivery) and the newborn (sex, birth weight, stillborns and malformations). Patients were requested to fill it in and return it to the clinic after delivery. To ensure that all data were collected, a person from each center was asked to complete any incomplete pregnancy reports, by means of individual phone calls. Before forwarding the questionnaires to GISE each clinic included information on ectopic pregnancies and pregnancy loss as well as data on the patients' age, cause of

infertility, use of egg or sperm donation, and treatment performed. This study do not need an institutional review board (IRB) approval because involve the collection of existing data and the information is recorded by the GISE in such a manner that subjects cannot be identified. Finally, two members of the GISE were responsible to collect and review the data.

The International Statistical Classification of Diseases and Related Health Problems [16], 10th Revision from WHO (version 2007) was used to describe congenital malformations. Prematurity and stillbirth were described following the Spanish Society of Obstetrics and Gynaecology (SEGO) definitions. We considered preterm babies as those delivered before completing 37 gestational weeks (or less than 259 days of pregnancy) and stillborn were those born dead after 20 weeks of pregnancy.

Statistical analysis

Descriptive data are given as numbers and percentage. Categorical variables like malformation, prematurity and stillbirth, in both multiple and singleton pregnancies obtained with different ART were compared. Other categorical variables such as maternal age groups (above or below 38 years old) and the use or not of egg donation in the different ART were also compared. In all cases the χ^2 test was used and a p -value <0.05 was considered significant. All analyses were performed with the commercial software SPSS version 13.0.

Results

14 119 pregnancies were analysed. From these, 1898 pregnancies were excluded (13.4 %) for several reasons: the final evolution of the pregnancy was unknown ($n=1,482$; 10.7 %), data were incomplete ($n=349$; 2.4 %) or the ART used was not reported ($n=67$; 0.4 %). Pregnancies from mixed IVF/ICSI treatments ($n=1,168$) were also excluded because it was impossible to establish the origin of the embryo generating the pregnancy. From the remaining 11 053 pregnancies, 2,371 (21.4 %) were lost (spontaneous miscarriage, abortion or ectopic pregnancy). Finally, data from 8,682 pregnancies were available for analysis. Data were analysed from 6,207 single pregnancies and 2,475 multiple pregnancies resulting in 10 653 babies (6,207 singletons and 4,446 babies from multiple pregnancies) (Fig. 2).

Pregnancies included in the study derived from IUI ($n=1,065$), IVF ($n=838$), ICSI ($n=5,080$), FET ($n=1,404$) and PGD ($n=295$).

Maternal age can affect pregnancy outcome. In order to compare results in our treatment groups, we analysed the number of cycles in each treatment for women aged above or below 38. We found that all treatments had a similar rate of

Fig. 1 Questionnaire given to pregnant women, to return to the Clinic after delivery**GENERAL DATA:**

Mother's name:

Father's name:

Telephone number:

e-mail:

ABOUT YOUR PREGNANCY (before week 20):

Your pregnancy was: Single Multiple (n° of sacs)

Did you have an amniocentesis/Chorionic biopsy performed? Yes / No Results:

Did you have a miscarriage before 20 week gestation? Yes / No If Yes, week of gestation:

- ☐ Spontaneous Miscarriage
☐ Ectopic pregnancy
☐ Embryo reduction
☐ Induced Abortion

DELIVERY (after week 20):

Date: oVaginal delivery o Caesarean section

FIRST NEWBORN:

Alive: Yes / No Male / Female Weight (g):

Malformations: Yes / No If Yes, specify:

SECOND NEWBORN:

Alive: Yes / No Male / Female Weight (g):

Malformations: Yes / No If Yes, specify:

THIRD NEWBORN:

Alive: Yes / No Male / Female Weight (g):

Malformations: Yes / No If Yes, specify:

Fig. 2 Flowchart pregnancies, drop outs and total babies born analyzed

women in the younger group (55.7 % in IVF, 58 % in ICSI, 55.2 % in FET and 52.4 % in PGD) except for IUI, in which they were 82.4 % of the sample ($p<0.05$). Consequently, in this study, the woman's age would affect gestational results in the same manner in all ART except for IUI. The use of donor eggs could also affect gestational results, as donors are generally younger than patients. Donor egg use was only recorded for the IVF and ICSI cycles, which had a similar rate of 35.8 % and 34.8 % respectively ($p=0.557$).

