CURRENT ASPECTS WITH REGARD TO THE LINK BETWEEN PREGNANCY AND INFLAMMATORY BOWEL DISEASE

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Abstract – Inflammatory bowel disease (IBD) has a high incidence predominantly in young individuals, it also affects family planning and pregnancy. In this review we will summarize a number of issues and challenges that arise from this, such as the chances of having a successful pregnancy, how IBD affects pregnancy, what investigations are needed during pregnancy, as well as what is the correct management of IBD (dietary, medical or surgical) in pregnant women with this disorder. IBD in pregnancy requires a multidisciplinary approach involving close collaboration between patient, gynecologist and gastroenterologist in order to increase treatment compliance and facilitate a successful pregnancy.

Key words: inflammatory bowel disease; pregnancy

INTRODUCTION

Inflammatory bowel disease (IBD) consists of ulcerative colitis (UC) and Crohn's Disease (CD). These are complex, chronic conditions featuring frequent relapses. They pose a diagnostic challenge, are of various levels of intensity and are incurable, and have an unpredictable therapeutic response. IBD predominantly affects younger individuals, and concurrent pregnancy is often found in this patient group. The issues and challenges arising in regard to the relationship between pregnancy and IBD will be examined.

The chances of having a successful pregnancy in the context of IBD

Current literature suggests that fertility in IBD sufferers is similar in both women and men when compared to the general population prior to surgical interventions (Lepistö et al., 2007), as well as during disease remission (van der Woude et al., 2010). The reduction in births in the IBD population does not appear to be directly linked to the disease itself. Moreover, the disease should be in remission for 3-6 months prior to conception. The chances of an acute exacerbation of IBD are around 33%, irrespective of pregnant status (Sunanda et al., 2010). The patient must be compliant with the treatment of any acute exacerbations, as the maintenance of disease remission is essential to a normal pregnancy. Additionally, the pregnant patient must be monitored every three months or more often if needed by a multidisciplinary team including both obstetricians and gynecologists.

In CD, the infertility seen during disease remission is also similar to that of the general population (5-14%) (Hudson et al., 2007). This is not the same during active forms of the disease, where fertility rates range between 40-80%. This may be explained by the inflammatory process that may involve the ovaries and annexes, and post-operative adhesions that may involve the anterior aspects of the pelvis. In addition, secondary amenorrhea may occur because of malabsorption or a severe episode of disease exacerbation, as well as by changes in sexual behavior patterns due to anoperineal lesions leading to dyspareunia (Munkholm et al., 2000).

In UC, fertility falls by 40-80% following surgical interventions such as proctocolectomies and especially ileoanal pouch reconstructions. This may be attributed to the higher incidence of hydrosalpynx, fimbria destruction or fallopian tube blockage (Vermeire et al., 2010). Consequently, females with severe forms of UC need to be actively involved in the decision-making process of choosing medical and surgical management options.

Controversy exists as to whether surgical intervention should be via an open or laparoscopic approach. There is also a lack of consensus regarding the role of laparoscopy in reducing the risk of infertility (Serafi et al., 2012). A possible explanation could be represented by the role of relaxin in inhibiting macrophage function and subsequently reducing the risk of adhesion formation (Munkholm et al., 2000).

Regarding male fertility, pelvic surgery and especially undergoing ileoanal pouch reconstruction can lead to ejaculatory or erectile dysfunction due to damage to the autonomic nervous system (Damgaard et al., 1995). Consequently, sperm storage must be considered prior to surgery. Sulfasalazine used in moderate forms of the disease can lead to a decrease in the number and motility of sperm cells; however, this is completely reversible at 6 months following therapy cessation (Levi et al., 1979). Methotrexate also leads to oligospermia and must be stopped for 4 months prior to conception (Sunanda et al., 2010).

The chances of having a healthy child

The etiology of IBD depends on genetic predisposition and environmental triggers; 5.5-22% of IBD sufferers have a family member already suffering from IBD.

