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Perinatal outcome in women with inflammatory bowel disease

Wyniki okołourodzeniowe u pacjentek chorujących na nieswoiste choroby zapalne jelit

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Abstract

Introduction: *Inflammatory bowel disease (IBD) is a lifelong, chronic inflammatory condition of the gastrointestinal tract. IBD morbidity rate in Europe has been steadily growing for the last six decades. Women with IBD are often diagnosed during the childbearing years, which makes the influence of the disease on pregnancy and birth outcomes an important clinical issue.*

Objectives: *The aim of the study was to estimate the influence of the IBD process among pregnant women on maternal, fetal and neonatal parameters. Material and methods: A retrospective analysis of data on patients suffering from IBD, diagnosed before pregnancy, who were admitted to the Department of Perinatology and Gynecology, Polish Mother's Memorial Hospital Research Institute for delivery between 2009-2013, was conducted. IBD was diagnosed in 10 cases. The control group consisted of 10 healthy, pregnant women near delivery.*

Results: *IBD activity status at conception in women receiving continuous mesalazine treatment does not correlate with gestational age, birth weight, Apgar score or maternal platelet count at delivery in comparison to controls.*

IBD patients under mesalazine management had lower: i) maternal body mass index and platelet count, ii) neonatal birth weight and Apgar score as compared to controls. However, no impact of IBD on the frequency of congenital anomalies was noted.

Conclusions: *To the best of our knowledge, this has been the first study conducted among pregnant women with IBD in Poland. The analysis demonstrates that pharmacological treatment has a deteriorating influence on maternal weight gain in pregnancy, as well as production and activity of platelets. Moreover, it diminishes fetal growth and worsens short-term neonatal condition. Further studies with larger sample size are necessary but the rarity of this complication limits the possibility of research.erapeutic perspectives.*

Key words: **inflammatory bowel disease** / **mesalazine treatment** / **perinatal outcomes** /

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Streszczenie

Wstęp: *Nieswoiste zapalenia jelita to grupa przewlekłych chorób zapalnych przewodu pokarmowego. W ostatnich sześciu dekadach w Europie odnotowano znaczny wzrost wskaźnika zachorowalności na nieswoiste choroby jelit. Rozpoznanie tej jednostki chorobowej często przypada u kobiet w okresie rozrodczym. Z tego względu niezwykle istotnym jest ocena wpływu choroby na przebieg ciąży oraz wyniki noworodkowe.*

Cel pracy: *Celem pracy było określenie wpływu nieswoistych zapaleń jelita na matczyne, płodowe i noworodkowe parametry kliniczne. Materiał i metody: Przeprowadzono analizę retrospektywną danych pacjentek hospitalizowanych w Klinice Perinatologii i Ginekologii Instytutu Centrum Zdrowia Matki Polki w Łodzi w latach 2009-2013, u których przed zajściem w ciążę rozpoznano niezapalne choroby jelit. Nieswoiste zapalenia jelit zdiagnozowano u 10 ciężarnych. Grupę kontrolną stanowiło 10 zdrowych pacjentek w terminie okołoporodowym.*

Wyniki: *Aktywność choroby w momencie zajścia w ciążę wśród pacjentek będących w trakcie ciągłej terapii mesalazyną w porównaniu z grupą kontrolną nie miała wpływu na wiek ciążowy w momencie porodu, masę urodzeniową, punktację w skali Apgar oraz liczbę płytek krwi u matek w momencie porodu. U pacjentek chorujących na nieswoiste zapalenia jelita, będących w trakcie ciągłej terapii mesalazyną w porównaniu z grupą kontrolną odnotowano niższą wartość indeksu masy ciała, niższe wartości płytek krwi oraz niższą masę urodzeniową i niższą punktację w skali Apgar. Nie odnotowano wpływu nieswoistych zapaleń jelita na częstość występowania wad wrodzonych u płodów.*

