Reunión Bibliográfica 14-4-2021

Sergio Ambiado

INDISA
CLINICA DE FAMILIA

INDISA - NEORED
Un Nuevo Concepto en Medicina Perinatal

Neo Red

Risk of Clinically Significant Chromosomal Microarray Analysis Findings in Fetuses With Nuchal Translucency From 3.0 mm Through 3.4 mm

Obstetrics & Gynecology: January 2021 - Volume 137 - Issue 1 - p 126-131

- Objetivo: Evaluar

  Riesgo de microarrays cromosómicos alterado en fetos con translucidez nucal de 3,0 a 3,4 mm

  Rendimiento de las pruebas prenatales no invasivas (NIPT) en dichos embarazos.

- Estudio de cohorte ,retrospectivo . Microarray realizados a embarazadas con fetos con translucidez nucal de 3,0 a 3,4 mm, sin anomalías ecográficas, recuperadas de la base de datos computarizada del Ministerio de Salud de Israel. 2013-2018
- Se calculó RR de resultados de análisis de microarrays clínicamente significativos (patógenos y probablemente patógenos)en fetos con aumento de la translucidez nucal y se comparó con una población de control local histórica de 2752 mujeres con embarazos de bajo riesgo (es decir, menores de 35 años, con hallazgos ecográficos normales y translucidez nucal de menos de 3,0 mm) sometidos a análisis de microarray a solicitud de la madre. Tasa 0,76%(21/2752) , cuatro de ellos detectables por NIPT (47, XXY; 45, X mosaicismo trisomía 21 y trisomía 13 mosaicismo
- Muestra tomada por punción vellosidades coriales en 32% y vía amniocentesis en 68%.

Clasificación resultados microarrays cromosómicos

- 1. **Clínicamente significativo**: Resultado patógeno y probablemente patógeno.
- 2. **Variantes de significado desconocido. H**allazgos de significado poco claro, así como variantes del número de copias con penetrancia clínica inferior al 10% (como duplicaciones en los loci 15q13.3, 16p11.2 y 16p11.13) .15,16
- 3. **Normal.**, incluye variantes sin número de copias, NVC benignas y probablemente benignas, hallazgos de NOS bajo umbral de informe de 1 Mb para deleciones y 2 Mb para duplicaciones.

Los resultados clínicamente significativos se subclasificaron en:

- 1. Hallazgos submicroscópicos (detectables solo mediante análisis de microarray y no mediante cariotipo): variantes de número de copias de tamaño inferior a 10 Mb.
- 2. Detección con pruebas prenatales no invasivas: trisomías 13, 18, 21 y aneuploidías de los cromosomas sexuales.
- 3. Hallazgos detectables por cariotipo : aberraciones iguales o superiores a 10 Mb.

Variantes clínicamente significativas en el número de copias en 619 fetos con medidas de translucidez nucal de 3 mm a 3,4 mm

Clinically Significant	3.0 mm	3.1 mm	3.2 mm	3.3 mm	3.4 mm	Overall
n/N	3/198	6/158	6/108	8/78	6/77	29/619
% (95% CI)	1.5 (0.03–4.6)	3.8 (1.6–8.2)	5.6 (2.3–11.8)	10.3 (5.1–19.2)	7.8 (3.3–16.3)	4.7 (3.3–6.7)
Description of clinically significant findings	22q11.21dup 1.5 Mb Xq21.21-q21.33 dup 8.9 Mb Trisomy 21	1q21.1q21.2 dup 1.7 Mb 4pdup 7 Mb Trisomy 21 mos Trisomy 21 (x3)	13q21.33q31.1del 18 Mb 16p11.2dup 0.6 Mb Trisomy 18+10 mos Trisomy 18 Trisomy 21 (x2)	8p23.1del 3 Mb chr7dup 159 Mb 47, XXX Trisomy 18 Trisomy 21 (x4)	16p11.2del 0.6 Mb 16p11.2dup 0.6 Mb 22q11.21del VCF 47, XXY Trisomy 2 mos Trisomy 21	
RR (95% CI)*	1.9 (0.6–5.4)	4.2 (2.0–8.7)	6.2 (3.0–12.8)	11.0 (5.9–20.8)	8.8 (4.2–18.4)	3.3 (2.6–4.2)
Karyotype or genome-wide NIPT-detectable	1 (33.3%)	4 (66.7%)	5 (83.3%)	7 (87.5%)	3 (50.0%)	20 (69.0%)
NIPT-detectable	1 (33.3%)	4 (66.7%)	4 (66.7%)	6 (75.0%)	2 (33.3%)	18 (62.1%)
Variants of unknown significance	2	2	0	1	0	5 (0.8%)
HFLP	0	1	0	1	1	3 (0.5%)

