Neurodevelopmental outcomes of preterm infants with very low birth weight conceived with the assistance of in vitro fertilization

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Objective: To compare the neurodevelopmental outcomes at 18–24 months of corrected age between preterm (<32 weeks of gestational age) infants with very low birth weight (VLBW) conceived with and without the assistance of in vitro fertilization (IVF).
Design: Prospective cohort study.
Setting: Not applicable.
Patient(s): In total, 4,940 infants with VLBW were born before 32 weeks of gestational age from January 2013 to December 2015.
Intervention(s): In vitro fertilization.
Main Outcome Measure(s): Neuromotor or sensory disability (primary outcome) and developmental delay assessed using the Bayley Scales of Infant and Toddler Development (secondary outcome) at 18–24 months of corrected age.
Result(s): Of the 4,940 infants with VLBW enrolled, 2,818 surviving infants who were followed up for neurodevelopmental assessment at 18–24 months of corrected age were included in the study. Of these 2,818 infants, 630 (22.4%) were conceived with the assistance of IVF, and 2,188 (77.6%) were not. After adjustment for potential confounders, no statistically significant differences were found in the rate of neuromotor or sensory disability at 18–24 months of corrected age between infants conceived with and without the assistance of IVF. After excluding infants with neuromotor or sensory disability, the rate of developmental delay was also comparable between those conceived with and without the assistance of IVF.
Conclusion(s): This study showed comparable neurodevelopmental outcomes at 18–24 months of corrected age between preterm infants with VLBW conceived with and without the assistance of IVF. (Fertil Steril® 2022;117:1214–22. ©2022 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: In vitro fertilization, assisted reproductive technology, very low birth weight infant, preterm infant

Assisted reproductive technology (ART), including in vitro fertilization (IVF), has been widely performed to facilitate conception in couples with infertility (1). Since the first delivery of an infant conceived by IVF in South Korea in 1985, the births of infants conceived through IVF have been increasing and accounted for 5.8% of live births in 2017 (2, 3). The number of live births occurring via IVF has increased 3.6-fold over the last decade since a national supporting program for infertility was implemented in 2006 (3). In 2017, 60,471 IVF cycles were performed, and the total number of live births occurring via IVF in South Korea was 20,864 (3).

In vitro fertilization has been associated with various obstetric and perinatal adverse outcomes, which are attributable primarily to an increased risk of multiple gestations with IVF (4–8). However, even in singleton pregnancy, IVF is not free from

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adverse outcomes (9, 10). Biologic characteristics underlying infertility of the mother, father, or both and epigenetic alternations of gametes and embryos from exposure to supraphysiologic estradiol levels and handling during the IVF process at critical stages of development have been discussed as potential drivers of adverse outcomes associated with IVF (11).

Brain development may be affected by these epigenetic alterations associated with IVF procedures. Therefore, concern has arisen regarding the neurodevelopmental outcomes of children conceived with the assistance of IVF. However, data on the neurodevelopmental outcomes of preterm infants conceived with the assistance of IVF have been described in only a few studies with conflicting results (12–14). One study reported a significant association between IVF and the risk of functional disability at 2–3 years of corrected age in preterm infants born at 22–26 weeks of gestational age (GA) (13). Other investigators demonstrated that assisted conception was significantly associated with a reduced probability of nonoptimal neurodevelopmental outcomes at 2 years in preterm infants born before 34 weeks of GA (14).

We hypothesized that the neurodevelopmental outcomes at 18–24 months of corrected age of infants with very low birth weight (VLBW) born before 32 weeks of GA conceived with the assistance of IVF are not worse than those of their peers conceived without the assistance of IVF.

MATERIALS AND METHODS

Study Population

Our cohort study used prospectively collected data from 70 neonatal intensive care units (NICUs) participating in the Korean Neonatal Network (KNN). The KNN registry includes approximately 70% of all infants with VLBW born in South Korea, and more than 97% of enrolled infants are ethnically Korean (15). We enrolled infants with VLBW registered in the KNN registry who were born at 23^{+0} to 31^{+6} weeks of GA between January 2013 and December 2015 and were followed up for neurodevelopmental assessment after discharge from the NICU at 18–24 months of corrected age. We excluded infants with major congenital anomalies, those who died during NICU admission or after NICU discharge, and those lost to follow-up.