Wnioski: *Jest to pierwsze badanie obejmujące ciężarne chorujące na nieswoiste zapalenia jelit przeprowadzone w Polsce. Wyniki przedstawionego badania wskazują na niekorzystny wpływ choroby w trakcie terapii mesalazyną na przyrost masy ciała ciężarnej i produkcję oraz aktywność trombocytów. Dodatkowo stwierdzono zwolnienie tempa wzrastania płodu oraz pogorszenie krótkoterminowych wyników noworodkowych. Niezbędne są dalsze badania obejmujące duże populacje pacjentek, jednakże rzadkość występowania tej jednostki chorobowej ogranicza możliwość przeprowadzania analiz.*

Słowa kluczowe: **nieswoiste choroby jelit** / **terapia mesalazyną** / **wyniki noworodkowe** /

Introduction

Inflammatory bowel disease (IBD) is a lifelong, chronic inflammatory condition of the gastrointestinal tract, with peak incidence between the ages of 15 and 35 years [1]. Women with IBD are often diagnosed during the childbearing years, which makes the effects of the disease on the neonatal outcome an important clinical issue. Retrospective studies demonstrated disease activity at conception to be the most important predictor of subsequent disease course during pregnancy [2]. If a woman has inactive disease at conception, her chances of relapse during pregnancy are identical to those of a woman who is not pregnant, i.e. 30% [3]. However, if a woman has an active disease at conception, she has a 60% chance of disease either remaining active or worsening [4].

A recent meta-analysis of research on women with IBD has revealed an increased overall risk for adverse pregnancy outcome [2], especially preterm delivery (before 37 weeks of gestation), with the relative risk of 1.87, and low birth weight (less than 2700g), with the relative risk of 2.1 [5-7]. As far as the delivery mode is concerned, most studies have also shown significantly increased frequency of cesarean sections [5, 8, 9]. Adverse pregnancy outcomes are more common in pregnant women with Crohn's disease (CD), as compared to ulcerative colitis (UC) [2].

Disease severity probably has an impact on pregnancy outcome, although most studies have not evaluated this effect [2]. One of the recent studies by Nguyen et al., purposely addressed the influence of CD activity and revealed a 3.4-fold higher risk of preterm birth [10].

Only few studies investigated the influence of IBD on the outcome of conception (miscarriage) and complication rates of pregnancy and labor (abruption of placenta, chorioamnionitis, eclampsia, placenta praevia, premature and prolonged membrane rupture, ectopic pregnancy) [8, 9, 11]. While the rate of early abortion up to 12 weeks is increased (both, spontaneous and induced), data on the frequency of complications of pregnancy and labor are very inconsistent, precluding meaningful conclusions.

Except for prematurity and low birth weight, maternal IBD seems to have no major adverse effects on term infants [2]. Apgar scores, death rate, hospitalization in an intensive care unit, and seizures were not more frequent in these infants. Data on the rates of congenital malformations are confusing, mostly due to inconsistencies in the diagnoses and the confounding influence of the used medications.

IBD morbidity rates have been growing for the last six decades in Europe and the USA [12]. Statistics show increasing CD rates, especially among children and teenagers, what is connected with growing morbidity among people of reproductive age. We estimate the number of IBD patients in Poland to be 50 000, with women of reproductive age as the vast majority of the affected individuals. Annually, about 700 new cases of UC and 200 new cases of CD are diagnosed in Poland.

Preterm birth affects 4-20% of all pregnancies around the world [13, 14]. In Poland, about 7% of all neonates are delivered prematurely, meaning that every year about 27 000 neonates face all dangers of prematurity. The risk of premature birth among mothers with IBD is about 12-14%. It is crucial for obstetricians to do their best and limit the risk of prematurity or other complications resulting from active inflammation in pregnant women with IBD. We believe that our study may help in estimating a

real correlation between IBD activity and adverse outcome of pregnancy. Moreover, the collected knowledge would be helpful in selecting appropriate treatment of IBD to limit the danger of problems in pregnancy, as well as morbidity and mortality in newborns. On the other hand, if the process is not reversible it would be achievable to prepare the mother and the fetus for a delivery in tertiary referral hospital to improve the conditions of intensive care, which is essential in case of prematurity or small for gestation age weight or other undefined obstacles.

