Inadequate gestational weight gain, the hidden link between maternal IBD and adverse pregnancy outcomes? Results from the Norwegian Mother and Child cohort

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Background: Mothers with inflammatory bowel disease (IBD) have an overall risk of adverse pregnancy outcomes. Knowing that weight loss and malnutrition are common features in IBD, we introduced inadequate gestational weight gain (GWG) as a predictor of adverse pregnancy outcomes among IBD mothers in the Norwegian Mother and Child Cohort Study (MoBa).

Methods: MoBa with 95200 mothers enrolled from 1999 to 2008, comprised 287 mothers with ulcerative colitis (UC) and 215 with Crohn's disease (CD). Demographics, IBD history and disease activity during pregnancy were ascertained.

Inadequate GWG was based on The US Institute of Medicine (IOM) recommendations.

The associations between IBD and inadequate GWG or adverse pregnancy outcomes, were explored, adjusted for diabetes, hypertension, smoking, maternal age, education and disease activity.

Results: The associations between IBD and small for gestational age (SGA) and between CD and preterm birth did not sustain, when inadequate GWG was added in the models.

CD (34.3%) and UC mothers (26.7%) were more frequently exposed to inadequate GWG compared to non-IBD mothers (19.4%) (OR = 2.02, 95% CI: 1.42, 2.86 and OR = 1.46, 95% CI: 1.04, 2.05, respectively).

IBD mothers with inadequate GWG (exposed) had a two-fold risk of SGA compared to exposed non-IBD mothers (adjusted OR = 1.93, 95% CI: 1.13, 3.29).

Exposed CD and UC mothers had a several-fold increased risk of SGA compared to non-exposed IBD mothers (OR = 4.5, 95% CI: 1.3, 16.2, OR = 5.5, 95% CI: 1.6, 18.5). Disease activity was associated with lower GWG.

Conclusion: Inadequate GWG was a strong independent predictor of adverse pregnancy outcomes in IBD.

INTRODUCTION

Inflammatory bowel disease (IBD) represents chronic complex disorders of the gastrointestinal tract, ulcerative colitis (UC) and Crohn's disease (CD), with highest incidence peak in fertile age. Several risk factors have been associated with adverse pregnancy outcomes in IBD mothers, such as disease activity[1, 2], bowel resections [3] and familial aggregation of IBD [4]. Although disease activity at conception and during pregnancy has been pointed out as the strongest predictor of adverse pregnancy outcomes in IBD mothers, having IBD has been demonstrated as a risk factor on its own, , independent of disease activity [5, 6]. The most consistent adverse outcomes described are preterm delivery (before 37 weeks of gestation), low birthweight (< 2500 g) and small for gestational age (SGA) birth [7-9].

It is well known that adequate gestational weight gain (GWG) during pregnancy is essential for fetal development and growth. Several investigations have revealed an association between inadequate GWG and preterm birth or SGA babies in the general population[10-12]. The influence of GWG on pregnancy complications depends on the pre-pregnancy body mass index (BMI). The institute of medicine (IOM) has established guidelines for GWG according to pre-pregnancy BMI [13], which has been adopted by the Norwegian directorate of health. IBD patients are vulnerable to weight loss and malnutrition, especially in period with active disease, but also in remission[14] Contributing factors to weight loss in remission are disease complications such as stenosis, bowel resections and food restriction, especially dairy products, to avoid symptoms like diarrhea and abdominal pain.[15-17].

Only two small studies have demonstrated an association between low GWG (< 12kg) and adverse perinatal outcomes in maternal IBD [18, 19].

We hypothesize that inadequate GWG, according to the IOM guidelines, is the link between IBD and adverse pregnancy outcomes, furthermore, that IBD mothers are more vulnerable to inadequate GWG compared to non-IBD mothers.

In the present study, we explored the impact of inadequate GWG on the risk of adverse pregnancy outcomes among IBD mothers in the population-based Norwegian Mother and Child Cohort (MoBa).