del, deletion; dup, duplication; mos, mosaicism; VCF, velocardiofacial syndrome; RR, relative risk; NIPT, noninvasive prenatal testing; HFLP, high-frequency low-penetrance findings.

* Compared with a previously published local control population, encompassing 2,752 fetuses with normal ultrasound findings. In this cohort, a 0.7% risk for clinically significant microarray findings was noted.

OBSTETRICS & GYNECOLOGY

29/619 (4,67%) población control 21/2752 (0.76%)
Diferencia estadísticamente significativa (RR 3,3; IC del 95%: 2,6–4,2).
Pruebas prenatales no invasivas detectaron en 17/29 58 %
12 Trisomías 21 3 Trisomías 13 2 aneuploidías 47, XXX and 47, XXY).

INDISA
CLINICA DE FAMILIA

INDISA - NEORED
Un Nuevo Concepto en Medicina Perinatal

Neo Red

Riesgo según muestra de vellosidades o amniocentesis

	NIPT-Detectable	Karyotype but Not NIPT-Detectable	Submicroscopic Findings
CVS 13/179 (7.3%, 95% CI 4.2–12.1)	n=7 (53.8%, 95% CI 29.1–76.8) Trisomy 18 (x3) Trisomy 21 (x4)	n=2 Trisomy 2 mosaicism 7p22.3q36.3 dup 159 Mb	n=4 1q21.1q21.2 dup 1.7 Mb 8p23.1del 3 Mb 4p16.1 + 4p15.33p15.32 dup 7 Mb 16p11.2 dup 0.6 Mb
Amniocentesis 16/440 (3.6%, 95% CI 2.2–5.9)	n=10 (62.5%, 95% CI 38.5–81.6) 47, XXY 47, XXX Trisomy 21 (x8)	n=1 13q21.33q31.1 del 18 Mb	n=5 Xq21.21-q21.33 dup 8.9 Mb 16p11.2 del 0.6 Mb x 2 22q11.21 del 2.8 Mb 22q11.23 dup 1.5 Mb

NIPT, noninvasive prenatal testing; CVS, chorionic villous sampling; del, deletion; dup, duplication. OBSTETRICS & GYNECOLOGY

Vellosidades (13/179, 7,3%)
Amniocentesis (16/440, 3,6%),
Sin diferencia estadísticamente significativa (p = 0,06).
En ambos grupos, el riesgo aumentó significativamente en comparación con control
RR 6,7 (4,2 a 10,5) vellosidad y RR 3,2 (2,2 a 4,7) amniocentesis

Appendix 2. Findings of Questionable Significance Detected by Microarray in 619 Pregnancies With Nuchal Translucency of 3-3.4 mm

CMA; chromosomal microarray analysis; CNV, copy number variant; NIPT, noninvasive prenatal testing; OMIM, *Online Mendelian Inheritance in Man*, updated catalog of human genes and genetic disorders and traits. OMIM-morbid – gene associated with clinical disorders.