The objective of the study was to estimate the influence of IBD process among pregnant women on maternal, fetal and neonatal parameters. Secondly, we aimed at determining the association between maternal IBD status at conception and perinatal outcomes.

Material and methods

Medical records of pregnant women suffering from inflammatory bowel diseases admitted for delivery to the Perinatology and Gynecology Department, Polish Mother's Memorial Hospital Research Institute between January 1, 2009 and December 31, 2013, were reviewed retrospectively. All patients were diagnosed with IBD before pregnancy. The IBD diagnosis included Crohn's disease and ulcerative colitis. The presence or absence of IBD was determined by a review of diagnoses listed in hospital discharge records associated with the delivery. IBD was diagnosed in 10 cases. The control group consisted of 10 healthy pregnant women near delivery. Detailed assessment of maternal and neonatal records was performed for each patient in the database. Charts were examined for standard demographic data such as age, body mass index, gravidity and parity, method of conception, and smoking. Route of delivery, birth weight, range of blood pressure, laboratory values and umbilical artery Doppler measurements were assessed. In addition, discharge time, comorbidities and major complications were documented.

Statistical analysis

In the analysis both parametric tests for differences between mean values from two samples for independent variances, called Student's t-test, as well as their nonparametric equivalent called Mann–Whitney U test were used. The criteria of choice for the suitable test category depended on the compatibility between the distribution of the examined parameter with the normal distribution in controls and the study group (a necessary condition for the Student's t-test selection). If not, then Mann–Whitney U test was used for the comparison between means. Levene's test for equality of variances was used to assess the variance comparison in both groups. If the result of Levene's test was the statement that variance of a variable in both groups does not vary significantly, then T statistic was used for comparison of means. If Levene's test showed variance heterogeneity, then Cochran-Cox test was used for comparison of means. The p-value of <0.05 was considered statistically significant.

Results

A total of 10 patients suffering from IBD delivered at the Department of Perinatology and Gynecology, Polish Mother's Memorial Hospital during the study period. The 10 patients with IBD represented 0.18% out of the 5513 deliveries that occurred during that time.

Demographic, clinical characteristics and fetal data are shown in Table I. General characteristics of the examined group were based on patient age, body mass index (BMI), gestational age, gravidity, mode of conception, IBD status at conception (remission or aggravation), and IBD course during pregnancy. Mean patient age was 30.8±4.37 years, what emphasizes mild differentiation of the feature. The majority (70%) of the women were primigravidas. Mean BMI was 25.52±4.31, what highlights moderate disparity of the quality as well. One patient from the study group suffered from cholestasis gravidarum and delivered at 36 weeks gestation because of fetal demise symptoms. None of the controls suffered from any chronic diseases or pregnancy-related disorders.

Prenatal diagnostics and assessment after delivery did not detect any congenital malformations of the fetuses, either in the study group or in controls. During hospitalization the fetuses were monitored by the use of non-stress test and fetal Doppler study of the umbilical artery, vein and ductus venosus flow. Fetal umbilical artery pulsatility index value (UmbA PI) did not correspond to newborn parameters such as birth weight, Apgar score at 5 minutes, or the umbilical artery pH value at delivery, either in study group or controls.

There were no differences in complication rates (e.g. a need for hospitalization during pregnancy because of imminent abortion, hyperemesis gravidarum) between IBD and control mothers. Mean gestational age at delivery was 37.6±2.31 weeks, with 30% of the fetuses born before 38 weeks of gestation. There was no statistically important difference between the studied patients and controls concerning this feature (p=0.353), despite one preterm delivery at 32 weeks of gestation among IBD mothers.

Mean birth weight was 2923±575.19g, with mean Apgar score of 8.9±0.86 (7-10) and pH value of 7.30±0.05(7.18-7.35). Birth weight (p=0.029) and Apgar score (p=0.005) were notably lower in the study group as compared to controls (Table V).