MATERIALS and METHODS

The Norwegian Mother and Child Cohort

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health[20]. The cohort now includes 114.500 children and 95.200 mothers recruited from all over Norway in the period 1999 to 2008. The pregnant women were included at 17 – 18 weeks gestation at the first ultrasound visit. Informed consent was obtained from all participants and they were asked to fill out comprehensive questionnaires at regular intervals. The basic questionnaire (Q1), at week 17-18, shortly before the first ultrasound visit, included information of mothers' socio-demographic data, such as education, age, height, pre-pregnancy weight and smoking history. Furthermore, they were asked about health, lifestyle, medication and pregnancy complications. In the fourth questionnaire (Q4), six months postpartum, the participants were asked to record weight at delivery and at 6 months postpartum. In the GWG analyses, mothers with plural birth and GWG less than -30 kg and higher than 50 kg were excluded from the analyses. Of the 739 mothers who claimed to suffer from IBD in the basic questionnaire (Q1), 655 mothers were available for the present study. We mailed out a questionnaire in 2013 to obtain information about the IBD history and disease activity 4 weeks before pregnancy and during the pregnancy. Disease activity was graded on a scale 1 to 4, from no symptoms to severe symptoms affecting daily activity with sick leave as a consequence. Furthermore, they

were asked to report treatment consequences of flares with three options; change of medication, IBD-related surgery or IBD-related hospital admissions. The fulfilment of one or more of these three options was defined as disease activity. Of the 328 responders, 136 and 192 mothers suffered from Crohn's disease (CD) and ulcerative disease (UC), respectively. Of the non-responders, 79 and 95 were recorded as CD and UC by the Norwegian Patient registry (NPR), which left the present study with 502 patients, 215 CD and 287 UC, for the analyses reflecting the association between GWG and pregnancy outcomes in IBD mothers. The cohort was linked to The Medical Birth Registry of Norway.

Ethics

The study was approved by The Regional Committee for Medical Research Ethics in South-Eastern Norway.

Outcomes variables

Small, for gestational age (SGA) was defined as birth weight below the 10^{th} percentile of population-based birthweight, based on gender and week of gestation. Preterm birth was defined as delivery at less than 37 weeks of gestation. Gestational age was based on the first trimester ultrasound, or the last menstrual period, if the measure from the ultrasound was missing.

Exposure variable

GWG was classified in three categories according to the IOM definitions; inadequate, below IOM recommendation, adequate, according to IOM recommendation and excessive, above IOM recommendation for all body mass index (BMI) groups (table 1) [13].

Table 1 The American Institute of Medicine (IOM) recommendations for gestational weight gain (GWG)	
Prepregnant 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

Other variables

Smoking history was defined in terms of non-smokers, occasional smokers and daily smokers, the latter two merged and considered to represent the smokers.

Education levels was divided in three categories by year of education; ≤ 12, 13 – 16, ≥ 17.

Maternal diabetic condition, recorded as a dichotomous variable, includes diabetes I and II as well as gestational diabetes. Maternal hypertension defined as; systolic blood pressure ≥ 140, or diastolic blood pressure ≥ 90. BMI was calculated, based on self-reported pre-pregnant weight and height in the basis questionnaire (Q1). The pre-pregnant BMI was categorized according to the WHO classification as underweight (18.5 kg/m^2), normal weight (18.5 – 24.9 kg/$m^{2)}$, overweight (25.0 – 29.9 kg/m^2) and obese (≥30 kg/m^2).

Statistical analyses

Kruskal-Wallis tests were used to compare continuous variables between the groups and Chi-squared tests for dichotomous variables.

Logistic regression models were fitted to estimate associations between adverse pregnancy outcomes and IBD. Inadequate GWG was added in separate models.

Furthermore, associations between IBD mothers exposed to inadequate GWG and adverse pregnancy outcomes were estimated, using dichotomous GWG, inadequate GWG or not, or adequate GWG as reference group. We adjusted for potential confounding by diabetes, hypertension, smoking history, maternal age and education. Disease activity was added as

confounder in separate models. We report odds ratio (OR) and corresponding 95% confidence intervals (CIs).