Case	CMA result (ISCN*) array GRCh37/hg19	CNV size [bp]	Syndromes/affected genes	Nuchal translucency	Inheritance
Variants of unknown significance					
1	6q14.3q15(85,958,544-88,235,246)x3	2,276,703	46 genes – 4 OMIM-morbid	3 mm	De novo
2	14q31.3(85,077,027-92,504,745)x3	7,427,719	69 genes – 10 OMIM-morbid	3 mm	Not reported
3	9p13.2(36,516,705-37,665,085)x3	1,148,381	21 genes – 2 OMIM-morbid	3.1 mm	Not reported
4	6q24.1(140,996,521-142,666,633)x1	1,670,113	10 genes – 1 OMIM-morbid	3.1 mm	Not reported
5	3p12.1(86,704,171-87,479,589)x1	775,419	8 genes – 2 OMIM-morbid	3.3 mm	Not reported
High-frequency low-penetrant findings					
1	15q13.2q13.3(30,936,285-32,620,127)x3	1,683,843	22 genes – 2 OMIM-morbid	3.1 mm	Maternal
2	15q13.3(32,003,537-32,439,251)x3	435,715	3 genes – 0 OMIM-morbid	3.3 mm	Paternal
3	15q13.2q13.3(31,104,220-32,915,723)x3	1,811,504	33 genes – 2 OMIM-morbid	3.4 mm	Paternal

Impaired motor performance in adolescentes with esophageal atresia

U.I. Møinichen a , ∗, A. Mikkelsen b , A. Faugli a , L. Mørkrid c , H. IJsselstijn d , R. Emblem

- Estudio prospectivo evaluando desarrollo motor durante la infancia hasta la adolescencia

Método:

- Evaluación desarrollo sicomotor al año . Bayley Scales Infant Development.

Score 85-114: normal 70- 84: riesgo de desarrollar retraso motor < 70: retraso motor

- Entrevista semiestructurada en adolescencia: SI/NO
  - Hubo seguimiento durante todo el período ó sólo en período lactante
  - Se les indicó kinesioterapia

Impaired motor performance in adolescentes with esophageal atresia

U.I. Møinichen a , ∗, A. Mikkelsen b , A. Faugli a , L. Mørkrid c , H. IJsselstijn d , R. Emblem

J Pediatric Surgery Abril 2021

Table 1
Demographic and clinical characteristics of the 33 esophageal atresia (EA) patients eligible for the follow-up study.

Variables	Included$n$ = 23	Not included$n$ = 10	p-value
Male, n (%)	16 (70)	6 (60)	.598
Birthweight, grams, median (range)	2820 (1690–4570)	3485 (585–4020)	.457
Prematurity, n (%)	6 (26)	4 (40)	.431
Gestational age, weeks, median (range)	38 (30–40)	41 (27–42)	.551
EA Gross A, n (%)	1 (4)	1 (10)	.538
EA Gross C, n (%)	19 (83)	8 (80)	.860
EA Gross D, n (%)	3 (13)	1 (10)	.808
CHD, n (%)	1 (4)	1 (10)	.538
VACTERL, n (%)	5 (22)	0 (0)	.115
Initial hospital stay, days, median (range)	21 (10–177)	21 (14–116)	.505
Mechanical ventilation, days, median (range)	0 (0–41)	0 (0–18)	.089
Rethoracotomy, n (%)	4 (17)[a]	2 (20)	.860
PDI score, median (range)[b]	102 (56–118)	90 (70–121)	.228
No. anesthesias < 12 months, median (range)	1 (1–30)		
No. anesthesias total, median (range)	1 (1–36)		
No. esophageal dilations < 12 months, median (range)	0 (0–25)		
No. esophageal dilations total, median (range)	0 (0–26)		

CHD, congenital heart disease. VACTERL, vertebral defect, anal atresia, cardiac defects, trachea-esophageal fistula, renal abnormalities, and limb abnormalities.