In cases where both parents are IBD sufferers, their children have a 36% lifetime risk of developing it (Bennet et al., 1991). If one parent suffers from IBD, offspring have a 2-13-fold higher risk of developing the disease compared to the general population (Mahadevan et al., 2006). The risk is higher for 1st degree relatives for developing CD (5.2%) compared to UC (1.6%). In addition, the risk for 1st degree relatives is slightly higher in the Jewish population (Serafi et al., 2012). Patients with IBD that have a positive family history tend to develop the disease at an earlier age compared to those without UC (Laharie et al., 2001).

The relationship between IBD and pregnancy

There is a lack of consensus regarding the role of IBD in pregnancy. Patients with disease remission or mild forms of IBD have normal pregnancies (Sunanda et al., 2010). It is known that surgical resection and ileal involvement are risk factors for complications of pregnancy. Some studies support the view that the presence of IBD is associated with a higher risk of complications, irrespective of disease severity, with CD being more detrimental than UC (Mahadevan et al., 2007). Consequently, premature birth (<37 weeks) is more often found in patients with active IBD. In CD sufferers, premature birth is 3.4 times more likely in those with active CD. Similarly, a reduced birth rate (2 500-2 700 g) occurs irrespective of disease severity, especially in those with CD (Sunanda et al., 2010). Delayed intra-uterine growth and spontaneous or therapeutic abortions are also seen more often than in the general population. Pregnant women suffering from IBD have fewer surgical procedures compared to those with IBD who are not pregnant. This may be explained by the role relaxin, a pregnancy hormone that leads to a reduction in adhesion formation

through macrophage inhibition during pregnancy (Nguyen et al., 2009).

If pregnancy occurs during a period of IBD remission, the risk of acute exacerbations is similar in both pregnant and non-pregnant patients (Serafi et al., 2012). In contrast, if the patient becomes pregnant during an episode of active disease, two thirds of the patients will maintain their active status during the entire pregnancy. This is an important factor in patient education, as individuals must be counseled regarding the need to commence a pregnancy during an episode of remission.

Investigations required during pregnancy

In this case as well there is a lack of consensus in the existing literature. Diagnostic and therapeutic endoscopy is a feasible alternative to radiological imaging in pregnant patients. Any invasive endoscopic procedure carried out requires perioperative fetal heart rate monitoring. A total colonoscopy is not advocated during pregnancy, where flexible sigmoidoscopy should be the first line investigation modality. A total colonoscopy may be justified if absolutely necessary to assess the severity of an acute exacerbation, an acute gastrointestinal bleed or to investigate diarrheal episodes only after a flexible sigmoidoscopy has been inconclusive. Bowel preparation is achieved using polyethylene glycol solution (Rimensberger et al., 1992). Intraprocedural monitoring may require maternal blood pressure monitoring and arterial blood gas analysis to insure adequate oxygenation and placental perfusion. The pregnant patient must be placed in the left lateral decubitus position to avoid compression of the inferior vena cava and hypotension (Sunanda et al., 2010). Upper gastrointestinal endoscopy poses an additional risk of aspiration due to the incompetence of the inferior esophageal sphincter during pregnancy. Endoscopic retrograde cholangiopancreatography (ERCP) is a relatively safe procedure if there are strong indications for its use; studies on a limited number of patients have not demonstrated a rise in fetal malformations or premature births due to its use (Cappell et al., 2003). The radiation dose used must be greater than 10mGy (Akcakaya et al., 2009). The risk of post-ERCP pancreatitis must always be considered in these cases. MRI may be used if indicated as it does not involve ionizing radiation and can diagnose IBD, as well as monitor its evolution in the second and third trimester of pregnancy.

The decision to sedate the patient must be carefully considered. Pethidine or meperidine may be used in the first trimester of pregnancy, as it is often used for analgesia and sedation during endoscopy. However, it can cause reversible bradycardia in the fetus. Fentanyl has also been reported to cause respiratory depression and rigidity of the respiratory muscles in preterm infants after childbirth (Lindemann et al., 1998).

