



CROHN'S DISEASE, PREGNANCY AND PSYCHIATRIC DISTURBANCES - A CASE REPORT

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ABSTRACT

Crohn's disease (CD) is a disorder characterized by transmural inflammation of the gastrointestinal tract. The peak onset of CD coexists with the reproductive period, but it doesn't seem to affect fertility. A course of pregnancy and mode of delivery comprise challenging clinical problem. An 18-year-old woman was diagnosed with CD involving terminal ileum and the left side of the colon. Due to intolerance of thiopurines and non-acceptance of methotrexate, maintenance therapy consisted only of mesalamine and budesonide. Ten years later presence of a fistula penetrating from sigmoid part of colon towards the left fallopian tube brought about a hemicolectomy with colostomy creation. As a next step infliximab was started, but it led to a severe exacerbation of psoriasis. Treatment with adalimumab was not effective. High doses of glucocorticoids resulted in an improvement but also in psychiatric complications. At the age of 30 the woman became pregnant. The pregnancy was uneventful from the gastrological point of view, but in 25/52 the woman experienced an acute psychotic disorder. In 40/52 she delivered vaginally a healthy child. After the delivery a disease flare appeared. The patient accepted methotrexate and achieved a temporary remission. The next flare presented with new fistulae. The patient was once again referred to a surgery. The course of CD may be extremely difficult to control. Standard treatment might lead to severe side effects. In majority of CD patients, the course of pregnancy is uneventful, but the post-delivery time is usually connected with a disease flare.

BACKGROUND

Crohn's disease (CD) is one of the inflammatory bowel diseases (IBDs), that is characterized by transmural inflammation that may involve whole gastrointestinal tract, from the oral cavity to the anus. However, the most common localization is the terminal ileum and colon. Usually there are inflammatory areas (mostly granulomatous), separated by not affected ones. The pathogenesis of CD is still unclear, but it is believed to be a combination of genetic, environmental, microbiological and immune factors [1, 2, 3].

CD is a chronic disease and patients usually experience recurrences and remissions. Symptoms may last constantly, debilitate patients' quality of life. Sometimes distress, complicated course of an illness may lead to early surgical interventions [4, 5].

Gastroenterologists play a crucial role in the treatment of patients suffering from IBD. However, because of wide, multiorgan symptomatology and often necessity of multidisciplinary approach, CD may become a challenge for great number of different specialists.

CASE DESCRIPTION

On 15th September 2015 a 30-year-old woman with CD at the beginning of pregnancy (17/52) was admitted to the Clinic of Gastroenterology and Hepatology University Hospital in Cracow to carry out routine laboratory tests and evaluate the disease activity.

The woman was diagnosed with CD in 2003. An inflammation was localised in the descending colon and distal ileum. The course of the disease was severe – with short remissions and extraintestinal manifestations (peripheral arthropathy, episcleritis, erythema nodosum, perianal lesion – fissure and condyloma) which involved multispecialistic care. As the patient did not tolerate thiopurines and refused to take methotrexate (MTX), initial maintenance therapy consisted only of mesalamine and budesonide. In 2013 the woman underwent extended left hemicolectomy with creation of transverse colostomy due to an abscess and sigmoid-gynaecological fistula penetrating towards left salpinx. Because of the severe disease course an anti-TNF- α treatment with infliximab (3 cycles) was started, but as it led to a severe exacerbation of psoriasis, it had to be withdrawn. As a next step the patient received injections of adalimumab (11 doses) but the therapy was not effective. Finally, the patient was treated with high doses of glucocorticoids that resulted in an improvement but also led to a transient worsening of her mental state (corticosteroid-induced psychosis). It was manifested by increased anxiety, strain and fear with nocturnal insomnia. In addition during psychiatric consultations labile affect, fretfulness and psychomotor agitation were noticed. Her statements indicating the presence of delusions and olfactory hallucinations. In June 2015 she had another surgical procedure – incision of abscesses in the postoperative scar and around the stoma. MR imaging (June 2015) showed chronic and active inflammatory changes in the colon. The patient hadn't informed the attending physician about her tries to get

pregnant. At the admission to the hospital the patient was in good general condition, although on the physical examination some abnormalities were observed (Table 1). Complete blood count revealed microcytic anaemia, elevated C-reactive protein (CRP), thrombocytopenia, decreased levels of albumins, iron and vitamin D (Table 2). The current treatment of CD (6-mercaptopurine, sulfasalazine) and schizophrenia (olanzapine) was maintained, and propranolol was implemented to reduce symptoms of hyperkinetic circulation. To reduce some deficits proper supplementation was prescribed.

In terms of obstetric the pregnancy was uneventful. Weight gain was adequate. The woman was only on sulfasalazine, iron and folic acid. She decided to discontinue the therapy with azathioprine on her own, although there were no contradictions.

