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Original article

Assessment of the procoagulant potential and associated risk factors in pregnant patients with inflammatory bowel diseases

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ABSTRACT

Objective: Both inflammatory bowel diseases (IBDs) and pregnancy are established risk factors for thrombotic complications, thus IBD pregnant patients can be considered at even greater risk for thrombosis as compared to non IBD pregnant women. We aimed to evaluate the risk factors associated with this prothrombotic tendency among IBD women throughout gestation.

Methods: Women with IBD attending a multidisciplinary clinic for the preconception,antenatal and postnatal treatment were prospectively recruited during 2017–2018. Prothrombotic tendency was assessed by thrombin generation, a global marker of the activation of the coagulation system, expressed as the endogenous thrombin potential (ETP).

Results: Overall, 145 IBD women and 50 healthy control subjects were enrolled in this study. Body mass index (BMI) and gestational age were comparable between the groups. ETP level was significantly higher in women with IBD compared to control subjects in all time period ($P < .0001$). Among women with IBD, ETP level positively correlated with disease activity, as assessed by physician global assessment ($P = .005$), gestational age ($P < .0001$), extra-intestinal involvement ($P = .04$), C-reactive protein level ($P < .0001$), erythrocyte sedimentation rate ($P < .0001$), white blood cell count ($P = .008$), BMI ($P = .02$) and was inversely correlated with hemoglobin level ($P < .0001$). ETP level did not correlate with the occurrence of adverse pregnancy outcomes. In a multivariate analysis, active disease ($\beta = 0.20$, $P = .009$), gestational age ($\beta = 0.45$, $P < .0001$), extra-intestinal involvement ($\beta = 0.17$, $P = .02$) and BMI ($\beta = 0.15$, $P = .05$) retained independent predictors of high ETP levels.

Conclusion: As determined by thrombin generation, the procoagulant potential among IBD pregnant patients was independently associated with disease activity, BMI and extra-intestinal disease involvement.

1. Introduction

Inflammatory bowel disease (IBD) is an established risk factor for thrombotic complications due to multifactorial mechanisms including platelet activation, elevated levels of fibrinogen, coagulation factors II, V, VII, VIII, X and XI, impaired fibrinolysis and endothelial dysfunction [1–3]. Pregnancy itself is marked by an increased hypercoagulable state [4], caused by pro-coagulant changes in the hemostatic system and a decrease in natural anticoagulants (e.g. protein C and S), which are further enhanced by pelvic venous compression from the gravid uterus, together with venous stasis in the lower extremities [4]. Therefore, pregnancy is an established risk factor for venous thromboembolism

Abbreviations: CD, Crohn's Disease; CRP, C reactive protein; DVT, deep vein thrombosis; ESR, erythrocyte sedimentation rate; ETP, endogenous thrombin potential; GA, gestational age; IBD, inflammatory bowel diseases; PE, pulmonary embolism; PGA, physician global assessment; UC, ulcerative colitis; VTE, venous thromboembolism; WBC, white blood cell.

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(VTE), including both deep vein thrombosis (DVT) and pulmonary embolism (PE). As such, IBD pregnant women are at particularly high risk for VTE events [5–8], a recognized leading cause of maternal morbidity and mortality [9]. Nevertheless, there is no consensus regarding the optimal thromboprophylaxis approach for preventing the occurrence of VTE among IBD patients. This is highlighted by the wide variability in recommendations of professional society guidelines [10–16].

In-vitro thrombin generation is a well-accepted tool in non-pregnant patients for assessing the procoagulant potential of plasma; and thus, may quantify the composite global effects of the multiple parameters of the coagulation system [17,18]. Moreover, enhanced thrombin generation, was previously found to correlate with VTE occurrence in non-pregnant subjects [19–22]. As the prothrombotic tendency among IBD pregnant women may result from several hemostatic mechanisms, related both to their underlying disease [1–3] and gestation itself [4] the assessment of a particular component of the coagulation system might not suffice to evaluate the overall hypercoagulable state. The observed complicated coagulopathy has led several authors to support the use of global coagulation tests in clinical practice and research of IBD-related VTE [23,24]. However, while few studies have investigated thrombin generation patterns in IBD patients [25,26], it has been understudied among IBD pregnant subjects. Furthermore, the specific factors associated with hypercoagulability in IBD patients in the setting of pregnancy are unclear. Given the paucity of data and the lack of consistent guidelines, we aimed to prospectively evaluate the procoagulant potential and its associated risk factors among IBD pregnant patients, in comparison to healthy pregnant control subjects.