The continuous variable GWG was split in quartiles based on the distribution of GWG among IBD mothers; GWG < 10 kg, 10 kg ≤ GWG < 13 kg, 13 kg ≤ GWG < 17.5 kg and GWG ≥ 17.5. The two first quartiles were collapsed and considered to represent the lowest GWG group. P-values less than 0.05 were considered statistically significant. The statistical analyses were performed using the software SPSS version 20.

RESULTS

The Norwegian MoBa Cohort

The cohort comprises 215 CD and 287 UC mothers, of whom 166 CD and 218 UC mothers and 79125 non-IBD mothers were available for the GWG analyses.

Disease activity before and during pregnancy

Of the responders to our mail-out questionnaire, 132 of 136 CD and 177 of 192 UC mothers completed questions about disease activity (88%). Sixty-five IBD mothers (65/309, 21%) reported flares during pregnancy with either change in medication (57/65), IBD-related hospital admission (16/65) or IBD-related surgery (5/65). There was a high correlation between disease activity four weeks before conceiving and disease activity during pregnancy, with highest correlation when reporting severe disease. The correlations between disease activity before and during pregnancy for those who experienced some disease activity, but with no consequences for daily activity and for those who experienced severe disease activity with sick leave, were estimated to 52 % and 81 %, respectively. Furthermore, there was a high correlation (75 %) between IBD mothers who experienced severe disease activity during pregnancy and the need of change of medication, IBD-related surgery or IBD-hospital admission.

GWG among IBD and non-IBD mothers

Demographics, mothers' disease, smoking history and adverse pregnancy outcomes in Maternal CD and UC compared to controls are listed in table 2.

The GWG for maternal CD varied from -16 kg to 43 kg, and the corresponding values for maternal UC were -2 kg to 37 kg. Maternal CD (34.3%) and UC (26.7%) had a higher risk of inadequate GWG compared to non-IBD (19.4%) (adjusted OR = 2.02, CI: 1.42, 2.86 and OR = 1.46, CI: 1.04, 2.05, respectively).

The distribution of BMI groups did not differ between IBD and non-IBD mothers (table 3). The significant higher risk of inadequate GWG among both UC and CD mothers compared to non-IBD, appeared in the normal BMI group, which comprised about 66% of the mothers. Maternal CD (57/166, 34.3%) demonstrated a trend for increased risk of inadequate GWG compared to maternal UC (58/217, 26.7%) (crude OR = 1.44, CI: 0.93, 2.23, p = 0.10).

Risk factors for adverse pregnancy outcomes in IBD mothers

CD mothers, but not UC mothers (data not shown), had a higher risk of preterm birth compared to non-IBD (adjusted OR = 1.30, 95 % CI: 1.00, 1.71, p = 0.05). IBD mothers had a significant higher risk of SGA compared to non-IBD mothers (adjusted OR = 1.47, 95% CI: 1.00, 2.15, p = 0.045). When inadequate GWG was added in separate regression models, the association between CD and preterm birth and between IBD and SGA did not maintain (adjusted OR = 1.26, 95% CI: 0.92, 1.73 and OR = 1.37, 95% CI: 0.93, 2.00, respectively). IBD mothers with inadequate GWG were more vulnerable of SGA compared to non-IBD mothers with inadequate GWG (adjusted OR = 1.93, 95% CI: 1.13, 3.29).

Weight gain was increasingly protective against preterm birth for maternal CD with inadequate GWG adjusted for BMI (OR = 0.66, 95 % CI: 0.45, 0.96), compared to non-IBD mothers with inadequate GWG (OR = 0.96, 95% CI: 0.94, 0.97). Mean difference in net

weight gain between IBD (7.8 kg) and non-IBD (7.4 kg) with maternal inadequate GWG was 0.443 g (p = 0.44).