Data Collection

The KNN is a nationwide multicenter registry of infants with VLBW that prospectively collects demographic and clinical data using a standardized operating procedure (15). Infants with VLBW registered in the KNN are scheduled to be followed up at 18–24 months of corrected age and at 3 years of postnatal age. The maternal data included age, education, hypertension, diabetes, premature rupture of membrane, and the use of antenatal corticosteroids. The neonatal data included GA, birth weight, sex, small for gestational age (SGA), multiple births, delivery mode, and Apgar scores at 1 and 5 minutes. The following clinical information was collected: respiratory distress syndrome; bronchopulmonary dysplasia; patent ductus arteriosus requiring medical or surgical treatment; necrotizing enterocolitis; sepsis; intraventricular hemorrhage; periventricular leukomalacia (PVL); and retinopathy of prematurity. The definition of each variable is listed separately in the supplementary materials (Supplemental Text 1, available online).

Comparison of the Baseline Characteristics and Neonatal Morbidities

The baseline characteristics, neonatal morbidities, and neurodevelopmental outcomes at 18–24 months of corrected age were compared between infants conceived with and without the assistance of IVF. Because neonatal morbidities and neurodevelopmental outcomes can differ by plurality, these were compared between infants conceived with and without the assistance of IVF stratified by plurality (singletons and multiplets).

Comparison of Neuromotor or Sensory Disability and Developmental Delay

Surviving infants with VLBW were followed up at 18–24 months of corrected age by pediatricians and/or rehabilitation doctors. Hearing and visual assessments included a hearing examination by an audiologist and a vision test by an ophthalmologist. Cerebral palsy was defined as a nonprogressive motor impairment characterized by abnormal control of movement or posture, or both, accompanied by neurologic signs (16).

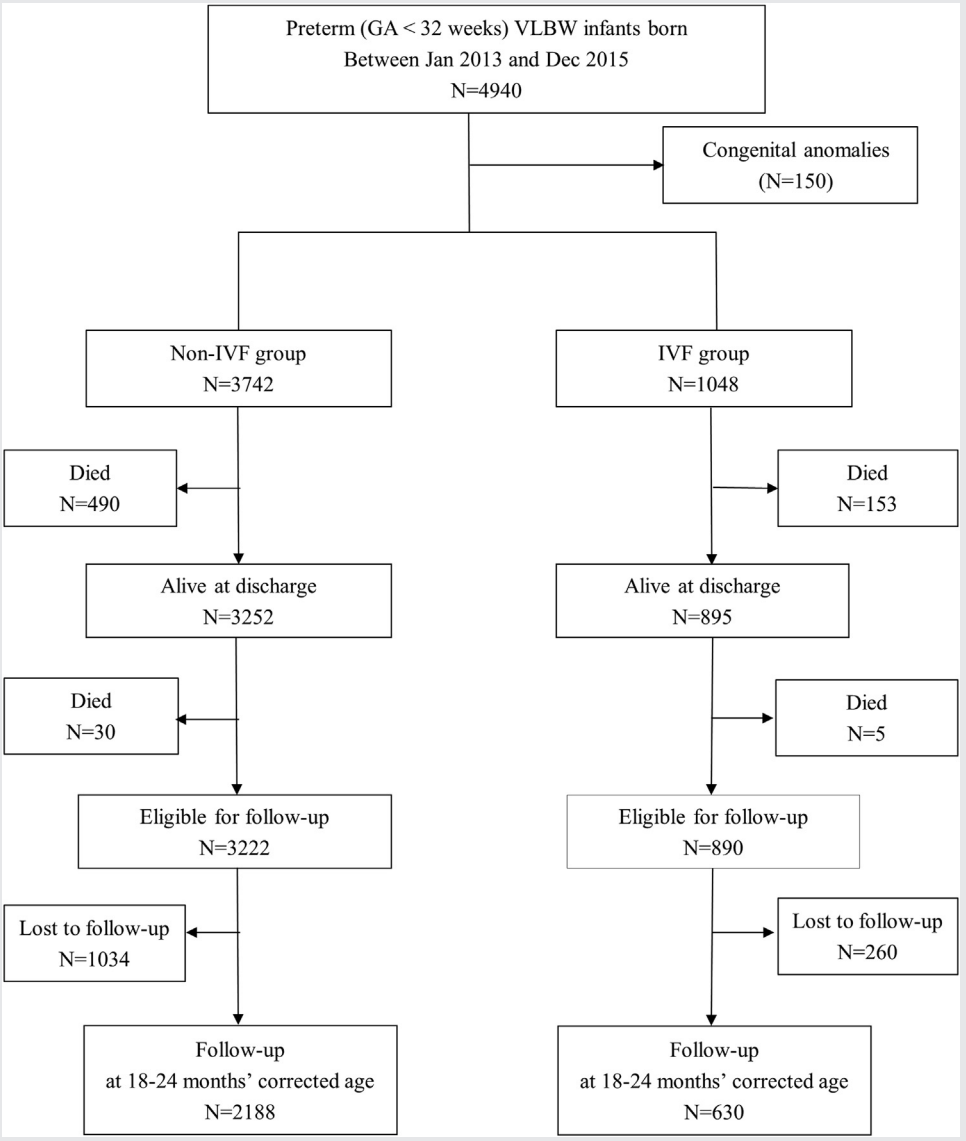
The primary outcome was neuromotor or sensory disability at 18–24 months of corrected age, defined as the presence of at least 1 of the following: cerebral palsy; deafness (unilateral or bilateral); and blindness (unilateral or bilateral).

