Gastroenterología y Hepatología 47 (2024):S70

Gastroenterología y Hepatología

https://www.elsevier.es/gastroenterologia

P-38 - UNVEILING THE IMPACT ON IN UTERO EXPOSURE TO BIOLOGIC TREATMENTS FOR INFLAMMATORY BOWEL DISEASE (IBD) ON CHILDREN&#39S PSYCHOMOTOR DEVELOPMENT: INSIGHTS FROM THE DUMBO REGISTRY OF GETECCU

Laura Palomino[1], Marta Velasco Rodríguez-Belvís[2], Yanire Brenes Ruiz[3], Eduardo Leo-Carnerero[4], Cristina Calviño Suarez[5], Montserrat Rivero[6], Marta Calvo[7], María Teresa Arroyo[8], Agnes Fernández-Clotet[9], Isabel Pérez-Martínez[10], Ángeles Masedo González[11], Vicent Hernández[12], Alexandra Ruiz-Cerulla[13], Pilar López Serrano[14], Pablo Vega[15], Iago Rodríguez-Lago[16], Raquel Vicente Lidón[17], Miguel Ángel de Jorge[18], Iván Guerra[19], Lara Arias García[20], Gema Molina Arriero[21], Daniel Hervías Cruz[22], David Busquets[23], Ana Gutiérrez Casbas[24], Manuel Van Domselaar[25], Gemma Valldosera Gomis[26], Juan María Vázquez Morón[27], Marta Piqueras Cano[28], Alfredo J Lucendo[29], María Dolores Martín Arranz[30], Patricia Ramírez de la Piscina[31], María del Pilar Martínez Tirado[32], Virginia Robles Alonso[33], Sandra Marín Pedrosa[34], Raquel Camargo Camero[35], Edisa Armesto González[36], Carlos Tardillo Marín[37], Esther Bernardos Martín[38], María Carmen Rodríguez Grau[39], José M. Huguet[40], Lucía Márquez-Mosquera[41], Pau Sendra Rumbeu[42], Luis Bujanda[43], Carlos Castaño-Milla[44], Empar Sáinz Arnau[45], Luis Hernández[46], Laura Ramos[47], M.M. Boscá-Watts[48], Noemí Manceñido Marcos[49], Miquel Sans[50], Victor Jair Morales[51], Sandra Hermida Vázquez[3], Pablo Parra Pineda[3], Almudena Durán Vegue[3], Ana Garre[3], Alberto García-Salido[52], Rosana Muñoz Codoceo[1], Javier P. Gisbert[3] and María Chaparro[3]

[1]Hospital Infantil Universitario Niño Jesús, Gastroenterology Unit, Madrid. [2]Hospital Infantil Universitario Niño Jesús Gastroenterology Unit, Madrid. [3]Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa IIS-IP and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas CIBEREHD, Gastroenterology Unit, Madrid. [4]Hospital Universitario Virgen del Rocío, Gastroenterology Unit, Sevilla. [5]Complexo Hospitalario Universitario de Santiago de Compostela, Gastroenterology Unit, Santiago de Compostela. [6]Hospital Universitario Marqués de Valdecilla e IDIVAL, Gastroenterology Unit, Santander. [7]Hospital Universitario Puerta de Hierro, Gastroenterology Unit, Majadahonda. [8]Hospital Clínico Universitario Lozano Blesa, IIS Aragón y CIBERehd, Gastroenterology Unit, Zaragoza. [9]Hospital Clinic de Barcelona, Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas CIBERehd, Institut d'Investigacions Biomèdiques August Pi i Sunyer IDIBAPS, Gastroenterology Unit, Barcelona. [10]Hospital Universitario Central de Asturias, Diet- Microbiota and Health Group, Instituto de Investigación Sanitaria del Principado de Asturias ISPA, Gastroenterology Unit, Oviedo. [11]Hospital Universitario 12 de Octubre, Gastroenterology Unit, Madrid. [12]Xerencia Xestión Integrada de Vigo- SERGAS, Grupo de Investigación de Patología Digestiva, Instituto de Investigación Sanitaria Galicia Sur IIS Galicia Sur, SERGAS UVIGO, Gastroenterology Unit, Vigo. [13]Hospital Universitario de Bellvitge-L'Hospitalet de Llobregat, Gastroenterology Unit, Barcelona. [14]Hospital Universitario Fundación Alcorcón, Gastroenterology Unit, Madrid. [15]Complexo Hospitalario Universitario de Ourense, Gastroenterology Unit, Ourense. [16]Hospital Universitario de Galdakao, Biobizkaia Health Research Institute, Gastroenterology Unit, Bizkaia. [17]Hospital Universitario Miguel Servet, Gastroenterology Unit, Zaragoza. [18]Hospital Universitario de Cabueñes, Gastroenterology Unit, Gijón. [19]Hospital Universitario de Fuenlabrada, Gastroenterology Unit, Madrid. [20]Hospital Universitario de Burgos, Gastroenterology Unit, Burgos. [21]Complejo Hospitalario Universitario de Ferrol, Gastroenterology Unit, A Coruña. [22]Hospital General Universitario de Ciudad Real, Gastroenterology Unit, Ciudad Real. [23]Hospital Trueta de Girona, Gastroenterology Unit, Girona. [24]Hospital General Universitario Dr. Balmis Alicante, ISABIAL-CIBERehd, Gastroenterology Unit, Alicante. [25]Hospital Universitario de Torrejón-Universidad Francisco de Vitoria, Gastroenterology Unit, Madrid. [26]Hospital Universitario Joan XXIII, Gastroenterology Unit, Tarragona. [27]Hospital Universitario Juan Ramón Jiménez, Gastroenterology Unit, Huelva. [28]Consorci Sanitari de Terrassa CST, Gastroenterology Unit, Barcelona. [29]Hospital General de Tomelloso, Instituto

