Pregnancy and inflammatory bowel diseases from conception to delivery

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Abstract

Background : **Chronic inflammatory bowel diseases frequently affect young people and are of major concern to them when envisaging parenthood.**

Materials and methods : **Using a literature review, we attempt to provide up-to-date solutions concerning conception, pregnancy, delivery and breastfeeding ; we also underline potential risks associated with such diseases, their treatment and management.**

Results and conclusion : **Inflammatory bowel diseases are not incompatible with maternity or paternity, but foresight is recommended and future parenthood should be discussed with gastroenterologists so as to adapt treatment and follow-up to ensure successful pregnancy outcome.** (Acta gastroenterol. belg., **2009**, 72, **238-244**).

Key words : inflammatory bowel diseases, pregnancy, conception, delivery, breastfeeding.

Introduction

Chronic inflammatory bowel diseases (IBD), which include Crohn's disease and ulcerative colitis, frequently affect young people, with a peak onset between the second and fourth decade of life (1-6). Thus, concerns have been raised about the quality of life of these young patients and their future prospects. Among the latter, the possibility of parenthood occupies an important position.

Via a literature review, we attempt to provide up-to-date answers to questions concerning pregnancy, from conception to delivery, and to provide general practitioners and gastroenterologists with the means of giving patients informed advice.

Conception

The capacity to conceive, the initial step in pregnancy, is a source of concern to patients suffering from IBD, who may often fear infertility. Up to 17.9% of such patients will consult for "fertility problems" (7) and undergo gynecological or andrological check-up, which is usually normal. It is interesting to note that around 25% of parents with IBD report having had fewer children than initially planned (6, 7).

The fertility rate in IBD is similar to that of the general population (3, 7, 8-14), except in the acute phase of Crohn's disease (2, 8, 13, 15). Previous history of surgical procedures would appear to be correlated with loss of fertility due to : 1) mechanical problems (tubal sterility secondary to adhesions (3, 8, 10, 12, 16)), with a cumulative 5-year incidence of pregnancy of 36% compared to 90% without surgery (16) ; 2) neurological lesions secondary to colectomy with ileoanal anastomosis (8, 17)) ; and 3) discomfort during intercourse (dyspareunia, soiling) (11, 12, 16, 18). However, these data are counterbalanced by contradictory studies showing a post-operative increase in frequency of intercourse and improved overall sexual satisfaction due to less symptomatic disease and better self-perception (19). Psychological concerns (difficulties with intimacy, shyness, delay in growth and onset of puberty, body-image problems, loss of self-esteem, fear of pregnancy, etc.) (3, 6, 12, 13) would appear to play a greater statistical role than mechanical problems in fertility problems reported by IBD patients. Finally, medication may also interfere with conception (see below).

Concomitantly with concern about fertility, the question of contraception is of crucial importance. Indeed, when conception occurs during an IBD active phase, there is a risk of poor obstetrical outcome which may be as high as 35% and a risk of up to 50% of clinical recurrence (8). Moreover, treatment of IBD can have teratogenic side-effects, which may contra-indicate conception (see below). Therefore, patients must be informed of these risks and advised to use efficient contraception, ideally a combination of two contraceptive methods. Indeed, while condoms are as effective as in the general population, caution is recommended when using oral contraception and possibly intrauterine devices as well. A conception rate of up to 12.2% has been reported under oral contraception due to malabsorption (diarrhea, previous history of intestinal resection) (8). Oral contraception is also correlated with greater risk of deep venous thrombosis, especially in an acute phase. Intrauterine devices may be less effective when associated with corticosteroids, but have thus far not been the object of preventive recommendations (8).

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Table 1. — **IBD effects on the fetus**
(References : see text)

	Relative risk (RR)
Transmission to the fetus Absolute risk if one parent is affected = 1.5 to 3.5% Absolute risk if both parents are affected = 33 to 67%	2 – 13
Abortion	1 – 35
Prematurity (birth before 37th week of gestation)	1.4 – 2.3
Hypotrophy	2 – 3.6
Congenital malformation	1 – 2.37

Pregnancy

Pregnancy represents a forty-week-long interaction between a woman and her fetus. In the case of IBD, a "third guest" is also present : IBD interferes both directly, through its impact on the fetus and the mother, and indirectly, via its management during pregnancy. Conversely, pregnancy itself may affect the course of IBD.

