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ORIGINAL ARTICLE

Assessment of psychomotor development of Spanish children up to 3 years of age conceived by assisted reproductive techniques: Prospective matched cohort study☆

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Received 21 March 2019; accepted 17 July 2019
Available online 20 March 2020

KEYWORDS
Assisted reproductive techniques;
Psychomotor development;
Sub-fertility;
Frozen embryo transfer

Abstract
Introduction: More than five million children have been conceived by assisted reproductive techniques (ART) around the world. Most authors agree that there are no differences in psychomotor development in comparison to naturally conceived children. However, these results are still contradictory.
Objectives: To determine whether children born from a cohort of ART-clinical gestations have a higher risk of suffering neurodevelopmental disorders in comparison to a control group. The potential associated ART-factors associated were also determined.
Material and methods: The study included the assessment of children up to 3 years old conceived by ART, and born from a cohort of women treated by the Reproduction Unit of a public Hospital from May 2012 to May 2014. A simultaneous assessment was made of matched controls, by following the newborn naturally conceived after the ART-case, of the same group of maternal age, gestational age, and type of gestation.

☆ Please cite this article as: Sánchez-Soler MJ, López-González V, Ballesta-Martínez MJ, Gálvez- Pradillo J, Domingo-Martínez R, Pérez-Fernández V, et al. Evaluación del desarrollo psicomotor hasta los 3 años de edad de niños españoles concebidos por técnicas de reproducción asistida (FIV/ICSI): estudio prospectivo de cohorte controlado. An Pediatr (Barc). 2020;92:200–207.

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Results: There were 243 clinical gestations and 267 ART-newborns, of which 231 were assessed (87%). A simultaneous assessment carried out 208/230 controls (90%). There were no differences in neurodevelopmental disorders (global developmental delay, autism spectrum or language delay). Multivariate analysis of potential ART factors only showed an association between transfer of frozen embryos with language delay that has not been previously described.
Conclusions: There were no differences between groups after adjusting the results according to maternal age, multiple pregnancy, and other possible confounding factors, supporting that the role of these factors may be more relevant than the ART itself. The association between frozen embryo transfer and language delay has not been previously described. Thus, more studies are needed to confirm or refute this relationship.

PALABRAS CLAVE
Técnicas de reproducción asistida;
Desarrollo psicomotor;
Subfertilidad;
Transferencia de embrión congelado

Evaluación del desarrollo psicomotor hasta los 3 añosde edad de niños españoles concebidos por técnicas dereproducción asistida (FIV/ICSI): estudio prospectivode cohorte controlado

Resumen
Introducción: Más de 5 millones de niños han sido concebidos por técnicas de reproducción asistida (TRA) a nivel mundial. Aunque la mayoría de autores no detecta diferencias en cuanto a desarrollo psicomotor, los resultados son aun contradictorios.
Objetivo: Conocer si los niños-TRA tienen más riesgo de trastorno del neurodesarrollo y describir posibles factores de la TRA asociados.
Material y Métodos: Evaluación de niños concebidos por TRA hasta los 3 años de edad, nacidos de una cohorte de mujeres tratadas en la Unidad de Reproducción Asistida de un hospital terciario desde mayo de 2012 hasta mayo de 2014; evaluación de controles apareados: siguiente recién nacido al caso concebido de forma natural, del mismo grupo de edad materna, gestacional y mismo tipo de gestación.
Resultados: Hubo 243 gestaciones clínicas y nacieron 267 niños-TRA. Fueron evaluados 231 (87%). Simultáneamente se evaluaron 208/230 controles (90%). No hubo diferencias estadísticamente significativas en trastornos del neurodesarrollo (retraso global del desarrollo, trastorno del espectro autista o retraso del leguaje). El análisis estadístico multivariante de posibles factores de la TRA asociados solo mostró asociación entre transferencia de embrión congelado y retraso del lenguaje.
Conclusiones: No se han detectado diferencias en trastornos del neurodesarrollo tras ajustar los resultados por edad materna, gemelaridad y otros posibles factores de confusión, lo que apoya que estos factores deben jugar un papel más importante que las propias TRA. La asociación entre transferencia de embrión congelado y retraso del lenguaje no ha sido descrita previamente. Son necesarios estudios a largo plazo en niños concebidos tras transferencia de embrión congelado para corroborar estos resultados.