de Investigación Sanitaria La Princesa- Instituto de Investigación Sanitaria de Castilla-La Mancha IDISCAM-Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas CIBERehd, Gastroenterology Unit, Ciudad Real. [30]Hospital Universitario La Paz, Gastroenterology Unit, Madrid. [31]Hospital Universitario de Álava, Gastroenterology Unit, Álava. [32]Hospital Clínico Universitario San Cecilio, Gastroenterology Unit, Granada. [33]Hospital Vall d´Hebron, Gastroenterology Unit, Barcelona. [34]Hospital Universitario Reina Sofía, Gastroenterology Unit, Córdoba. [35]Hospital Universitario Virgen de la Victoria, Gastroenterology Unit, Málaga. [36]Hospital Universitario San Agustín, Gastroenterology Unit, Avilés. [37]Hospital Universitario Nuestra Señora de Candelaria, Gastroenterology Unit, Tenerife. [38]Hospital Mancha Centro, Gastroenterology Unit, Álcazar de San Juan. [39]Hospital Universitario del Henares, Gastroenterology Unit, Coslada. [40]Hospital General Universitario de Valencia, Gastroenterology Unit, Valencia. [41]Hospital del Mar, IMIM (Hospital del Mar Medical Research Institute), Gastroenterology Unit, Barcelona. [42]Hospital Universitario Son Espases, Gastroenterology Unit, Palma de Mallorca. [43]Bioodonostia Health Research Institute - Donostia University Hospital, Universidad del País Vasco (UPV/EHU), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Gastroenterology Unit, San Sebastián. [44]Hospital Universitario Rey Juan Carlos, Gastroenterology Unit, Móstoles. [45]Hospital Sant Joan de Déu, Manresa; Hospital Universitario de La Princesa and CIBEREHD, Madrid. [46]Hospital Santos Reyes Aranda de Duero SACyL, Gastroenterology Unit, Burgos. [47]Hospital Universitario de Canarias, Gastroenterology Unit, La Laguna. [48]Hospital Clínico Universitario de Valencia, Gastroenterology Unit, Valencia. [49]Hospital Universitario Infanta Sofía, Gastroenterology Unit, San Sebastián de los Reyes. [50]ISADMU Centro Médico Teknon, Gastroenterology Unit, Barcelona. [51]Hospital de Granollers, Gastroenterology Unit, Barcelona. [52]Hospital Infantil Universitario Niño Jesús, Intensive Care Unit, Madrid.

Resumen

Introduction: Our aim was to evaluate the impact of the exposure of biologics in utero on the psychomotor development of children during the first year of life.