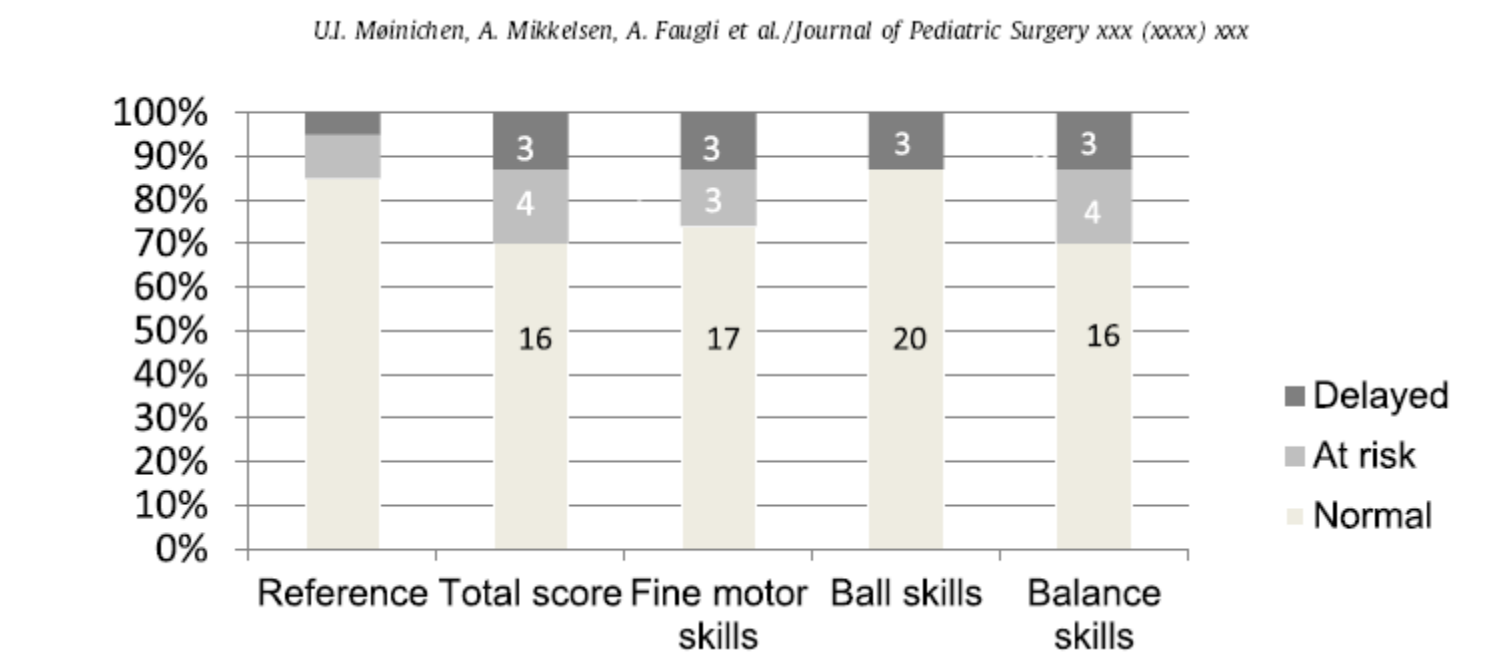
[a] Rethoracotomy: complex cardiac anomaly (n = 1), anastomotic revision (n = 3).

[b] Two missing PDI (Psychomotor Developmental Index) data in the included group and three missing in the not included group.

Impaired motor performance in adolescentes with esophageal atresia

U.I. Møinichen a , ∗, A. Mikkelsen b , A. Faugli a , L. Mørkrid c , H. IJsselstijn d , R. Emblem

J Pediatric Surgery Abril 2021



Se ofreció o no kinesioterapia:

- 70%f en período neonatal,
- 35% en período de lactante
- 17% en adolescencia

Sólo 17 % tuvieron kinesioterapia durante todo el período

Ninguno recibió terapia motora gruesa sistemática

INDISA
CLINICA DE FAMILIA

Un Nuevo Concepto en Medicina Perinatal

Neo Red

Original Research

Association of Breastfeeding and Child IQ Score at Age 5 Years

Beth A. Plunkett, MD, MPH, Lisa Mele, ScM, Brian M. Casey, MD, Michael W. Varner, MD, Yoram Sorokin, MD, Uma M. Reddy, MD MPH, Ronald J. Wapner, MD, John M. Thorp Jr, MD, George R. Saade, MD, Alan T.N. Tita, MD, PhD, Dwight J. Rouse, MD, Baha Sibai, MD, Brian M. Mercer, MD, Jorge E. Tolosa, MD, MSCE, and Steve N. Caritis, MD, for the Eunice Kennedy Shriver *National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network**

