

Digestive Diseases and Sciences

Inadequate gestational weight gain predicts adverse pregnancy outcomes in mothers with inflammatory bowel disease: Results from a prospective US pregnancy cohort --Manuscript Draft--

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Full Title:	Inadequate gestational weight gain predicts adverse pregnancy outcomes in mothers with inflammatory bowel disease: Results from a prospective US pregnancy cohort	
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Funding Information:	South-Eastern Norway Regional Health Authority	Dr May-Bente Bengtson
Abstract:	<p>Background: Malnutrition and weight loss are common features of patients with inflammatory bowel disease (IBD).</p> <p>Aim: To explore the impact of inadequate gestational weight gain (GWG) on adverse outcomes among IBD mothers in the prospective US Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) cohort.</p> <p>Methods: The PIANO cohort comprises 559 and 363 pregnant mothers with Crohn's disease (CD) and ulcerative colitis (UC), respectively, enrolled between 2006 and 2014. The mothers were followed during and after pregnancy to ascertain medication, measurement of disease activity and complications during pregnancy and at delivery. Inadequate GWG was based on US Institute of Medicine recommendations. The associations between inadequate GWG and adverse pregnancy outcomes in maternal IBD were analyzed, adjusted for diabetes, hypertension, smoking, maternal age, education and disease activity.</p> <p>Results: Maternal CD and UC with inadequate GWG had a 2.5-fold increased risk of preterm birth (OR = 2.5, CI: 1.3, 4.9 and OR = 2.5, CI: 1.2, 5.6). Furthermore, an increased risk for intrauterine growth restriction (IUGR) and a trend for small for gestational age (SGA) were demonstrated in CD but not in UC (OR = 3.3, CI: 1.1, 10.0, OR = 4.5, CI: 0.8, 24.3, p=0.08). Flares increased risk of inadequate GWG (OR = 1.6, CI: 1.2, 2.3 p = 0.002) but did not change the associations between inadequate GWG and adverse pregnancy outcomes in our models.</p> <p>Conclusion: The US PIANO cohort demonstrated that inadequate GWG was a strong independent predictor of adverse pregnancy outcomes in IBD mothers.</p>	
Author Comments:	<p>Dear Editor</p> <p>I hereby submit the manuscript "Inadequate gestational weight gain predicts adverse pregnancy outcomes in mothers with inflammatory bowel disease: Results from a prospective US pregnancy cohort" and hope that you will find it suitable for publication in Dig. Dis. Sci. A number of studies have demonstrated that IBD mothers have a substantial risk of adverse pregnancy outcomes, such as low birth weight, <2500 g, preterm birth and small for gestational age (SGA) babies. Searching for predictors of adverse pregnancy outcomes in IBD has been an important task for adequate follow-up of IBD patients before and during pregnancy. Disease activity has been shown to</p>	

be the most consistent predictor of adverse pregnancy outcomes among IBD mothers. However, having IBD has been shown to be a risk factor of its own. The most common feature in IBD patients are weight loss. We hypothesized that being prone to weight loss in general influence GWG in maternal IBD, and that GWG might be the link between IBD mothers and adverse pregnancy outcomes. The aim of the present study was therefore to explore the impact of inadequate GWG on adverse pregnancy outcomes among IBD mothers in the prospective United States Pregnancy in Inflammatory Bowel Disease (PIANO) IBD cohort (922 IBD mothers).

We demonstrated for the first time, to our knowledge, that inadequate GWG according to the IOM recommendations, is a strong independent predictor for adverse pregnancy outcomes. Maternal CD and UC with inadequate GWG had a 2.5-fold increased risk of preterm birth. Although disease activity contributed significantly to inadequate GWG, disease activity did not influence the strong association between inadequate GWG and adverse pregnancy outcomes.

Only two studies, both relatively small retrospective from tertiary level, 1, 2 have revealed an association between IBD mothers with weight gain < 12 kg and adverse pregnancy outcomes.

The findings in the present study suggest that preconception counseling should include a discussion of gestational weight gain and assessment of caloric-protein intake in IBD patients before and during pregnancy. Inadequate GWG should be considered both as a marker of possible disease activity as well as an independent predictor of adverse outcomes.

This manuscript, including related data and tables, has not been previously published, and the manuscript is not under consideration elsewhere. We now submit the article to your journal exclusively.

