Psychomotor Development in Infants Following Maternal Exposure to Biologics: Results From the DUMBO Registry

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Abbreviations used in this paper: ASPEN, American Society for Parenteral and Enteral Nutrition; ASQ-3, Ages and Stages Questionnaire 3rd edition; BMI, body mass index; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; GETECCU, Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa; GW, gestational weeks; IBD, inflammatory bowel disease; IL, interleukin; IQR, interquartile range; OR, odds ratio; REDCap, Research Electronic Data Capture tool; SD, standard deviation; TNF, tumor necrosis factor; UC, ulcerative colitis.

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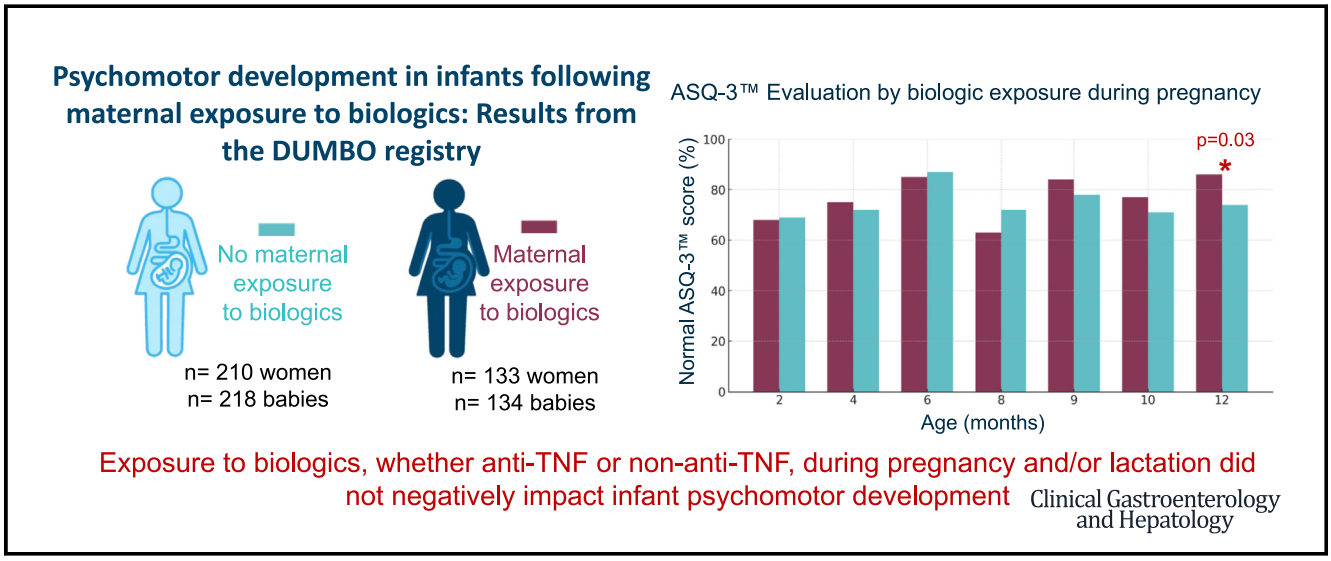

BACKGROUND & AIMS: **The impact of biologic treatment for inflammatory bowel disease (IBD) during pregnancy and lactation on infant psychomotor development is barely studied. We investigated the effect of exposure to biologics in utero or during breastfeeding on the psychomotor development of offspring during their first year.**

METHODS: **The study included patients and infants from DUMBO, an ongoing prospective, observational registry of GETECCU enrolling pregnant women (aged ≥18 years) with IBD from 60 centers across Spain. Mothers were followed up at each trimester during pregnancy and after delivery. Psychomotor development of infants was assessed using the Spanish version of the Ages and Stages Questionnaire 3rd edition (ASQ-3) during the first year of life. An ASQ-3 score below the normal limit in any domain was considered abnormal.**

RESULTS: **In total, 352 children born to 343 women were assessed; 134 infants (38.1%) were exposed to biologics during pregnancy and 80 (22.7%) during lactation, including 5 who were exclusively breastfed. At 12 months, the proportions of infants with normal ASQ-3 total scores (86% vs 74%; $P = .031$) and normal gross motor domain scores (91% vs 81%; $P = .033$) were significantly higher in the biologics-exposed vs nonexposed subgroups. Multivariate analysis revealed that preterm birth (odds ratio, 0.3; 95% confidence interval, 0.1–0.6) and maternal ulcerative colitis (odds ratio, 0.5; 95% confidence interval, 0.3–0.9) were associated with an increased risk of abnormal ASQ-3. Other variables, including exposure to biologics in utero, had no impact on ASQ-3 scores at month 12.**

CONCLUSIONS: **Exposure to biologics for IBD in utero or during breastfeeding has no negative impact on psychomotor development in infants.**

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Keywords: Biologic; Inflammatory Bowel Disease; Offspring; Pregnancy; Psychomotor Development.

A significant proportion of inflammatory bowel disease (IBD) cases are diagnosed during reproductive years,[1] yet few patients receive adequate preconception or perinatal counselling.[2] IBD treatment is critical in pregnancy, as active disease during the periconceptional period and gestation increases the risk of adverse outcomes, including low birth weight, preterm birth, small for gestational age, miscarriage, and stillbirth.[3,4] Biologics are increasingly used early in IBD management; up to 50% of patients receive them within 5 years of diagnosis,[5] leading many pregnant women to be exposed.