INDISA
CLINICA DE FAMILIA

INDISA - NEORED
Un Nuevo Concepto en Medicina Perinatal

Neo Red

Association of Breastfeeding and Child IQ Score at 5 Years
Obstetrics & Gynecology Abril, 2021

- Objetivo primario: IQ score < 85 en Test WPPSI-III a los 5 años Weschler Preschool and Primary Scale of Intelligence III
- Objetivo secundario:
  - IQ a los 5 años
  - DAS-II general conceptual score < 85 a los 3 años
  - DAS-II specific conceptual scoree < 85 a los 4 años
  - Bayley III Cognitive, Motor and Languaje
    - score 1 y 2 años
    - Score < 85 1 y 2 años
  - CBCL Child Behavorial Checklist
    - T score > 60 a los 3 y 5 años
  - Conners´ Rating Scales-Revised for assessment
  - T score > 60 a los 3 y 5 años
    - T score > 60 a los 3 y 5 años

INDISA
CLINICA DE FAMILIA

INDISA - NEORED
Un Nuevo Concepto en Medicina Perinatal

Neo Red

Association of Breastfeeding and Child IQ Score at 5 Years
Obstetrics & Gynecology Abril, 2021

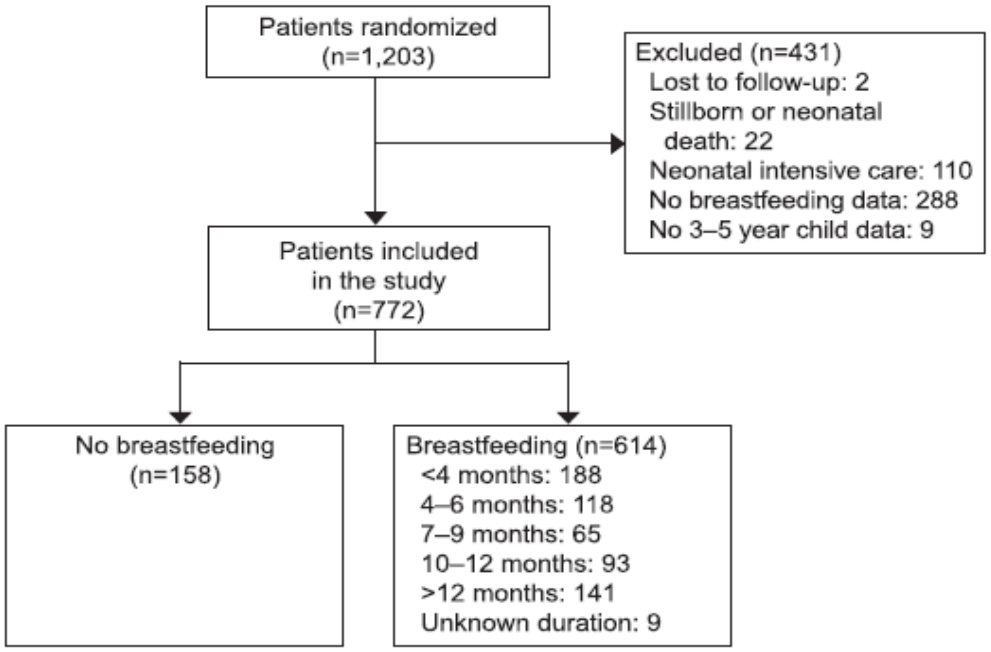


Fig. 1. Patient inclusion a exclusion.