Developmental delay was assessed as the secondary outcome using either the Bayley Scales of Infant Development-Second Edition (BSID-II) or the cognitive, language, and motor composites of the Bayley Scales of Infant and Toddler Development-Third Edition (Bayley-III) depending on the routine procedure of the individual follow-up center (17, 18). Developmental delays were assessed only for infants without cerebral palsy, deafness, or blindness because significant physical and sensory impairments could preclude the proper use of the BSID-II or Bayley-III (19). We defined developmental delay as a mental developmental index or psychomotor developmental index of <70 on the BSID-II or a Bayley-III composite score of <85 on the components (cognitive, language, and motor) according to the studies by Jary et al. (20) and Johnson et al. (21).

Statistical Analysis

Continuous variables are expressed as means ± standard deviation, and categorical variables are expressed as numbers and proportions. Continuous variables between the groups were compared using Student's *t* test for normally distributed variables and the Mann-Whitney *U* test for variables with nonnormal distributions. Categorical variables were compared using Pearson's χ^2 test. Multivariable logistic

FIGURE 1



Flow diagram of the study population. GA = gestational age; IVF = in vitro fertilization; VLBW = very low birth weight.

Kim. Neurodevelopmental outcomes after IVF. Fertil Steril 2022.

regression analysis was performed to adjust for potential confounding variables, and adjusted odds ratios (aORs) and their 95% confidence intervals (CIs) were calculated. The potential confounders adjusted in the multivariable analyses were those identified in previous studies, observed from the comparison of baseline characteristics, or chosen using clinical judgment. These factors included maternal age, maternal education, antenatal steroids, male sex, GA, and SGA. However, GA and SGA were not adjusted because they may act as intermediate variables that lie on the causal pathway from IVF to adverse neurodevelopmental outcomes. Statistical analyses were performed using SPSS software, version 26.0 (IBM Corp., Armonk, NY). A P value of $<.05$ was considered statistically significant.

Ethical Approval and Informed Consent

The KNN registry was approved by the Institutional Review Board of the CHA Bundang Medical Center, CHA University (Institutional Review Board No. CHAMC 2013-08-082). Informed consent was obtained from the parents of each infant before participation in the KNN registry.

RESULTS

Study Population

Information on the study population is presented in Figure 1. Overall, 4,940 infants with VLBW born before 32 weeks of GA were registered in the KNN from January 2013 to December

TABLE 1

Comparisons of the baseline characteristics and neonatal morbidities between infants conceived with the assistance of IVF (IVF group) and infants conceived without the assistance of IVF (non-IVF group) among preterm infants with very low birth weight (< 1,500 g) born earlier than 32 weeks of gestational age from the Korean Neonatal Network.