To ensure remission, European guidelines recommend continuing biologics (tumor necrosis factor [TNF] and non-TNF inhibitors) throughout pregnancy.[6] As these cross the placenta, fetal in utero exposure occurs.[7,8] Breast milk transmission is minimal (<1% of maternal serum levels).[6,9,10] Evidence suggests a low risk to both mother and infant during pregnancy and lactation; however, follow-up remains limited—particularly for newer agents—and most studies focus on infection risk[6,11] and immune response to vaccination, in line with evolving clinical guidelines.[12,13]

Fetal exposure to maternal inflammation, including IBD, may increase neurodevelopmental disorder risk,[14,15] underscoring the importance of disease control during pregnancy. However, the impact of in utero biologic exposure on psychomotor development remains unclear. Existing studies are few, often underpowered, use nonvalidated tools, or assess only at a single time point, typically at 12 months, without domain-specific analysis or adjustment for confounders.[7,16–19]

Early psychomotor milestones are crucial for global development. Therefore, more data are needed on the effects of in utero and breastfeeding-related biologic exposure. The DUMBO (Safety of IBD Drugs During Pregnancy and Breastfeeding: Mothers' and Babies' Outcomes) registry evaluates long-term effects of in utero exposure up to age 4, including psychomotor development.[20] This study examines the first year of life, evaluating the relationship between maternal biologic exposure and infant psychomotor development, while identifying contributing factors. It offers insights into key developmental milestones in children born to mothers with IBD and reinforces current management recommendations during pregnancy and lactation.

What You Need to Know

Background

The use of biologics during pregnancy to treat inflammatory bowel disease is increasing, but data on their potential impact on infant psychomotor development remain limited.

Findings

Infants exposed to biologics in utero or during breastfeeding showed no differences in psychomotor development at 1 year compared with nonexposed infants. Preterm birth and maternal ulcerative colitis increased the risk of abnormal development.

Implications for patient care

These findings support the safety of biologics use during pregnancy and breastfeeding, providing reassurance for clinicians managing inflammatory bowel disease in pregnant patients.

Methods

Study Design

DUMBO (NCT03894228) is an ongoing, prospective, multicenter, observational registry study supported by Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU) which includes women with IBD whose pregnancy was known to the investigator before the 28th week of gestation. The study was approved by the Ethics Committee for Research with Medicines of Hospital Universitario de La Princesa (Spain) and is being conducted in accordance with the Declaration of Helsinki (2013 version) and current Spanish legislation. Patients provided written informed consent to participate in the study, in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice, and with local legal and administrative regulations.

The design of the study was described previously.[20] The present analysis included data collected up to July 2023. Follow-up visits were conducted during pregnancy (first 4 weeks after conception and at the end of each trimester), in the post-partum period (first 4 weeks after birth), and at 3, 6, 9, and 12 months following delivery.

The sample size for this analysis was calculated based on an estimated global prevalence of psychomotor development disorders of 5% to 15%.[21] To obtain a significance level of 5% and an 80% power, 121 person-years per group were required. Taking into account a 5% loss to follow-up, the final sample size was 127 person-years per group.

Outcomes

The main study endpoint was the psychomotor development of infants at 12 months of life according to the Spanish version of the Ages and Stages Questionnaire 3rd edition (ASQ-3).[22] ASQ-3 is a validated parent-completed questionnaire consisting of 30 age-appropriate questions regarding infants' daily activities grouped into 5 developmental domains: communication, gross motor, fine motor, problem solving, and personal-social. Questions refer to an ability/behavior and may be answered "yes" (10 points), "sometimes" (5 points) or "not yet" (0 points). Cutoff points to determine the lower limit of normality were obtained from the ASQ-3 manual.

Additional endpoints included psychomotor development during the first year of life and potential factors associated with it. In the case of the children, the factors analyzed were birth condition (based on Apgar scores), anthropometric development, dietary information, nutritional status, and serious adverse events. For the mothers, the factors considered included IBD activity (assessed using the Crohn's Disease Activity Index [CDAI for Crohn's disease (CD)] or the Mayo Index [for ulcerative colitis (UC) or unclassified IBD]), treatments, weight gain during pregnancy, and serious adverse events.

Data Collection

Electronic data were collected and stored using the Research Electronic Data Capture tool (REDCap),[23] which is hosted by the Spanish Association of Gastroenterology. For assessment of the psychomotor development of infants, ASQ-3 was completed by parents when infants were 2, 4, 6, 8, 9, 10, and 12 months old (or by corrected gestational age in the case of premature infants). IBD activity in mothers was assessed at conception and at each trimester of gestation.

Both in-person and remote monitoring of the data were performed. From birth onwards, monitoring was carried out by the coordinating team based on telephone contact with the mothers every 3 months during the first year.

Definitions

Maternal biologics exposure was defined as $\geq$1 dose of TNF inhibitors (adalimumab, infliximab, certolizumab, golimumab) or non-TNF agents (vedolizumab, ustekinumab) during pregnancy or within 3 months preconception. Discontinuation was based on half-life: last dose before gestation week (GW)30 (infliximab, vedolizumab, ustekinumab), GW34 (certolizumab, golimumab), or GW36 (adalimumab). Lactation exposure referred to biologic use during partial or exclusive breastfeeding.

Active IBD was defined as CDAI >150 (CD) or partial Mayo >2 (UC/IBD-U), with activity in $\geq$1 trimester.