Methods: Data from children included in the DUMBO registry with complete AQS-3 available up to 12 months of age were analysed. DUMBO is a prospective, observational, and multicentre registry endorsed by GETECCU, which enrolls pregnant women with IBD throughout 5 years in 70 centres in Spain. Study protocol is summarized in figure 1a. Normal psychomotor development was defined by ASQ-3 scores above the lower limit of normality (referral zone) in all domains. Serious adverse events (SAE) were defined in accordance with the ICH Topic E 2 A Clinical Safety Data Management.

Results: 352 children born to 343 mothers were included (9 pair of twins) (tables 1a, 1b and 1c). 134 children (38%) had been exposed to biologics in utero; from them, 50 (37%) had been exposed to adalimumab, 44 (32%) to infliximab, 3 (2.2%) to certolizumab, 1 (0.7%) to golimumab, 28 (20%) to ustekinumab, and 10 (7.5%) to vedolizumab. 8% of the mothers were smokers during pregnancy; no other toxic consumption (alcohol or drugs) was recorded. The ASQ-3 results across different domains are presented in figure 1b, and the impact of the different factors associated with the neurodevelopment is summarised in table 1d. In the multivariate analysis, to have been born to a mother with CD (vs. UC) was associated with higher likelihood (OR = 2, 95%CI = 1.1-3.9), while to be premature was associated with lower likelihood (OR = 0.3, 95%CI = 0.1-0.6) of having ASQ-3 scores above the limit of normality in all domains at 12 months of age.

Table 1a. Characteristics of mothers at conception depending on the presence of biologic treatment.

		Non exposed to biologics	Exposed to biologics	
	Maternal age (years), mean ± SD	33 ± 5	32 ± 6	**p<0.001**
	Time since IBD diagnosis (years), mean ± SD	8.2 ± 6.3	9.8 ± 6.7	**p<0.05**
Type of IBD	Crohn´s disease, n (%)	88 (42)	104 (78)	**p<0.001**
	Ulcerative colitis, n (%)	120 (58)	29 (22)	
	Non classified, n (%)	2 (1)	0	
Crohn´s disease	Ileal (L1), n (%)	50 (57)	48 (45)	ns
	Colonic (L2), n (%)	8 (9)	12 (12)	
	Ileocolonic (L3), n (%)	30 (34)	45 (42)	
	Upper digestive tract involvement, n (%)	6 (7)	9 (9)	ns
	Perianal disease, n (%)	11 (13)	25 (24)	**p<0.05**
	Inflammatory behavior (B1), n (%)	61 (70)	62 (60)	ns
	Stenosing behavior (B2), n (%)	20 (23)	25 (24)	
	Fistulizing behavior (B3), n (%)	7 (8)	17 (16)	
Ulcerative colitis	Proctitis (E1) n (%)	52 (43)	2 (7)	**p<0.001**
	Left colitis (E2), n (%)	36 (30)	7 (24)	
	Extensive colitis (E3), n (%)	34 (28)	20 (69)	
	IBD activity (baseline), n (%)	10 (4.6)	4 (3)	ns
Maternal history	Previous surgical interventions, n (%)	30 (14)	36 (27)	**p<0.05**
	Comorbidities, n (%)	71 (34)	49 (37)	ns
	Anemia, n (%)	173 (84)	113 (86)	ns
	Previous pregnancies, mean ± SD	0.9 ± 1.3	0.8 ± 0.9	ns
	Previous miscarriages, n (%)	55 (25)	34 (25)	ns
	Previous fetal anomalies, n (%)	2 (1)	0	ns
	Previous fetal deaths, n (%)	3 (1)	1 (0.8)	ns
	Multiparous, n (%)	93 (43)	53 (40)	ns
Maternal weight at conception	Body Mass Index (BMI), mean ± SD	24 ± 5	24± 3.9	ns
	Normoweight (BMI 18.5-24.9), n (%)	134 (64)	82 (62)	
	Overweight (BMI 25-29.9), n (%)	39 (19)	32 (24)	
	Obesity (BMI <30), n (%)	19 (9)	9 (6.8)	
	Underweight (BMI <18.5), n (%)	18 (8.6)	9 (6.8)	

SD, standard deviation; IBD, inflammatory bowel disease; n.s., non-statistically significant.