As far as maternal parameters at delivery such as hemoglobin level, HCT, RBC, WBC, APTT were concerned, there was no important difference between the study and the control groups. Additionally, the above mentioned factors did not differ when comparing active IBD at conception to non-active patients. The only maternal blood parameter that was significantly lower in the study group than in controls was the PLT level (p=0.008; Table V), but it did not correspond to IBD activity (p=0.916; Table II).

Studying UmbA PI prenatally, birth weight, Apgar score and gestational age at delivery among IBD women, we found no correlation to inflammation activity at conception (Table V).

All patients from the study group were diagnosed with IBD before pregnancy. The majority (60%) of pregnant women with IBD were in deterioration at conception (despite pharmacological therapy), while 40% had inactive disease. Every patient in remission at conception continued this status for the rest of pregnancy. Five out of 6 women with active IBD at the beginning of pregnancy deteriorated during gestation, whereas 1 out of that group improved during the second and third trimester (Table III). All patients received continuous mesalazine treatment since the preconception period until delivery but 1 of the women was put on infliximab (a chimeric monoclonal antibody against tumor necrosis factor alpha) during gestation because of severe decline.

None of the patients from the study group required surgery or any other invasive procedures due to IBD. Moreover, none

Table I. Values of descriptive statistics and Kolmogorov-Smirnov normality test with Lilliefors correction for parameters included in our analysis (study group).

Parameters	Mean	Median	SD	x_{min}	x_{max}	Normality of distribution
Age	30.80	30.50	4.37	25.0	39.0	YES
BMI	25.52	26.70	3.41	20.2	30.1	YES
Age at delivery	37.6	38.0	2.31	32.0	40.0	NO
UmbA PI	0.787	0.795	0.07	0.66	0.88	YES
HGB	11.58	11.90	1.24	9.40	13.0	YES
HCT	33.76	34.90	3.63	27.20	37.40	NO
RBC	3.86	3.93	0.43	3.03	4.33	YES
WBC	10.74	11.03	3.01	6.35	16.07	YES
PLT	205.2	202.5	25.5	171.0	240.0	YES
APTT	28.02	26.99	2.31	25.60	33.02	YES
Birth weight	2923.0	3035.0	575.19	1666.0	3650.0	YES
APGAR	8.90	9.00	0.86	7.0	10.0	NO

Table II. Outcomes of Fisher's test, one-way analysis of variance (ANOVA), division into groups based on the disease state at conception (H0 hypothesis sets up equality of means in both groups).

Parameters	Remission (n=4)		Resurgence (n=6)		Outcome of test F	p_{value}
	Mean	SD	Mean	SD		
UmbA PI	0.80	0.098	0.777	0.053	0.299	0.599
HGB	11.65	1.33	11.53	1.30	0.019	0.894
HCT	33.78	4.23	33.75	3.61	0.0001	0.992
RBC	3.81	0.55	3.90	0.39	0.082	0.781
WBC	10.36	2.61	11.00	3.47	0.098	0.762
PLT	211.75	50.49	188.00	102.1	0.013	0.916
APTT	28.12	3.33	27.94	1.73	0.013	0.913
Birth weight	3087.5	421.14	2813.33	671.94	0.516	0.493
APGAR	9.0	0.81	8.83	0.98	0.078	0.787

Table III. Cross tabulation of patient state at conception and the state of the IBD status.

CHZ State / Conception	Recovery	Relapse	Total
Remission	4	0	4
Resurgence	1	5	6
Total	5	5	

of the women with IBD had undergone surgery due to intestinal problems before pregnancy. There was no disparity relating to smoking, drinking or other addictions among the populations (all women denied any addictions).