Normal gestational weight gain followed prepregnancy body mass index (BMI): 13 to 18 kg (<18.5), 11 to 16 kg (18.5–24.9), 7 to 11 kg (25–29.9), 5 to 9 kg ($\geq$30); for twins: 17 to 25, 14 to 23, and 11 to 19 kg, respectively.[24]

Newborns with Apgar $\geq$7 at 5 and 10 minutes were considered normal.[25]

Normal psychomotor development: ASQ-3 scores within age-appropriate range in all 5 domains; abnormal: $\geq$1 domain below cutoff.

Prematurity: birth <37 GW.[26]

Low birth weight: <2500 g at term.[27]

Small for gestational age: preterm infants <10th percentile by Fenton scale.[27]

Nutritional status was based on weight-for-height z-scores according to the American Society for Parenteral and Enteral Nutrition (ASPEN): adequate (−1.0 to +1.0); undernutrition classified as mild (−1.0 to −1.9), moderate (−2.0 to −2.9), or severe ($\leq$−3.0).[28]

Serious adverse events were defined per International Council for Harmonisation guidelines.[29]

Statistical Analysis

Quantitative variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR) depending on whether data were normally distributed or not. The Kolmogorov-Smirnov test was used to assess the normality of data distribution. Qualitative variables are presented as number of events and percentage.

In sensitivity analyses, the characteristics of mother-infant pairs who did or did not submit the ASQ-3 were analyzed to rule out delivery bias a priori. For ASQ-3 forms completed during the first year of infants' lives, the frequency of abnormal development was compared between exposed and nonexposed infants in each evaluation.

Associations between mother/infant characteristics and alterations in psychomotor development were assessed by univariate analysis using normal ASQ-3 status at 12 months as the dependent variable. The Wilcoxon signed rank test was used for paired samples, and the χ^2 test was used to compare proportions of patients. The Student's *t*-test was used to compare normally distributed variables, and the Mann-Whitney *U* test was used for non-normally distributed variables, with $P < .05$ indicating statistical significance. All percentage values are presented as observed frequencies with no imputation of missing data.

A predictive model was constructed using multivariate logistic regression analysis. In the multivariate analysis, the dependent variable was having normal/abnormal psychomotor development at 12 months, whereas independent variables included biologic exposure, IBD activity, preterm birth, exposure duration, and other relevant variables or those significant in the univariate analysis. The magnitude of the association between the variables of the predictive model and the dependent variable was determined by calculation of the odds ratio (OR) and its corresponding 95% confidence interval (CI).

All statistical analyses were performed using STATA/SE version 16.0 software.

Results

Study Population

At the time of data collection, 702 mothers with IBD during pregnancy had been enrolled in the DUMBO study

and had given birth. Of these, 343 had submitted ASQ-3 questionnaire results during their child's first year. The distribution of the main variables was similar between those who completed the ASQ-3 questionnaire and those who did not (Supplementary Table 1).

The main characteristics of the 343 mothers who assessed 352 infants (including 9 twin pairs) during pregnancy and the infants' first year are summarized in Supplementary Tables 2 and 3.

Biologics Exposure

In total, 133 women (38.1%) received biologics during pregnancy. Most of the maternal and paternal characteristics were similar across groups, except for the extent and severity of disease (Supplementary Table 4).

Of 352 infants, 134 (38.1%) were exposed to biologics during pregnancy, including 50 (14.2%) to adalimumab, 44 (12.5%) to infliximab, 28 (8%) to ustekinumab, 10 (2.8%) to vedolizumab, 3 (0.8%) to certolizumab, and 1 (0.2%) to golimumab. Two infants were exposed to 2 biologics: one to adalimumab and infliximab and the other to certolizumab and ustekinumab. Of 134 infants with biologics exposure, 39 (29.1%) were also exposed to immunosuppressants, including 38 (28.4%) to azathioprine and 1 (0.7%) to mercaptopurine; none were exposed to methotrexate.

Eighty infants (22.7%) were exposed to biologics during lactation, including 31 (8.8%) exposed to adalimumab, 29 (8.2%) to infliximab, 12 (3.4%) to ustekinumab, 7 (2.0%) to vedolizumab, and 1 (0.3%) to golimumab. The mean ± SD duration of exposure was 39.8 ± 17.4 weeks for adalimumab, 46.8 ± 13.7 weeks for infliximab, 39.5 ± 20.6 weeks for ustekinumab, 30.4 ± 21.4 weeks for vedolizumab, and 52.1 weeks for golimumab. Five infants were exposed to biologics exclusively during breastfeeding as their mothers started biologic treatment after childbirth.

There were no significant differences in infant characteristics at birth and through the first year of follow-up according to maternal biologics exposure, with the exception of serious adverse events and low birth weight, which occurred more frequently in the nonexposed vs exposed group (33% vs 19%; $P = .011$ and 17% vs 8.2%; $P = .044$, respectively) (Table 1).

Psychomotor Development

Most ASQ-3 domain scores were similar for biologics-exposed vs nonexposed children during 12 months of follow-up. However, biologics-exposed children had significantly higher ASQ-3 scores than nonexposed children for the personal-social domain at 4 months (51.6 vs 49.6; $P = .031$) and the gross (46.8 vs 40.7; $P = .004$) and fine (52.4 vs 49.7; $P = .024$) motor domains at 12 months (Table 2).

Similarly, the proportion of infants with normal ASQ-3 scores was not significantly different in the biologics-exposed vs nonexposed subgroups during 1 year of follow-up across most domains and time points; however, among the 242 infants with data at 12 months, the proportions of infants with normal ASQ-3 total scores (86% vs 74%; $P = .031$) and normal gross motor domain scores (91% vs 81%; $P = .033$) were significantly higher in the biologics-exposed vs nonexposed groups (Table 2; Figure 1).

