Inflammatory Bowel Disease Best of DDW 2021

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Ustekinumab vs Adalimumab in Moderate-Severe Crohn's disease: The SEAVUE Study

- Background:
  - Multiple biologic therapies with different mechanisms are available to treat patients with Crohn's disease (CD)
  - Head to head trials are needed to inform treatment decisions

- Aim:
  - To study the efficacy and safety of ustekinumab (UST) vs adalimumab (ADA) for induction and maintenance therapy in biologic-naïve patients with moderate-severe CD

Sands et al. DDW. May 23, 2021

Ustekinumab vs Adalimumab in Moderate-Severe Crohn's disease: The SEAVUE Study

- Methods:
  - Multicenter, randomized, blinded trial in adult patients with moderate-severe CD with CD activity index (CDAI) scores ≥ 220 and ≤ 450
  - Patients were biologic naïve, had failed prior corticosteroids or immunomodulators, and had an ulcer of any size on baseline colonoscopy
  - Patients randomized to standard dosing UST (6 mg/kg IV at baseline, 90 mg SC q8w) or ADA (induction 160/80 mg SC, 40 mg SC q2w), no dose modifications, no immunomodulators

Sands et al. DDW. May 23, 2021

Ustekinumab vs Adalimumab in Moderate-Severe Crohn's disease: The SEAVUE Study

- Primary outcome:
  - Clinical remission at week 52 with CDAI < 150

- Secondary outcomes:
  - Corticosteroid free remission at week 52
  - Clinical response (≥100 point CDAI decrease from baseline) at week 52
  - Remission in patient reported CDAI outcomes (abdominal pain and stool frequency)
  - Endoscopic remission (SES-CD ≤ 3) at week 52
  - Clinical remission at week 16

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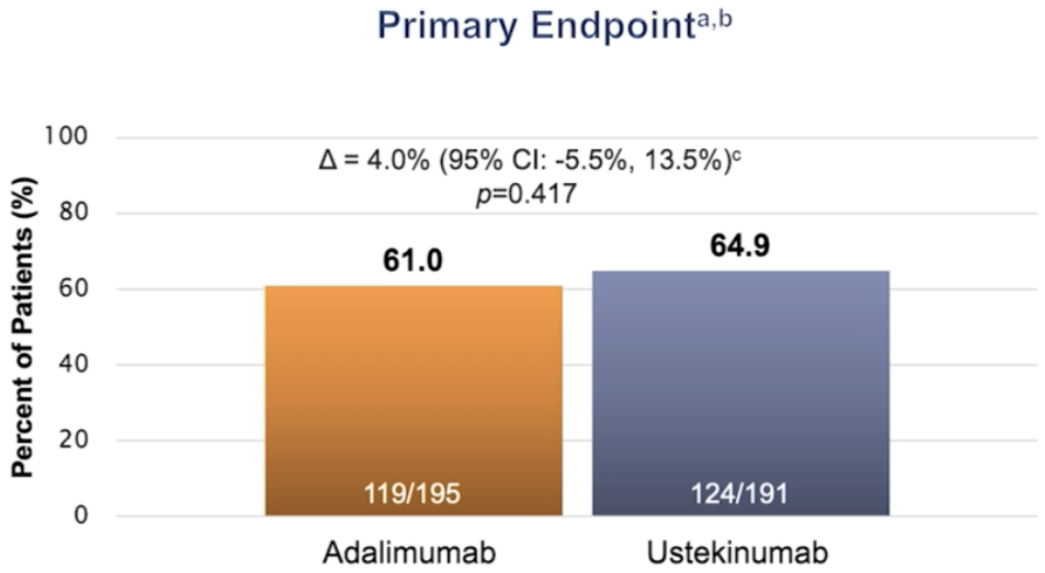
Ustekinumab vs Adalimumab in Moderate-Severe Crohn's disease: The SEAVUE Study

- Results
  - 386 patients were randomized to UST or ADA
  - Primary outcome: 64.9% of UST-treated patients and 61.0% of ADA-treated patients achieved clinical remission (p=0.417) at week 52