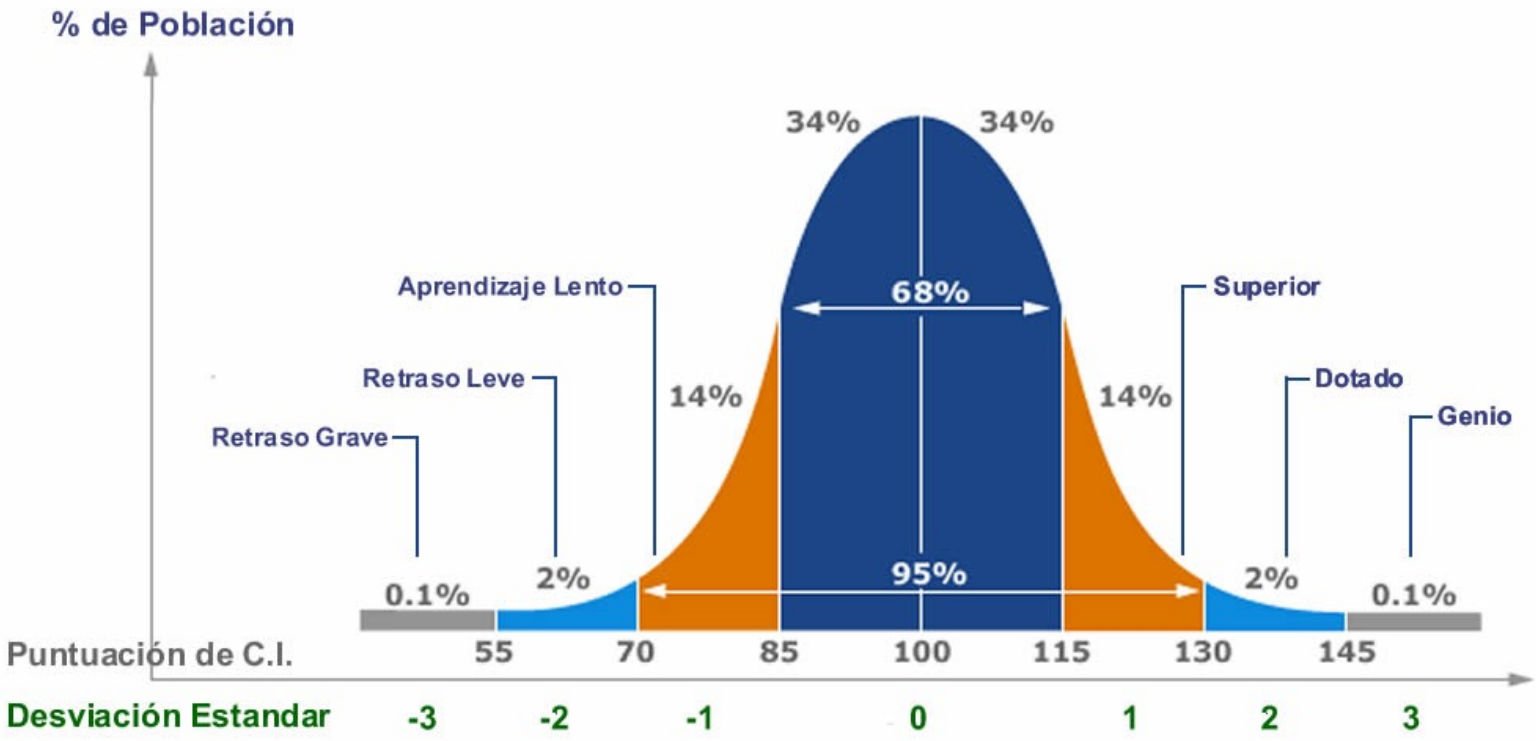
Plunkett. Breastfeeding and IQ Scor Obstet Gynecol 2021.