Yours sincerely

May-Bente Bengtson

1. Oron G, Yogeve Y, Shcolnick S, et al. Inflammatory bowel disease: risk factors for adverse pregnancy outcome and the impact of maternal weight gain. *J Matern Fetal Neonatal Med* 2012;25:2256-60.

2. Raatikainen K, Mustonen J, Pajala MO, et al. The effects of pre- and post-pregnancy inflammatory bowel disease diagnosis on birth outcomes. *Aliment Pharmacol Ther* 2011;33:333-9.

4/3-17

Dear Editor

Thank you so much for the possibility to correct and revise our manuscript “Inadequate gestational weight gain predicts adverse pregnancy outcomes in mothers with inflammatory bowel disease: Results from a prospective US pregnancy cohort” (DDSJ-D-16-01683).

We have uploaded the manuscript with significant corrections highlighted in yellow.

Furthermore, we have responded to the reviewers’ comments point by point referring to paragraph and page number in the manuscript.

We hope that our response to the reviewers’ comments and the following corrections made in the manuscript will be considered as an appropriate revision of the manuscript.

Your sincerely

May-Bente Bengtson

Comments to Reviewer 1:

- 1) A “t” has been added to the word “weigh” in **line 2** in the abstract
- 2) The sign has been corrected from above (>) to below (<) regarding 18.5 kg/m² in the second last line, sub-capture “**Other variables**” **page 5**.
- 3) The reviewer states that:” *It has to be discussed that current disease activity indexes during pregnancy are not accurate. In the study the authors rely on HBI and SCCAI indexes to assess disease activity during pregnancy. HBI for example is based on some parameters including: assessment of general well being, abdominal pain, existence of abdominal mass etc. Almost all these parameters can be influenced by the pregnancy itself and sometimes it is very challenging to differentiate between symptoms related to the IBD or to the pregnancy.*”

We agree with the statement that it is difficult to differentiate between symptoms of IBD flares and the pregnancy itself based on some of the parameters of the indexes. However, disease activity was not based only on HBI and SCCAI indexes alone, but also on change in medication for disease activity, and IBD-related hospitalization or surgery between the visits. To clarify this, we have rephrased the last three sentences in the Methods section, **The PIANO cohort, page 4:**” *Furthermore, separate questions about IBD-related hospitalizations, surgeries and intensified treatment with steroid or biological therapy due to flares in between study visits were asked.*”

We have also included a paragraph about the disease activity indexes in the discussion section, last sentence, **page 10** and first paragraph, **page 11:** “*Current disease activity indexes are not accurate and rely on parameters that might be influenced by the pregnancy itself, such as assessment of general well-being, abdominal pain and existence of abdominal mass. It is sometimes challenging to differentiate between symptoms related to IBD versus the pregnancy. However, disease activity was not only based on HBI or SCCAI indexes in the present study. Additional questions including IBD related hospitalization or intensified IBD treatment due to IBD disease activity in between the visit were queried.*”

- 4) The reviewer states that since the study has revealed that inadequate GWG was associated with adverse pregnancy outcomes, not only related to disease activity, the authors should add that “*inadequate GWG can be also related to worsening of obstructive symptoms during pregnancy because of mechanical and hormonal effects in CD patients with obstructing phenotype*” in the discussion chapter. We have therefore added a paragraph in the discussion chapter, the two last sentences, **page 9**, and the first paragraph, **page 10:** “*Bowel resections and strictures are contributing factors to malnutrition and weight loss before pregnancy [11, 12] among CD mothers, and likely also to inadequate GWG during pregnancy. The reason why factors like disease activity, bowel resections, and ileal disease [2, 3, 14] have been reported as predictors of adverse pregnancy outcomes in IBD, might be that they all are possible contributors to lower GWG. Furthermore, inadequate GWG might also be related to worsening of obstructive symptoms due to mechanical effect of the pregnant uterus among CD mothers with obstructive phenotype.*”

We have corrected the affiliation connected to the first and fourth authors from “ *EpiGen-Institute, Faculty Division Akershus University Hospital, University of Oslo*”, Norway to “ *EpiGen-Institute, Faculty Division Akershus University Hospital **and** University of Oslo, Norway*”