Discussion

IBD is usually first diagnosed during the reproductive years of female patients and the effects of IBD *per se*, disease activity and therapy on pregnancy and its outcomes, are of foremost concern [1, 15, 16]. To the best of our knowledge, this has been the first case-control study on pregnancy outcome in women with IBD in Poland. All patients from the study group were diagnosed with IBD at least 3 years before pregnancy. Also, gastroenteral disorder was confirmed by histopathology in all cases. Moreover, all women with IBD received continuous mesalazine treatment at conception until the end of pregnancy.

Table IV. Values of descriptive statistics and Kolmogorov-Smirnov normality test with Lilliefors correction for parameters included in the study (control group).

Parameters	Mean	Median	SD	X_{min}	x_{max}	Normality of distribution
Age	31.0	33.0	4.06	22.0	35.0	NO
BMI	28.84	29.05	1.26	27.2	31.2	YES
Age at delivery	38.7	39.0	1.42	37.0	41.0	YES
UmbA PI	0.807	0.785	0.112	0.640	0.990	YES
HGB	11.88	11.45	0.90	11.0	14.0	NO
HCT	34.84	33.90	2.86	31.90	41.40	NO
RBC	4.05	3.87	0.44	3.58	4.99	NO
WBC	9.25	9.36	1.35	6.55	11.68	YES
PLT	285.5	289.0	81.49	136.0	388.0	YES
APTT	27.73	27.13	1.35	26.23	30.12	YES
Birth weight	3444.0	3480.0	385.2	2790.0	3970.0	YES
APGAR	9.90	10.0	0.32	9.0	10.0	NO
pH	7.32	7.33	0.06	7.28	7.35	YES

Table V. Outcomes of tests comparing mean values of selected parameters in the study and the control groups.

Parameters	Study group		Control group		Value of statistical tests	p_{value}	Type of test
	Mean	SD	Mean	SD			
Age	30.80	4.37	31.0	4.06	44.0	0.684	U Mann-Whitney
BMI	25.52	3.41	28.84	1.26	-2.88	0.009	Cochran-Cox
Age at delivery	37.60	2.31	38.7	1.42	37.0	0.353	U Mann-Whitney
UmbA PI	0.79	0.07	0.81	0.11	-0.47	0.637	t-test
HGB	11.58	1.24	11.88	0.90	46.50	0.756	U Mann-Whitney
HCT	33.76	3.63	34.84	2.86	50.0	0.970	U Mann-Whitney
RBC	3.86	0.43	4.05	0.44	50	0.970	U Mann-Whitney
WBC	10.74	3.01	9.25	1.35	1.432	0.169	Cochran-Cox
PLT	205.2	25.50	285.5	81.50	2.973	0.008	Cochran-Cox
APTT	28.02	2.31	27.73	1.35	0.33	0.742	t-test
Birth weight	2923.0	575.19	3444.0	385.18	-2.38	0.029	t-test
APGAR	8.90	0.86	9.90	0.32	14.0	0.005	U Mann-Whitney
pH	7.30	0.05	7.32	0.03	-1.453	0.163	t-test

In this retrospective population-based cohort study of live children born to women with IBD, 40% of the mothers had inactive disease at conception, out of which 100% stayed in remission until the end of pregnancy (Table III), whereas 60% of the patients with IBD suffered from aggravation at the time of conception. The classification of disease activity in each trimester was based on well-defined criteria and thorough review of the medical records, allowing a detailed classification of each pregnancy. In our study, the exacerbation of IBD was observed mainly in the late second trimester and third trimester, what is consistent with other reports in the literature [15-18].

We did not detect any differences between the groups in terms of patient age, gestational age, maternal blood parameters just before delivery (hemoglobin level, HCT, RBC, WBC, APTT), fetal parameters before delivery (UmbA PI), and fetal umbilical artery blood pH at birth (Table V). Women with IBD, particularly with Crohn's disease, may have an increased risk of adverse outcome of pregnancy, especially preterm delivery, low birth weight, and increased risk of cesarean section [18, 19].