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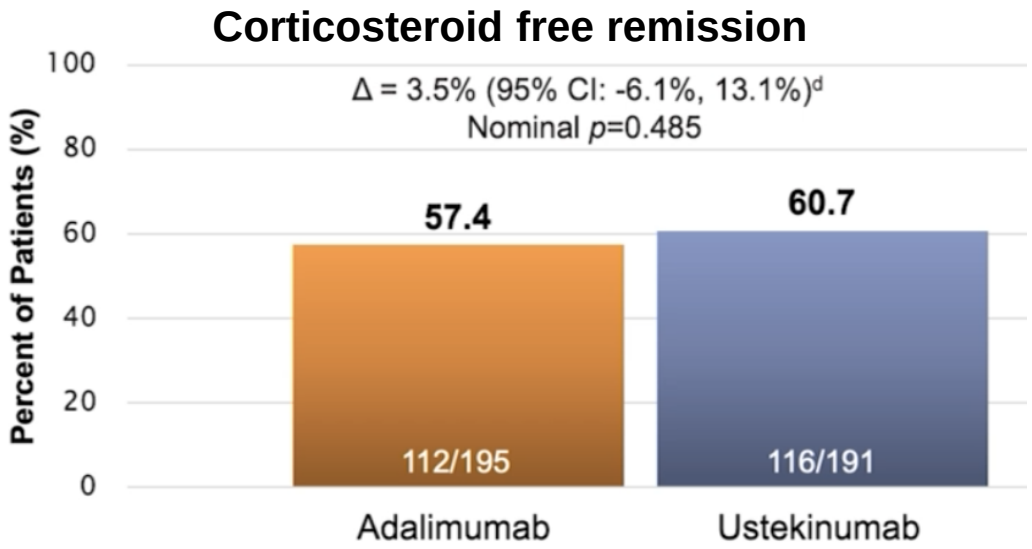
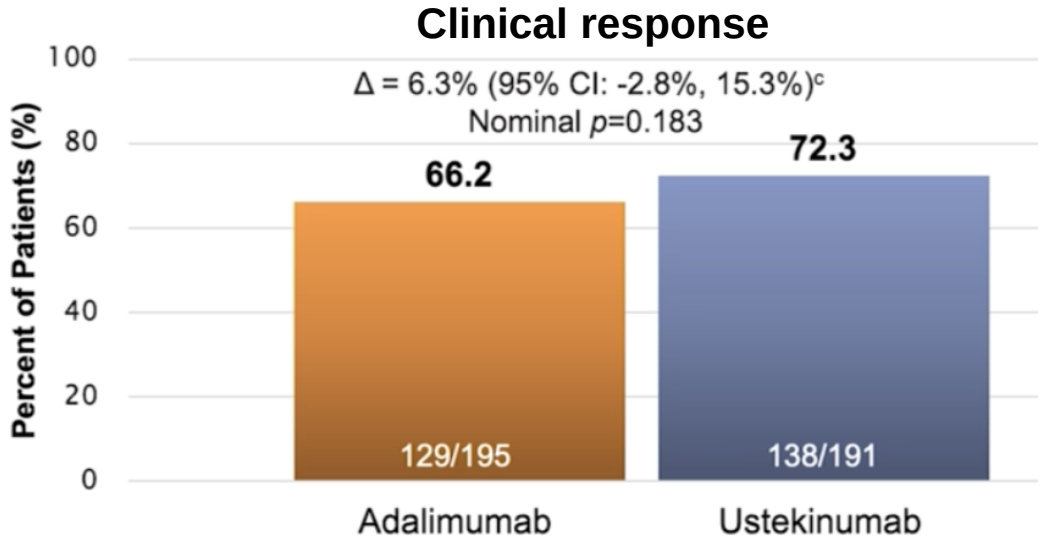
Ustekinumab vs Adalimumab in Moderate-Severe Crohn's disease: The SEAVUE Study

- Results – secondary outcomes:
  - Corticosteroid free remission at week 52, clinical response at week 52, endoscopic remission at week 52, and patient reported outcome symptom remission at week 52 were similar between the two groups





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Ustekinumab vs Adalimumab in Moderate-Severe Crohn's disease: The SEAVUE Study

- Results - safety events:
  - Infections: 34% in UST, 40.5% in ADA
    - Opportunistic infections – active tuberculosis and disseminated herpes zoster in one patient on ADA, paracoccidioides in one patient on UST
  - Most common serious adverse events was worsening CD: 2.6% in UST, 7.2% in ADA
  - Injection site reactions: 1.0% in UST, 10.3% in ADA