Introduction

Assisted reproductive technology (ART) treatments have been used for more than 30 years[1]. The first child conceived with in vitro fertilization (IVF) in the world was born in 1978, and the first one in Spain was born in 1984. Since then, more than 5 million individuals have been conceived with ART, amounting to 1.3%–6.1% of the total live births in Europe each year.[2] The success rate of ART has been increasing since the early days of the field thanks to the experience accrued and scientific advances, but concerns remain about the potential impact in child health of conception through these means.

There is an ample body of evidence on the psychomotor development and cognitive skills of children conceived with ART, and to date most authors have not found statistically significant differences relative to the general population.[3–7] However, the evidence regarding the incidence of autism spectrum disorder (ASD) is contradictory.[8–11] Although the aetiology of ASD can still not be determined in most cases, epidemiological studies suggest that, in addition to the genetic factors that have already been identified, other factors such as the health of mothers before pregnancy, exposure to toxic substances, parental infertility problems and fertility treatments, among others, play an important role.[12]

In this context, the primary objective of our study was to determine whether there is an increased risk of neurodevelopmental disorders in children up to age 3 years conceived with ART compared to naturally conceived (NC) children, independently of maternal age, the number of foetuses and preterm birth. In addition, we performed an analysis to identify factors specific to ART potentially associated with disorders diagnosed in the group conceived with ART.

Material and methods

We designed an observational prospective matched cohort study to compare psychomotor development in children conceived with ART (a group we will from now on refer to as ''ART children'') and NC children of similar characteristics. The study was approved by the Ethics Committee of the Hospital Clínico Universitario Virgen de la Arrixaca. The signing of an informed consent form was required for participation in the study, in adherence with the principles of the Declaration of Helsinki.

Sample selection

Selection of the cohort of children conceived by means of ART

First we selected a cohort of clinical pregnancies (evidence of a heart beat on week 7–8 of gestation) in women who underwent IVF, intracytoplasmic sperm injection (ICSI) or preimplantation genetic testing between May 2012 and May 2014 in the reproductive health unit of the Hospital Clínico Universitario Virgen de la Arrixaca, a public tertiary care hospital that has a contract with 5 private fertility clinics. Our purpose was to select a representative cohort of children born following the use of ART. Based on data for 2012–2014 published in the Nationwide Activity Register of the Sociedad Española de Fertilidad (Spanish Society on Fertility), we estimate that of a total of 32 000 births in our region during this period,[13] approximately 2.5% were the result of IVF/ICSI. Based on these figures, a sample of 230–240 children conceived with ART would correspond to an absolute precision of 2% with a confidence level of 95%.

During this phase, we collected the following data:

Epidemiological variables: nationality, age of the conceiving couple at initiation of treatment, family and personal history of the parents, maternal body mass index, duration and causes of infertility, exposure to toxic substances (including tobacco and alcohol use).

Treatment-related variables: type of ART, ovarian stimulation and ovulation suppression protocol used, complications, number of oocytes retrieved and fertilised, embryo quality, day of embryo transfer, cryopreservation and others.

Selection of the sample of newborns from the identified cohort of clinical pregnancies

In a second stage, we telephoned the couples that had successful pregnancies 6–10 months post birth and asked them to participate in the study. We informed them of the objectives of the study and our intent to carry out 2 health evaluations before the third birthday of the child. For all families that agreed to participate, we scheduled appointments to evaluate the child, and all evaluations were carried by a paediatrician with specialised training in clinical genetics and dysmorphology.

Selection of matched controls

We also analysed a cohort of NC children selected as follows:

Naturally conceived child born consecutively after a case for who we obtained consent for participation and matched for:

- Maternal age ($\leq$30; 31–34; 35–39 years).
- Gestational age at birth ($\leq$30, 31–36, $\geq$37 weeks' gestation)
- Type of pregnancy (singleton or multiple).

We excluded families in the control group that had initially consented to participate but in which one of the following applied after the first phone call:

- Missed at least 2 of the scheduled appointments.
- Children originally identified as controls that had actually been conceived with some form of ART (ovarian stimulation, artificial insemination, IVF etc.).
- Chose to drop out of the followup.

Clinical evaluation and followup of ART children and NC children

During this phase, we carried out the clinical evaluations: the first one at age 12–20 months and the second at 26–40 months, between September 2014 and June 2017.