Contrary to the results of Norgard and Nguyen, who determined that preterm delivery was notably more frequent and depended on disease activity [10, 17], our analysis found no significant differences in gestational age between IBD patients and healthy controls (Table V). Disease severity probably has an impact on pregnancy outcome. However, most studies did not estimate this effect because it is difficult to evaluate. Randomization

would be essential, including controls without pharmacological treatment, what would be unethical. Similarly to our findings, Bortoli et al., revealed no differences in preterm birth rates [19], although in their study 86% of the patients stayed in remission for most of the pregnancy, whereas in our revision the group in remission accounted for 50%. Mean gestational age over 37 weeks may be the result of pharmacological treatment at conception and continued throughout pregnancy in all subjects from our study as well as that of Bortoli. It must be emphasized that our study group included one preterm birth at 32 weeks of gestation which occurred in a patient put on anty-TNF-α treatment in the first trimester because of severe course of IBD. Data published so far on anty-TNF-α treatment in IBD patients deny any negative influence on pregnancy outcome [17].

Women with IBD, particularly with CD, may have an increased probability of low birth weight (LBW) in their neonates [10]. Dominitz et al., as well as Moser et al., and a few other authors proved significantly higher risk of LBW among women with CD [5, 10, 15]. Our study disclosed the average birth weight of children born to mothers with IBD to be at the level of 2923±575.19g, and was significantly lower than in controls. None of the newborns demonstrated symptoms of intrauterine growth restriction or other adverse consequences of low birth weight. Nevertheless, the effect of IBD or mesalazine may reduce natural potential of intrauterine weight gain. Contrary to the above mentioned findings, Bortoli et al., revealed no difference in terms of birth weight among IBD patients as compared to healthy controls [19]. They explained these results with high remission rate during the observed pregnancies. It has a logical connection to our outcome, where lower birth weight might be the consequence of aggravation among most patients from the study group.

Another potential effect of maternal IBD on their offspring is the risk for congenital anomalies (CAs). None of the newborns from our study population manifested congenital malformations (analogously to the control group). Nevertheless, the occurrence of CAs in offspring of IBD patients is controversial, mostly due to inconsistencies in medical records and confounding influence of the used medications [5, 15, 18]. Furthermore, only studies with large sample sizes may reveal statistically significant rise in risk rates of CAs. The predominant anomalies mentioned in the literature include limb deformations, obstructive urinary malformations, neurological development anomalies, and multiple congenital abnormalities. During our 5-year observation of children born to mothers from the study group no problems with gastroenteral, neurological or psycho-motoric development were observed.

BMI was one of the assessed parameters whose predictably was meaningfully lower in the IBD group as compared to controls. This may imply that special attention should be paid to normalized and high-quality diet for such patients during pregnancy.

Another important finding was a significantly lower platelet count among patients with IBD in continuous mesalazine treatment [20]. This is probably the effect of mesalazine *per se*, but differential diagnosis of low PLT, a symptom of potentially great impact on the pregnancy course, should always be considered.

Our study is not without limitations, especially the small sample size. Statistical analysis was composed in such a way as to conclude as objectively as possible on the basis of 10 patients. Secondly, all IBD patients received pharmacological treatment during the entire course of pregnancy, what counterfeits the results. In fact, we evaluated pregnancy outcomes of IBD patients in mesalazine treatment rather than IBD patients.

Conclusions

To the best of our knowledge, this has been the first case-control study performed among pregnant women with IBD in Poland. We found that activity status of IBD at conception among woman on continuous mesalazine treatment does not correspond to gestational age, birth weight, Apgar score, or maternal platelet count at delivery. The study demonstrated that IBD under mesalazine management affected maternal BMI and platelet count, as well as fetal birth weight and Apgar score. This demonstrates that disease under pharmacological treatment has a deteriorating influence on maternal weight gain in pregnancy, as well as production and activity of platelets. Moreover, it diminishes fetal growth and worsens short-term neonatal condition. However, IBD has no effect on gestational age at delivery or frequency of congenital anomalies. Further studies are necessary to warrant current findings but rarity of IBD limits the possibility of conducting unbiased analysis.

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