	Adalimumab[a] (N=195)	Ustekinumab (N=191)
Avg duration follow-up (weeks)	45.8	47.6
Avg number of administrations	28.0	29.0
Patients with ≥1, n (%)		
Adverse events	152 (77.9%)	153 (80.1%)
Serious adverse events	32 (16.4%)	25 (13.1%)
Serious adverse events of worsening CD	14 (7.2%)	5 (2.6%)
Infections	79 (40.5%)	65 (34.0%)
Serious infections	5 (2.6%)	4 (2.1%)
Deaths	0[b]	0
Malignancies	1 (0.5%)[c]	0
Infusion-related adverse events	6 (3.1%)	3 (1.6%)
Injection site reactions	20 (10.3%)	Active UST: 2 (1.0%) PBO: 4 (2.1%)
Adverse events that led to discontinuation of study drug	22 (11.3%)	12 (6.3%)

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Ustekinumab vs Adalimumab in Moderate-Severe Crohn's disease: The SEAVUE Study

- Conclusions
  - Both UST and ADA are highly effective as induction and maintenance therapy for moderate-severe CD in biologic naïve patients
  - Clinical remission rates at week 52 were not significantly different between the two groups (64.9% for UST and 61.0% for ADA)
  - Discontinuation rates and injection site reactions were numerically lower for UST
  - **Clinical key point: No difference in efficacy between UST and ADA in moderate-severe CD**

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Comparative Effectiveness of Mediterranean Diet and Specific Carbohydrate Diet for CD: **D**iet to **IN**duc**E** Remission in **CD** (**DINE CD**) **Study**

- Background:
  - Therapeutic diets have been used to treat symptomatic CD
  - Specific Carbohydrate Diet (SCD) is **high** in unprocessed meats, poultry, fish, shellfish, eggs, vegetables, fruits, nuts, legumes, and **low** in grains, dairy, sweeteners other than honey
  - Mediterranean Diet (MD) **high** in olive oil, fruits, vegetables, nuts, cereals, and **low** in red and processed meat and sweets

- Aim:
  - To compare the effectiveness of the MD and SCD for mild to moderate CD

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Comparative Effectiveness of Mediterranean Diet and Specific Carbohydrate Diet for CD: **DINE CD Study**

- Methods:
  - Adult patients with CD and **mild-moderate** symptoms defined as short CDAI score 176-499
  - Patients were randomly assigned to SCD or MD for 12 weeks
  - Weeks 1-6, participants received meals and snacks compliant with their assigned diet
  - Weeks 7-12, participants could purchase some or all of their food while following the diet on their own

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Comparative Effectiveness of Mediterranean Diet and Specific Carbohydrate Diet for CD: **DINE CD Study**

- Primary Outcome:
  - Symptomatic remission (sCDAI < 150) in the absence of initiation or increase of any CD medications at week 6

- Secondary Outcomes:
  - Clinical remission (CDAI<150)
  - Fecal calprotectin response (<250 ug/g and reduction by > 50% from baseline)
  - C-reactive protein response (<5 mg/L and >50% reduction from baseline)
  - Short IBDQ and PROMIS measures of fatigue, pain, sleep and social isolation

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Comparative Effectiveness of Mediterranean Diet and Specific Carbohydrate Diet for CD: **DINE CD Study**

- Results:
  - SCD n=99, MD n=92
  - Majority of participants were White females
  - Participants predominantly had non-stricturing, non-penetrating disease involving the ileum or the ileum and colon
  - More than 50% of participants were on biologics
  - Approximately 50% of participants had evidence of active inflammation at baseline

Characteristic	Mediterranean Diet (n=92)	Specific Carbohydrate Diet (n=99)
CD behavior		
Non-stricturing, nonpenetrating	56 (60.9)	60 (60.6)
Stricturing	19 (20.7)	17 (17.2)
Penetrating	9 (9.8)	13 (13.1)
Stricturing and Penetrating	8 (8.7)	9 (9.1)
CD disease distribution[a]		
Ileum alone	22 (23.9)	30 (30.6)
Colon alone	17 (18.5)	13 (13.3)
Ileum+Colon	53 (57.6)	55 (56.1)
History of perianal fistula	24 (26.1)	20 (20.2)
History of intestinal surgery	34 (37.0)	29 (29.3)

Characteristic	Mediterranean Diet (n=92)	Specific Carbohydrate Diet (n=99)
Evidence of ongoing inflammation	38 (41.8)	50 (52.1)
hsCRP > 5 mg/L	28 (30.4)	37 (37.4)
FC > 250 µg/g	13 (14.6)	23 (24.0)
Inflammation on colonoscopy		
Not performed	80 (87.0)	89 (89.9)
Yes	8 (8.7)	8 (8.1)
Probably	1 (1.1)	0 (0.0)
Probably not	1 (1.1)	1 (1.0)