Table 1b. Characteristics of babies depending on the exposure to biologic treatment.

		Non exposed to biologics	Exposed to biologics	
Birth	Female sex, n (%)	113 (52)	69 (51)	ns
	Gestational age (weeks), mean ± SD	38.4 ± 2.5	39 ±1.8	ns
	Vaginal delivery, n (%)	114 (75)	56 (52)	**p<0.05**
	Cesarean delivery, n (%)	38(25)	34 (38)	
	Size at birth (cm), mean ± SD	49 ± 3	50 ± 2.6	ns
	Birth weight (kg), mean ± SD	3.1 ± 0.6	3.21 ± 0.5	ns
	Low birth weight, n (%)	31 (14)	10 (7.5)	ns
	Apgar ≥7 at 5 minutes, n (%)	213 (98)	129 (96)	ns
	Apgar ≥7 at 10 minutes, n (%)	217 (99.5)	134 (100)	ns
Feeding in the 1st month of life	Exclusive breastfeeding, n (%)	141 (65)	78 (58)	ns
	Mixed breastfeeding, n (%)	28 (13)	19 (14)	
Feeding in the 6th month of life	Exclusive breastfeeding, n (%)	43 (22)	23 (21)	ns
	Mixed breastfeeding n (%)	19 (9.7)	5 (4.5)	
Feeding (with complementary feeding) in the 12th month of life	Exclusive breastfeeding, n (%)	9 (6)	4 (4.4)	ns
	Mixed breastfeeding, n (%)	2 (1.3)	1 (1)	
Follow-up first 12 months of life	Hearing impairment, n (%)	16 (7.3)	12 (9)	ns
	Visual impairment, n (%)	1 (0.5)	2 (1.5)	ns
	Family concern about behavior, mean ± SD	0.5 ± 1	0.2 ± 0.6	ns
	Health problems according to parents, mean ± SD	1.6 ± 1.9	1.4 ± 1.5	ns
	Daycare attendance, n (%)	88 (40)	45 (34)	ns
	Serious adverse events, n (%)	61 (28)	25 (19)	**p<0.05**
	Hospital admission, n (%)	58 (27)	24 (18)	ns
	ICU admission, n (%)	14 (6.4)	5 (3.7)	ns
	Surgical intervention, n (%)	8 (3.7)	5 (3.7)	ns
	Complete vaccination, n (%)	215 (99)	131 (98)	ns
	Allergies, n (%)	12 (5.5)	7 (5.2)	ns
	Infections, n (%)	17 (7.8)	9 (6.7)	ns
	Malformations, n (%)	2 (0.9)	0	ns
	Neoplasms, n (%)	0	0	

SD, standard deviation; ICU, intensive care unit; n.s., non-statistically significant.

Table 1c. Characteristics of pregnancies depending on the presence of biologic treatment.

		Non exposed to biologics	Exposed to biologics	
Mother´s information during pregnancy	Natural pregnancy, n (%)	185 (88)	120 (90)	ns
	Fertility treatment, n (%)	26 (12)	14 (10)	
	Difference in BMI from baseline on last ultrasound scan, mean ± SD	0.1 ± 0.9	0.1 ± 0.7	ns
	Hospital admission, n (%)	8 (3.7)	9 (6.7)	ns
	Surgical interventions, n (%)	6 (2.8)	1 (0.8)	ns
	IBD activity, n (%)	28 (13)	11 (8.2)	ns
	Smoking habit, n (%)	15 (6.9)	13 (9.7)	ns
	Daily cigarettes consumption, mean ± SD	3.8 ± 4.5	3.4 ± 3.4	ns
Paternal antecedents	Relevant disease, n (%)	24 (11)	13 (10)	ns
	Known genetic alteration, n (%)	1 (0.5)	0	ns
	Treatment at the time of conception, n (%)	22 (10)	11 (8.2)	ns

SD, standard deviation; BMI, Body Mass Index; n.s., non-statistically significant.

Table 1d. Distribution of factors according to psychomotor development at 12 months, according to normality in all domains of the ASQ-3 questionnaire.