IBD effects upon the fetus

Many studies mention unfavorable effects of IBD upon the fetus (1, 3, 4, 6, 8-15, 20-23) (Table 1), but incidence rates vary considerably from one study to another.

IBD is not genetically transmitted from parents to children as an autosomal dominant, recessive or X-linked model. Nevertheless, some genetic patterns seem to define a predisposition to IBD, and these patterns may be transmitted during the random process of gene distribution occurring during fecundation. Via this mechanism, the relative risk of transmission of IBD to the fetus ranges from 2 to 13 (8, 9), with an absolute risk of 1.5 to 3.5% if one parent is affected and up to 33 to 67% if both parents are affected (8, 9, 12, 13). The risk of inheriting IBD is also higher in Jewish (7.8%) families compared to non-Jewish (5.8%) families (12, 13).

IBD is also associated with greater risk of spontaneous abortion (1, 8, 10-15, 20), which can rise to 35% when conception occurs during the active phase (8, 10, 12).

When pregnancy is brought to completion, the most frequently described adverse effects of IBD upon the fetus are prematurity (birth before 37th week of gestation), with a relative risk of 1.4 to 2.3 (1, 3, 4, 6, 8-13, 20-23), and hypotrophy (mean birth weight 134 to 185 g less than that of the general population (8)), with a relative risk of 2.0 to 3.6 (1, 4, 6, 8, 11-13, 15, 20-23). It is interesting to note that both risks are significantly increased by smoking ; thus, pregnant women suffering from IBD should be firmly advised not to smoke.

Data are not clear concerning possible congenital malformations. Some studies report a risk similar to that of the general population (3, 8, 10, 15), whereas others mention a relative risk of up to 2.37 (1, 6). This is difficult to assess, as many congenital malformations lead to spontaneous abortion and are therefore not taken into account.

Effect of pregnancy upon IBD

It is interesting to note that, contrary to previously held notions, contraception does not interfere with the course of IBD : it neither increases nor decreases the risk of exacerbation of the disease (8). During pregnancy, the risk of IBD exacerbation has been reported to range from 8.9 to 25% (3, 8, 20) if the disease is inactive at the time of conception, but this rises to 45-50% when IBD is active (1, 3, 8, 10). This justifies the need for effective contraception during the acute phase. Conversely, pregnancy has also been reported to be beneficial to the IBD natural history : a decrease in both clinical activity and need for surgery (8, 9, 11, 12, 16) has been observed and could be explained by pregnancy-related production of relaxin, a hormone which inhibits macrophage function and thereby reduces fibrosis and stricture formation (12), and by immunological tolerance which develops during pregnancy (12) in order to protect the fetus, viewed as a "foreign body". This particular status could also explain the "spontaneous" (though relatively rare) improvement in the disease (3) observed during some pregnancies.

Management of IBD during pregnancy

In case of clinical exacerbation during pregnancy, diagnosis must be confirmed and the disease treated. However, adaptations must be made so as to protect pregnancy outcome.

Diagnostic procedures

Diagnostic procedures to be used during pregnancy in the case of IBD do not differ from those used in normal pregnancy.

Ultrasonography is the key procedure because of its safety for the fetus (12) and its diagnostic value.