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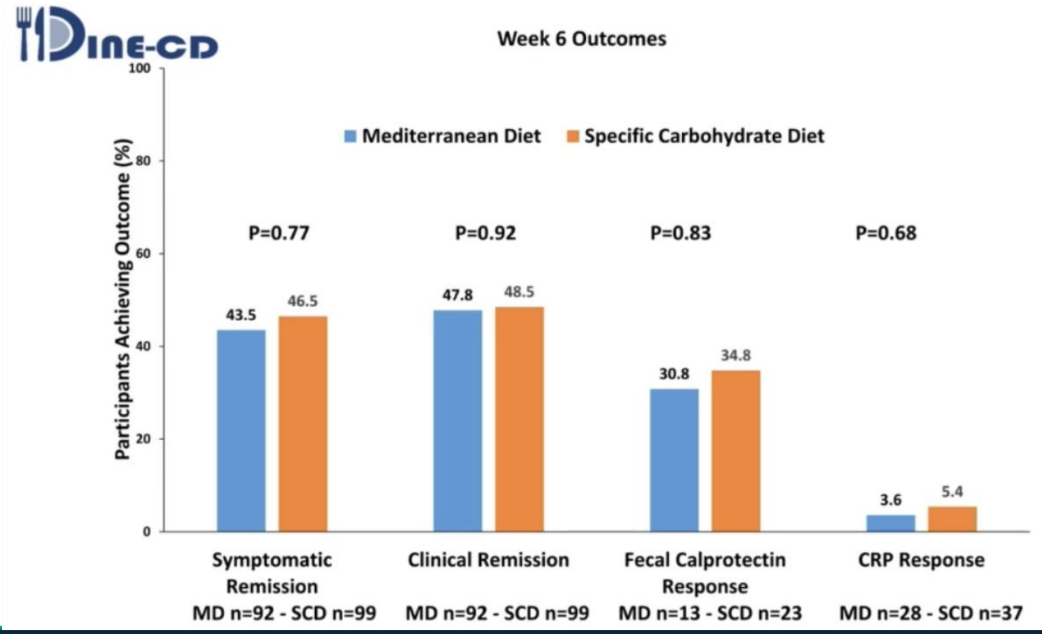
Comparative Effectiveness of Mediterranean Diet and Specific Carbohydrate Diet for CD: **DINE CD Study**

- Results:
  - The percentage of participants who achieved symptomatic remission and clinical remission at week 6 did not differ by diet
  - CRP response was uncommon
  - No difference in comparative effectiveness of the two diets based on the presence or absence of inflammation at screening



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Comparative Effectiveness of Mediterranean Diet and Specific Carbohydrate Diet for CD: **DINE CD Study**

- Results:
  - There was similar improvement in the sCDAI, CDAI, short IBDQ and PROMIS measures from week 0 to week 6 in both groups

Outcome	MD (change to week 6)	P value	SCD (change to week 6)	P value	Change in MD vs. Change in SCD P value
sCDAI	-59.33 (64.53)	<.0001	-71.78 (75.94)	<.0001	0.23
CDAI	-55.54 (72.45)	<.0001	-67.47 (78.11)	<.0001	0.28
Short IBDQ	8.21 (10.66)	<.0001	8.85 (10.04)	<.0001	0.56
Fatigue	-5.24 (8.35)	<.0001	-5.37 (7.10)	<.0001	0.91
Pain interference	-5.10 (8.48)	<.0001	-5.73 (8.19)	<.0001	0.60
Sleep disturbance	-3.82 (7.87)	<.0001	-3.28 (7.76)	<.0001	0.63
Social isolation	-3.02 (7.56)	0.0002	-1.75 (7.21)	0.02	0.24

Results are presented as mean (s.d.)
sCDAI – Short Crohn's Disease Activity Index
MD – Mediterranean Diet; SCD – Specific Carbohydrate Diet

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Comparative Effectiveness of Mediterranean Diet and Specific Carbohydrate Diet for CD: **DINE CD Study**

- Conclusions:
  - Symptomatic remission was common with both diets regardless of confirmed inflammation at baseline
  - Both diets were well tolerated despite increased consumption of fruits and vegetables
  - CRP normalization was uncommon with both diets
  - **Clinical key point: SCD was not superior to MD for achieving symptomatic remission**