	Singletons (N = 1,813)			Multiplets (N = 1,005)		
	IVF N = 109	Non-IVF N = 1,704	*P* value	IVF N = 521	Non-IVF N = 484	*P* value
Maternal age (years)	34.7 ± 3.6	32.9 ± 4.3	<.001	33.5 ± 3.2	31.8 ± 3.8	<.001
Maternal education (≥college)[a]	73 (83.0)	1,028 (72.9)	.037	353 (77.8)	320 (75.8)	.500
Primigravida	55 (50.5)	620 (36.4)	.003	312 (59.9)	250 (51.7)	.009
Maternal hypertension	20 (18.3)	409 (24.0)	.178	43 (8.3)	46 (9.5)	.486
Gestational diabetes	13 (11.9)	140 (8.2)	.177	43 (8.3)	45 (9.3)	.558
PROM	49 (45.0)	696 (41.0)	.415	201 (39.3)	147 (30.5)	.004
Antenatal steroids	58 (53.2)	843 (50.4)	.564	259 (50.8)	200 (41.8)	.004
Gestational age (weeks^{+days})	$27^{+4} \pm 2^{+0}$	$28^{+0} \pm 2^{+0}$	.043	$28^{+1} \pm 2^{+1}$	$28^{+4} \pm 2^{+0}$	.028
Birth weight (g)	991 ± 283	1,055 ± 259	.013	1,085 ± 268	1,102 ± 261	.309
Male sex	60 (55.0)	869 (51.0)	.412	271 (52.0)	254 (52.5)	.883
SGA	16 (14.7)	188 (11.0)	.243	30 (5.8)	42 (8.7)	.073
Cesarean section	85 (78.0)	1,208 (70.9)	.113	422 (81.0)	404 (83.5)	.306
1-minute Apgar score	4.1 ± 1.8	4.4 ± 1.9	.061	4.6 ± 1.9	4.6 ± 1.9	.909
5-minute Apgar score	6.5 ± 1.7	6.7 ± 1.8	.148	6.8 ± 1.7	6.9 ± 1.6	.523
RDS	98 (89.9)	1,527 (89.6)	.922	422 (84.8)	412 (85.3)	.826
BPD	44 (40.4)	586 (34.5)	.209	174 (33.5)	158 (32.8)	.819
PDA requiring medical or surgical treatment	49 (45.0)	732 (43.0)	.683	211 (40.5)	204 (42.1)	.596
NEC (≥stage II)	10 (9.2)	89 (5.2)	.078	23 (4.4)	24 (5.0)	.683
Culture-proven sepsis	27 (24.8)	372 (21.8)	.473	94 (18.0)	113 (23.3)	.038
High-grade IVH	11 (10.1)	120 (7.0)	.233	37 (7.1)	38 (7.9)	.651
PVL	8 (7.3)	137 (8.0)	.794	29 (5.6)	55 (11.4)	.001
ROP (≥stage 3)	20 (18.3)	217 (12.7)	.092	91 (17.5)	63 (13.0)	.054

Note: The data are presented as numbers (percentage) or means ± standard deviation. BPD = bronchopulmonary dysplasia; IVF = in vitro fertilization; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; PROM = premature rupture of membranes; PVL = periventricular leukomalacia; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity; SGA = small for gestational age.

[a] The data were available for 1,498 singletons and 876 multiplets.

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2015. Among these infants, 150 with major congenital anomalies and 643 who died during NICU admission were excluded. Of the 4,147 infants discharged home from the NICU, 35 died after NICU discharge, and 1,294 were lost to follow-up assessments at 18–24 months of corrected age. Thus, 2,818 surviving infants who participated in follow-up assessments at 18–24 months of corrected age comprised our study population. Their mean GA was $28^{+1} \pm 2^{+0}$ weeks, and their mean birth weight was 1,066 ± 263 g. Of these 2,818 infants, 630 (22.4%) were conceived with the assistance of IVF, and 2,188 (77.6%) were not.

Profiles of Infants Who Were Lost to Follow-up Compared With Those Who Were Followed up at 18–24 Months of Corrected Age

The baseline characteristics of the infants who were lost to follow-up at 18–24 months of corrected age and those of the infants who were followed up (study population) are compared in Supplemental Table 1 (available online). The mothers of both singleton and multiplet infants lost to follow-up were more likely to be younger, and the mothers of singleton infants were less educated. Compared with infants who were followed up, infants lost to follow-up were born at a higher GA and had a higher birth weight and 1- and 5-minute Apgar scores. The rate of IVF did not significantly differ between infants who were followed up and those lost to follow-up whether they were born as singletons or multiplets.