In these evaluations, we collected data related to the pregnancy, delivery and neonatal period (Fig. 1) and performed a full physical examination, including exhaustive anatomical and neurologic assessments.

We used the following materials for the neuropsychological evaluation:

none- Haizea-Llevant development chart (ages 0–5 years)[14,15]
none- Modified V. Vaughan scale.[16]
none- Modified Checklist for Autism in Toddlers (M-CHAT)[17]

In addition, patients with abnormal results of screening were assessed by paediatric neurologists and/or educational psychologists as needed and classified applying the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).[18] The variables under study were presence of global developmental delay (GDD; with impairment in at least 2 of the following areas: socialization, language, motor skills and body posture), language disorder and ASD. We also collected data on the metabolic and genetic tests performed and laboratory-confirmed genetic diagnoses.

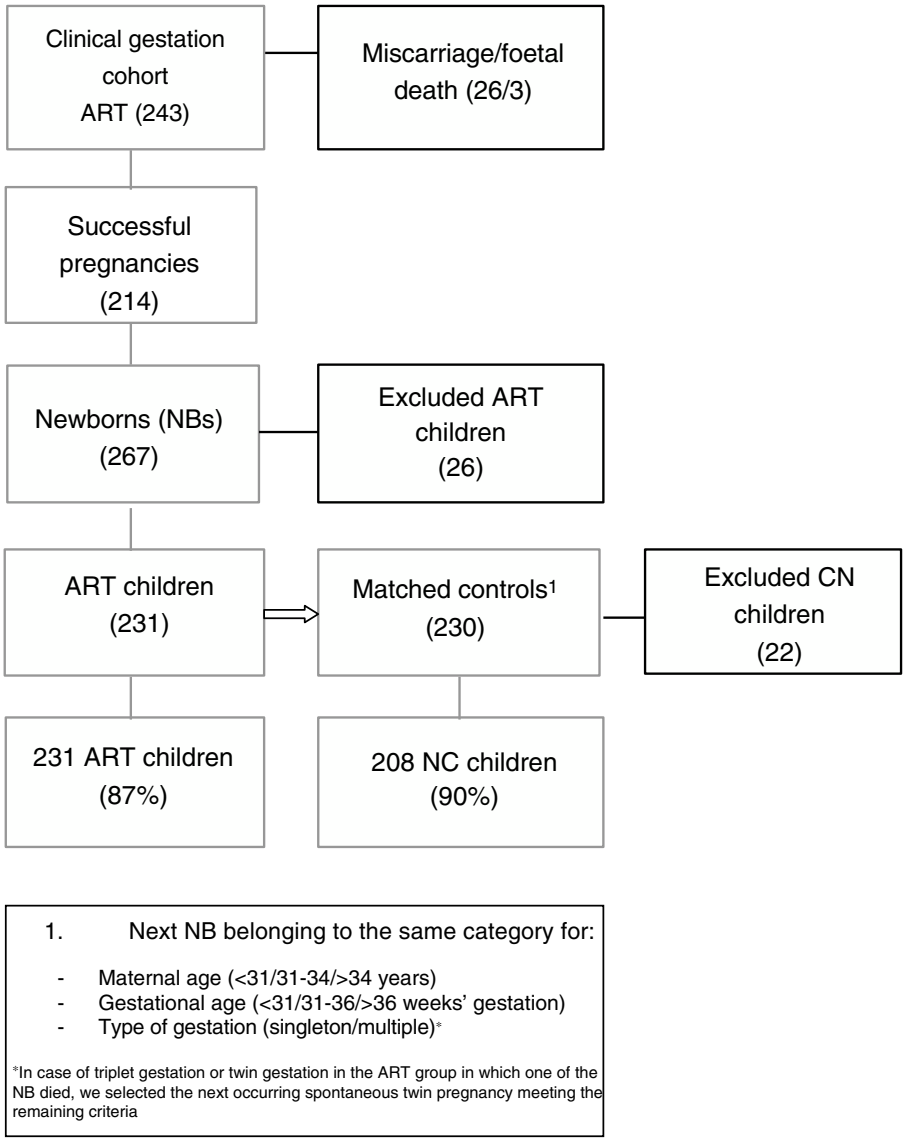

Figure 1 XXX.

Statistical analysis

To meet the objectives of the study, we carried out a statistical analysis in 2 phases.