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Exposure to Corticosteroids in Pregnancy is Associated with Adverse Perinatal Outcomes Among Infants of Mothers with IBD: Results from the PIANO Registry

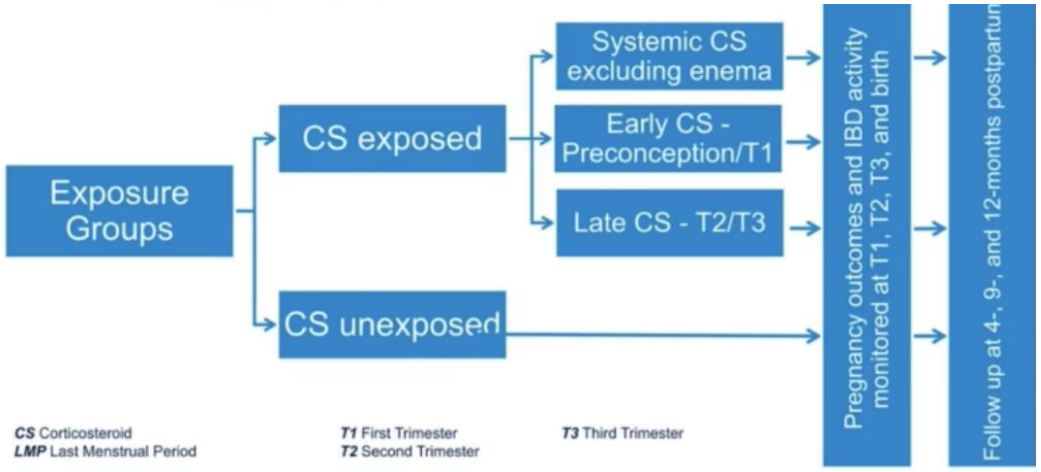
- Background:
  - IBD flares complicate approximately 30% of pregnancies, and steroids may be required for management
  - Active IBD is associated with adverse perinatal outcomes such as pre-term birth, spontaneous abortion and infant infection
  - Exposure to biologics and thiopurines during pregnancy is not associated with increased maternal or infant adverse events

- Aim:
  - To determine the impact of in utero exposure to corticosteroids on adverse pregnancy outcomes, congenital malformations, infant infections, and neurocognitive development among offspring of mothers with IBD

Mahadevan et al. Gastroenterology. 2020
Odufalu et al. DDW. May 23, 2021

Exposure to Corticosteroids in Pregnancy is Associated with Adverse Perinatal Outcomes Among Infants of Mothers with IBD: Results from the PIANO Registry

- Methods:
  - Prospective, multicenter, observational cohort study
  - Data was collected at each trimester, delivery, and at 4, 9, and 12 months post-partum
  - Corticosteroid use was defined as any use during the 3 months prior to conception or during pregnancy
  - Serious infant infections were defined as infections requiring hospitalization



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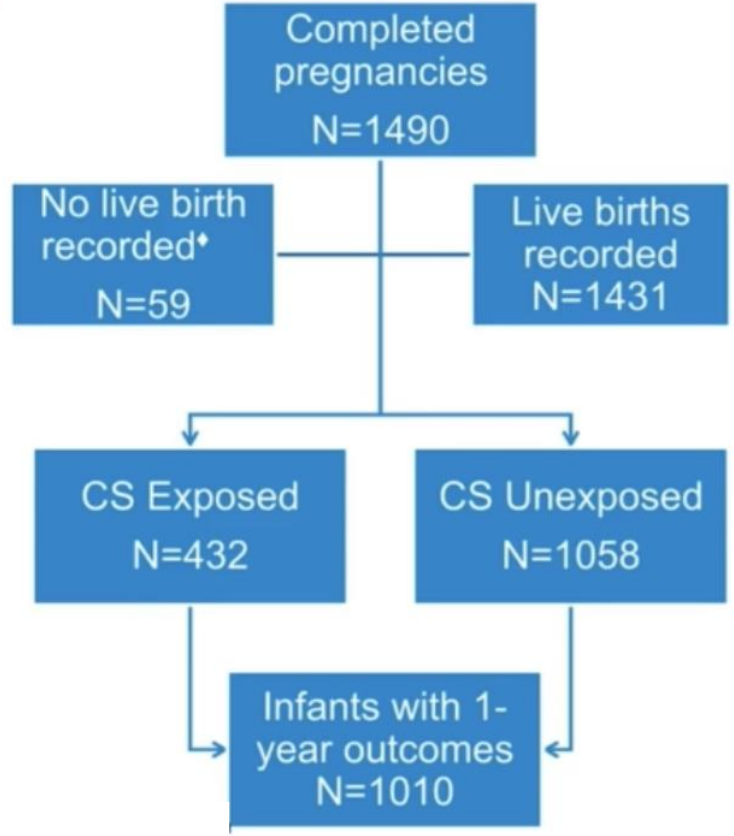
Exposure to Corticosteroids in Pregnancy is Associated with Adverse Perinatal Outcomes Among Infants of Mothers with IBD: Results from the PIANO Registry