The crude and adjusted odds for preterm birth or SGA babies among CD and UC mothers exposed to inadequate GWG, are listed in Table 4. In these analyses, using GWG as a dichotomous variable, inadequate or not, we compared IBD mothers who were exposed to inadequate GWG with non-exposed IBD mothers. Exposed UC and CD mothers were associated with 5.5 and 4.5 increased risk for SGA, respectively,

The distribution of pregnancy outcomes, mothers' disease and sociodemographic data according to GWG groups among IBD mothers are listed in table 5.

Using adequate GWG as a reference group did not change the strong association between inadequate GWG and SGA in IBD. IBD mothers with inadequate GWG had a four-fold increased risk of SGA compared to IBD mothers with adequate GWG (adjusted OR = 4.01, 95 % CI: 1.39, 11.88). The odds for SGA did not differ between IBD mothers with adequate GWG and IBD mothers with excessive GWG (OR = 0.73, 95% CI: 0.22, 2.41).

IBD mothers with excessive GWG tend to be current smokers compared to IBD mothers with inadequate GWG (OR = 2.33, 95 % CI: 0.88, 6.09, p = 0.07).

Disease activity, GWG and adverse pregnancy outcomes

IBD mothers with flares demonstrated a trend for inadequate GWG (36.8%) compared to excessive GWG (28.1%) (OR = 2.08, 0.90, 4.79, p = 0.09), but flares were similarly distributed among mothers with inadequate GWG and adequate GWG (35.1%). However, the risk of low GWG (< 13kg) compared to high GWG (> 17.5kg) was higher among IBD mothers with flares compared to those without flares (adjusted OR = 3.34, 95 % CI: 1.33, 8.38). Flares were reported twice as often among UC (47/177, 26.6%) compared to CD mothers (18/132, 13.6%) (crude OR = 1.95, CI: 1.19, 3.19, p = 0.006). Maternal UC with inadequate GWG (15/45, 33.3%) demonstrated a trend for flares compared to maternal CD

with inadequate GWG (6/35, 17.1%) (crude OR = 1.94, CI: 0.84, 4.49, p = 0.10).

Disease activity was neither linked to preterm birth, nor SGA among IBD mothers (adjusted OR = 0.64, 95 % CI: 0.14, 3.01 and OR = 0.87, 95% CI: 0.28, 2.72, respectively).

The strong association between IBD mothers with inadequate GWG and SGA did not change when disease activity was added in second models for the association between inadequate GWG and adverse pregnancy outcomes (table 4).

Table 2 The Norwegian Mother and Child Cohort
Demographics, mothers' disease, smoking history and pregnancy outcomes in maternal CD and UC compared to controls

		IBD (%)	CD (%)	p-value*	UC (%)	p-value*
Mothers' age	N (mean, std)	489	209 (30.35, 4.13)	0.49	280 (30.96, 4.15)	0.003*
Education groups	High school or less	154 (33.6)	72 (37.3)		82 (30.9)	
	College 3 years	210 (45.9)	86 (44.6)	0.15	124 (46.8)	0.56
	Master or higher	94 (20.5)	35 (18.1)	0.87	59 (22.3)	0.24
Diabetes	Yes	6 (1.2)	1 (0.5)	0.23	5 (1.8)	0.69
	No	483 (98.8)	208 (90.5)		275 (98.2)	
Hypertension	Yes	25 (5.1)	10 (4.8)	0.56	15 (5.4)	0.79
	No	464 (94.9)	199 (95.2)		265 (94.6)	
Smoking history	Current	43 (9.7)	28 (14.4)	0.02*	15 (6.0)	0.07
	Never	401 (90.3)	166 (85.6)		236 (94)	
Gestational weight gain	N (mean, std)	384	13.56 (6.7)	0.006*	13.97 (5.8)	0.04*
Prepregnant BMI groups (p-values with normal BMI; 18.5 < BMI < 24.9 as reference group)	BMI < 18.5	16 (3.4)	9 (4.4)	0.38	7 (2.6)	0.53
	18.5 < BMI < 24.9	326 (68.5)	139 (68.5)		187 (68.5)	
	25 < BMI < 29.9	95 (20.7)	42 (20.7)	0.57	53 (19.4)	0.29
	BMI > 30	39 (8.2)	13 (6.4)	0.10	26 (9.5)	0.93
Preterm	Yes	31 (6.3)	17 (8.1)	0.06	14 (5.0)	0.85
	No	458 (93.7)	192 (91.9)		266 (95.0)	
SGA	yes	45 (9.2)	21 (10.1)	0.05*	24 (8.6)	0.20
	No	442 (90.8)	186 (89.9)		256 (91.4)	