In the first phase, we assessed for potential differences between ART children and CN children in the frequency of GDD, language disorder and ASD at age 12-to-20 and 26-to-40 months, as well as other characteristics that could have an impact on the interpretation of results (perinatal disease, exposure to substances, etc.). In the second phase, we analysed the cohort of cases and aspects related to ART to try to identify factors that could be associated with the neurodevelopmental disorders detected in this cohort.

The variables that we analysed as potential risk factors were the following:

- At least 4% of sperm with normal morphology (Kruger's criteria).
- Cause of infertility: male factors, female factors, combination of male and female factors, unknown cause.
- Baseline levels of follicle-stimulating hormone (FSH) and oestradiol.
- Preconception folic acid supplementation.
- Type of ART: IVF, ICSI, frozen embryo transfer (FET) or preimplantation genetic testing.
- Day of embryo transfer.
- Number of embryos transferred: 1, 2 or 3.
- Ovarian stimulation and ovulation suppression protocol.
- Previous history of ovarian hyperstimulation (oestradiol >3000 pg/mL and compatible sonographic features).
- Mean number of retrieved oocytes, fertilised oocytes and viable embryos.
- Embryo quality (ASEBIR morphological criteria).

We analysed the association between qualitative variables using the χ^2 test and the Fisher exact test for 2×2 contingency tables. We compared quantitative variables

between 2 groups using the Student *t* test if the data followed a normal distribution or the Mann–Whitney *U* test otherwise. We compared quantitative variables between more than 2 groups by means of analysis of variance (ANOVA) in case the data were normally distributed or the Kruskal–Wallis test otherwise.

We also performed regression analyses: multivariate logistic regression if the dependent variable was dichotomous, multinomial regression if the dependent variable was polytomous and multivariate linear regression if the dependent variable was quantitative and normally distributed. We used normalization techniques as needed. The independent variables included in the regression analyses were those that had exhibited a statistically significant association with the dependent variable in the preceding univariate analyses.

We defined statistical significance as a *P*-value of less than 0.05 in any of the tests. The statistical analysis was performed with the software StataCorp. 2017 (Stata Statistical Software, Release 15; StataCorp. LLC, College Station, TX, USA).

Results

During the period under study, we evaluated 231 ART children and 208 NC children ($N = 439$; Fig. 2). The comparative analysis of the general characteristics of both cohorts did not detect any significant differences in mean maternal age, the proportion of multiple gestation, the mean gestational age at birth, family history or exposure to substances during gestation. We found a higher proportion of mothers that received folic acid supplementation before conception, of mothers who became pregnant after more than 1 year of trying and of female babies in the ART group, and a higher proportion of monochorionic twin pregnancy in the control group (Table 1).

Having completed the 2 evaluations before age 3 years in ART children, we found that 9% had some type of neurodevelopmental disorder of unknown aetiology:

- GDD in 3%.
- Language disorder in 7.8%.
- ASD in **3.4%**.

All patients that received a diagnosis of GDD or ASD were further assessed with the fragile X DNA test and array comparative genomic hybridization (aCGH), and some underwent blood and urine tests for metabolic assessment. These tests only detected a disorder in 1 child conceived with ART: trisomy 47, XXY compatible with Klinefelter syndrome.

The comparative analysis did not identify any difference between the 2 groups in the frequency of diagnosis of neurodevelopmental disorders (Table 2).

We did find differences in the number of children that underwent assessment with aCGH (7.3 in the ART group vs 1.9% in the NC group; $P = .026$), mainly due to the association of neurodevelopmental disorders and/or congenital malformations with craniofacial dysmorphic features, which were more frequent in the ART group.

In cases in which additional tests were performed because the clinical manifestations matched those of a specific genetic disorder (assessment of methylation status at 14q32, 11p15, sequencing of the *EFNB1* gene), the results were normal.

Other specific disorders were also diagnosed in 3 children in the ART group, and these patients were eliminated from the subsequent analysis because they could have neurodevelopmental disorders as a result of their underlying disease: 1 girl with Steinert syndrome inherited from the mother (antenatal diagnosis), 1 case of Beckwith-Wiedemann syndrome with IC2 hypomethylation and 1 girl with hypohidrotic ectodermal dysplasia carrier status.