2. Materials and methods

2.1. Patients

This clinical trial was designed as a prospective cohort study. IBD patients who attended our single-center multidisciplinary clinic (IBD MOM) from February 2017 to July 2018 were assessed consecutively for eligibility to participate. Exclusion criteria were: age < 18 years, known bleeding or thrombotic disorders, hepatic or renal failure, active inflammatory condition (other than the IBD), multifetal gestation, endocrine disorders (i.e. thyroid dysfunction, Cushing syndrome), current or recent (< 7 days) use of any antiplatelet therapy or anticoagulants, non-steroidal anti-inflammatory drug (NSAID) use and heavy alcohol consumption. Fifty healthy volunteers (in the pre-pregnancy period, 1st trimester, 2nd trimester, 3rd trimester and end of postpartum period, 10 women each), without any medical condition or medications use, served as a control group for the laboratory analysis performed.

2.2. IBD MOM clinic description

The IBD MOM multidisciplinary clinic was established in June 2011 as part of the Digestive Diseases Institute at the Shaare Zedek Medical Center (SZMC) [27]. SZMC is a single, general referral center with over 20,000 deliveries per year. The IBD MOM clinic is a joint unit of the Digestive Diseases Institute and the Maternal–Fetal Medicine Division of the Obstetrics and Gynecology Department. The team in the IBD MOM clinic includes a gastroenterologist, a maternal-fetal medicine specialist, an IBD nurse coordinator, a dietitian and a psychologist. The clinic provides a comprehensive consultation for the preconception period, conception planning, medication safety, and management throughout pregnancy and postpartum periods.

2.3. Data collection

Blood samples were taken from all women enrolled in the study and tested for complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and thrombin generation. Blood samples were collected from an antecubital vein, by using a 23-gauge needle without stasis. For coagulation assays, blood was collected in vacutainer tubes containing trisodium citrate (final concentration 0.32%) (Becton Dickinson and Company, Franklin Lakes, NJ, United States). All analyses were performed immediately, except for the thrombin generation assay, which was carried out using platelet poor plasma samples stored at -80 °C. In addition, stool samples for calprotectin were collected.

In addition to the laboratory evaluation performed, the following data were prospectively recorded for each participant at clinic admission: time of admission (prior to pregnancy, 1st trimester < 13 weeks, 2nd trimester 13–27 weeks, 3rd trimester > 27 weeks, end of postpartum period > 6 weeks following delivery), age, anthropometric parameters, obstetric history, IBD diagnosis, age at IBD onset, intestinal, extra-intestinal and perianal involvement, current disease activity, current IBD treatment, personal and family known thrombophilia, use of assisted reproductive technologies (ART), gestational age (if pregnant), and pregnancy and delivery outcomes. Disease activity was defined by clinical evaluation including clinical scores, Harvey–Bradshaw index for Crohn's Disease (CD) and partial Mayo score for ulcerative colitis (UC) as well as by a physician global assessment (PGA), and evaluated as either active or in remission [28]. The PGA, a reliable and informative marker of active inflammation, is widely used to guide clinical decisions in IBD patients [28], and acknowledges the clinical scores, laboratory and physical examination findings and patient's performance status. Gestational age (GA) was based on ultrasonography performed during the 1st trimester. If the pregnancy was the result of in vitro fertilization (IVF), GA was determined from the date of embryo transfer. Preterm delivery was defined as GA < 37 completed weeks. Gestational hypertension was defined as systolic blood pressure > 140 mmHg and/or diastolic pressure > 90 mmHg, or the use of antihypertensive medications. A composite adverse pregnancy outcome required at least one of the following- preterm delivery, gestational hypertensive disorders, pregnancy loss or the delivery of a small-for gestational-age (SGA) infant. SGA was defined as < 10th percentile using birth weight z-scores calculated with the formulas published by Dollberg et al. on a similar population in Israel, adjusting for GA and the offspring's sex [29].