Malformations

Of the 10,653 newborns from ART in Spain between 2008 and 2009 there were 89 reported malformations, affecting 0.83 % of ART newborns. Congenital malformations and deformations of the musculoskeletal system are the most frequent ($n=20$; 22.4 % of malformations, 0.18 % of all ART births) followed by malformations of the circulatory system ($n=14$; 15.7 % of malformations, 0.13 % of all ART births), digestive system ($n=10$; 11.2 % of malformations, 0.09 % of all ART births), chromosomal abnormalities ($n=10$; 11.2 % of malformations, 0.09 % of all ART births), urinary system ($n=8$; 8.9 % of malformations, 0.07 % of all ART births), nervous system ($n=5$; 5.6 % of malformations, 0.04 % of all ART births), eye, face and neck ($n=4$; 4.4 % of malformations, 0.03 % of all ART births), genital organs ($n=4$; 4.4 % of malformations, 0.03 % of all ART births) and syndromes affecting multiple systems ($n=4$; 4.4 % of malformations, 0.03 % of all ART births). In 7 cases (7.8 %) the malformations were not appropriately recorded (Table 1).

Malformation frequency was compared between singleton (44/6,207; 0.7 %) and multiple pregnancy babies (45/4,446; 1.01 %) and no significant difference was found ($p=0.09$).

When comparing the ART used, in single pregnancies, malformations were observed in 0.4 % (4/927) of babies derived from IUI, 0.7 % (4/555) of those from IVF, 0.9 % (32/3,510) of those from ICSI, 0.2 % (3/1,027) of those from FET and in 0.5 % (1/188) of those from PGD. Differences were not significant ($P=0.224$). In multiple pregnancies, malformations were observed in 1.1 % (3/271) of babies derived from IUI, 0.3 % (2/509) of those from IVF, 0.9 % (28/2,820) of those from ICSI, 1.5 % (10/653) of those from FET and 1 % (2/193) of those from PGD. Again, differences were not significant ($P=0.442$) (Table 2). Analysis showed no significant associations between any type of malformation and any ART technique (data can be supplied on request).

Prematurity

Frequency of prematurity was analyzed in singleton (730/6,207; 11.7 %) versus multiple (1,258/2,475; 50.8 %) pregnancies, and there was as expected, a significant difference ($p<0.05$).

Table 1 Malformations (ICD-10 WHO code)

Congenital malformations of Nervous System	
Q03.9 hydrocephalus	
Q04.0 malf. of corpus callosum	
Q05.9 Spina bifida	Total: 5 (5.6 %)
Malformations of eye, ear, face and neck:	
Q10.0 Congenital ptosis	
Q12.0 Congenital cataract	
Q17.0 Accessory auricle	Total: 4 (4.4 %)
Congenital malformations of circulatory system:	
Q 20.0 Common arterial trunk	
Q 20.9 Congenital malformation of cardiac chambers, unspecified	
Q21.0 Ventricular septal defect	
Q21.1 Atrial septal defect	
Q21.2 Atrioventricular septal defect	
Q21.3 Tetralogy of Fallot	
Q21.4 Aortopulmonary septal defect	
Q21.8 Other congenital malf. of cardiac septa	
Q25.0 Patent ductus arteriosus	
Q25.3 Stenosis of aorta	
Q25.4 Other congenital malformations of aorta	Total: 14(15.7 %)
Congenital malformations of the respiratory system	
Q30.1 Agenesis and underdevelopment of nose	
Q30.9 Congenital malformation of nose, unspecified	
Q 37.0 Cleft hard palate with bilateral cleft lip	Total: 3 (3.3 %)
Other congenital malformations of the digestive system	
Q38.1 Ankyloglossia	
Q39.0 Atresia of oesophagus without fistula	
Q40.0 Congenital hypertrophic pyloric stenosis	
Q41 Congenital absence, atresia and stenosis of duodenum	
Q44.7 Other congenital malformations of liver	Total: 10 (11.2 %)
Congenital malformations of genital organs	
Q53.1 Undescended testicle, unilateral	
Q54.9 Hypospadias, unspecified	
Q55.1 Hypoplasia of testis and scrotum	Total: 4 (4.4 %)
Congenital malformations urinary system:	
Q 60.3 Renal hypoplasia, unilateral	
Q61.3 Polycystic kidney	
Q61.4 Renal dysplasia	
Q62.1 Atresia and stenosis of ureter	
Q63.1 Lobulated, fused and horseshoe kidney	
Q63.2 Ectopic kidney	Total: 8 (8.9 %)
Congenital malformations and deformations of the musculoskeletal system:	
Q65.6 Unstable hip	
Q65.8 Other congenital deformities of hip	
Q66.0 Congenital deformities of feet -Talipes equinovarus	
Q66.2 Metatarsus varus	
Q66.8 Other congenital deformities of feet	