During following gastrological assessment (29/52) the presence of an enterocutaneous fistula in abscess incision location was suspected due to increasing excretion of air and faeces. In 37/52 medical case conference were organised to choose the most appropriate mode of delivery. Taking into consideration all the circumstances the vaginal delivery was chosen. The labour was on time. The patient gave birth to a healthy, female child (Figure 1).

A check-up after delivery (in May 2016) revealed enterocutaneous fistulae and pus near the stoma. From an April 2016 arthropathy and skin complication (erythema nodosum and areas of discoloration) had intensified. Because of the presence of active inflammation in computed tomography (CT) the patient was disqualified from surgical intervention. The woman did not agree for therapy with anti-TNF- α agents due to infliximab induced psoriasis in history, but she finally decided to start MTX (at first 25 mg per week, then reduced to 15 mg per week).

In August 2016 the patient was admitted to psychiatric hospital for 6 weeks with paranoid schizophrenia (for the same reason she was treated between 2012 and 2014). MTX therapy led to achievement of clinical remission in 4 weeks, but it lasted only 6 months. The next disease flare presented with an occurrence of new enterocutaneous fistulae and severe abdominal pain. The patient was once again referred to a surgery (Figure 2).

DISCUSSION

CD is slightly more common among women and the peak of incidence falls between 15 and 25 years of age coexisting with the reproductive period [3]. It has been observed that patients with IBD have fewer offspring than the general population, but this seems to primarily reflect a voluntary childlessness [6, 7]. This tendency may result from the fear of passing the disease to a child, although the incidence of foetal developmental disorders (about 1% of cases) and long-term morbidity are not different from that observed in healthy women [8, 9, 10].

It seems that CD does not affect fertility, especially during remission, but an active disease may reduce the chances of conception [8, 11, 12]. All surgical interventions during the course of the disease involve the risk of disrupting the function of the fallopian tubes, mainly due to adhesions

leading to their obstruction [8, 12]. Other factors that may reduce reproductive potential are protein-calorie malnutrition and deficiencies of micronutrients and vitamins [3]. Our patient met some of the above risk factors. The disease was severe, and achieving remission was very difficult despite the use of various medications. Therapeutic possibilities were limited because of an intolerance, lack of effectiveness, intensification of comorbidity (psoriasis) and refusal to use certain drugs (MTX).

TNF-alfa inhibitors, for example infliximab, are useful in many diseases including psoriasis and psoriatic arthritis. However, used in other autoimmune disorders it may cause paradoxical induction of psoriatic plaques [13]. This adverse drug reaction was observed in the patient during anti-TNF-alfa treatment. De novo psoriasis seems to be more frequent during therapy with infliximab and adalimumab than etanercept. The latter leads to an increased risk of psoriasis exacerbation among patients with a history of this disease [14]. In the most of cases discontinuation of the treatment is accompanied by remission of the skin lesions, and re-use of the same drug contributes to its relapse. Sometimes, in case of de novo psoriasis, change of administered TNF-alfa inhibitor to another one leads to improvement of clinical state or regression of skin lesions [14, 15].

As the patient had to undergo a surgical procedure due to an abscess and a fistula of splenic flexure and a sigmoid fistula penetrating towards the left fallopian tube, it could have reduced fertility. Not only the moment of conception was inadequate but also the attending physician had not been informed in advance, so the patient could not be provided with an advice as well as the optimal therapy.

Although the uncomplicated course of pregnancy and childbirth concerns the majority of women suffering from CD (about 85%), such successful results are observed when conception occurred during the remission [8, 11, 12]. In case of the discussed patient, it occurred in a short period of time after immediate surgical intervention. In addition, active inflammatory changes were visualized in the abdominal and pelvic MR imaging preceding the conceiving. There is an increased risk of spontaneous abortion, preterm delivery (PD), small for gestational age (SGA), low birth weight (LBW) and labor complications [9, 16, 17, 18, 19]. Also ileal disease and previously undergone bowel resection are associated with worse prognosis [20].

Considering the influence of pregnancy on the course of CD, one may say that the activity of the disease at the time of conceiving is also the most important predictor [8,18]. If conception occurs during a period of quiescent disease, the risk of exacerbation is 15%, not diverging from that expected in non-pregnant CD patients over a period of nine months. If a relapse appears, it is most likely to occur in the first trimester and puerperium [21, 22]. About two-third women who have clinically active CD at the time of conception will stay active during the pregnancy or will deteriorate [21]. Therefore, it is important to plan conceiving in CD remission.