		Anormal ASQ-3	Normal ASQ-3	
Mother´s factors	Biologic treatment, n (%)	13 (25)	77 (41)	**p<0.05**
	Thiopurine treatment, n (%)	20 (38)	60 (32)	ns
	Crohn´s disease, n (%)	23 (43)	112 (59)	**p<0.05**
	Ulcerative colitis, n (%)	30 (57)	75 (40)	**p<0.05**
	IBD mother activity during pregnancy, n (%)	3 (5.7)	18 (9.2)	ns
	Comorbidities	10 (19)	24 (13)	ns
	Natural pregnancy n (%)	44 (83)	167 (88)	ns
	Fertility treatment n (%)	9 (17)	22 (12)	
	Multiparous, n (%)	30 (57)	92 (49)	ns
	Miscarriages, n (%)	0.3 (0.6)	0.3 (0.7)	ns
	Smoking habit n (%)	2 (3.8)	15 (8)	ns
Father´s factors	Known genetic alteration, n (%)	0	1 (0.5)	ns
	Father´s treatment at the time of conception, n (%)	1 (1.9)	16 (8.5)	ns
Babies factors	Male sex, n (%)	28 (53)	92 (49)	ns
	Female sex, n (%)	25 (47)	97 (51)	
	Prematurity, n (%)	13 (25)	18 (9.5)	**p<0.05**
	Vaginal delivery, n (%)	38 (72)	132 (70)	ns
	Cesarean delivery, n (%)	15 (28)	57 (30)	
	Low birth weight, n (%)	11 (21)	21 (11)	ns
	Apgar ≥7 at 5 minutes, n (%)	50 (94)	182 (96)	ns
	Apgar ≥7 at 10 minutes, n (%)	52 (98)	189 (100)	ns
	Exclusive breastfeeding ≤ 3months, n (%)	7 (33)	31 (33)	ns
	Daycare attendance, n (%)	24 (45)	79 (42)	ns
	Hearing impairment, n (%)	5 (9.4)	23 (12)	ns
	Visual impairment, n (%)	1 (1.9)	2 (1)	ns
	Family concern about behavior, mean ± SD	0.7 ± 1.2	0.3 ± 0.8	**p<0.001**
	Other family concerns, mean ± SD	0.9 ± 1.7	0.5 ± 1.4	**p<0.05**
	Health problems according to parents n (%)	1.7 ± 1.9	1.5 ± 1.7	ns
	Serious adverse events n (%)	21 (40)	40 (21)	p<0.05
	Hospital admission n (%)	19 (36)	41 (22)	**p<0.05**
	ICU admission n (%)	6 (11)	9 (4.8)	ns
	Surgical intervention n (%)	2 (3.8)	6 (3.2)	ns
	Complete vaccination n (%)	50 (100)	188 (99.5)	ns
	Allergies, n (%)	3 (5.7)	11 (5.8)	ns
	Infections, n (%)	5 (9.4)	16 (8.5)	ns
	Malformations, n (%)	1 (1.9)	0	ns
	Neoplasms, n (%)	0	0	

SD, standard deviation; ICU, intensive care unit; IBD, inflammatory bowel disease; n.s., non-statistically significant.

Figure 1a. Summary of the DUMBO registry protocol.

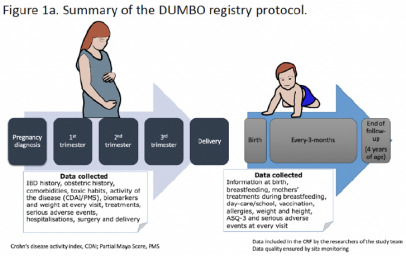
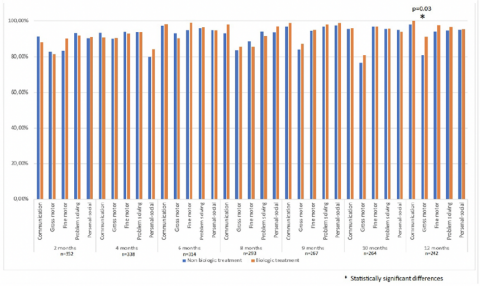


Figure 1b. Normal neurodevelopment based on ASQ-3 questionnaires.



Conclusions: In the multicenter, prospective DUMBO registry, the exposure to biologics for the treatment of IBD in utero (including anti-TNF and non-anti-TNF agents) did not impair the psychomotor development of the children.