Comparisons of the Baseline Characteristics and Neonatal Morbidities Between Infants Conceived With and Without the Assistance of IVF

The mothers of infants conceived with the assistance of IVF were significantly older and more often primiparous than those of infants conceived without the assistance of IVF, whether they were pregnant with singletons or multiplets. The mothers of infants conceived with the assistance of IVF were more educated than those of infants conceived without the assistance of IVF only among those who were pregnant with singletons. Maternal premature rupture of membrane occurred more often in infants conceived with the assistance IVF than in infants conceived without the assistance of IVF only in multiplet pregnancies. Antenatal steroids were used more often in infants conceived with the assistance of IVF than in infants conceived without the assistance of IVF only in multiplet pregnancies. Infants conceived with the assistance of IVF were born at an earlier GA than infants conceived without the assistance of IVF, whether they were born as singletons or multiplets. However, the birth weights of infants conceived with the assistance of IVF were lower than those of infants

TABLE 2

Comparisons of neurodevelopmental outcomes between infants conceived with the assistance of IVF (IVF group) and infants conceived without the assistance of IVF (non-IVF group) among preterm infants with very low birth weight (< 1,500 g) born earlier than 32 weeks of gestational age from the Korean Neonatal Network.

	Singletons (N = 1,813)				
	IVF N = 109	Non-IVF N = 1,704	*P* value	Adjusted OR (95% CI)[a]	Adjusted *P* value[a]
Corrected age at assessment (months)	20.8 ± 2.1	20.6 ± 2.2	.250	—	—
Cerebral palsy	8/109 (7.3)	97/1704 (5.7)	.475	1.801 (0.830–3.907)	.136
Hearing					
Bilateral deafness	1 (0.9)	13 (0.8)	.582	1.260 (0.158–10.067)	.828
Unilateral deafness	2 (1.8)	18 (1.1)	.341	0.839 (0.108–6.495)	.867
Vision					
Bilateral blindness	0 (0.0)	3 (0.2)	1.000	—	
Unilateral blindness	0 (0.0)	6 (0.5)	1.000	—	
Neuromotor or sensory disability[b]	11 (10.1)	125 (7.3)	.290	1.606 (0.798–3.230)	.184
Infants assessed by the BSID-II or Bayley-III[c]	46/98 (46.9)	485/1579 (30.7)	< .001	2.320 (1.456–3.697)	< .001
BSID-II MDI of <70	9/29 (31.0)	56/320 (17.5)	.073	1.648 (0.619–4.388)	.317
BSID-II PDI of <70	6/29 (20.7)	42/319 (13.2)	.261	1.672 (0.565–4.952)	.353
Bayley-III composite cognition score of <85	2/17 (11.1)	16/165 (9.7)	.786	1.126 (0.210–6.055)	1.126
Bayley- II composite language score of <85	7/17 (41.2)	42/165 (25.5)	.164	2.102 (0.704–6.277)	.183
Bayley-III composite motor score of <85	4/17 (23.5)	14/165 (8.5)	.070	3.083 (0.793–11.989)	.104
Developmental delay[d]	19/46 (41.3)	119/485 (24.5)	.013	1.986 (0.999–3.948)	.050
	Multiplets (N = 1,005)				
	IVF N = 521	Non-IVF N = 484	*P* value	Adjusted OR (95% CI)[a]	Adjusted *P* value[a]
Corrected age at assessment (months)	20.87 ± 2.2	20.7 ± 2.1	.984	—	—
Cerebral palsy	43 (8.3)	49 (10.1)	.304	0.910 (0.550–1.506)	.715
Hearing					
Bilateral deafness	7 (1.3)	6 (1.2)	.884	1.232 (0.393–3.866)	.721
Unilateral deafness	4 (0.8)	6 (1.2)	.534	0.753 (0.190–2.985)	.686
Vision					
Bilateral blindness	1 (0.2)	0 (0.0)	1.000	—	
Unilateral blindness	1 (0.2)	1 (0.2)	1.000	—	
Neuromotor or sensory disability[b]	50 (9.6)	57 (11.8)	.263	0.905 (0.571–1.437)	.673
Infants assessed by the BSID-II or Bayley-III[c]	161/471 (34.2)	129/427 (30.2)	.204	1.190 (0.872–1.626)	.273
BSID-II MDI of <70	18/95 (18.9)	19/79 (24.1)	.413	0.951 (0.421–2.151)	.904
BSID-II PDI of <70	15/95 (15.8)	10/79 (12.7)	.558	1.548 (0.606–3.953)	.361
Bayley-III composite cognition score of <85	7/66 (10.6)	5/50 (10.0)	.915	0.793 (0.185–3.399)	.755
Bayley-III composite language score of <85	15/66 (22.7)	9/50 (18.0)	.534	1.182 (0.427–3.268)	.748
Bayley-III composite motor score of <85	10/66 (15.2)	6/50 (12.0)	.626	1.570 (0.450–5.474)	.479
Developmental delay[d]	38/161 (23.6)	32/129 (24.8)	.812	1.041 (0.577–1.875)	.895