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3 Inadequate gestational weight gain predicts adverse pregnancy
4 outcomes in mothers with inflammatory bowel disease: Results from a
5 prospective US pregnancy cohort
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21 **Short running title:** Inadequate weight gain and pregnancy outcomes
22

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42 **Abbreviation:** BMI, body mass index; CI, confidence interval; CD, Crohn's disease; GWG,
43 gestational weight gain; HBI, Harvey Bradshaw Index; IBD, inflammatory bowel disease;
44 IOM, The US Institute of Medicine; IUGR, intrauterine growth restriction; OR, odds ratio;
45 PIANO, Pregnancy IBD and Neonatal Outcomes; REE, resting energy expenditure; SCAI,
46 Short Colitis Activity Index; UC, ulcerative colitis
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Abstract

Background: Malnutrition and weight loss are common features of patients with inflammatory bowel disease (IBD).

Aim: To explore the impact of inadequate gestational weight gain (GWG) on adverse outcomes among IBD mothers in the prospective US Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) cohort.

Methods: The PIANO cohort comprises 559 and 363 pregnant mothers with Crohn's disease (CD) and ulcerative colitis (UC), respectively, enrolled between 2006 and 2014. The mothers were followed during and after pregnancy to ascertain medication, measurement of disease activity and complications during pregnancy and at delivery.

Inadequate GWG was based on US Institute of Medicine recommendations. The associations between inadequate GWG and adverse pregnancy outcomes in maternal IBD were analyzed, adjusted for diabetes, hypertension, smoking, maternal age, education and disease activity.

Results: Maternal CD and UC with inadequate GWG had a 2.5-fold increased risk of preterm birth (OR = 2.5, CI: 1.3, 4.9 and OR = 2.5, CI: 1.2, 5.6). Furthermore, an increased risk for intrauterine growth restriction (IUGR) and a trend for small for gestational age (SGA) were demonstrated in CD but not in UC (OR = 3.3, CI: 1.1, 10.0, OR = 4.5, CI: 0.8, 24.3, $p=0.08$). Flares increased risk of inadequate GWG (OR = 1.6, CI: 1.2, 2.3 $p = 0.002$) but did not change the associations between inadequate GWG and adverse pregnancy outcomes in our models.

Conclusion: The US PIANO cohort demonstrated that inadequate GWG was a strong independent predictor of adverse pregnancy outcomes in IBD mothers.

Keyword: IBD, inadequate gestational weight gain; adverse pregnancy outcome, PIANO cohort, disease activity

Introduction

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2
3 Inflammatory bowel disease (IBD) represents a chronic complex disorder of the
4
5 gastrointestinal tract. The peak incidence of IBD coincides with the prime fertility years. The
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7 course of IBD is characterized by episodes of exacerbations and remissions, but pregnancy, in
8
9 general, does not influence disease activity [1]. Disease activity has been demonstrated as the
10
11 strongest predictor of adverse pregnancy outcomes among IBD mothers [2]. However,
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13 having IBD has been shown to be a risk factor of its own [1, 3]. The most consistent adverse
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15 outcomes described are preterm delivery (before 37 weeks of gestation), low birthweight (<
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17 2500 g) and small for gestational age (SGA) birth [4-6].
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21 Adequate gestational weight gain (GWG) is important for fetal development and growth.

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23 Research indicates that both excessive and inadequate GWG are associated with maternal and
24
25 neonatal complications in the general population [7]. The institute of medicine (IOM) has
26
27 established guidelines for GWG according to pre-pregnancy BMI [8], and the terms excessive
28
29 and inadequate GWG depend on the pre-pregnancy BMI.
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33 Little is known about the impact of inadequate GWG on adverse pregnancy outcomes among
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35 IBD mothers, only two small studies have suggested an association between insufficient
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37 GWG (< 12 kg) and adverse perinatal outcomes [9, 10].
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41 Malnutrition and weight loss are common features of patients with IBD in periods of active
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43 disease as well as in remission. [11-13]. Complications of disease, such as small bowel
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45 inflammation, fistulas and bowel resections are all contributing factors to weight loss among
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47 IBD patients. Furthermore, many IBD patients restrict intake of specific food product, such as
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49 dairy products, to avoid abdominal symptoms, also in quiescence period of disease [12].
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53 We hypothesize that being prone to weight loss in general influences GWG in maternal IBD,
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55 and furthermore, that GWG acts as a link between IBD and adverse pregnancy outcomes.
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1 The aim of this study was therefore to explore the impact of inadequate GWG on adverse
2 pregnancy outcomes among IBD mothers in a large prospective ongoing pregnancy cohort,
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4 the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) IBD cohort.
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7 **Methods**