There was no significant difference in the mean duration of biologics exposure during pregnancy for infants with normal vs abnormal ASQ-3 scores at 12 months (32 vs 33.3 weeks; $P = .285$). Details of exposure to each biologic are outlined in Table 3.

Of 80 infants exposed to biologics during breastfeeding, 55 had reached 12 months of age and were evaluated using ASQ-3. There was no significant difference in the proportion of breastfed infants with normal vs abnormal ASQ-3 scores at 12 months of age. For each biologic agent, there was no significant difference in exposure times for infants with normal vs abnormal ASQ-3 scores at 12 months of age (Supplementary Table 5).

Main maternal characteristics of children with normal vs abnormal ASQ-3 are summarized in Table 4. The proportion of mothers who received biologics during pregnancy was significantly higher in the normal vs abnormal ASQ-3 subgroups (41% vs 25%; $P = .031$). No differences were observed in psychomotor development in relation to biologics exposure, regardless of whether the biologic was administered as monotherapy or in combination with other immunosuppressants. The proportion of mothers with CD diagnosis was higher (59% vs 43%; $P = .04$) and the proportion with UC diagnosis was lower (40% vs 57%; $P = .028$) in the normal vs abnormal ASQ-3 group.

In the global ASQ-3 assessment at 12 months, the proportion of infants with a normal ASQ-3 total score was lower in those born to mothers with UC vs CD (71% vs 83%; $P = .033$); however, individual ASQ-3 domain scores were not affected by the mother's IBD diagnosis (Supplementary Table 6).

Infants' characteristics according to psychomotor development are summarized in Table 5. At 12 months of age, infants with abnormal ASQ-3 exhibited higher proportions of premature birth (ie, <37 GW; 25% vs 11%; $P = .013$), at least one serious adverse event (45% vs 26%; $P = .009$), and admission to hospital (36% vs 22%; $P = .035$) compared with infants with normal ASQ-3.

Both the proportion of infants with a normal ASQ-3 total score at 12 months (62% vs 81%; $P = .013$) and the mean ASQ-3 domain scores were lower for premature infants compared with infants reaching full term, despite correction for gestational age (Supplementary Table 7). Of the 49 preterm infants, 9 were classified as extremely preterm, all of whom were born from twin

Table 1. Infant Characteristics at Birth and Through 1 Year of Follow-Up According to Maternal Exposure to Biologics During Pregnancy

Characteristic	Maternal exposure to biologics n = 134	No maternal exposure to biologics n = 218	*P* value
Female sex	69 (51)	113 (52)	.916
At birth			
Gestational age, *weeks*	39 ± 1.8	38.4 ± 2.5	.064
Vaginal delivery	89 (66)	161 (74)	.135
Cesarean section	45 (34)	57 (26)	
Height at birth, *cm*	50 ± 2.6	49 ± 3	.099
Birth weight, *kg*	3.2 ± 0.5	3.1 ± 0.6	.153
Low birth weight	11 (8,2)	34 (17)	**.044**
Apgar score ≥7			
At 5 minutes	120 (96)	197 (98)	.436
At 10 minutes	123 (100)	198 (99.5)	.431
Feeding during the first month of life			
Breast feeding	78 (58)	141 (65)	.457
Mixed feeding (breast + formula)	19 (14)	28 (13)	
Formula feeding	37 (28)	49 (22)	
Feeding at 6 months of age[a]			
Breast feeding	18 (20)	33 (22)	.414
Mixed feeding (breast + formula)	5 (5.6)	15 (10)	
Formula feeding	24 (27)	45 (30)	
Feeding at 12 months of age[a]			
Breast feeding	2 (2.4)	8 (5.6)	.365
Mixed feeding (breast + formula)	1 (1.2)	2 (1.4)	
Formula feeding	1 (1.2)	6 (4.2)	
Follow-up during the first year			
Hearing problems	12 (9.0)	16 (7.3)	.509
Visual problems	2 (1.5)	1 (0.5)	.288
Family concern about behavior	0.2 ± 0.6	0.5 ± 1	.051
Health problems according to caregivers	1.4 ± 1.5	1.6 ± 1.9	.802
Nursery school attendance	45 (34)	88 (40)	.202
Complete vaccination	131 (98)	215 (99)	.544
Serious adverse events	25 (18.7)	73 (33)	**.011**
Hospital admission	24 (17.9)	58 (27)	.061
No. of hospital admissions	1.2 ± 0.7	1.2 ± 0.6	.582
Admission to ICU	5 (3.7)	14 (6.4)	.278
Duration of admission to ICU, *days*	21 ± 21	19 ± 18	.915
Surgery	5 (3.7)	8 (3.7)	.976
Allergy	7 (5.2)	12 (5.5)	.910
Infection	10 (7.5)	26 (12)	.180
No. infections	1 ± 0	1.2 ± 0.5	.195
Duration of infections, *days*	14 ± 22	27 ± 73	.595
Malformation	0	2 (0.9)	.266
Neoplasm	0	1 (0.5)	.432

NOTE. Data are presented as number (%) or mean ± standard deviation.
ICU, intensive care unit; SD, standard deviation.
[a]With complementary feeding.

pregnancies. No significant differences in ASQ-3 overall status or across individual domains were observed between moderately and extremely preterm infants (Supplementary Table 8).