*Compared to controls

Table 3 The Norwegian Mother and Child Cohort
Maternal CD and UC, compared to control, allocated by gestational weight gain in BMI groups according to the American Institute of Medicine (IOM) recommendations

	Controls	**CD**		**UC**	
Underweight BMI < 18.5	N (%)	N (%)	p-value (vs controls)	N (%)	p-value (vs controls)
Inadequate (< 12.5)	713 (30.5)	4 (66.7)	0.06	1 (16.7)	0.46
Adequate (12.5<GWG< 18)	1075 (46.4)	2 (33.3)	0.54	3 (50)	0.84
Excessive (>18)	529 (22.8)	0 (0)	0.17	2 (33.3)	0.58
Normal weight 18.5 < BMI < 24.9					
Inadequate (< 11.5)	11518 (21.1)	46 (39.3)	<0.0001*	50 (32.6)	0.001*
Adequate (11.5<GWG< 15)	21134 (40.5.)	35 (29.9)	0.02*	55 (36.9)	0.38
Excessive (>15)	19555 (37.4)	36 (30.8)	0.14	44 (29.5)	0.05*
Overweight 25 < BMI < 29.9					
Inadequate (< 7)	1568 (9.1)	5 (15.2)	0.23	3 (7.0)	0.63
Adequate (7<GWG< 11.5)	3733 (21.6)	12 (36.4)	0.04*	8 (18.6)	0.63
Excessive (>11.5)	11957 (69.4)	16 (48.5)	0.01*	33 (75)	0.47
Obese BMI > 30					
Inadequate (< 5)	1318 (18)	2 (20.0)	0.86	4 (21.1)	0.73
Adequate (5<GWG< 9)	1603 (21.6)	4 (40.0)	0.16	3 (15.8)	0.54
Excessive (>9)	4422 (60.5)	4 (40.0)	0.19	12 (63.2)	0.79
Plural birth excluded 50kg > GWG > -30 kg					

Table 4 The Norwegian Mother and Child Cohort

ORs for preterm birth and SGA among IBD mothers with inadequate gestational weight gain

	N (obs)	Inadequate GWG	Preterm birth	OR (95 %CI)	p-value	Adjusted OR (95% CI)	p-values	Adjusted OR (95% CI) *
IBD	383	115	23	1.87 (0.78, 4.39)	0.15	1.79 (0.62, 5.11)	0.28	0.56 (0.098, 3.16)
CD	166	57	13	1.71 (0.55, 5.37)	0.35	1.50 (0.37, 6.10)	0.57	
UC	217	58	10	1.89 (0.51, 6.95)	0.33	1.3 (0.43, 8.23)	0.40	
	N (obs)	**Inadequate GWG**	**SGA**	**OR (95 %CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-values**	
IBD	383	115	35	3.55 (1.74, 7.22)	< 0.0001	4.96 (2.09, 11.74)	< 0.0001	5.48 (1.91, 15.73)
CD	166	57	17	3.10 (1.11, 8.65)	0.025	4.53 (1.27, 16.18)	0.02	
UC	217	58	18	3.93 (1.47, 10.53)	0.004	5.46 (1.61, 18.48)	0.006	