8 **The PIANO Cohort**

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10 The (PIANO) study is an ongoing, prospective population-based cohort study of pregnant
11 women with IBD based at University of California, San Francisco.
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15 Between 2006 and 2014 over 1100 pregnant women have been enrolled at 33 clinical IBD
16
17 centers in the United States. Women were typically consented during first trimester of
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19 gestation, at which time demographic and anthropometric data, health and lifestyle habits,
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21 IBD history, reproductive history, and history of the current pregnancy, including previous
22
23 and current IBD medication history, was obtained. Questionnaires were completed during
24
25 each subsequent trimester and at delivery to update information on disease activity,
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27 medication use, and pregnancy complications. The post-partum visit captured data on
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29 pregnancy outcomes, including birth weight and gestational age. Only women with singleton
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31 pregnancies were included in the cohort, and only those who delivered a live birth were
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33 included in analyses.
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37 The Harvey Bradshaw Index (HBI) and Walmsley Simple Clinical Colitis Activity Index
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39 (SCCAI) for Crohn's disease (CD) and Ulcerative Colitis (UC) patients, respectively, were
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41 used at each visit to capture information on disease activity during gestation. **Furthermore,**
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43 **separate questions about IBD-related hospitalizations, surgeries and intensified treatment with**
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45 **steroid or biological therapy due to flares in between study visits were asked.**
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53 **Ethics**

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55 The study was approved by the University of California, San Francisco Committee on Human
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57 Research.
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Outcomes variables

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2 Small, for gestational age (SGA) was defined as birth weight below the 10th percentile of
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4 population-based birthweight, based on gender and week of gestation. Preterm birth was
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6 defined as delivery at less than 37 weeks of gestation. Gestational age was based on the first
7
8 trimester ultrasound, or the last menstrual period, if the measure from the ultrasound was
9
10 missing. Intrauterine growth restriction (IUGR) was self-reported based on medical visits.
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Exposure variable

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16 GWG was based on self-reported pre-pregnancy weight at the intake questionnaire in the first
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18 trimester and weight reported in the questionnaire done at the time of delivery. GWG was
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20 classified in three categories according to the IOM definitions; inadequate, below IOM
21
22 recommendation, adequate, according to IOM recommendation and excessive, above IOM
23
24 recommendation for all BMI groups (table 1) [8].
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Other variables

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31 Smoking history was defined as non-smokers, former and daily smokers. Education levels
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33 were split in five categories: high school, some college, graduated from college, graduated
34
35 school and unknown. Maternal diabetic condition, recorded as a 0,1 variable, includes
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37 diabetes I and II as well as gestational diabetes. Maternal hypertension defined as; systolic
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39 blood pressure ≥ 140 , or diastolic blood pressure ≥ 90 and categorized into a 0,1 variable.
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43 BMI based on self-reported pre-pregnant weight and height at the intake questionnaire in the
44
45 first trimester. The pre-pregnant BMI was categorized according to the WHO classification as
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47 underweight ($< 18.5 \text{ kg/m}^2$), normal weight ($18.5 - 24.9 \text{ kg/m}^2$), overweight ($25.0 - 29.9$
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49 kg/m^2) and obese ($\geq 30 \text{ kg/m}^2$).
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Statistical analyses

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56 Kruskal Wallis tests were used to compare continuous variables between the groups and Chi-
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58 squared tests for dichotomous variables.
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1 Logistic regression models were fitted to estimate associations between adverse pregnancy
2 outcomes and inadequate GWG, using dichotomous GWG, inadequate GWG or not. We
3
4 adjusted for potential confounding by diabetes, hypertension, smoking history, maternal age
5
6 and education. Disease activity was added as confounder in separate models. The association
7
8 between inadequate GWG and preterm birth was stratified by disease activity to explore
9
10 potential effect modification of disease activity. We report odds ratio (OR) and corresponding
11
12 confidence intervals (CIs). P-values less than 0.05 were considered statistically significant.
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17 The statistical analyses were performed using SAS version 9.