2.4. Laboratory investigations

2.4.1. Thrombin generation assay

Thrombin generation was measured in duplicate using a commercially available fluorogenic assay kit (Technothrombin®, Vienna, Austria) on a fully automated coagulation analyser (Ceveron®, Alpha, Technoclone, Vienna, Austria). Briefly, coagulation is initiated through the addition of tissue factor (3 pM) and phospholipids (30 μM). The concentration of thrombin is measured in platelet-poor plasma with a fluorescent peptide substrate, which is cleaved by thrombin to release a fluorophore. The rate of thrombin generation is measured over time, resulting in a thrombin formation curve. The endogenous thrombin potential (ETP), equals the area under the curve, and represents the total amount of thrombin generated (nM).

2.5. Other laboratory parameters

Complete blood count (Beckman Coulter Counter), ESR and CRP (by ELISA) were determined by employing standard laboratory procedures. Fecal calprotectin levels were determined with a commercially available quantitative enzyme-linked immunoassay (IDK® Calprotectin, Immundiagnostik AG, Bensheim, Germany).

2.6. Statistical analysis

Patient characteristics are described as proportions for categorical variables and as medians and interquartile ranges for continuous variables. Significant differences between subgroups were assessed using

the chi-square test and Fisher's exact test for categorical variables, while the Mann-Whitney *U* test was used for continuous variables, after testing for a normal distribution using the Kolmogorov-Smirnov Test. Correlations were calculated by the Spearman test with the correspondent ρ_s and *P* values. A univariate regression model was applied to all clinical and laboratory parameters. In addition, a multivariable logistic regression analysis was performed to assess factors independently associated with the procoagulant potential. A 2-sided *P*-value < .05 indicated statistical significance. The data were analyzed using Software Package for Statistics and Simulation (IBM SPSS version 22, IBM Corp, Armonk, NY).

2.7. Ethical approval

The study was approved in October 2016 by the Human Investigation Review Board of SZMC (IRB approval number: 176–14).

3. Results

One-hundred and forty-five consecutive women with IBD were enrolled in this study; 100 had Crohn's Disease (CD), 43 Ulcerative Colitis (UC) and 2 indeterminate colitis. The median age of this cohort was 29 [26–33] years. Seven women had known personal thrombophilia including: heterozygous factor V Leiden ($n = 4$), heterozygous prothrombin 20,210 mutation ($n = 2$), and protein C deficiency ($n = 1$). None of the patients used either vaginal progesterone or 17-alpha hydroxyprogesterone caproate during gestation. Patient baseline and laboratory characteristics are summarized in Tables 1 and 2. The gestational age ($P = .16$) and body mass index (BMI) (median 22.2 vs. 23.0 kg/m^2, $P = .86$) did not differ between the IBD group of patients and the control group. Higher levels of ETP were found among women with IBD compared to the control group in all time periods (median ETP: pre-pregnancy 3928 vs. 2094 nM, 1st trimester 4186 vs. 2302 nM, 2nd trimester 4474 vs. 2495 nM, 3rd trimester 4527 vs. 2568 nM, end of postpartum period 3937 vs. 2229 nM, $P < .0001$ for all comparisons).

In univariate analysis that included all measured clinical and laboratory parameters, ETP levels in CD disease patients were directly correlated with disease activity as assessed by PGA ($P = .003$), gestational age ($P < .0001$), CRP level ($P < .0001$), ESR ($P < .0001$), white blood cell (WBC) count ($P = .05$), BMI ($P = .01$) and inversely correlated with hemoglobin level ($P < .0001$).

In univariate analysis of data for UC patients, ETP levels were positively associated with disease activity as assessed by PGA ($P = .005$), gestational age ($P < .0001$), CRP level ($P < .0001$) and WBC count ($P = .04$).