The multivariate analysis of factors related to ART that could be associated with the neurodevelopmental disorders detected in the ART group revealed the following:

When it came to the presence of some form of neurodevelopmental disorder of unknown cause (9%), logistic regression did not detect an association with any ART-related factors, but it did detect an association with multiple gestation (OR, 3.19; 95% confidence interval [CI], 1.00–10.13; $P = .049$).

In the case of GDD (3%), we also did not find an association with any ART-related factor, but we found an association with a positive history of neonatal hypoglycaemia, defined as a blood glucose concentration of less than 25 mg/dL in the first 4 h of life and less than 35 mg/dL thereafter, as specified in the protocol of our hospital,[19] and with infertility of unknown cause (Table 3).

We found evidence of language disorder in 7.8% of the ART group by age 3 years. Although the univariate analysis found an association between language disorder and a positive history of ovarian hyperstimulation, neonatal hypoglycaemia and FET, the logistic regression analysis only found an association with FET (Table 4) independent of preterm birth, maternal age and multiple gestation.

Autism spectrum disorder was diagnosed in 3.4% of ART children. The univariate analysis did not detect an association with any ART-related factor or with multiple pregnancy, preterm birth etc.

Discussion

Our analysis did not reveal any statistically significant differences in psychomotor development through age 3 years between children conceived with ART and NC children, which was consistent with the majority of the evidence published to date. The increasing use of fertility treatments and their known association with a higher incidence of perinatal disease (mainly low birth weight and prematurity) raised concerns that these children could consequently suffer from neurologic problems more frequently. Some authors have also proposed the hypothesis that the use of ARTs could have a direct effect on neurodevelopment through epigenetic mechanisms at play in the early stages of embryonal development.[20] These hypotheses notwithstanding, most studies conducted to date and the most recent systematic review on the subject[21] have not found significant differences in psychomotor development (gross and fine motor skills, communication and language, problem solving and cognitive skills) between the ART and the NC populations.

GESTATION
Type of gestation: singleton, twin, triplet
Selective reduction: YES/NO_____
Foetal death in utero (after 20 weeks gestation) YES/NO_____
Cause: chromosomal disorder, maternal disease, sonographic abnormalities (malformations), unknown_____

Disease during pregnancy: YES/NO
- Fever Infection, high blood pressure, pre-eclampsia, HELLP syndrome
- Premature rupture of membranes, threatened premature delivery, gestational diabetes
- Other _____

Substance use: Mother: YES/NO Father: YES/NO
Amount and frequency (times/week)
- Alcohol, tobacco, illicit drugs
Discontinuation of substance use

☐ While

Substance use: Mother: YES/NO Father: YES/NO

Amount and frequency (times/week)
- Alcohol, tobacco, illicit drugs
Discontinuation of substance use

☐ While trying to conceive (months)_____

☐ At pregnancy diagnosis (weeks'gestation) or later

Medication during pregnancy YES/NO, (dose and frequency)_____
Exposure to environmental factors YES/NO (frequency)_____
Sonographic abnormalities: YES/NO _____

Figure 2 Flowchart of sample selection.

Table 1 Comparative analysis of the cohorts: general characteristics.

	ART children	NC children	*P*
Sex (female), %	55.8	40.0	<.001
Maternal age (years), mean	33.4	33.4	.40
Multiple pregnancy, %	23.5	24.0	.35
Monochorionic multiple pregnancy, %	11.0	31.0	.17
Preterm birth, %	24.6	23.5	.78
Gestational age at birth (weeks), mean	37.7	37.8	.69
Maternal smoking, %	13.8	17.8	.25
Consumption of toxic substances (tobacco, alcohol or other), %	16.0	19.0	.30
Time to conception > 1 year, %	94.0	7.9	<.001
Preconception folic acid supplementation, %	65.0	42.0	<.001
Family history of genetic disorder*, %	2.6	2.4	.89

ART, assisted reproductive technology; NC, naturally conceived.
* First-degree relative.

Table 2 Comparative analysis of the cohorts: neurodevelopmental disorders.

	ART children	NC children	*P* (χ^2)
Neurodevelopmental disorder	9.0	9.6	.85
GDD	3.0	2.9	.93
Language disorder	7.8	7.7	.98
ASD	3.4	1.9	.32

ART, assisted reproductive technology; ASD, autism spectrum disorder; GDD, global developmental delay; NC, naturally conceived.

Table 3 Logistic regression analysis of potential ART-related risk factors: global developmental delay.