18 19 **Results**

20 21 **The PIANO IBD cohort:**

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23 The PIANO cohort included 559 CD and 363 UC mothers at the time of analysis.

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25 Demographics, mothers' disease, smoking history and adverse pregnancy outcomes according
26
27 to GWG groups are listed in table 2.
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31 32 **Risk factors for adverse pregnancy outcomes in IBD mothers**

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34 Approximately 20% of the IBD mothers were classified with inadequate GWG. The majority
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36 of IBD mothers with inadequate GWG (82.4%) had normal pre-pregnant BMI. Inadequate
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38 GWG was slightly more frequent among UC mothers (83/363, 22.9%) compared to CD
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40 mothers (104/599, 17.4%) (OR = 1.29, 95% CI: 0.94, 1.79), $p = 0.12$). Crude and adjusted
41
42 odds ratios for adverse pregnancy outcomes among CD and UC mothers with inadequate
43
44 GWG are listed in table 3. Maternal CD and UC with inadequate GWG had a 2.5-fold
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46 increased risk of preterm birth. Furthermore, an increased risk for IUGR and a trend for SGA
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48 were demonstrated in CD mothers, but not among UC mothers.
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52 53 **Disease activity, adverse pregnancy outcomes and GWG**

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55 Approximately thirty percent of the IBD mothers experienced flares during pregnancy, UC
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57 mothers more frequently (37%) compared to CD mothers (26%), $p = 0.0004$.
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1 Disease activity was significantly associated with inadequate GWG among IBD mothers (OR
2 = 1.61, 95% CI: 1.15, 2.25, $p = 0.002$). A trend for disease activity associated with preterm
3 birth among IBD mother was seen (OR = 1.61, 95% CI: 0.99, 2.61, $p = 0.054$), but no
4 associations were found between disease activity and SGA or IUGR (OR = 2.37, 95% CI:
5 0.59, 9.57 and OR = 1.51, 95% CI: 0.64, 3.52, respectively).
6

7 The strong association between inadequate GWG and preterm birth did not change when
8 disease activity was added to the adjusted models (table 3).
9

10 The association between inadequate GWG and preterm birth was stratified by disease activity,
11 in adjusted models. The significant association between inadequate GWG and preterm birth
12 (adjusted OR = 2.4, 95% CI: 1.4, 3.9) (table 3) did not sustain in the analysis including only
13 mothers with disease activity (adjusted OR= 2.0, 95% CI: 0.9, 4.6). Among mothers without
14 disease activity, the association between inadequate GWG and preterm birth increased (OR =
15 2.7, 95% CI: 1.4, 5.0).
16