The risk of venous thromboembolism in pregnant women with IBD

IBD carries a 4- to 6-fold increased risk of thromboembolism during pregnancy, which is an important cause of maternal death (Heit et al., 2005). This risk is highest in the first 6 weeks of pregnancy and in the postnatal period. Consequently, during an acute flare of IBD, thromboprophylaxis with low molecular-weight heparin is recommended during hospitalization and in the perioperative period. This has been shown to reduce the risk of thromboprophylaxis by 60-70% (National Clinical Guideline Centre, 2010).

The optimal method of childbirth

IBD is not an indication for caesarean section. Despite this, retrospective studies have suggested that in CD with perianal involvement there is a risk of disease flare-up following vaginal delivery in 18% of cases (Kane et al., 2011). A growing trend for caesarean sections has however been noted in IBD sufferers (van der Woude et al., 2010).

Management of pregnant women with IBD?

As regards diet, in the severe forms of IBD corrections of electrolytes and fluid balance are essential.

Bowel rest and parenteral nutrition may be used in certain cases. Smoking is contraindicated during pregnancy for fetal and maternal health reasons, despite its impact on UC.

The major risk to pregnancy is caused by IBD activity rather than its medical management. There are a limited number of studies investigating the impact of IBD pharmacotherapy on pregnancy. Drugs used can be divided in four categories: A – no risk for the fetus; B – no risk demonstrated on humans; possible but low risk; C – high risk to the fetus; and D – contraindicated during pregnancy. Mesalazine, corticosteroids, infliximab and adalimumab are classified as category B drugs. Ciprofloxacin and cyclosporin are class C agents, whilst azathioprine and 6-mercaptopurine are classified as category D drugs.

Thus, sulfasalazine and 5-ASA agents are used in the treatment of moderate forms of IBD, as well as in maintaining disease remission. They are classified as class B agents and although they cross the placental barrier, they do not lead to fetal malformations. Sulfasalazine is one of the oldest drugs used in the management of IBD and carries the same risk profile irrespective of pregnant status. This may include nausea, vomiting, rashes, anorexia, interstitial nephropathy and hepatotoxicity. Consequently, the initial starting dose of 500 mg needs to be gradually increased. Sulfasalazine can be used in women that are breastfeeding. It can interfere with folate absorption and it must be used in conjunction with folate supplementation (2g once daily) prior to conception and for the entire duration of the pregnancy (Vermeire et al., 2010).

In regards to 5-aminosalicylic acid agents, they have a similar side-effect profile to sulfasalazine. Nevertheless, their side effects are less frequent and severe. Mesalazine can be administered in different forms in order to target selectively the part of the GI tract affected by IBD. Asacol releases 5-aminosalicylic acid in the distal ileum and colon, and can be used in IBD affecting the distal digestive tract. Pentasa causes drug release throughout the entire gastrointestinal tract and is used in the management of CD affecting the stomach and small bowel. In contrast, balsalazine releases 5'-aminosalicylic acid in the colon. Pentasa and balsalazine can be given to pregnant women at a maximum dose of 3 g per day, as suggested by meta-analytical work and the ECCO Consensus, without increasing the risk of teratogenicity or complications of pregnancy (Kowitz et al., 2004). Recently, Asacol has been reclassified from a class B to a class C agent due to compounds in its coating (van der Woude et al., 2004). The use of mesalazine requires further investigation.

Corticosteroid therapy can be used in the treatment of acute flares of IBD in pregnant patients. These cross the placenta and are converted into less active compounds by 11-hydroxygenase, leading to a lower fetal serum concentration. Corticosteroids with a short half-life should be administered (prednisolone and methylprednisolone) rather than those with longer half-lives (e.g. dexamethasone). Oral prednisolone (40 mg) can be used as a first-line agent. In severe cases or in the presence of drug tolerance, intravenous hydrocortisone (300 mg) or methylprednisolone can be administered. These may be converted to oral prednisolone (30 mg) after 7 days. In IBD cases involving the left colon, hydrocortisone enemas may be used. The side effects of prednisolone are well known; however, it is important to mention the need to actively monitor electrolytes and reduce salt intake during pregnancy as hyponatremia, electrolyte disturbance and hypervolemia can lead to preeclampsia. There is also a risk of premature membrane rupture and corticosuprarenal insufficiency in the newborn if prednisolone is administered in the last trimester of pregnancy, due to suppression of the adrenal gland medulla (Homar et al., 2008). In the first trimester, the use of corticosteroids can lead to orofacial malformations (cleft lip and palate) (Moffat et al., 2007). Prednisolone and methylprednisolone can however be given during lactation. In addition, budesonide, a synthetic steroid, may be used in pregnant women with IBD without complications to the pregnancy or teratogenic effects. However, its administration cannot be fully endorsed due to its relatively limited use (Beaulieu et al., 2009).