Table 1 (continued)

Q66.9 Congenital deformity of feet, unspecified	
Q67.3 Congenital musculoskeletal deformities of head, face, spine and chest - Plagiocephaly	
Q67.4 Other Depressions in skull	
Q69.0;Q69.2 Accessory finger(s) Accessory toe(s)	
Q70.9 Syndactyly, unspecified	
Q70.0 Fused fingers	
Q70.4 Polysyndactyly	
Q79.2 Exomphalos	
Q79.0 Congenital diaphragmatic hernia	
Q79.9 unspecified Displasia esquelética	Total: 20 (22.4 %)
Other specified congenital malformation syndromes affecting multiple systems:	
Q87.0 predominantly affecting facial appearance	
Q87.1 predominantly associated with short stature	
Q89.9 other, not classified	Total: 4 (4.4 %)
Chromosomal abnormalities, not elsewhere classified	
Q90 Down's syndrome	
Q91.4 Trisomy 13, meiotic nondisjunction	
Q95.0 Balanced translocation and insertion in normal individual	
Q96.3 Mosaicism, 45,X/46,XX or XY	
Q97.1 Female with more than three X chromosomes	Total: 10 (11.2 %)
Not reported	Total: 7 (7.8 %)

Singleton delivery was premature in 8.3 % (96/927) of IUI pregnancies, 8.5 % (64/555) of IVF pregnancies, 8.2 % (387/3,510) of ICSI pregnancies, 9.4 % (148/1,027) of FET pregnancies and 14.7 % (35/188) of PGD pregnancies. There was a significant difference between treatments ($p=0.001$) with the highest rate of prematurity in PGD babies (14.7 %). In multiple pregnancies, delivery was premature in 44.9 % (62/138) of IUI pregnancies, 52.2 % (148/283) of FIV pregnancies, 49.8 % (783/1,570) of ICSI pregnancies, 54.6 % (206/377) of FET pregnancies and 55.1 % (59/107) of PGD pregnancies. Differences were not significant ($P=0.220$) (Table 3).

Stillbirth

The frequency of stillbirth was compared between singleton (45/6,207; 0.72 %) and multiple pregnancies (81/4,446; 1.82 %) and differences were significant ($p<0.05$).

Stillbirth in singleton pregnancies were recorded for all groups: IUI (8/927; 0.8 %), IVF (1/555; 0.1 %), ICSI (25/3,510; 0.7 %), FET (9/1,027; 0.8 %) and PGD (2/188; 1 %). Differences between ART were not significant ($p=0.530$). For multiple pregnancies, 1.4 % (4/271) of the babies from IUI were stillborn, 3.7 % (19/509) of those from IVF, 1.5 % (45/2,820) of those from ICSI, 1.6 % (11/653) of those from FET and 1 % (2/193) of those from PGD. Stillbirths in multiple pregnancies show a significant difference between techniques ($p=0.017$) with the highest rate found in conventional IVF (3.7 %) (Table 4).

Discussion

This is the first analysis of data on pregnancy outcome from the Spanish Fertility Society's GISE Registry. Many parameters regarding the gestation (cause of infertility, female and male age, miscarriages, voluntary embryo reduction, presence of donors and gestational type of delivery) and the newborns (sex and birth weight and presence or absence of malformations) were recorded (Fig. 1) and annually published in the Spanish Fertility Society Journal [10, 11]. The present analysis focuses only on crucial issues of ART, such as neonatal malformation, prematurity, and stillbirth in both singleton and multiple pregnancies derived from different ART.

Our data in terms of percentage of miscarriages (data not shown) and prematurity are similar to those reported in the international literature, so we can assume that our data collection method was adequate. This is important since our results for malformations are lower than those in the literature. The available literature mainly classifies malformations as minor or major defects [5]. There is an international classification [19], but it ignores several minor congenital anomalies [7, 40], making difficult the comparison among them. In fact, there is no generally accepted malformation classification system. Our study has used an internationally recognized code developed by the WHO (International Classification of Diseases - ICD). The basic ICD is a single coded list of three-character categories, each of which can be further divided into up to ten four-character subcategories that denote the severity of the problem [16]. Each Spanish center systematically recorded congenital malformations, deformations and chromosomal abnormalities using the ICD code (code Q00-Q99), and no minor anomalies were excluded.