Note: The data are presented as numbers (percentage), numbers/total numbers (percentage), or means ± standard deviation. Bayley-III = Bayley Scales of Infant and Toddler Development-Third Edition; BSID-II = Bayley Scales of Infant Development-Second Edition; CI = confidence interval; IVF = in vitro fertilization; MDI = mental developmental index; OR = odds ratio; PDI = psychomotor developmental index.

[a] The ORs and *P* values were calculated with adjustment for maternal age, maternal education, antenatal steroids, and male sex.

[b] Neuromotor or sensory disability was defined as the presence of at least 1 of the following: cerebral palsy; auditory impairment (unilateral or bilateral); and visual impairment (unilateral or bilateral).

[c] Infants with cerebral palsy, deafness, or blindness were excluded (N = 81).

[d] Developmental delay was defined as an MDI or PDI of <70 in the BSID-II assessment or a Bayley-III composite score of <85 on the cognitive, language, and motor components.

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conceived without the assistance of IVF only when they were born as singletons (Table 1).

Among the 1,813 infants with VLBW born as singletons, no differences in neonatal morbidities were found between infants conceived with and without the assistance of IVF. Among the 1,005 infants with VLBW born as multiplets, sepsis and PVL occurred less often in infants conceived with the assistance of IVF than in infants conceived without

the assistance of IVF. Otherwise, no differences in neonatal morbidities were found between infants conceived with and without the assistance of IVF (Table 1).

Comparisons of Neuromotor or Sensory Disability and Developmental Delay Between Infants Conceived With and Without the Assistance of IVF

The corrected age at neurodevelopmental assessment was comparable between the 2 groups. After adjusting for potential confounders, no differences were found in the rates of cerebral palsy, unilateral or bilateral deafness, unilateral or bilateral blindness, or neuromotor or sensory disability between infants conceived with and without the assistance of IVF, whether they were born as singletons or multiplets (Table 2).

Among the 2,818 infants who were followed up at 18–24 months of corrected age, 902 had undergone the BSID-II or Bayley-III assessment. The profiles of infants who did not undergo the BSID-II or Bayley-III assessment among those who were followed up at 18–24 months compared with those who had undergone the BSID-II or Bayley-III assessment are presented in Supplemental Table 2 (available online). After excluding 81 infants with cerebral palsy, unilateral or bilateral deafness, or unilateral or bilateral blindness, which precluded the proper use of the BSID-II or Bayley-III assessment, 821 infants were subjected to the assessment of developmental delay. Of these 821 infants, 531 were born as singletons, and 290 were born as multiplets. After adjusting for potential confounders, no statistically significant differences were found in the rate of developmental delay assessed using the BSID-II or Bayley-III between infants conceived with and without the assistance of IVF, whether they were born as singletons or multiplets (Table 2).

DISCUSSION

In this multicenter cohort study of infants with VLBW born before 32 weeks of GA, no significant differences were found between infants conceived with and without the assistance of IVF in the rate of neuromotor or sensory disability at 18–24 months of corrected age. After excluding infants with cerebral palsy, blindness, or deafness, no significant differences in the rate of developmental delay evaluated using the BSID-II or Bayley-III assessment were found between infants conceived with and without the assistance of IVF.