Anthropometric development was largely comparable between ASQ-3 normal and abnormal groups during the first year. However, severe short stature was more prevalent at 3 months in the abnormal group, and normal weight was more frequent at 9 months in the normal group (73% vs 56%; $P = .010$). Univariate analysis revealed significant group differences in malnutrition subcategories at 3 and 12 months. No differences in height-for-weight ratio were found (Supplementary Table 9).

In the first year, no significant differences were observed in vaccine administration status between infants with normal vs abnormal ASQ-3 scores (Supplementary Table 10).

Table 2. ASQ-3 Results by Domain Throughout the First Year According to Maternal Exposure to Biologics During Pregnancy

	2 months (n = 352)			4 months (n = 338)			6 months (n = 314)			8 months (n = 293)		
	Exposed to biologics	Not exposed to biologics	*P* value	Exposed to biologics	Not exposed to biologics	*P* value	Exposed to biologics	Not exposed to biologics	*P* value	Exposed to biologics	Not exposed to biologics	*P* value
Normal ASQ-3 total score, n/N (%)	91/134 (68)	150/218 (69)	.860	96/127 (75)	152/211 (72)	.551	98/115 (85)	173/199 (87)	.670	67/106 (63)	135/187 (72)	.127
Communication domain												
Normal score, n (%)	118 (88)	199 (91)	.326	118 (93)	197 (93)	.873	113 (98)	194 (97)	.655	104 (98)	174 (93)	.059
Mean ± SD score	44.6 ± 14.5	44.5 ± 14.3	.916	51.5 ± 7.6	51.1 ± 9.1	.855	50.4 ± 9.9	50.4 ± 9.3	.829	51.7 ± 9.3	51.6 ± 9.8	.918
Gross motor domain												
Normal score, n (%)	109 (81)	181 (83)	.687	115 (91)	190 (90)	.880	104 (90)	185 (93)	.425	91 (86)	158 (84)	.680
Mean ± SD score	50.3 ± 11.8	50.5 ± 10.9	.966	52.8 ± 10.2	52 ± 11.3	.744	40.7 ± 13.3	40.5 ± 12	.740	46.8 ± 12.2	46.3 ± 13.4	.999
Fine motor domain												
Normal score, n (%)	121 (90)	182 (83)	.073	118 (93)	198 (94)	.738	114 (99)	189 (95)	.054	91 (86)	166 (89)	.464
Mean ± SD score	47.2 ± 11	45.8 ± 11.1	.188	49.7 ± 12.2	49.6 ± 11.1	.551	50.9 ± 9.4	52.3 ± 10.7	.434	54.4 ± 8.2	53.9 ± 9.2	.643
Problem-solving domain												
Normal score, n (%)	123 (92)	203 (93)	.644	119 (94)	197 (94)	.968	111 (97)	191 (96)	.809	97 (92)	175 (94)	.402
Mean ± SD score	43.5 ± 13.4	43.9 ± 12.5	.928	53.2 ± 9.1	52.9 ± 10	.875	51.9 ± 8.8	51.4 ± 10.8	.704	52.4 ± 9.5	54.1 ± 8.6	.101
Personal-social domain												
Normal score, n (%)	122 (91)	196 (90)	.822	108 (84)	168 (80)	.313	109 (95)	189 (95)	.941	103 (97)	174 (94)	.178
Mean ± SD score	48.3 ± 10.5	48.4 ± 11.3	.742	51.6 ± 9.4	49.6 ± 10.1	**.031**	50.6 ± 11	50.1 ± 10.6	.469	53.1 ± 7.3	51.2 ± 9.2	.181

	9 months (n = 267)			10 months (n = 264)			12 months (n = 242)		
	Exposed to biologics	Not exposed to biologics	*P* value	Exposed to biologics	Not exposed to biologics	*P* value	Exposed to biologics	Not exposed to biologics	*P* value
Normal ASQ-3 total score, n/N (%)	87/102 (84)	128/165 (78)	.168	77/100 (77)	116/164 (71)	.265	77/90 (86)	112/152 (74)	**.031**
Communication domain									
Normal score, n (%)	101 (99)	160 (97)	.272	96 (96)	157 (96)	.916	90 (100)	149 (98)	.180
Mean ± SD score	44.3 ± 13.3	44.9 ± 13.3	.666	49.6 ± 11.5	48.9 ± 12.1	.654	52.1 ± 10	50.7 ± 12	.493
Gross motor domain									
Normal score, n (%)	89 (87)	139 (84)	.498	81 (81)	126 (77)	.424	82 (91)	123 (81)	**.033**
Mean ± SD score	38.6 ± 16.5	36.6 ± 16.3	.310	47 ± 15.1	44 ± 15.7	.077	46.8 ± 16.6	40.7 ± 18.3	**.004**
Fine motor domain									
Normal score, n (%)	98 (95)	156 (95)	.830	97 (97)	159 (97)	.982	88 (98)	143 (94)	.182
Mean ± SD score	53.3 ± 9.3	52.9 ± 9.5	.503	56 ± 7.1	55.9 ± 6.5	.472	52.4 ± 8.5	49.7 ± 9.5	**.024**