Association of Breastfeeding and Child IQ Score at 5 Years
Obstetrics & Gynecology Abril, 2021

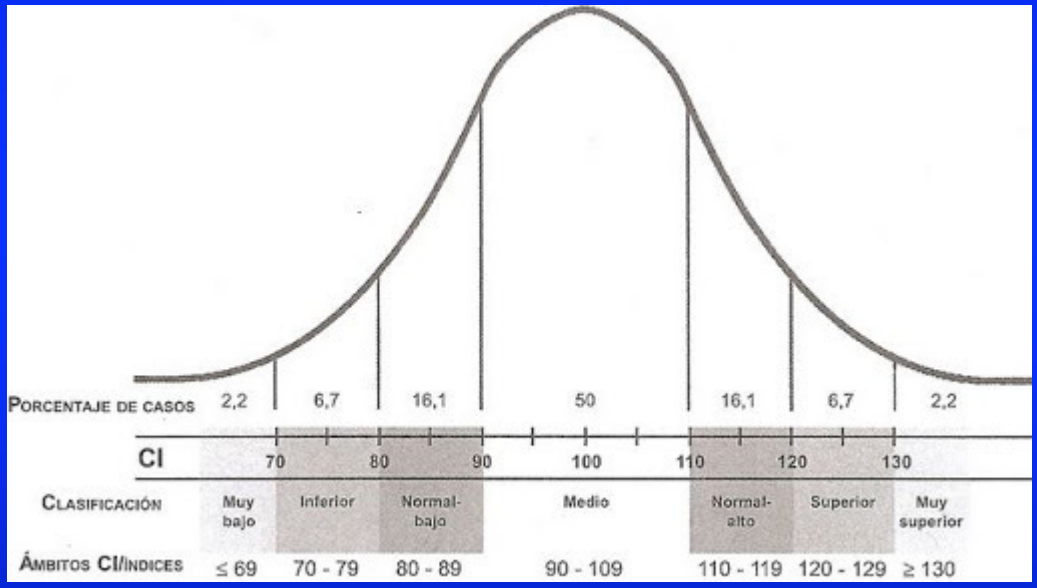
- Es una análisis secundario de 2 estudios randomizados, controlados de embarazadas con hipotiroidismo subclínico o con hipotiroxinemia fueron tratados con tiroxina o placebo
- Análisis univariable y multivariable fue realizado para evaluar asociación entre lactancia y neurodesarrollo

- Se utilizaron modelos de regresión logística para desarrollar los modelos finales ajustados

Distribución del Coeficiente de Inteligencia Escala de Weschler



Testdeinteligencia.com.ar



INDISA
CLINICA DE FAMILIA

INDISA - NEORED
Un Nuevo Concepto en Medicina Perinatal

Neo Red

Association of Breastfeeding and Child IQ Score at 5 Years
Obstetrics & Gynecology Abril, 2021

Table 1. Baseline Demographic and Clinical Characteristics by Breastfeeding Status

Characteristic	Breastfeeding (n=614)	No Breastfeeding (n=158)	*P*
Age (y)	28.4±5.7	26.5±5.7	**<.001**
Race and ethnicity*			**<.001**
Non-Hispanic White	210 (34.2)	36 (22.8)	
Non-Hispanic Black	51 (8.3)	58 (36.7)	
Hispanic	335 (54.6)	63 (39.9)	
Other or unknown	18 (2.9)	1 (0.6)	
Prepregnancy BMI (kg/m^2)†	27.2±6.1	29.5±7.8	**.002**
Nulliparity	203 (33.1)	43 (27.2)	.16
Insurance			**<.001**
Public	322 (52.4)	128 (81.0)	
Private	208 (33.9)	20 (12.7)	
Self-pay	84 (13.7)	10 (6.3)	
Maternal education			**<.001**
Less than high school	258 (42.0)	75 (47.5)	
High school or some college	192 (31.3)	71 (44.9)	
College graduate or higher	164 (26.7)	12 (7.6)	
Smoked during pregnancy	23 (3.7)	34 (21.5)	**<.001**
Alcohol use during pregnancy	37 (6.0)	10 (6.3)	.89
Illicit drug use during pregnancy	3 (0.5)	5 (3.2)	**.01**
Gestational hypertension or preeclampsia	56 (9.1)	13 (8.2)	.73
Thyroid status			**<.001**
Subclinical hypothyroidism	372 (60.6)	66 (41.8)	
Subclinical hypothyroxinemia	242 (39.4)	92 (58.2)	
Levothyroxine treatment group	312 (50.8)	77 (48.7)	.64
Gestational diabetes	41 (6.7)	13 (8.2)	.50
Gestational age at delivery (wk)	39.4±1.3	39.4±1.4	.81
Preterm birth before 37 wk	24 (3.9)	13 (8.2)	.02
Route of delivery			.32
Spontaneous vaginal	429 (69.9)	101 (63.9)	
Operative vaginal	20 (3.3)	5 (3.2)	
Cesarean	165 (26.9)	52 (32.9)	
SGA birth weight less than the 10th percentile	45 (7.3)	15 (9.5)	.36
Male sex	322 (52.4)	94 (59.5)	.11