In the entire cohort of patients, ETP levels were directly correlated with disease activity as assessed by PGA (median ETP: active disease 4489 nM, inactive disease 4252 nM, $P = .005$), gestational age (median ETP: pre-pregnancy 3928 nM, 1st trimester 4186 nM, 2nd trimester 4474 nM, 3rd trimester 4527 nM, end of postpartum period 3937 nM, $P < .0001$), extra-intestinal involvement (median ETP: extra-intestinal involvement 4391 nM, no extra-intestinal involvement 4217 nM, $P = .04$), CRP level ($P < .0001$), ESR ($P < .0001$), WBC count

Table 1
Baseline characteristics of IBD patients.

Characteristics	Overall	Crohn's disease	Ulcerative colitis	*P* value
	$n = 145$[a]	$n = 100$	$n = 43$	
Current age (years)	28.8 [25.5–33.0] (29.1)	28.7 [24.1–31.8] (28.6)	30.5 [25.8–33.7] (29.8)	0.16
BMI (kg/m^2)	22.2 [20.1–24.5] (23.0)	22.6 [19.8–25.2] (23.1)	21.7 [20.4–23.0] (22.4)	0.24
Age at IBD onset (years)	20.9 [15.6–26.5] (21.3)	20.9 [15.6–26.5] (21.3)	22.4 [19.6–27.2] (22.6)	0.16
Intestinal involvement[e] (%)	–	L1–48 (48.0%) L2–9 (9.0%) L3–42 (42.0%) L4–1 (1.0%)	Proctitis- 8 (18.6%) Left-sided colitis- 21 (48.8%) Extensive- 14 (32.6%)	–
Extra-intestinal involvement (%)	52 (35.9%)	44 (44.0%)	8 (18.6%)	0.004
Perianal disease (%)	37 (25.5%)	34 (34.0%)	2 (4.7%)	< 0.0001
Active disease[b] (%)	47 (32.4%)	35 (35.0%)	10 (23.3%)	0.18
Scoring for disease activity[c]	–	2 [0–5] (3)	0 [0–2] (2)	–
Current IBD treatment				
None (%)	14 (9.7%)	12 (12.0%)	2 (4.7%)	< 0.0001
Conventional (%)	53 (36.7%)	29 (29.0%)	22 (51.2%)	
Anti-TNF (%)	56 (38.6%)	50 (50.0%)	6 (14.0%)	
Other biologic treatment[d] (%)	22 (15.2%)	9 (9.0%)	13 (30.2%)	
Time of sampling				
Pre-pregnancy	19 (13.1%)	14 (14.0%)	5 (11.6%)	0.46
1st trimester	22 (15.2%)	12 (12.0%)	10 (23.3%)	
2nd trimester	50 (34.5%)	35 (35.0%)	14 (32.6%)	
3rd trimester	37 (25.5%)	26 (26.0%)	11 (25.6%)	
End of postpartum period	17 (11.7%)	13 (13.0%)	3 (7.0%)	
Family history of VTE (%)	14 (9.7%)	10 (10.0%)	4 (9.3%)	1.0
Known personal thrombophilia (%)	7 (4.8%)	4 (4.0%)	2 (4.7%)	1.0
Parity	1 [0–3] (2)	1 [0–3] (2)	1 [0–3] (2)	0.48
Nulliparous (%)	46 (31.7%)	32 (32.0%)	13 (30.2%)	1.0
≥2 recurrent miscarriages (%)	8 (5.5%)	4 (4.0%)	4 (9.3%)	0.24
ART conceived pregnancy (%)	18 (12.4%)	15 (15.0%)	2 (4.7%)	0.10

ART-assisted reproductive technologies; BMI-body mass index; GI-gastrointestinal; IBD-inflammatory bowel disease; VTE-venous thromboembolism;
All continuous variables are expressed as median [interquartile range] (mean). The Mann-Whitney *U* test, a non-parametric test was used for continuous variables without a normal distribution.