Table 2. Continued

	9 months (n = 267)			10 months (n = 264)			12 months (n = 242)		
	Exposed to biologics	Not exposed to biologics	*P* value	Exposed to biologics	Not exposed to biologics	*P* value	Exposed to biologics	Not exposed to biologics	*P* value
Problem-solving domain									
Normal score, n (%)	101 (98)	159 (97)	.582	95 (96)	157 (96)	.929	87 (97)	143 (95)	.480
Mean ± SD score	52.4 ± 10	51.6 ± 10.3	.451	55.3 ± 8.7	54.4 ± 9	.338	50.5 ± 10.7	49.2 ± 10.6	.204
Personal-social domain									
Normal score, n (%)	102 (99)	160 (98)	.389	93 (94)	156 (95)	.679	86 (96)	144 (95)	.945
Mean ± SD score	46.8 ± 11.1	44.9 ± 12.3	.279	50.4 ± 10.4	49.9 ± 10	.488	47.1 ± 12	45.7 ± 12.5	.429

NOTE. Boldface *P* values indicate statistical significance.
ASQ-3, Ages and Stages Questionnaire third edition; SD, standard deviation.

Factors Associated With Impaired Psychomotor Development at 12 Months

In the multivariate analysis, prematurity (OR, 0.3; 95% CI, 0.2–0.8) and being born to a mother with UC (vs CD; OR, 0.5; 95% CI, 0.3–0.9) were the only independent factors associated with impaired psychomotor development at 12 months of age. Notably, in utero exposure to biologics was not associated with impaired psychomotor development at 12 months.

Discussion

To our knowledge, this is the most comprehensive analysis of psychomotor development of children born to mothers with IBD to date. Our data suggest there is no adverse impact of biologics exposure in utero or during breastfeeding on the psychomotor development of infants.

Active maternal inflammation during the periconception period and pregnancy has been associated with low birth weight, preterm delivery, small size for gestational age, spontaneous abortion, and stillbirths.[3,4] Although it is unclear how maternal inflammation impacts fetal neuronal development specifically, proinflammatory cytokines are known to play a role in various neurodevelopmental processes, including neuronal and glial cell proliferation and differentiation, microglial activation, and neuronal plasticity.[30] Prolonged exposure to inflammatory cytokines is associated with an increased risk of psychomotor developmental disorders and conditions such as autism spectrum disorder, attention deficit hyperactivity disorder, and Tourette syndrome.[31] Furthermore, elevated levels of interleukin (IL)-6, IL-8, and TNF-α in infants at birth, and in the early weeks post-partum, are linked to poorer neurodevelopmental outcomes.[32]

In infants born to mothers with IBD, exposure to biologics would be expected to reduce their exposure to inflammatory cytokines in utero, which could potentially mitigate the impact of maternal inflammation on psychomotor development. In support of this hypothesis, our study found no negative impact of biologics exposure on the psychomotor development of infants, either from exposure in utero or during breastfeeding. Furthermore, we observed higher ASQ-3 scores in the personal-social domain at 4 months and in the gross and fine motor domains at 12 months in biologics-exposed vs nonexposed children, possibly reflecting a beneficial effect of treatment in reducing maternal inflammation.

Prematurity and maternal UC were the only independent factors associated with impaired psychomotor development at 12 months. Preterm infants showed significantly lower ASQ-3 scores across all domains, particularly in gross motor and total scores, supporting established links between prematurity and motor delays, even after gestational age correction.[33] Multivariate