BMI, body mass index; SGA, small for gestational age.
Data are mean±standard deviation or n (%) unless otherwise specified.
Bold indicates statistical significance.
* Race was determined by participant self-identification as either White, Black, Asian, Native Hawaiian or Pacific Islander, other, not reported. Ethnicity was self-reported as Hispanic or non-Hispanic. Owing to small numbers, Asian, Native Hawaiian or Pacific Islander, other and not reported were collapsed into Other.
† Nineteen missing prepregnancy BMI.

INDISA
CLINICA DE FAMILIA

Neo Red

Table 2. Neurodevelopmental Outcomes by Breastfeeding Status

	Breastfeeding (n=614)	No Breastfeeding (n=158)	Mean Difference in Scores (95% CI)
Primary outcome			
WPPSI III IQ score less than 85 at age 5 y	130 (21.5)	55 (36.2)	
Secondary outcomes			
WPPSI III IQ score at age 5 y (n=756)	96.7±15.1	91.2±15.0	**5.49 (2.80 to 8.17)**
CBCL T-score higher than 60 at age 5 y (n=760)	56 (9.2)	25 (16.3)	
Conners' Rating Scales-Revised ADHD score T-score higher than 60 at age 4 y (n=747)	86 (14.5)	29 (19.0)	
DAS II subtests at age 4 y			
Recall of digits forward less than the 25th percentile (n=737)	141 (24.0)	32 (21.5)	
Picture recognition less than the 25th percentile (n=742)	104 (17.6)	45 (30.0)	
DAS II general conceptual ability score at age 3 y (n=757)	92.0±15.8	88.2±15.4	**3.77 (0.99 to 6.56)**
DAS II general conceptual ability score less than 85 age 3 y	194 (32.2)	67 (43.5)	
CBCL T-score higher than 60 at age 3 y (n=761)	54 (8.9)	19 (12.3)	
Bayley III scores at age 2 y			
Cognitive (n=764)	91.1±12.4	89.1±13.1	1.93 (−0.31 to 4.16)
Cognitive less than 85	135 (22.1)	39 (25.7)	
Motor (n=754)	98.4±12.5	95.8±13.0	**2.61 (0.33 to 4.89)**
Motor less than 85	54 (8.9)	16 (10.9)	
Language (n=746)	92.5±15.7	88.7±15.0	**3.74 (0.92 to 6.57)**
Language less than 85	189 (31.4)	47 (32.6)	
Bayley III scores at age 1 y			
Cognitive (n=758)	99.5±13.2	99.1±14.3	0.39 (−1.99 to 2.77)
Cognitive less than 85	53 (8.8)	17 (11.1)	
Motor (n=756)	96.6±11.0	97.7±12.5	−1.10 (−3.12 to 0.91)
Motor less than 85	56 (9.3)	15 (9.9)	
Language (n=754)	94.9±11.9	94.9±14.7	0.03 (−2.21 to 2.27)
Language less than 85	101 (16.7)	34 (22.5)	

Conclusiones

- Lactancia y su duración se asocian a riesgo de < IQ a los 5 años

- ?
- Objetivo primario era encontrar diferencia significativo en tasa score < 85 y no se encontró
- No se encontró diferencia en ninguno de objetivos secundarios
- Hay diferencias en madres grupo lactancia y no lactancia