Table 2 Malformations in singletons and multiples in different ART

	IUI	IVF	ICSI	FET	PGD	P
% Malformations in singletons (n)	0.4 (4/927)	0.7 (4/555)	0.9 (32/3,510)	0.2 (3/1,027)	0.5 (1/188)	0.224
% Malformations in multiples (n)	1.1 (3/271)	0.3 (2/509)	0.9 (28/2,820)	1.5 (10/653)	1 (2/193)	0.442

Table 3 Prematurity in singleton and multiple pregnancies in different ART

	IUI	IVF	ICSI	FET	PGD	P
% Prematurity in singleton pregnancies (n)	8.3 (96/927)	8.5 (64/555)	8.2 (387/3,510)	9.4 (148/1,027)	14.7 (35/188)	0.001
% Prematurity in multiple pregnancies (n)	44.9 (62/138)	52.2 (148/283)	49.8 (783/1,570)	54.6 (206/377)	55.1 (59/107)	0.220

The percentage of malformations observed in newborns in our registry was 0.83 %, which is similar to the rate of malformations observed in the latest published National Spanish Report (1.19 %) [2]. More recently, the prevalence of major congenital anomalies recorded in Europe was 2.4 % [7], coinciding with a retrospective cohort study that found a similar prevalence of major congenital anomalies in singletons (2.1 %) and twins (2.4 %) from natural conceptions [31]. The percentage of malformations observed in our study is similar to that reported by recent authors. In this sense, the meta-analysis by Rimm et al. [30] concludes that ART does not increase the risk of major malformation as much as previously reported by others [18, 31]. Furthermore, The Spanish Collaborative Study of Congenital Malformations (ECEMC) has published an annual report since 1980. Their report is based on data culled from a case-controlled hospital-by-hospital report that covers only 20.4 % of all births in Spain. The epidemiological surveillance reports a significant decrease of congenital defects in our population over time, going from 2.2 % in 1985 to 0.98 % in 2009, and attributes the decrease to elective abortion after diagnosis of foetal anomalies. Our results are similar to the rate of malformations reported in the ECEMC publication in the same years (0.98 %) [2]. Furthermore, one interesting point that arises in the ECEMC report is geographical heterogeneity. They report regional variations in the incidence of malformations, something that is also reflected all over the world. Allen et al. [1] in Canada found a 4.2 % rate of malformation, in Japan the malformation rate in the normal conception population is 1.16 % [25], and 5.8 % in normal conception was recently reported in the South Australia Registry [6]. Furthermore Källén et al. [18] in their adjusted analysis suggest that, among sub fertile couples (defined as those that need more than a year for natural conception), the relative risk of major malformation in the offspring of ART treated couples is not significantly different from that of untreated ones [30], concluding therefore, that the malformations could well be linked to the subjacent cause of sub fertility rather than the ART technique employed.

In our study the frequency of malformations in multiple pregnancies is higher than in singleton pregnancies although the differences do not reach significance (1.01 % vs. 0.7 %; $p=0.09$). The literature assessing possible differences in malformations between multiple and singleton pregnancies is also controversial. Conclusions might depend on the number of cases observed. When analyzing a smaller sample some have found a significantly higher malformation rate in multiple compared with singleton pregnancies (1,139 infants; [36]), while differences are not observed with bigger samples (German IVF Registry from 2001, 30 000 pregnancies; [23, 28]). The Japanese national data (2004–2008) show a higher percentage of birth defects in multiples if analysed per pregnancy, but not if the analysis is per live birth (25). Some report no significant differences when analyzing only major birth defects [40], while others find a higher rate of malformations in multiple pregnancies when both minor and major anomalies are considered [27].

We found no significant differences in the malformation rate between any reproductive technique considered, both for singleton and multiple babies ($p=0.224$ and $p=0.442$ respectively). Most literature compares results between IVF and ICSI not finding any differences [5, 22, 35], although a recent publication showed no differences either for singletons or twins derived from IUI or IVFT (IVF+ICSI+FET) [31].

Lastly, the incidence of malformations found the most frequent being those of the musculoskeletal system followed by malformations of the circulatory system and third, the digestive system, as has also been reported elsewhere [8, 29]. We found an incidence of 11.7 % for prematurity in singleton pregnancies, similar to the rate reported for the general Spanish newborn population in 2004 (9.4 %), (n.b: 2.1 % of that population consisted of multiple pregnancies. [13]. Among multiple pregnancies, 50.8 % had premature delivery, which is consistent with the 42–68 % rate reported by other European countries [4]. Other studies, however, have estimated a two-fold increased risk of preterm birth

Table 4 Stillbirth in singletons and multiples in different ART

	IUI	IVF	ICSI	FET	PGD	P
% Stillbirth in singletons (n)	0.8 (8/927)	0.1 (1/555)	0.7 (25/3,510)	0.8 (9/1,027)	1 (2/188)	0.530
% Stillbirth in multiples (n)	1.4 (4/271)	3.7 (19/509)	1.5 (45/2,820)	1.6 (11/653)	1 (2/193)	0.017

both in singletons (in IVF) [15, 17, 24] and for twins (in ART) compared with spontaneous pregnancies [15].