Limited data are available regarding the neurodevelopmental outcomes of preterm infants conceived with the assistance of IVF (12–14). In a study specifically examining preterm infants born as multiplets, the neurodevelopmental outcomes were similar between infants conceived with and without the assistance of IVF (12). An Australian cohort study evaluated functional disability at 2–3 years of corrected age in preterm infants (<29 weeks of GA) conceived with and without the assistance of IVF or hyperovulation (13). In that study, infants in both groups had comparable rates of functional disability. However, in the subgroup analysis, the investigators reported that the risk of functional disability in infants born at 22–26 weeks of GA was significantly higher for infants conceived with the assistance of IVF than for those conceived without the assistance of IVF (aOR, 1.79; 95% CI, 1.05–3.05; $P=.03$). Molines et al. (14) assessed the association between assisted conception and neurodevelopmental outcome at 2 years of corrected age in preterm infants born before 34 weeks of GA. Assisted conception was associated with a significantly reduced probability of nonoptimal neurodevelopment at 2 years after adjusting for maternal age, maternal socioeconomic status, and parity (aOR, 0.26; 95% CI, 0.09–0.80; $P=.019$). These discrepancies among the studies, including ours, may be attributable to different study populations and different definitions of ART.

No differences were found in the risk of cerebral palsy between infants conceived with and without the assistance of IVF, whether they were born as singletons or multiplets. Our finding of the absence of an association between IVF and cerebral palsy is consistent with those of previous studies that assessed the risk of cerebral palsy in children conceived with ART (13, 22–25). In contrast, IVF has been associated with an increased risk of cerebral palsy even after the association was adjusted for prematurity and plurality in other studies (26, 27). In a cohort study from Western Australia, the odds of cerebral palsy in children conceived with ART were doubled only in singletons born earlier than 32 weeks of GA (27).

Because the primary outcome of our study was neurodevelopmental outcome at 18–24 months of corrected age, dropout issues were expected. First, 643 infants who died during NICU admission and 35 infants who died after NICU discharge were excluded from the study population. Death before 18–24 months of corrected age can act as a competing event with poor neurodevelopmental outcomes at 18–24 months of corrected age. Although no significant differences were found in the rates of death during NICU admission or after NICU discharge between infants conceived with and without the assistance of IVF regardless of plurality, these dropouts before the neurodevelopmental assessment at 18–24 months of corrected age due to death are a potential source of bias in our study. Second, dropouts from the neurodevelopmental assessment at 18–24 months of corrected age due to loss to follow-up are another source of bias. Overall, 1,294 infants were lost to follow-up at 18–24 months of corrected age. As shown in Supplemental Table 1, infants who were lost to follow-up were born at later GAs and had greater birth weights than those who were followed up and, thus, were at a lower risk for poor neurodevelopmental outcomes at 18–24 months of corrected age than those who were followed up (28–30). These dropouts of low-risk infants from the neurodevelopmental assessment at 18–24 months of corrected age may also represent a selection bias in our study.

We observed no differences in the rate of developmental delay evaluated using the BSID-II or Bayley-III assessment at 18–24 months of corrected age, which was our secondary outcome. This finding is consistent with that of the Australian cohort study, which showed that the rate of developmental delay (defined as the Griffiths Mental Developmental Scales General Quotient or the BSID-II mental developmental index of >2 standard deviations less than the mean) in infants conceived with ART was comparable to that in infants

conceived without ART (13). However, the BSID-II or Bayley-III assessment of developmental delay was performed only in 32.0% of infants who were followed up at 18–24 months of corrected age. Given the small numbers in the developmental assessment, our results on developmental delay should be interpreted with caution.

Similar to previous studies, the mothers of infants conceived with the assistance of IVF were older and more likely to be primiparous than the mothers of infants conceived without the assistance of IVF (10, 13, 31). No differences were found in neonatal morbidities between infants conceived with and without the assistance of IVF among infants born as singletons, whereas sepsis and PVL occurred less often in infants conceived with the assistance of IVF than in infants conceived without the assistance of IVF among infants born as multiplets. Because sepsis and PVL are major risk factors for motor delay and cerebral palsy (32–34), better long-term neurodevelopmental outcomes were expected in multiplets conceived with the assistance of IVF. However, no significant difference was observed in the rate of neuromotor or sensory disability or developmental delay at 18–24 months of corrected age between infants conceived with and without the assistance of IVF.

In the present study, we restricted the study population to preterm infants with VLBW born earlier than 32 weeks of GA. Although this group of infants is at a higher risk for adverse neurodevelopmental outcomes and is considered an appropriate study population to evaluate the association between IVF and adverse neurodevelopmental outcomes, our primary concern, this approach raises concern for collider-stratification bias (35). Because the comparison between infants conceived with and without the assistance of IVF was restricted to a stratum of a post-IVF variable, which was preterm delivery (<32 weeks of GA) with VLBW in this study, comparability issues arise. Infants conceived with and without the assistance of IVF may differ by unmeasured factors that influence the likelihood of preterm delivery (<32 weeks of GA) with VLBW and are unequal for infants conceived with the assistance of IVF (e.g., factors related to infertility) and infants conceived without the assistance of IVF (e.g., chorioamnionitis), in addition to differing by IVF itself. Our results should be interpreted after considering the comparability issue and the resulting potential collider-stratification bias.