With regard to immunosuppressants, azathioprine and its metabolite, 6-mercaptupruine, are used in cases that do not respond to 5-ASA and/or maintenance of long-term remission. These are classified as class D drugs from a complications profile perspective. Most studies have shown that their use is safe during pregnancy and does not lead to an increased risk of malformations in the newborn (Cleary et al., 2009). These agents cross the placenta and their metabolites can be found in similar quantities in maternal and fetal erythrocytes (Jharap et al., 2008). Side effects occur in pregnant and non-pregnant women to a similar extent. These include leucopoenia, pancreatitis, nausea and vomiting. It is difficult to determine to what extent spontaneous abortions, premature births and low birth weight are due to therapy with ASA and 6-mercaptopurine or IBD itself. The largest study to date was performed on a small number of patients, with no significant difference in prematurity, spontaneous abortions or congenital anomalies in patients with and without 6-mercaptupurine therapy during pregnancy (Francella et al., 2003). Current literature does however suggest that chromosomal anomalies may occur secondary to immunosuppression (Coelho et al., 2010). Breastfeeding is theoretically contraindicated due to the risk of toxicity, infection and pancreatitis in the newborn. Despite this, other evidence suggests that breastfeeding can be carried out at 4-6 h from the last dose of 6-mercaptopurine (the maximal interval for excretion of 6-mercaptopurine in maternal milk) (Serafi et al., 2012).

Cyclosporin is used in treating fulminant UC as an alternative to colectomy, which is associated with an increased fetal mortality (Branche et al., 2009). Cyclosporin is not thought to be teratogenic but it is reserved for severe cases and its use in pregnancy is extremely rare (Bar-Oz et al., 2001). There are no teratogenic side effects described for tacrolimus. Furthermore, it is difficult to determine whether the low birth weight and prematurity noted are caused by the severity of the disease or the medical therapy administered. Currently, there is one case of IBD (UC) treated with tacrolimus in a pregnant patient (Baunergart et al., 2005).

Methotrexate and thalidomide are used in patients with IBD that are resistant to conventional management. Importantly, they are teratogenic and contraindicated in pregnancy. Methotrexate given in the first trimester of pregnancy leads to abortion, congenital malformation and development abnormalities of the nervous system (Kozlowski et al., 1990). It is important to note that methotrexate has a long half-life and its use is contraindicated for 3-6 months prior to conception in both men and women. Accidental pregnancies during methotrexate therapy may require a therapeutic abortion. Thalidomide is an alternative IBD treatment modality through its anti-tumor necrosis factor (TNF) and anti-angiogenic effects. It leads to fetal malformations and a high rate of neonatal mortality (approximately 40%) (Smithells et al., 1992). Female IBD patients on thalidomide therapy should be on a dual contraceptive therapy.

Regarding antibiotics, ciprofloxacin and metronidazole are used electively in the treatment of pouchitis and perianal CD. Metronidazole is class B agent used in the management of IBD in pregnancy; its use is safe in the second and third trimesters of pregnancy, although the development of facial malformations have been documented (Piper et al., 1993). Ciprofloxacin is considered a class C agent. It has not been shown to lead to spontaneous abortions or the development of congenital anomalies in clinical studies. Animal studies have suggested the possible development of skeletal muscle anomalies following its use. During pregnancy, the use of safer antimicrobials is recommended for the treatment of pouchitis. These include ampicillin, cephalosporins and amoxicillin with clavulanic acid.