[a] Two patients had indeterminate colitis.
[b] Based on physician global assessment (PGA).
[c] Harvey–Bradshaw index for Crohn's Disease and partial Mayo score for Ulcerative Colitis.
[d] Including-vedolizumab ($n = 18$) and ustekinumab ($n = 4$).
[e] Montreal classification was used among those with Crohn's Disease.

Table 2
Laboratory data of the study participants.

	Overall	Crohn's disease	Ulcerative colitis	*P* value
	n = 145[a]	*n* = 100	*n* = 43	
Hemoglobin (g/dl)	11.6 [10.8–12.5] (11.7)	11.9 [11.0–12.5] (11.8)	11.2 [10.8–12.3] (11.4)	0.05
WBC count (X10^9/l)	7.9 [6.3–9.6] (8.2)	7.8 [6.3–9.5] (7.9)	8.2 [7.0–10.3] (8.9)	0.08
Platelet count (X 10^9/l)	244 [205–290] (250)	245 [204–290] (250)	252 [214–285] (250)	0.76
C-reactive protein (mg/dl)	0.90 [0.42–2.03] (1.47)	0.97 [0.50–2.11] (1.58)	0.72 [0.18–1.19] (1.23)	0.09
Erythrocyte sedimentation rate (mm/h)	34 [21–49] (37)	37 [24–48] (38)	29 [20–52] (33)	0.32
Calprotectin (μg/g)	298 [90–1998] (903)	373 [102–1836] (981)	168 [68–2100] (658)	0.36
Endogenous thrombin potential (nM)	4365 [4012–4639] (4329)	4323 [3996–4648] (4306)	4394 [3979–4588] (4372)	0.46

WBC-white blood cell.
All continuous variables are expressed as median [interquartile range] (mean). The Mann-Whitney *U* test, a non-parametric test was used for continuous variables without a normal distribution.
[a] Two patients had indeterminate colitis.

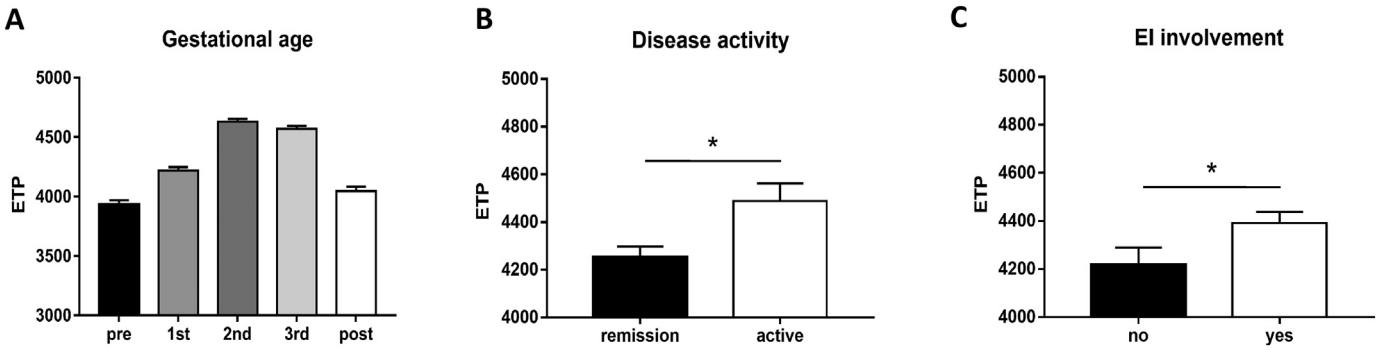

Fig. 1. Thrombin generation was estimated by ETP (nM) for the entire cohort (*n* = 145) for correlation to gestational age (pre-conception, 1st trimester, second trimester, 3rd-third trimester and end of postpartum period) (A), disease activity (B) and extra-intestinal (EI) involvement (C). * indicates $P < .05$.

Parameter	Points		
	0	1	2
Gestational age	Not-pregnant	1st trimester	2nd trimester and above
BMI (kg/m^2)	<25	>25	-
Active disease as assessed by PGA	No	Yes	-
Extra-intestinal disease involvement	None	Yes	-

0-1 points-low risk; 2-3 points-intermediate risk; 4-5 points-high risk.