The present study is distinct from other studies in several aspects. First, it focused on IVF outcomes as opposed to previous outcomes that contain other treatment modalities, such as intrauterine insemination and/or ovulation induction. Second, our data were derived from a large national database prospectively collected from an ethnically homogeneous population. Third, we analyzed the association between IVF and neurodevelopmental outcomes stratified by plurality considering the associations of IVF with various obstetric and perinatal adverse outcomes primarily due to multiple gestations (11). Finally, we focused on defined parameters to assess neurodevelopmental outcomes, such as cerebral palsy, deafness, blindness, and the Bayley Scales of Infant and Toddler Development.

The weaknesses of our study were the low follow-up and implementation rates of the BSID-II or Bayley-III assessment. For the unbiased interpretation of our results, we provided information about infants who were lost to follow-up and did not undergo the BSID-II or Bayley-III assessment at 18–24 months of corrected age in Supplemental Tables 1 and 2, respectively. The comparability issue and the ensuing potential collider-stratification bias resulting from restricting analysis to the stratum of preterm infants with VLBW are also weaknesses of our study. A further limitation of our study is the lack of information concerning parental socioeconomic status and parenting environment at home, which can influence the neurodevelopmental outcomes of children (36).

CONCLUSION

In conclusion, the results of our cohort study showed no significant differences in the neurodevelopmental outcomes at 18–24 months of corrected age between preterm infants with VLBW conceived with and without the assistance of IVF. Our results could help clinicians counsel couples planning IVF and parents with preterm infants conceived with the assistance of IVF. Further long-term follow-up studies are required to evaluate the cognitive, motor, socioemotional, and behavioral developments of preterm infants conceived with the assistance of IVF from childhood to young adulthood.

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Data Availability Statement: The KNN Publication Ethics Policy adheres to the following research data management and access guidelines. All information regarding patients and participating NICUs is confidential and only available to individuals who have access for the purposes of the permitted research activities. Access is allowed only for the purpose of collecting data for the first time, and no access for any other purpose is allowed.

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Resultado del neurodesarrollo de niños pretermino con bajo peso al nacer concebidos con asistencia de fertilización in vitro.

Objetive: comparar el resultado del neurodesarrollo a los 18- 24 meses de edad corregida entre niños preterminos (< 32 semanas de gestación) con muy bajo peso al nacer (VLVW) concebidos con o sin asistencia de fertilización in vitro (FIV).

Diseño: Estudio de cohorte prospectivo.

Ubicación: No aplicable.

Paciente(s): E n total, 4,940 niños registrados con VLBW nacidos antes de la 32 semanas de edad gestacional entre Enero 2013 a Diciembre 2015.

Intervención (s): Fertilización in vitro.

Principal medida de resultado(s): Discapacidad neuromotora o sensorial (resultado primario) y desarrollo retrasado evaluado usando la Escala de Bayley para niños y desarrollo Toddler (resultado secundario) a las 18-24 meses de edad corregida.

Resultado(s): De los 4,940 niños registrados con VLBW, 2818 niños quienes fueron seguidos para evaluar neurodesarrollo a los 18-24 meses, fueron incluidos en este estudio. De esos 2,818 niños ,630 (22,4%) fueron concebidos con la asistencia de FIV, y 2,188 (77,6%) no fueron. Después de ajustar potenciales factores de confusión, no significancia estadística fueron encontradas en la tasa de discapacidad neuromotora o sensorial a los 18-24 meses de edad corregida entre los niños concebidos con o sin asistencia de FIV. Después de excluir niños con discapacidad motor o sensorial, la tasa de desarrollo retrasado fue comparable entre aquellos concebidos con o sin asistencia de FIV.

Conclusión(s): El estudio mostró resultados comparables en el neurodesarrollo a los 18-24 meses de edad corregida entre los niños pretermino con VLBW concebidos con o sin asistencia de FIV.