Agents with anti-TNFα activity (infliximab, adalimumab, certolizumab pegol) actively cross the placental barrier by using specific fetal receptors. This occurs most significantly in the third trimester and can be detected in the newborn for up to 6 months, often at a higher level than in the maternal blood (Mahadevan et al., 2007). Consequently, in patients in remission, infliximab therapy should be stopped in the 26th-30th week of gestation. Newborns should

not be vaccinated for 6 months with agents using live or live attenuated micro-organisms (rotavirus, measles, rubella, BCG, mumps and chickenpox) (Zelinkova et al., 2011). In addition, the GETAID and TREAT studies did not identify any differences in fetal or maternal complication in patients treated with or without infliximab (Reddy et al., 2008). The same applies for adalimumab therapy despite a more limited evidence basis (Vesga et al., 2009). The use of certolizumab in pregnant IBD-suffers is even scarcer. It is believed that the placental transport is minimal and passive and does not lead to fetal abnormalities. Consequently, a normal vaccination pattern may be adopted (Kane et al., 2011).

Adjuvant therapy with an antidiarrheal agent, such as loperamide, can be used in pregnant IBD-suffers.

Regarding surgical management, this is relatively safe throughout the duration of the pregnancy. A small number of patients have identified a risk of abortion during the first trimester and premature birth in the third trimester in IBD patients undergoing surgery (Serafi et al., 2012). Indications for surgery are the same in pregnant and non-pregnant IBD patients, i.e. bowel obstruction in CD, intestinal bleeding, perforation and abscesses in fulminant UC that do not respond to medical therapy and where the risk posed by the disease severity is greater than that of the surgery (van der Woude et al., 2010).

Breastfeeding in patients with IBD

Breastfeeding is beneficial for both mother and baby in healthy individuals. It has a variable impact on conditions with an immune etiology. In cases such as multiple sclerosis or rheumatoid arthritis, breastfeeding may lead to exacerbations of the disease, whilst in IBD it can have a protective role for the mother, as well as for the fetus. In the mother, this is manifested as a longer duration of disease remission and in the fetus by a delay in the onset of IBD (American Academy of Pediatrics Work Group on Breastfeeding, 1997). These can be explained by a reduction in estrogen and progesterone levels during lactation, leading to a reduction in the pro-inflammatory response sustained by the intestinal mucosa (Bergstrand et al., 2003). Another explanation is the psychosomatic effect of breastfeeding during which women experience reduced levels of stress and postpartum anxiety. This leads to raised levels of corticotropin-releasing factor, which can modulate inflammatory responses and reduces the onset of acute exacerbations (Moffat et al., 2004). 14-85% of mothers with IBD self-interrupt their medical therapy during lactation. Clinicians need to explain to patients that breastfeeding is safe when taking certain classes of drugs. 5-ASA (sulfasalazine, mesalazine; 3 g/day) are compatible with breastfeeding. Possible complications are diarrhea in the fetus (Hart et al., 2010). Corticosteroids with a short half-life (prednisolone, methylprednisolone) can be used safely during lactation (Moffat et al., 2004). Traditionally, azathioprine and 6-marcaptopuine were contraindicated during breastfeeding. Pharmacokinetic studies suggest that breastfeeding can take place 4-5 h after the use of immunomodulator therapy, as there is limited excretion in maternal milk (Christensen et al., 2008). Cyclosporine, methotrexate, tacrolimus and thalidomide are also contraindicated during breastfeeding (Hart et al., 2010). Biological agents are not excreted in maternal milk and can be safely used (Stengel et al., 2008). The most commonly studied agent is infliximab. In addition, antibiotic use needs to be adjusted, with ciprofloxacin and metronidazole being exchanged for ampicillin and amoxicillin, which have less toxic side effects during lactation.

CONCLUSIONS

IBD has a high incidence predominantly in young individuals and therefore has a concomitant impact on family planning and pregnancy. Ideally, conception needs to occur during remission of IBD and clinicians must strive to maintain this throughout the entire pregnancy. The highest risk to the pregnant patient and fetus is posed by the disease, not by disease therapy. In the postnatal period, management of IBD needs to be tailored to lactation priorities. IBD management in pregnancy requires a multidisciplinary approach, involving close collaboration

between patient, gynecologist and gastroenterologist in order to increase treatment compliance and a successful pregnancy.

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