BMI-body mass index; IBD-inflammatory bowel diseases; PGA-physician global assessment; VTE-venous thromboembolism.

Fig. 2. Suggested VTE risk score in IBD pregnant patients.

Table 3
Adverse pregnancy outcomes of IBD patients.

	Overall	Crohn's Disease	Ulcerative Colitis	*P* value
	n = 145[a]	*n* = 100	*n* = 43	
Preterm delivery (< 37 weeks) (%)	10 (6.9%)	7 (7.0%)	3 (7.0%)	1
Gestational hypertensive disorders (%)	4 (2.8%)	3 (3.0%)	1 (2.3%)	1
Pregnancy loss (%)	5 (3.4%)	3 (3.0%)	2 (4.7%)	0.64
Small for gestational age (< 10th percentile) (%)	7 (4.8%)	5 (5.0%)	2 (4.7%)	1
At least one adverse pregnancy outcome[b] (%)	24 (16.6%)	16 (16.0%)	8 (18.6%)	0.81

WBC-white blood cell.
All continuous variables are expressed as median [interquartile range] (mean). The Mann-Whitney *U* test, a non-parametric test was used for continuous variables without a normal distribution.
[a] Two patients had indeterminate colitis.
[b] Two patients had two adverse outcomes (one patient had experienced gestational hypertensive disorder and delivered preterm and the other delivered preterm a small for gestational age infant).

($P = .008$), BMI ($P = .02$) and inversely correlated with hemoglobin level ($P < .0001$). ETP level did not correlate with any of the other clinical and laboratory characteristics including the presence of personal thrombophilia (median ETP 4528 vs. 4358 nM, $P = .98$), fecal calprotectin level ($P = .72$) and disease activity scores (Harvey–Bradshaw index, $P = .12$ and partial Mayo score, $P = .63$) in the entire cohort, as well as in those with CD or UC. In multivariate analysis, disease activity as assessed by PGA ($\beta = 0.20$, $P = .009$) (Fig. 1A), gestational age ($\beta = 0.45$, $P < .0001$) (Fig. 1B), extra-intestinal involvement ($\beta = 0.17$, $P = .02$) (Fig. 1C) and BMI ($\beta = 0.15$, $P = .05$) were independent predictors of ETP level. A suggested risk score based on these 4 parameters (Fig. 2), which categorizes patients into low, intermediate and high risk for VTE, was highly correlated in the current cohort with ETP level ($\beta = 0.58$, $P < .0001$).

Notably, ETP level did not correlate with the occurrence of an adverse pregnancy outcome ($P = .68$), GA at delivery ($P = .74$) or neonatal birthweight ($P = .63$). No thrombotic events were encountered in the cohort during study period throughout gestation and the postpartum period. The adverse pregnancy outcomes encountered in the current cohort are summarized in Table 3.

4. Discussion

In the current study, we investigated the procoagulant potential in relation to pregnancy among IBD patients, based on thrombin generation testing. The procoagulant potential was directly correlated with the gestational age, disease activity, BMI and the presence of extra-intestinal disease involvement. A risk score based on these 4 parameters was highly correlated with the ETP level.

There is no consensus regarding the role of thromboprophylaxis during pregnancy among IBD patients. Among non-pregnant IBD patients, the guidelines of the Canadian Association of Gastroenterology [10] and European Crohn's and Colitis Organization [11,12] support pharmacological prophylaxis in all hospitalized IBD patients. This is contrast to the recommendations of the American College of Chest Physicians [13], American College of Gastroenterology [14] and the British Society of Gastroenterology [15] which advocate the administration of thromboprophylaxis only to in-patients with moderate and severe disease activity. This variation in recommendations is apparently due to the lack of evidence-based data to guide optimal thromboprophylaxis. Most importantly, while none of the aforementioned guidelines addressed the population of IBD pregnant patients, in whom VTE risk is substantially increased, the Royal College of Obstetricians and Gynaecologists guidelines refer to IBD as an intermediate risk factor and suggest that antenatal thromboprophylaxis should be considered in this subset of patients [16].