In contrast, X-rays and computer tomography are contraindicated, particularly during embryogenesis and organogenesis (8, 12), because of teratogenic side-effects. They should not be performed unless absolutely necessary and at low irradiation doses during the third trimester of pregnancy (8). Magnetic resonance imaging may be a safe alternative, but because of absence of data,

Table 2. — **Medical therapy during pregnancy in women suffering from IBD**
(References : see text)

	Safety	*Risk / precautions*
Quinolones	No	Risk of fetal arthropathy
Loperamide	Yes	Stop just before delivery (risk of fetal ileus)
Corticosteroids		
Prednisone	Yes	–
Bethamethasone	No	Risk of fetal surrenal insufficiency
Dexamethasone	No	Risk of fetal surrenal insufficiency
Budesonide	?	Data lacking in IBD, safe in asthma
Sulfasalazine and mesalazine	Yes	Maximal daily dose of 3 g and 2.4 g/day Folate supplements
Azathioprine	Yes	Maximal daily dose of 1.5 to 2.5 mg/kg/day Follow mother's leucocytosis
Cyclosporine	?	Only recommended in severe ulcerative colitis to avoid colectomy
Methotrexate	No	Risk of severe congenital malformation Stop at least 3 months before conception
Thalidomide	No	Risk of severe congenital malformation Stop at least 3 months before conception
Anti-TNF antibodies		
Infliximab	Yes	–
Adalimumab	?	Data lacking, seems safe according to first reports

guidelines recommend not using it during the first trimester (8).

Endoscopy is allowed during pregnancy, but should be used with caution (8, 11-13). Sedation should be adapted to fetal monitoring during the procedure (12), taking into account transplacental passage of certain sedatives (8, 11, 13). To date, there is no evidence that endoscopy induces premature labor or delivery (12).

Medical treatment

As mentioned above, the risk of exacerbation of IBD during pregnancy ranges from 8.9 to 25%, if the disease is inactive at the time of conception, to 34% (1) if maintenance treatment of the disease is interrupted. Moreover, risk of obstetric complications increases during acute inflammatory processes (2, 9). These data outline the importance of maintaining remission and controlling active phases occurring during pregnancy. However, the transplacental passage of most medication raises safety questions. Recommendations have been made (Table 2) solely on the basis of observational data, due to ethical restrictions concerning randomized controlled trials.

Regarding *antibiotics*, *quinolones* must be avoided, as they have been associated with fetal arthropathy (2, 8, 12). It is widely considered that fetal risk outweighs benefits to the mother (2), especially in light of other available therapies which may be safer.

Loperamide, the most frequently used antidiarrheal drug, is safe (2) and can be used without precautions, except during the period just prior to delivery, in order to prevent fetal ileus (8, 12).

The safety of *corticosteroids* depends on the type of molecule. *Prednisone* undergoes placental metabolization, so that the fetal dose attains only 10% of the total dose absorbed by the mother (8, 12), rarely resulting in fetal surrenal insufficiency (13). Some studies reported a higher incidence of cleft-lip and cleft-palate [odds ratio 3.35 (2) to 3.69 (23)], but this mainly affects laboratory animals (8, 9, 17) ; in humans, it is generally considered that benefits to the mother largely outweigh possible fetal risk (2). Thus, prednisone represents the first choice treatment of IBD exacerbation during pregnancy. Premature delivery due to early rupture of membranes has been reported with prednisone (2, 23), but a causal relationship has not been demonstrated. In contrast to prednisone, *bethamethasone* and *dexamethasone* are contraindicated during pregnancy because of the absence of placental metabolization, exposing the fetus to high levels of corticosteroids leading to surrenal insufficiency (8, 11). As concerns *budesonide*, data are lacking concerning safety in pregnancy in the setting of IBD, but it has been proven safe in the case of asthma (2, 11). Rectal preparations may be used up until the third trimester, despite concern about preterm delivery (13).

Sulfasalazine and *mesalazine* are safe during pregnancy even when fetal serum levels are equivalent to maternal levels due to transplacental passage (1, 2, 6, 8-12, 17, 23). Some authors consider that the daily dose should not exceed 3 g and 2.4 g/day respectively (8, 11, 12, 17). One case of severe fetal nephropathy was reported with mesalazine, but at a dose largely exceeding recommendations (8, 11, 17). The relative risk of congenital malformation, abortion and hypotrophy is not significantly increased (RR = 1.16, 1.14 and 0.93 respectively (1)).

Nevertheless, folate supplements are generally recommended (2 to 4 mg/day, ideally to be initiated before conception), especially with sulfasalazine (2, 6, 9, 11, 13, 23). This is to avoid the risk of neural tube disorder due to a lack of folate following enzymatic inhibition of the folate conjugase enzyme by sulfapyridine, a metabolite of sulfasalazine (2).