17 Discussion

18 A number of studies have demonstrated that IBD mothers have a substantial risk of adverse
19 pregnancy outcomes. Searching for predictors of adverse pregnancy outcomes in IBD has
20 been an important task for adequate follow-up of IBD patients before and during pregnancy.
21 Potential predictors like disease activity, ileal CD, bowel resections, and strong family history
22 have been suggested, with disease activity as the most consistent predictor [1, 2, 4, 14, 15].
23 However, having IBD has been shown to be a risk factor on its own, independent of disease
24 activity [1, 3, 16]. Research regarding the impact of inadequate GWG on adverse pregnancy
25 outcomes in IBD is modest. Knowing that IBD patients are prone to weight loss in general,
26 the present study explored the impact of inadequate GWG on adverse pregnancy outcomes
27 among IBD mothers in the prospective ongoing PIANO IBD cohort, based on the
28 recommendations of the US Institute of Medicine.
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1 We demonstrated for the first time, to our knowledge, that maternal inadequate GWG is a
2 strong independent predictor of adverse pregnancy outcomes in IBD. IBD mothers exposed to
3 inadequate GWG, had a 2.5-fold increased risk of preterm birth compared to unexposed IBD
4 mothers, similarly increased in CD and UC mothers (OR = 2.5, 95% CI: 1.3, 4.9 and OR =
5 2.5, 95% CI: 1.2, 5.6, respectively) (table 3). Furthermore, a 3-fold increased risk for IUGR
6 and a trend for SGA was demonstrated in CD mothers with inadequate GWG but not in UC.
7 Disease activity was associated with inadequate GWG (OR = 1.61, 95% CI: 1.15, 2.25, p =
8 0.002) and considered as a potential confounder for inadequate GWG. However, adding flares
9 to the adjusted models, did not change the associations between inadequate GWG and adverse
10 pregnancy outcomes.
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23 Since our analyses revealed that disease activity during pregnancy was associated with
24 preterm birth as a trend (OR = 1.61, 95% CI: 0.99, 2.61, p = 0.054), we explored the relation
25 between inadequate GWG and preterm birth, stratified by disease activity in adjusted models.
26 The association between inadequate GWG and preterm birth (OR = 2.4, 95% CI: 1.5, 4.1)
27 (table 3) did not sustain in the analysis including only IBD mothers with disease activity
28 (OR= 2.0, 95% CI:0.9, 4.6), probably due to low statistical power.
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39 Furthermore, among mothers without disease activity, the association between inadequate
40 GWG and preterm birth was strengthened (OR = 2.7, 95% CI: 1.4, 5.2), indicating that
41 inadequate GWG in women with IBD may be caused by other factors than disease activity,
42 and this can strongly influence the risk of preterm birth. It may be that disease activity is
43 associated with preterm birth particularly because of the association with GWG.
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51 The most commonly presenting feature of newly diagnosed IBD children is weight loss,
52 especially in CD (60%), but also in UC (35%) [13]. Weight loss is also usually observed
53 during relapse of disease [17]. Many factors could contribute to inadequate weight gain
54 during pregnancy among IBD mothers, such as chronic diarrhea, inflammation and bowel
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1 resections. Furthermore, specific food avoidance to minimize symptoms has been suggested
2 as the main mechanism to low caloric-protein intake and micronutrition deficiencies in
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4 periods of active disease as well as in remission [11, 12, 18].
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7 Maternal protein, especially from dairy sources, in the periconceptual and early pregnancy
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9 period has been associated with increased birth weight in both developing and developed
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11 countries [19, 20]. Several investigations have revealed an association between anemia and
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13 preterm birth and low birth weight deliveries [21]. IBD patients, with disease activity as well
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15 as in remission, are exposed to both low protein diet especially from dairy sources [22], and to
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17 anemia [23]. Raatkainen et al. demonstrated three times increased risk of third trimester
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19 anemia in IBD mothers compared to controls [10].
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23 Although malnutrition is a well-known problem in IBD patients, it is generally accepted that
24
25 the prevalence of nutritional deficiencies and malnutrition is higher in CD compared to UC
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27 patients. This has been explained by bowel resections and transmural inflammation in CD,
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29 while inflammation in UC patients affects mucosa only in the large bowel. A recently
30
31 published paper compared the nutritional status and resting energy expenditure (REE)
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33 between hospitalized CD and UC patients found no differences in nutritional parameters and
34
35 energy metabolism between CD and UC patients. However, REE correlated with disease
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37 activity only in UC [24], which might suggest that malnutrition in UC patients is usually
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39 associated with disease activity.
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46 Although disease activity was reported significantly more often among UC mothers (39%)
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48 compared to CD mothers (28%) in the present study, inadequate GWG increased the risk of