GDD	OR	*P*	95% CI
Sex	4.42	.172	0.52–37.43
Maternal age	0.86	.271	0.66–1.11
Multiple gestation	1.60	.701	0.14–18.01
Preterm birth	2.26	.491	0.22–23.07
Gestational diabetes	0.24	.380	0.01–5.60
Infertility of unknown cause	25.22	.013	1.98–320.16
Neonatal hypoglycaemia	68.97	.016	2.22–2142.20

ART, assisted reproductive technology; CI, confidence interval; GDD, global developmental delay; OR, odds ratio.

Table 4 Logistic regression analysis of potential ART-related risk factors: language disorder.

Language disorder	OR	*P*	95% CI
Sex	1.50	.440	0.53–4.25
Maternal age	0.95	.575	0.81–1.12
Multiple gestation	1.41	.580	0.41–4.76
Preterm birth	0.69	.634	0.16–3.05
Gestational diabetes	2.86	.426	0.21–38.12
Neonatal hypoglycaemia	1.22	.794	0.26–5.58
FET	3.84	.035	1.10–13.37

ART, assisted reproductive technology; CI, confidence interval; FET, frozen embryo transfer; OR, odds ratio.

We found a high proportion of ASD (3.4%) in the ART cohort in our study, but the multivariate analysis did not find differences between the ART and NC groups. A recent review and meta-analysis that included 11 studies and a total of 8 161 225 patients found a relative risk of ASD of 1.35 (95% CI, 1.09–1.68; *P* = .007) in ART children.[22] However, the authors noted that further studies were necessary to take into account potential confounders such as maternal age, preterm birth, multiple gestation etc., as most studies did not analyse their potential impact. Our findings support this conclusion. Although the sample size may also have an impact on the results, our data suggest that the criteria used to select the control group (maternal age, type of pregnancy and gestational age at birth) should be considered the most important risk factors associated to the morbidity found in the population of ART children, as opposed to the use of ART itself. This supports the currently growing practice of single-embryo transfer,[23,24] which minimises the frequency of multiple gestation and, as a secondary effect, the frequency of preterm birth, something that should be discussed with couples.

On the other hand, the analysis of ART-specific factors potentially associated with the neurodevelopmental disorders detected in the ART cohort only identified FET as a risk factor for language disorder that was independent of multiple gestation, preterm birth and maternal age, an association not previously described in the literature. Among the limitations of the study, we ought to highlight the young age of our sample and the fact that we did not ask participating couples whether either partner had had language delays in childhood. Given the known familial component in isolated cases of language disorder, this history could have an impact on the results. However, there is a scarcity of long-term longitudinal data on the FET population, and given the current generalised practice of vitrifying all embryos, performance of studies on the subject is of the essence, with particular emphasis on psychomotor development.[25] We did not find an association of any neurodevelopmental disorder with the type of ART used (IVF or ICSI), nor with the different stimulation protocols or the duration of embryo culture, contrary to the findings of other authors.[26]

We ought to highlight the association we found between infertility of unknown cause and GDD, which supports previous descriptions in the literature of an association between subfertility in couples and poorer psychomotor development outcomes and coordination in their children.[27,28] The results of these studies evince that difficulties in conception have a more relevant impact on neurodevelopment that the ARTs that these couples may come to use.

Conclusions

This is the first prospective cohort study analysing the psychomotor development of children conceived with ART through age 3 years in comparison with a control group of similar characteristics in terms of multiple pregnancy, maternal age and preterm birth. We did not find a difference between groups in the incidence of the neurodevelopmental disorders under study through age 3 years, which was consistent with most of the previous literature. Our findings suggest that the criteria used for selection of control groups and subfertility should be considered potential risk factors, as opposed to ART itself. These results should be conveyed to couples planning to attempt conception with ART to improve counselling and promote elective single-embryo transfer, thus reducing the risk of multiple pregnancy and preterm birth, which are 2 known risk factors for neurodevelopmental abnormalities. The association between FET and

language disorder has not been described in the past. Long-term longitudinal studies on the health of children conceived by means of FET are needed to confirm this finding.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

These data are part of the doctoral dissertation titled *Evaluación de salud y desarrollo hasta los 3 años de edad de niños concebidos por técnicas de reproducción asistida* (Assessment of health and development through age 3 years in children conceived by assisted reproductive FEThnology). We thank all participants, parents and children for their availability and cooperation.

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