Most of medications used to induce or maintain remission are said to be safe during pregnancy, including

sulfasalazine, mesalazine, azathioprine, 6-mercaptopurine and glucocorticoids [8, 18]. It seems that biological treatment (anti-TNF- α) also might be used during pregnancy, but it is recommended to discontinue the therapy in 24/52. For this reason, treatment of pregnant patients is nearly the same as for non-pregnant women [3, 8, 18]. Only methotrexate and thalidomide are in Pregnancy Category X so they are contraindicated (Table 3). Resignation from treatment of MTX also concerns women with maternal plans. Our patient consistently refused therapy with the use of MTX, so she was probably aware of its teratogenic and embryotoxic activity. During pregnancy the woman was only on maintenance therapy with sulfasalazine. Folic acid and iron supplementation was prescribed. The patient decided to stop taking azathioprine on her own. Resignation from some medications usually reflects the patient concern about its negative impact on the developing fetus [23]. Irrational withdrawal may lead to exacerbation of inflammation and may increase the risk of relapse after labor which the patient experienced. The most important for the disease control and proper development of pregnancy is continuation of the therapy applied so far. The active disease is worse for the mother and the child than medicines used to control it. Special attention should be given to folic acid, vitamin B12 and iron supplementation in women waiting to conceive and during pregnancy [3, 8].

There are not any clear guidelines concerning mode of delivery [3, 8, 18, 24]. During the remission period there are no contraindications for vaginal delivery. There are two gastroenterological situations when cesarean section is recommended: active perianal disease and the presence of an ileoanal pouch [3, 8, 25]. In any other situation decision about mode of delivery should be made on purely obstetric grounds [8]. If a patient has inactive perianal disease or no history of perianal disease, there risk for perianal disease after a vaginal delivery is not increased. Amid the reports about perianal complications of CD after episiotomy, it is necessary to protect the perineum and avoid this obstetric procedure. Patients with colostomy, ileostomy or continent ileostomy can deliver vaginally [3, 8].

In this case doctors decided about vaginal delivery based on obstetric recommendation. There were not gastroenterological contraindications such as perianal disease. Moreover, the patient was suspected of enterocutaneous fistulae which was associated with a similar risk of complications for both methods of delivery. Skin incision procedure could conduce to complications during surgery and affect postoperative wound healing. Therefore, vaginal delivery seemed to be the optimal solution.

Psychological disturbances in patients with IBD may be a consequence of underlying disease, a complication of the treatment or a comorbid condition [26, 27, 28, 29]. There is a correlation between the degree of psychological distresses, disease severity and health related quality of life (HRQoL) [4, 30]. Patients with CD seem to have slightly higher frequency of psychological disabilities than those who suffer from ulcerative colitis or other chronic conditions [8]. There is also an increased incidence of mood disorders, including depression [28, 29, 31].

Especially children and adolescents with IBD are at high risk of developing psychiatric disorders [30].

Psychiatric adverse effects of corticosteroid use include euphoria, delirium, confusion, insomnia, emotional lability, personality changes, severe depression, mania, sensory flooding, suicide ideation and corticosteroid-induced psychosis [31, 32]. The latter may develop in 5% to 18% of patients treated with corticosteroids, especially in high dose. The risk of psychosis is likely to be dose related. High dose with a sharp increase is said to be the primary risk factor [33], but it is impossible to predict time of onset, severity, type or duration of symptoms basing on the dose size [31]. It is still unclear if patients who have experienced a previous psychiatric reaction to steroids have higher probability for recurrence with psychotic features [31, 33]. A history of prior psychiatric illness does not necessarily predict a susceptibility to steroid-induced psychiatric symptoms [33]. Females may have a slightly higher risk of steroid-induced psychiatric symptoms [31, 32].

It is not well understood whether corticosteroid-associated psychiatric disturbances are related to hippocampal effects (suppression of the hypothalamo-pituitary-adrenal axis by dopamine neurotransmission) or to other direct or indirect effects of corticosteroids [31, 33].

Symptoms of corticosteroid-induced psychosis range from subtle mood changes and memory deficits to frank psychosis that can occur at any time during treatment. Condition is reported to manifest in mania and hypomania (35%), depressive symptoms (28%) and psychotic reactions (24%). Symptoms typically develop within 3 to 4 days (median - 11 days) following the initiation of corticosteroid therapy, but they can occur at any time, including after accomplishment or cessation of treatment [32, 33].

Our patient experienced variety of psychological disturbances: anxiety and depressive mood caused by difficulties in getting pregnant, corticosteroid-induced psychosis and delirium and paranoid schizophrenia.

In a patient with a chronic disease, the psychological aspect should not be marginalized, because it can significantly affect the cooperation with the doctors, limit therapeutic options and, therefore, deteriorate the control of the illness.

Summary

Crohn's disease with incidence rate in European countries around 5/100 000/year and prevalence rate at the level of approximately 50/100 000 is classified as a rare disease [1, 34]. Therefore, not every obstetrician will have the opportunity to come across a pregnant woman with that condition. Although some studies suggest that CD may predispose to the development of depression, it seems that there is no correlation between inflammatory bowel disease and the paranoid schizophrenia [35]. Taking into consideration all the mentioned arguments, the described case combining various clinical problems looks certain to be rather an unique observation.