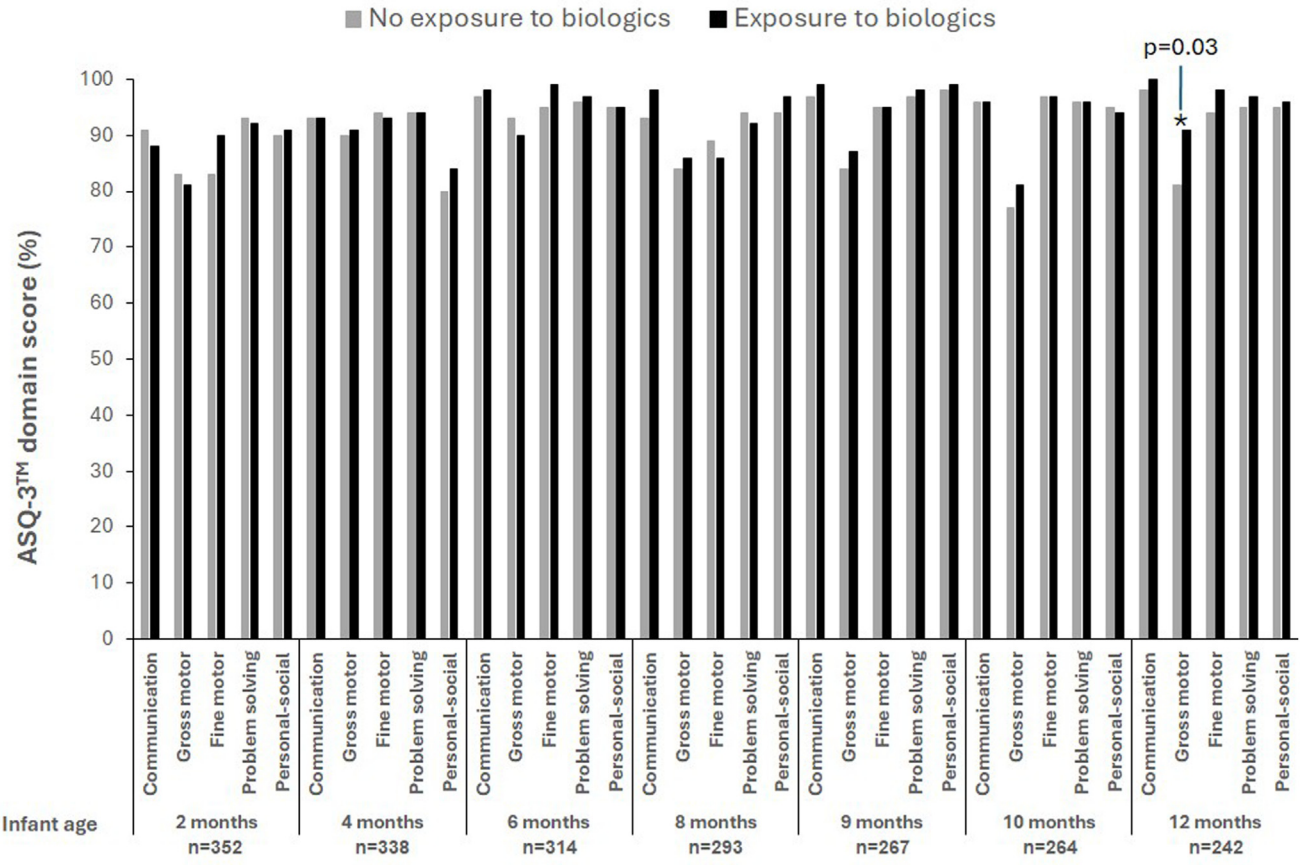

Figure 1. Proportion of infants with abnormal ASQ-3 domain scores at each follow-up visit according to maternal exposure to biologics.

analysis confirmed that UC (vs CD) was linked to lower psychomotor development, although causality cannot be inferred due to the lack of maternal inflammatory markers (eg, cytokine levels). Despite this association, the proportion of children with normal psychomotor development remained high and comparable to the general population.

Table 3. Exposure to Biologics During Pregnancy Among Infants With Normal or Abnormal ASQ-3 Status at 12 Months of Age

Biologics exposure	ASQ-3 normal n = 189	ASQ-3 abnormal n = 53	*P* value
Adalimumab	29 (15)	4 (7.6)	.114
Exposure time, *weeks*	33.9 ± 9.4	37 ± 4.9	.407
Infliximab	22 (12)	4 (7.6)	.395
Exposure time, *weeks*	33.9 ± 7.6	33.7 ± 6.9	.374
Ustekinumab	22 (12)	3 (5.7)	.206
Exposure time, *weeks*	31.7 ± 11.4	22.1 ± 5.7	.094
Vedolizumab	3 (1.6)	2 (3.8)	.323
Exposure time, *weeks*	20.6 ± 17.4	33.2 ± 8.4	.248
Certolizumab	2 (1.1)	0	.577
Exposure time, *weeks*	38.5 ± 1.1	–	–
Golimumab	0	0	–
Exposure time, *weeks*	–	–	–

NOTE. Data are presented as number (%) or mean ± standard deviation.
ASQ-3, Ages and Stages Questionnaire third edition; SD, standard deviation.

In recent years, interest in the effects of intrauterine exposure to biologic drugs administered to mothers with IBD has increased significantly, but most studies focused on the risk of infection. In accordance with our findings, the few studies that have analyzed psychomotor development have reported no negative impact of biologic exposure, including both anti-TNF and non-anti-TNF agents, on psychomotor development in infants.[2,6]

Studies focusing on anti-TNF biologics, such as the work by Bortlik et al, observed normal psychomotor development in 24 of 25 children exposed to anti-TNFs (eg, adalimumab, infliximab) during pregnancy.[16] Larger studies, by Duricova et al (including 72 exposed and 69 unexposed children)[18] and Julsgaard et al (including 72 exposed children)[7] also reported normal psychomotor outcomes in children exposed to anti-TNFs in utero. However, these assessments did not use the ASQ-3 or any other validated questionnaire, and details on specific items or degrees of psychomotor impairment were lacking.

Other research has also explored the impact of non-TNF biologics on infant psychomotor development. Julsgaard et al evaluated psychomotor outcomes at 12

Table 4. Parental Characteristics of Infants Born to Women With IBD According to ASQ-3 Status at 12 Months of Age

	ASQ-3 normal n = 189	ASQ-3 abnormal n = 53	*P* value
Maternal characteristics			
Treatment during pregnancy			
Biologics	77 (41)	13 (25)	**.031**
Corticosteroids	16 (8.5)	4 (7.6)	.830
Thiopurines	60 (32)	20 (38)	.413
Type of IBD			
CD	112 (59)	23 (43)	**.040**
UC	75 (40)	30 (57)	**.028**
IBD activity during pregnancy	22 (12)	5 (9.4)	.632
Previous comorbidities	24 (13)	10 (19)	.253
Natural pregnancy	167 (88)	44 (83)	.304
Fertility treatment	22 (12)	9 (17.0)	
Multiparity	92 (49)	30 (57)	.308
Previous abortion	40 (21)	11 (21)	.949
Maternal smoking	15 (8)	2 (3.8)	.295
Cigarette daily consumption	0.5 ± 2.4	0.1 ± 0.7	.281
Paternal factors			
Known genetic alterations	1 (0.5)	0	.791
Medical treatment at conception	16 (8.5)	1 (1.9)	.239

NOTE. Data are presented as number (%) or mean ± standard deviation.
NOTE. Boldface P values indicate statistical significance.
ASQ-3, Ages and Stages Questionnaire third edition; CD, Crohn's disease; IBD, inflammatory bowel disease; SD, standard deviation; UC, ulcerative colitis.