- Results:
  - 1,490 mothers enrolled, with 1,431 live births recorded
  - 432 enrolled mothers had exposure to corticosteroids: up to 1/3rd of patients with UC
  - On multivariate models adjusted for biologic, combination or immunomodulator use, corticosteroid use was associated with:
    - Preterm birth (OR 1.79, 95% CI1.18-2.73)
    - Low birth weight (OR 1.76, 95% CI 1.07-2.88)
    - NICU stay (OR 1.54, 95% CI 1.03-2.30)



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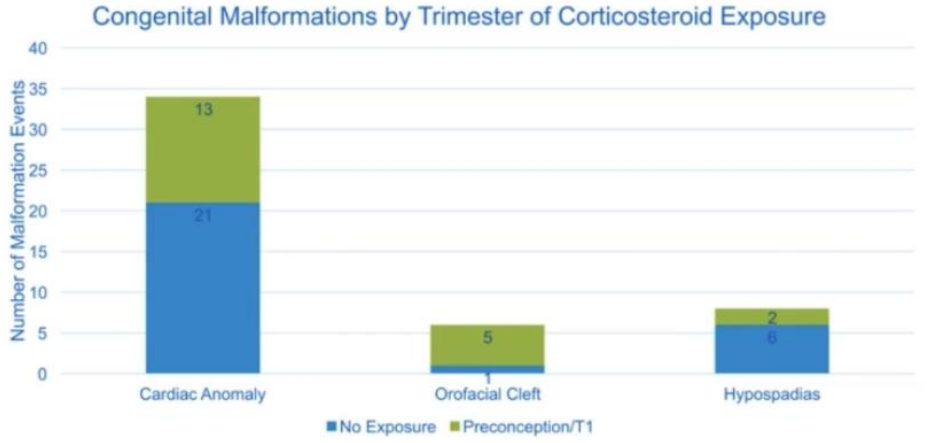
Exposure to Corticosteroids in Pregnancy is Associated with Adverse Perinatal Outcomes Among Infants of Mothers with IBD: Results from the PIANO Registry

- Results:
  - Overall, 9% of infants had congenital malformations
  - Congenital malformations were only observed in infants born to mothers with corticosteroid exposure in the 1st trimester
  - There were 6 infant with orofacial clefts - 5 born to mothers with corticosteroid exposure



Congenital Malformation	Total (%)	No Exposure	Pre-conception/T1	T2/T3	*P* Value
Any Congenital Malformation	126 (9%)	86 (9%)	37 (11%)	0 (0%)	0.04

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Exposure to Corticosteroids in Pregnancy is Associated with Adverse Perinatal Outcomes Among Infants of Mothers with IBD: Results from the PIANO Registry

- Conclusions:
  - Corticosteroid use among pregnant women with IBD was associated with significant increased risk of low birth weight, preterm birth and neonatal ICU stay
  - First trimester corticosteroid exposure was associated with a significant increased rate of congenital malformations in the infant
  - No increased risk of neurocognitive deficits or infections during the first 12 months of life among infants exposed to corticosteroids in utero
  - **Key clinical point: It is imperative to control disease activity before and during pregnancy with steroid sparing therapy**

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Conclusions

- The SEAVUE Study: Both UST and ADA are highly effective as induction and maintenance therapy for moderate-severe CD in biologic naïve patients
- DINE-CD Study: Symptomatic remission in patients with mild-moderate CD was common with both Specific Carbohydrate Diet and Mediterranean Diet regardless of confirmed inflammation at baseline
- The PIANO Registry: Corticosteroid use among pregnant women with IBD was associated with significant increased risk of low birth weight, preterm birth and neonatal ICU stay