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50 preterm birth similarly in CD and UC, independent of disease activity (table 3), suggesting
51
52 that factors other than disease activity contribute to inadequate GWG in UC as well as in CD.
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54 **Bowel resections and strictures are contributing factors to malnutrition and weight loss before**
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56 **pregnancy [11, 12] among CD mothers, and likely also to inadequate GWG during pregnancy.**
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1 The reason why factors like disease activity, bowel resections, and ileal disease [2, 3, 14] have
2 been reported as predictors of adverse pregnancy outcomes in IBD, might be that they all are
3 possible contributors to lower GWG. Furthermore, inadequate GWG might also be related to
4 worsening of obstructive symptoms due to mechanical effect of the pregnant uterus among
5 CD mothers with obstructive phenotype.
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11 Two earlier investigations have included net GWG as a risk factor for adverse pregnancy
12 outcomes among IBD mothers [9, 10], both relatively small retrospective studies from a
13 tertiary university level. The Finish study by Raatikainen et al. [10], showed, that IBD
14 mothers gain less weight during pregnancy compared to controls. The Israeli study by Oron et
15 al, included 28 maternal UC and 47 maternal CD with matched controls [9]. The authors
16 demonstrated that $GWG < 12$ kg was significantly associated with adverse pregnancy
17 outcomes. The Finish study did not include disease activity in their analyses and the Israeli
18 study used proxies for disease activity, such as change in medication and IBD related surgery
19 during pregnancy.
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33 Differences in study design, definitions of adverse pregnancy outcomes and measurement of
34 disease activity might explain the inconsistency of results of IBD investigation.
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38 The strengths of the present study include exploring the potential impact of maternal
39 inadequate GWG on adverse pregnancy outcomes in IBD using GWG according to the IOM
40 recommendations to correct for BMI groups, instead of net GWG. Furthermore, the cohort
41 includes a large number of IBD mothers who have been followed prospectively by
42 measurement of disease activity each trimester using HBI and SCAI for CD and UC,
43 respectively. This is unique for the PIANO cohort, as most pregnancy studies of importance,
44 term the number of pregnancies, are registry studies that had to use different proxies for
45 disease activity like, change of medication or IBD related surgery or IBD hospital admission
46 [5, 6]. Current disease activity indexes are not accurate and rely on parameters that might be
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1 influenced by the pregnancy itself, such as assessment of general well-being, abdominal pain
2 and existence of abdominal mass. It is sometimes challenging to differentiate between
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4 symptoms related to IBD versus the pregnancy. However, disease activity was not only based
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6 on HBI or SSCAI indexes in the present study. Additional questions including IBD related
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8 hospitalization or intensified IBD treatment due to IBD disease activity in between the visit
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10 were queried.
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14 The recording of anthropometric data in the first trimester and at delivery are advantages of
15
16 the PIANO cohort, due to the avoidance of recall bias using questionnaire several months
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18 after delivery. Moreover, the tendency to underestimate pre-pregnant weight would be
19
20 minimized when being asked about weight and height at hospital consultation [25].
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24 In conclusion, this is the first study to demonstrate that inadequate GWG according to the
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26 IOM recommendations is an independent predictor of adverse pregnancy outcomes in women
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28 with IBD. Disease activity was significantly associated with inadequate GWG, but did not
29
30 influenced the strong association between inadequate GWG and adverse pregnancy outcomes.
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34 Our findings suggest that part of preconception counseling and pregnancy monitoring in the
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36 pregnant IBD patient should be around appropriate weight gain, understanding that first
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38 trimester is a risk period difficult to interpret due to low weight gain, if any at all in this
39
40 period [26]. Inadequate GWG should be consider as a marker of disease activity and as an
41
42 independent risk factor for adverse outcomes and referral to a nutritionist for correction of
43
44 calorie-protein intake and micronutrition deficiencies should be made.
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9 The concept and design was worked out by MBB, UM and MHV. Analysis and interpretation
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11 of data by CFM and GAA. MBB wrote the paper. All authors contributed to the drafting and
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13 editing of the manuscript. All authors have read and approved the manuscript for publication.
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Table 1 The American Institute of Medicine (IOM) recommendations for gestational weight gain	
Pre-pregnant categories of BMI	GWG (kg) according to IOM recommendations
BMI < 18.5	12.5 < GWG < 18
18.5 < BMI < 24.9	11.5 < GWG < 15
25 < BMI < 29.9	7 < GWG < 11.5
BMI > 30	5 < GWG < 9