In our population singleton prematurity varied with the technique used to achieve pregnancy ($p=0.001$) and the highest prematurity rate was observed in PGD (14.7 %). We must be cautious when interpreting this finding, because the PGD sample size was very small but this point has not been mentioned elsewhere. Others have related IUI to an increase incidence of preterm birth in singleton pregnancies compared with naturally conceived singletons, suggesting that intrinsic factors in sub fertile couples predispose them to having smaller infants [12, 34]. For multiples, in our study, there are no differences in prematurity depending on the ART used. This is consistent with other authors that found no differences comparing prematurity between twin pregnancies from IVF or ICSI [5]. It is possible that the negative effect of multiplicity itself on perinatal outcome is stronger than any individual ART effect.

In our study the rate of stillborn babies was 0.72 % in singleton, which is similar to the rates observed in the Spanish population in 2004 (0.55 %) [13]. We found significantly more stillbirth in multiple pregnancies (1.82 %). It is important to take into account that definitions of stillbirth differ by country or study (between 20 and 27 week of gestational age) additionally, some include early neonatal death while others do not, and this causes a particular lack of inconsistency in results across the studies [33]. A higher rate of stillbirth in singletons and multiples has been widely reported [5, 15, 17, 19, 26], nevertheless a systematic review showed a 40 % lower perinatal mortality in twin pregnancies from assisted conception compared with spontaneous twins [15].

In our results we observed no differences in stillbirth rate in singletons between ARTs. In multiple pregnancies, however, there are differences with the highest rate observed in IVF (3.7 %). Previous publications report stillbirth rate in IVF population ranging between 1.7 and 3.9 % [20, 38] which is in accordance with our stillbirths rate. A recent study in singleton pregnancies compared the risk of stillbirth between fertile women, sub fertile women and women pregnant after fertility treatment (IVF and non-IVF ART). Only women who conceived with IVF had a statistically significant fourfold increased risk of stillbirth compared with fertile women [39]. This would suggest that the increased risk of stillbirth is associated with treatment-related factors to a greater degree than infertility/subfertility itself. Others have associated PGD with a substantial increased risk of perinatal death compared with standard ICSI in multiple pregnancies, which we have not observed [32].

We are aware that there are some weaknesses in this study. First of all, the lack of an adequate control group is a major drawback for this report. Our study would have been strengthened if it had been feasible to include a nationwide control sample of children born after spontaneous conception in the same time period. We have compared our results with the

official data published on spontaneous pregnancy outcomes in Spain [2] in the same time period but that report cannot strictly be considered a true control group. Second, we have taken into consideration women's age and the use of donor eggs in IVF and ICSI as the most important confounding factors affecting our results. However, we cannot exclude the influence that other factors such as diagnosis, male age, duration of infertility and others might also have on neonatal outcome. Third, an adequate nationwide registry should include nearly all ART pregnancies during the study period. However, our study includes 38.1 % of reported cycles in Spain (14 119/36 979) performed by 20.5 % of the ART clinics (29/141). We hope to improve participation in the registry in future years although, in our opinion, the present study is already relevant. Fourth, we only collect neonatal information, and we lack a follow up for children up to 3 months of age. Two-thirds of major malformations are detected within the first 7 days of life [14], so we can assume that our results in malformations are not far from the actual situation. Last, most information regarding neonates was reported by the parents. Therefore it is possible that it might be clinically inaccurate or incomplete. Nevertheless all data were supervised by the individual clinics and monitored by GISE members.

In conclusion, this is the first report of a large-scale ART neonatal outcome study from Spain. The percentage of malformations observed in newborns was 0.83 %, which is similar to the rate of malformations observed in the Spanish population in 2009 (0.98 %). No differences in malformation rate were observed either in singletons or multiples independently of the ART used. Multiplicity seems to be the most important factor behind the increased incidence of newborn complications such as preterm birth or mortality. Taking into account the low rate of malformations and stillbirths, it is imperative to increase the number of observations in order to obtain an even more precise picture of the possible neonatal risks linked to ARTs.

We are conscious that a good register should contemplate a truly nationwide registry including all IVF units, and we do need to have an adequate group control with spontaneous pregnancies in couples without any fertility problem.

If every country did the same, it would make comparisons between countries possible and quite probably reveal other factors implicated in the development of congenital malformations in assisted and normal pregnancies.

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