Plural birth excluded. Adjusted for education, mothers' age, diabetes, hypertension, smoking history

*Disease activity added as a confounder in a second regression model

Table 5 The Norwegian Mother and Child Cohort

Demographics, mothers' disease, smoking history in maternal IBD allocated by GWG groups

		N (%, mean, SD)	Inadedequate GWG	Adequate GWG	Excessive GWG	p-value
Mothers' age	N (mean, SD)	387 (30.69, 4.15)	29,92 (4.56)	31.08 (3.94)	30.08 (3.87)	0.14
Education	High school or less	114 (31.6)	38 (33.3)	25 (21.9)	51 (44.7)	0.048
	College 3 years	172 (47.6)	49 (28)	58 (33.1)	68 (38.9)	
	Master or higher	75 (20.8)	25 (21.9)	33 (42.9)	58 (33.1)	
BMI groups	Underweight	12 (3.1)	5 (41.7)	5 (41.7)	2 (16.7)	< 0.0001
	Normal	26.6 (69.5)	96 (35.6)	92 (34.1)	82 (30.4)	
	Overweight	76 (19.8)	8 (10.4)	20 (26,0)	49 (63.6)	
	Obese	29 (7.6)	6 (20.7)	7 (24.1)	16 (55.2)	
Diabetes	No	384 (99)	112 (29.2)	123 (32.0)	149 (38.8)	0.12
	Yes	4 (1)	3 (75)	1 (25)	0	
Hypertension	No	368 (95.1)	112 (30.4)	118 (32.1)	138 (37.5)	0.25
	Yes	19 (4.9)	3 (15.8)	5 (26.3)	11 ((57.9)	
Smoking history	Never	312 (91.0)	93 (29.8)	104 (33.3)	115 (36.9)	0.07
	Current	31 (9.0)	6 (19.4)	7 (22.6)	18 (58.1)	
Preterm birth	No	362 (93.5)	105 (29)	117 (32.3)	140 (38.7)	
	Yes	23 (6.5)	10 (43.5)	5 (21.7)	8 (34.8)	0.24
SGA	No	351 (90.7)	95 (27.1)	116 (33)	140 (39.9)	
	Yes	35 (9.3)	20 (57.1)	7 (20.0)	8 (22.9)	0.001

Plural birth excluded from the analyses

DISCUSSION

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. Although disease activity has been pointed out as the strongest predictor of adverse pregnancy outcomes in IBD [1, 2], having IBD has been shown to be a risk factor on its own, independent of disease activity [6, 21, 22]. Based on the knowledge that IBD patients are prone to weight loss in general [15, 16], we introduced inadequate GWG as a predictor of adverse pregnancy outcomes among IBD mothers, in The Norwegian Mother and Child cohort (MoBa). Our study revealed that inadequate GWG occurred more often among IBD mothers compared to non-IBD mothers, and furthermore, modified the association between IBD and adverse pregnancy outcomes. Inadequate GWG appeared as a strong independent predictor of adverse pregnancy outcomes among IBD mothers. Although disease activity contributed to low weight gain during pregnancy, it did influence the association between inadequate GWG and adverse pregnancy outcomes.

Like several large Scandinavian population-based studies [8, 9], we showed an association between IBD mothers and SGA babies and between preterm birth and CD mothers However, when inadequate GWG was included in separate models, these associations did not sustain, which is explained by the significant higher prevalence of inadequate GWG among mothers with CD (34.3%) and UC (26.7%) compared to non-IBD (19.4%).