BMI: Body mass index, GWG: Gestational weight gain

Table 2		The PIANO cohort				
Demographic, disease at risk and pregnancy outcomes in maternal IBD allocated by gestational weight gain groups						
		N (%)	Inadequate GWG	Adequate GWG	Excessive GWG	p-value
Mother's age	N (mean, Std)	922 (31.00, 4.62)	187 (30.61, 4.57)	296 (31.72, 4.56)	439 (30.67, 4.63)	0.0014
Education	High school	28 (5.1)	7 (25.0)	4 (14.3)	17 (60.7)	0.1803
	Some college	75 (13.6)	17 (22.7)	16 (21.3)	42 (56.0)	.
	Graduated from college	196 (35.5)	35 (17.9)	65 (33.2)	96 (49.0)	.
	Graduate school	211 (38.2)	46 (21.8)	74 (35.1)	91 (43.1)	.
	Unknown	42 (7.6)	6 (14.3)	14 (33.3)	22 (52.4)	.
BMI groups	1 underweight	51 (5.5)	15 (29.4)	30 (58.8)	6 (11.8)	<.0001
	2 normal	631 (68.4)	154 (24.4)	223 (35.3)	254 (40.3)	.
	3 overweight	175 (19.0)	11 (6.3)	39 (22.3)	125 (71.4)	.
	4 obese	65 (7.0)	7 (10.8)	4 (6.2)	54 (83.1)	.
Diabetes	no	865 (93.8)	173 (20.0)	270 (31.2)	422 (48.8)	0.0179
	yes	57 (6.2)	14 (24.6)	26 (45.6)	17 (29.8)	.
Hypertension	no	870 (94.4)	180 (20.7)	281 (32.3)	409 (47.0)	0.2696
	yes	52 (5.6)	7 (13.5)	15 (28.8)	30 (57.7)	.
Smoking history	Current	22 (2.4)	3 (13.6)	6 (27.3)	13 (59.1)	0.0749
	Former	266 (28.9)	46 (17.3)	76 (28.6)	144 (54.1)	.
	Never	633 (68.7)	138 (21.8)	214 (33.8)	281 (44.4)	.
Preterm birth	no	847 (91.9)	160 (18.9)	269 (31.8)	418 (49.4)	0.0002
	yes	75 (8.1)	27 (36.0)	27 (36.0)	21 (28.0)	.
IUGR	no	899 (97.5)	178 (19.8)	289 (32.1)	432 (48.1)	0.0604
	yes	23 (2.5)	9 (39.1)	7 (30.4)	7 (30.4)	.
SGA	No	898 (99.1)	180 (20.0)	287 (32.0)	431 (48.0)	0.1053
	Yes	8 (0.9)	4 (50.0)	2 (25.0)	2 (25.0)	.

BMI: body mass index, GWG: gestational weight gain, PIANO: Pregnancy in inflammatory Bowel Disease and Neonatal Outcomes, IUGR: intrauterine growth restriction, SGA: small for gestational age, Std: standard deviation

Table 3								
The PIANO Cohort								
ORs for preterm birth, SGA and UIGR among IBD mothers with inadequate gestational weight gain								
	N (obs)	Inadequate GWG	Preterm birth	OR (95% CI)	p-value	Adjusted OR (95% CI) ^a	p-value	Adjusted OR (95% CI) ^b
All	922	187	75	2.41 (1.46, 3.99)	0.0006	2.48 (1.49, 4.11)	0.0005	2.36 (1.42, 3.94)
CD	559	104	46	2.31 (1.19, 4.45)	0.0128	2.50 (1.28, 4.90)	0.0072	2.34 (1.19-4.60)
UC	363	83	29	2.62 (1.19, 5.72)	0.0163	2.53 (1.15, 5.62)	0.0217	2.50 (1.12-5.58)
	N (obs)	Inadequate GWG	SGA	OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	
All	906	184	8	3.98 (0.98, 16.10)	0.052	4.11 (0.99,17.01)	0.0506	3.99 (0.96, 16.42)
CD	549	102	6	4.49 (0.89, 22.55)	0.069	4.49 (0.83,24.35)	0.0810	4.33 (0.80-23.51)
UC	357	82	2	3.38 (0.21, 54.68)	0.39	4.11 (0.25, 68.16)	0.324	4.28 (0.26-71.78)
	N (obs)	Inadequate GWG	UIGR	OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	
All	922	187	23	2.60 1.11, 6.11)	0.028	2.51 (1.05, 5.99)	0.038	2.39 (0.99, 5.77)
CD	559	104	14	3.42 (1.16,10.08)	0.026	3.32 (1.09, 10.04)	0.034	3.07 (1.00-9.37)
UC	363	83	9	1.71 (0.42, 7.00)	0.45	1.51 (0.35, 6.57)	0.58	1.71 (0.38-7.65)

a: Adjusted for education, mother's age, mother's disease such as hypertension and diabetes, smoking history
b: Disease activity was added in separate regression models
CD: Crohn's disease, CI: confidence interval, GWG: gestational weight gain, IBD: inflammatory bowel disease, OR: odds ratio, PIANO: Pregnancy in inflammatory Bowel Disease and Neonatal Outcomes, SGA: small for gestational age, UIGR: intrauterine growth restriction, UC: ulcerative colitis