Disease activity as assessed clinically by the PGA, and as reflected by the various laboratory parameters (CRP, ESR, WBC and hemoglobin) was shown in the current study to correlate with the procoagulant potential (ETP). This is in accordance, with previous studies in IBD patients which demonstrated a higher thrombotic risk during a disease flare-up [5,25,30–32].

Moreover, an interesting finding of our study is the independent association found between the ETP and extra-intestinal disease involvement, which probably reflects an increased disease burden. Interestingly, no association between fecal calprotectin and thrombin generation was found. This may be at least partially explained by the lack of established correlation of this biomarker with clinical disease activity throughout gestation [33,34]. Finally, the absence of correlation found between ETP and the traditional clinical scores (i.e. Harvey–Bradshaw index and partial Mayo score) may be accounted for by their lack of validation throughout gestation.

ETP level was directly correlated with the gestational age. This finding may relate to the gradually increasing ETP levels and VTE risk throughout gestation shown in non-IBD pregnant patients [35–38]. The lack of association found in the current report between the ETP levels and the presence of personal or family history of thrombophilia, concurs with previous studies which demonstrated that acquired risk factors (e.g. pregnancy, disease activity, hospitalization etc.), rather than congenital features, play a more prominent role in the etiopathogenesis of IBD-related thrombosis [23].

In addition, we report that the procoagulant potential, as determined by thrombin generation, independently correlated with patients' BMI. Although none of the women in the current was obese, this finding is consistent with the hypercoagulability associated with increased body weight and its associated thromboembolic risk [39–41].

Lastly, our results may have implications for the treatment of IBD pregnant patients. The identification of patients at increased risk of thrombosis would facilitate individualization of thromboprophylaxis and may improve thrombosis rates, while avoiding the potential adverse effects and high costs of overtreatment. Moreover, as VTE has been reported as one of the leading causes of death among pregnant patients, and to negatively affect IBD patients' outcomes [42], preventing VTE occurrence may affect survival. Treating physicians, including both obstetricians and gastroenterologists, who encounter IBD pregnant patients in their practice, should be aware of the high prevalence of thrombotic complications, and routinely assess the patient-specific thrombotic risk. Applying our suggested risk score for VTE risk assessment among IBD pregnant patients may be of particular benefit and should be further validated in future clinical studies. It is possible that the combination of clinical risk factors with the results of thrombin generation, as a global marker of the coagulation system, would even better predict the occurrence of thrombotic events.

The main limitation of the current study was that the magnitude of the prothrombotic tendency found is likely underestimated as we excluded those under anticoagulation therapy or with previous thrombotic events, and there was a minority of patients with known thrombophilia, in whom the prothrombotic potential may have been even higher. Moreover, the adequate thromboprophylaxis regimen, in terms of dose and duration, remains undetermined and should be delineated in future studies. Despite these potential caveats, we believe our results add valuable information to the current literature, as it may aid in patients' risk stratification in the implementation of adequate thromboprophylaxis policies in this subset of patients.

In conclusion, the procoagulant potential among IBD pregnant patients, based on thrombin generation testing, was independently associated with gestational age, disease activity, as well as with patients' BMI and the presence of extra-intestinal disease involvement. Future prospective studies are warranted to confirm our findings, evaluate the correlation between thrombin generation and the occurrence of IBD-related thrombosis and tailor the optimal antithrombotic prophylactic strategy in these patients.

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Disclosure of conflicts of interest

The authors declare that they have no conflicts of interest.

Authors' contributions

AR, MD, ABGS, EG, SGG, TM, BR, GS and YK study conception and design, data collection, data analysis and interpretation, drafting the article. ABGS, SGG and TM treated the patients. AR performed the laboratory evaluation of patients. All authors approved the final version of the manuscript.

Compliance with ethical standards

All procedures performed in studies involving human participants

were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the local institutional review board of Shaare Zedek Medical Center Helsinki Committee (IRB approval number No. 176–14).

Informed consent

Informed consent was obtained from all individual participants included in the study.

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