By introducing maternal inadequate GWG as a predicting factor of adverse pregnancy outcomes in IBD, we unraveled a several-fold increased risk of adverse pregnancy outcomes in CD and UC mothers when exposed to inadequate GWG independent of disease activity (table 4). The risk of SGA was increased with a factor of 4.5 and 5.5 in exposed CD and UC mothers, respectively, compared to non-exposed CD and UC mothers. These results suggest

that inadequate GWG might have acted as a "hidden link" between IBD mothers and adverse pregnancy outcomes in earlier investigations which have not accounted for inadequate GWG. The most commonly presenting feature of new-diagnosed IBD children is weight loss, especially in children with CD (60%), but also in UC (35%) [14]. Weight loss is also usually observed during relapse of disease [23]. Many factors could explain why mothers with IBD are more exposed to inadequate weight gain during pregnancy compared to mothers without IBD. Enteric loss of nutrition and malabsorption due to chronic diarrhea, inflammation and bowel resections are contributing factors of malnutrition in IBD patients. However, reduced food intake, to minimize symptoms of abdominal pain and diarrhea, has been suggested as one of the main mechanisms to low caloric-protein intake as well as micronutrition deficiencies in IBD, even in remission [16]. One study showed that approximately 33% of IBD patients avoid dairy products in remission[17]. Protein intake from diary sources, especially in early period of pregnancy, has been shown to correlated with birth weight both in developed and developing countries [24-27]. Furthermore, anemia, which occurs in approximately 25 % of the IBD patients [28, 29], has been linked to adverse pregnancy outcomes like preterm birth and low birth weight [30, 31].

An earlier MoBa study revealed a link between SGA and inadequate GWG in the general population in Norway[11]. The present MoBa-IBD study showed that inadequate GWG had a higher impact on adverse pregnancy outcomes among IBD compared to non-IBD. Maternal CD with inadequate GWG reduced the risk of preterm birth with 34% per kg weight gain compared to 4% in non-IBD mothers with inadequate GWG. Furthermore, IBD mothers with inadequate GWG had twice as high risk for SGA babies compared to non-IBD mothers with inadequate GWG (OR = 1.93, 95% CI: 1.13, 3.29). This vulnerability of preterm birth and SGA among IBD mothers exposed to inadequate GWG compared with exposed non-IBD mothers cannot be explained by lower net weight gain among IBD mothers (mean difference

0.443 g, p = 0.44). The explanation might be that IBD mothers are prone to malnutrition before conceiving and in the periconceptional and early pregnancy periods. Nutrition related influences on adverse pregnancy outcomes are captured especially in this period, the stage of rapid placental development[32-34].

The increased risk of inadequate GWG among IBD mothers compared to non-IBD appeared especially in the normal pre-pregnant BMI group, which included approximately 66 % of the IBD mothers. However, the tendency to gain lower weight compared non-IBD was seen in all BMI groups for maternal CD. Mothers without IBD had a higher risk to gain excessive weight when placed in the overweight or obese pre-pregnant BMI group compared to UC and CD, respectively.

A higher proportion of UC mothers (27%) reported disease activity during pregnancy defined as; change of medication, IBD-related hospital admission or surgery during pregnancy, compared to CD mothers (17%). Maternal UC with inadequate GWG (15/45, 33.3%) demonstrated a trend for disease activity compared to maternal CD with inadequate GWG (6/35, 17.1%) (p = 0.10), which might suggest that that inadequate GWG in UC patients is associated with disease activity. A recently published study reflects similar association between disease activity and malnutrition only in UC, by comparing the nutritional status and resting energy expenditure (REE) between hospitalized CD and UC patients. [35]. This study did not find any differences in nutritional parameters and energy metabolism between CD and UC patients. IL-6 correlated with disease activity in both CD and UC, but REE correlated with disease activity only in UC.

Malnutrition in CD patients could be explained by several factors, unrelated to disease activity, like small bowel resections and transmural inflammation. Al-Jaouni et al. showed altered metabolism with higher REE in combination with increased fat oxidation in CD patients with active disease as well as in remission [36] .

Disease activity was not associated with adverse pregnancy outcomes in IBD mothers in this cohort. Furthermore, disease activity did not influence the strong association inadequate GWG and SGA in maternal IBD. When disease activity was included in the second regression model, the risk of SGA remained high, and even increased, from 5.0 to 5.5, among exposed IBD mothers compared with unexposed IBD mothers.