Table 5. Characteristics of Infants Born to Women With IBD According to ASQ-3 Status at 12 Months of Age

	ASQ-3 normal n = 189	ASQ-3 abnormal n = 53	*P* value
Sex			
Male	92 (49)	28 (53)	.593
Female	97 (51)	25 (47)	
Prematurity	21 (11)	13 (25)	**.013**
Type of delivery			
Vaginal	132 (70)	38 (72)	.794
Caesarean section	57 (30)	15 (28)	
Low birth weight	21 (11)	11 (21)	.067
Apgar score ≥7			
At 5 minutes	174 (96)	47 (94)	.512
At 10 minutes	178 (100)	48 (98)	.056
Breastfeeding			
≤3 months	31 (33)	7 (33)	1.000
>6 months[a]	47 (51)	12 (57)	.584
Follow-up during the first year			
Nursery school attendance	79 (42)	24 (45)	.650
Hearing problems	6 (18)	22 (10.6)	.232
Visual problems	1 (1.1)	1 (1.9)	.630
Serious adverse events	50 (26)	24 (45)	**.009**
Hospital admission	41 (22)	19 (36)	**.035**
No. admissions	1.4 ± 0.8	1.1 ± 0.3	.085
ICU admission	9 (4.8)	6 (11)	.080
Surgery	11 (5.8)	2 (3.8)	.559
Complete vaccination	188 (99.5)	53 (100)	.596
Allergy	11 (5.8)	3 (5.7)	.965
Infection	23 (12)	8 (15)	.573
No. infections	1.2 ± 0.5	1 ± 0	.214
Malformation	0	1 (1.9)	.058
Neoplasm	0	0	–

NOTE. Data are presented as number (%) or mean ± standard deviation.
NOTE. Boldface P values indicate statistical significance.
ASQ-3, Ages and Stages Questionnaire third edition; ICU, intensive care unit.
[a]With complementary feeding.

months in 34 children exposed to vedolizumab, and, consistent with our findings, found no increased risk of psychomotor delay.[34] Interestingly, vedolizumab-exposed infants showed higher communication scores compared with reference means. Although this study used ASQ-3, their criterion for normal development was less stringent; they required normal scores in 4 of 5 domains, whereas our study required normal scores in all domains. Another study evaluating 63 infants exposed to ustekinumab in utero found no association with psychomotor delays, although some assessments were made by pediatricians in outpatient clinics rather than using validated scales.[35]

Chugh et al examined non-TNF biologic exposure (12 children exposed to ustekinumab and 22 to vedolizumab), reporting normal developmental milestones across communication, motor, and problem-solving domains compared with population norms. Personal-social milestones were also consistent with, or exceeded, ASQ-3 cutoffs, supporting our findings.[17] A smaller study by Mitrova et al reported normal psychomotor development in 36 children exposed to ustekinumab or vedolizumab in utero, but detailed methods for assessment of psychomotor development were not provided.[19]

Finally, data from the PIANO study further supports our findings. Mahadevan et al assessed psychomotor development in 206 children exposed to biologics (both anti-TNF and non-anti-TNF) in utero, and 92 controls, finding higher ASQ-3 scores in the exposed group. Despite its size and prospective nature, the study relied on self-reported data and did not evaluate factors that might affect development.[36] Another subanalysis of the same cohort found no increased risk of psychomotor delay in children exposed to biologics during breastfeeding in the first year, though it did not address in utero exposure.[37]

Our study has some limitations. Despite close contact with the mothers and requests to complete the ASQ-3 questionnaire, a proportion of mothers included in the registry did not provide the questionnaire to the research team, although we found no significant differences between the characteristics of the mother-infant pairs who completed the forms and those who did not. Secondly, we were not able to reliably assess certain social and cultural factors; therefore, their potential impact on psychomotor development was not included

in the analysis. Similarly, the possible influence of circulating levels of biologic therapies could not be evaluated, as no biological samples were available in the study; nonetheless, it is unlikely that such exposure would have had a detrimental effect. Lastly, disease activity was assessed solely using clinical indices (CDAI and partial Mayo scores). Although objective inflammatory markers such as C-reactive protein were available and their potential impact on psychomotor development was analyzed, C-reactive protein may be an unreliable indicator of disease activity during pregnancy due to physiological changes. Other biomarkers, such as fecal calprotectin and ILs, were not included in the study to maintain the feasibility of conducting a multicenter investigation.

Notably, our study has several strengths. It is the most detailed study on the effects of exposure to biologics on infant psychomotor development conducted to date; data were not only collected at 12 months but throughout the first year of life, and a validated and standardized questionnaire was used, allowing better detection of psychomotor development risks compared with familial and pediatrician assessments.[38] Moreover, this is the first study to perform multivariate analysis to take into account independent factors that may influence developmental milestones beyond exposure to biologics, including maternal, disease, paternal, and infant characteristics. Furthermore, we were able to assess not only the impact of exposure to biologics but also its impact based on the duration of exposure. Finally, the study included a large sample size, encompassing both anti-TNF and non-anti-TNF biologics, as well as remote and in-person monitoring, thereby ensuring a comprehensive and robust dataset.

Conclusion

In an area that has been poorly studied, the results of our study demonstrate that exposure to biologics, whether anti-TNF or non-anti-TNF, during pregnancy and/or lactation did not negatively impact infant psychomotor development, supporting the recommendation that women with IBD should continue biologic therapy during the periconception period, as well as during pregnancy and lactation.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2025.05.012.

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Data Availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.