CONCLUSIONS

1. Crohn's disease is a rare disease, therefore, its presence in a pregnant woman might be a clinical challenge.
2. Treatment of pregnant women is nearly the same as for non-pregnant women.
3. Influence of pregnancy on CD is difficult to predict, however conception in remission period provides the same chance to deliver healthy child as for women in general population.
4. Due to complexity of this problem, a decision about mode of delivery should be made by the patient, obstetrician and gastroenterologist.
5. Psychological disturbances in patients with IBD may be a consequence of underlying disease, a complication of the treatment or a comorbid condition. Systemic corticosteroid use is an example of therapeutic option that may affect mental health.

CITE THIS AS

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ABBREVIATIONS

- CD** – Crohn's disease
CRP – C-reactive protein
CT – computed tomography
HRQoL – health related quality of life
IBD – inflammatory bowel disease
LBW – low birth weight
MTX – methotrexate
PD – preterm delivery
SGA – small for gestational age

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TAB. 1. PHYSICAL EXAMINATION FINDINGS.

Table I

Physical examination findings	
Mental state	mood significantly lowered, tearfulness
Skin	numerous psoriatic lesions on the skin of the abdomen and scalp
Cardiovascular system	irregular heartbeat(extrasystoles), tachycardia - >100 beats per minute; hyperdynamic circulation
Abdomen	stoma bag in the left lumbar region; scar after surgical procedure (median incision) healed per primam

TAB. 2. LABORATORY TESTING.

Table II

Laboratory testing		
Parameter	Result	Reference range
Hb [g/dl]	10.10	11,00 - 15,00
Hct [%]	30.90	37,00 - 47,00
MCV [fl]	77.10	82,00 - 92,00
RDW-CV [%]	17.70	12,10 - 14,10
PLT [/ul]	513 000	125 000 - 340 000
CRP [mg/l]	33,79	< 5,00
Albuminy [g/l]	33,00	35,00 - 52,00
Želazo [μmol/l]	2.80	5,83 - 34,50
Witamina D [ng/ml]	17.41	30 - 80

TAB. 3. SAFETY OF MEDICINES USED TO TREAT CROHN'S DISEASE IN PREGNANT WOMEN ACCORDING TO THE FDA CLASSIFICATION.

Table III

Safety of medicines used to treat Crohn's disease in pregnant women according to the FDA classification		
SAFE ¹	RISK NOT RULED OUT ²	CONTRAINDICATED ³
5-ASA Infliximab Probiotics Prednisone Prednisolone Loperamide Colestyramine	Budesonide Azathioprine 6-Mercaptopurine Cyclosporine Tacrolimus Ciprofloxacin Metronidazole	Methotrexate Thalidomide

¹ Pregnancy Category B
² Pregnancy Category C (potential benefits may warrant use of the drug despite potential risks)
³ Pregnancy Category X

Rutgeerts P, Vermeire S, Van Assche G: Mucosal healing in inflammatory bowel disease: impossible ideal or therapeutic target? Gut. 2007; 56: 453-455.
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FIG. 1. PREGNANCY.

Figure 1 – pregnancy

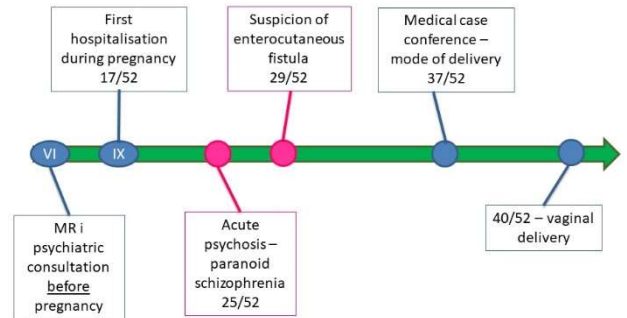
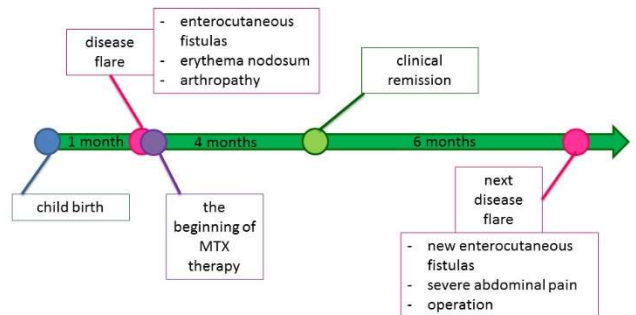


FIG. 2. AFTER DELIVERY.

Figure 2 – after delivery





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