Our study revealed that disease activity was a risk factor of low GWG. The risk of low GWG (< 13kg) compared to high GWG (> 17.5kg) was higher among IBD mothers with flares compared to those without flares (adjusted OR = 3.34, 95 % CI: 1.33, 8.38).

We speculate, based on these results, that inadequate GWG is predictor of adverse pregnancy outcomes in IBD, independent of disease activity. Disease activity should be considered as a risk factor of inadequate GWG, or low GWG, as should bowel resections and ileal disease.

Two earlier investigations have included net GWG as a risk factor for adverse pregnancy outcomes among IBD mothers [19, 37], both relatively small retrospective designed studies from tertiary university level. The Finish study by Raatikainen et al, showed like the present study, that IBD mothers gain lesser weight during pregnancy compared to controls. The Israeli study by Oron et al, included 28 maternal UC and 47 maternal CD with matched controls [37]. Data on disease activity before and during pregnancy was collected by reviewing medical charts. The authors demonstrated that GWG < 12 kg as well as disease exacerbation were significantly associated with adverse pregnancy outcomes.

The strengths of the present study include the large and nationwide sample size, the linkage to the national birth registry, and the use of GWG according to the IOM recommendations to correct for BMI groups, instead of net GWG. Limitations of this study include the fact that weight change and pre-pregnant weight class were based on self-reported weight. Epidemiological studies on GWG have shown that women, especially women who are overweight or obese, underestimate their pre-pregnant weight, which might place them in a

lower BMI group with overestimated GWG [38]. However, being placed in excessive instead of adequate GWG group in the normal and overweight group, respectively, has probably not influenced the association between inadequate GWG and adverse pregnancy outcomes in the present study because we used GWG as a dichotomous variable, inadequate or not, merging adequate and excessive GWG in the same group. Introducing the exposure variable as a dichotomous variable, inadequate GWG or not, is another concern of this study, because the association between SGA and inadequate GWG might be overestimated due a usually lower risk of SGA in the excessive GWG group. However, the distribution of SGA was similar in the adequate (20.0%) and the excessive group of GWG (22.9%), among the IBD mothers in contrast to the results in the background population [11], which revealed a reduced risk of SGA in the excessive GWG group in all BMI groups. We did perform analyses comparing the occurrence of preterm birth and SGA among IBD mothers exposed to inadequate GWG using adequate GWG as the reference group, with similar results as in the analyses using GWG as a dichotomous variable. In these analyses, we collapsed CD and UC mothers to increase statistical power.

Another limitation was self-reported disease activity several years after delivery. They were asked to report disease activity before and during pregnancy in two ways, by symptoms scale, range from no symptoms to severe symptoms with sick leave as a consequence, and by change in treatment. There was a high correlation between disease activity before and during pregnancy in line with earlier investigations [39] and between reported severe disease and change of treatment, which demonstrated consistency of the reported disease activity.

In conclusion, this study revealed, for the first time to our knowledge, that IBD mothers are more exposed to inadequate GWG, compared to non-IBD mothers, and when exposed to inadequate GWG, more vulnerable to adverse pregnancy outcomes. Furthermore, we showed that inadequate GWG is a strong independent predictor of SGA among IBD mothers. Disease

activity contributed to low GWG, suggesting that inadequate GWG has been the "hidden" link between IBD and adverse pregnancy outcomes in earlier investigations. The reason why factors like disease activity, bowel resections, and ileal disease [1-3] have been pointed out as predictors of adverse pregnancy outcomes in IBD, might be that they all are possible contributors to low GWG.

Our findings suggest careful follow-up of caloric-protein intake in IBD patients before pregnancy and during pregnancy, having in mind that the first trimester is a risk period difficult to interpret, due to low weight gain, if any at all in this period [40]. Inadequate GWG should be consider as a risk factor on its own or as a marker of disease activity leading to disease activity measurement and nutritional correction of calorie-protein intake and micronutrition deficiencies.

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