Azathioprine, a purine analogue which interferes with synthesis of adenine and guanine ribonucleosides, could theoretically be responsible for genetic abnormalities leading to congenital malformation or abortion. However, this potential risk is not confirmed by studies showing a risk similar to that observed in the general population (2, 8, 9, 10, 11, 13, 17, 24), at daily doses of 1.5 to 2.5 mg/kg (17, 24). Azathioprine could also result in fetal immunodepression due to abnormal turnover of white blood cells. In practice, maternal and fetal leucocytes have been proven to be well-correlated, so that maternal leucocytosis is a reliable marker of the fetal immune system. A decrease of 50% in the dose of azathioprine is recommended from the 32nd gestational week if maternal leucocytosis falls below the -1 standard deviation from the normal mean (usually a drop of above 1500/ml) (8, 11). It must be pointed out that such a deficiency has been rarely reported up to now (25). Despite the demonstrated safety of azathioprine during pregnancy, some experts still advise stopping use of this drug three months before conception and during the first stage of pregnancy, unless absolutely necessary for treatment of the mother (2, 8, 12, 13, 17, 25). This important matter must be discussed with the patient.

The safety of *cyclosporine*, a fungus-derived calcineurin inhibitor, is unclear. Some studies reported possible fetal nephropathy and hepatopathy, as well as bone marrow suppression, but this has not been proven (8). Other studies are more reassuring, showing no significant increase in the fetal malformation rate (2, 11, 17). Cyclosporine crosses the placenta but seems to be rapidly cleared from the fetus. Accordingly, the only recommended indication for cyclosporine use during pregnancy is in treatment of severe ulcerative colitis, to avoid colectomy (2, 6, 13).

Methotrexate and *thalidomide* are contraindicated in pregnancy (2, 6, 8, 11, 12) because of very severe teratogenic effects, affecting limbs, eyes, heart, kidneys, bone marrow and brain. Patients treated with these drugs should be clearly informed of the absolute necessity of contraception (2, 8). Some authors recommend that women treated with these drugs undergo a pregnancy test every two months (8) and that abortion be advised in case of pregnancy (8, 11). Methotrexate should be stopped at least three months (or even six months according to some authors (6, 11)) before envisaging conception, because of the lengthy persistence of the drug in the liver (2, 8) and the time span required for spermatogenesis (12).

Finally, and up until now, new *biologic therapies (anti-TNF antibodies)* seem to be safe. *Infliximab*, a chimeric anti-TNF antibody, does not cross the placenta during the first or second trimester of pregnancy (2) and therefore does not affect embryogenesis or organogenesis (2, 6, 8, 11, 13, 23). Only one case of severe prematurity with pulmonary and cerebral hemorrhage has been reported (2), but a causal link was not demonstrated. Transplacental passage may occur during the third trimester of pregnancy (2, 26), but without obvious effects on the future child's immune system, as shown by a satisfactory response of the newborn to vaccination (2). Furthermore, theoretical data suggest that anti-TNF antibodies could even play a protective role against premature rupture of membranes (15), as TNF is implicated in that process. Regarding *adalimumab*, a 100% human anti-TNF antibody, its fetal innocuity cannot be confirmed as data are lacking. However, studies have shown that this drug is safe in laboratory animals, and recent human reports tend toward the same conclusion (2, 27).

Surgical treatment

Surgical treatment is not recommended during pregnancy because of a 60% risk of fetal loss (13). Medical management is preferred except in life-threatening situations. Among these, toxic megacolon occupies a major position and justifies a first-line surgical procedure (16), generally colostomy until delivery. It is interesting to note that there is no current consensus for recommending caesarean delivery in case of colostomy. Vaginal delivery seems to be safe (12, 16, 22), but this must be confirmed by more wide-scale studies. Peritonitis and occlusion may also require rescue surgery and are followed by poor fetal and maternal outcome (11). In contrast, surgical drainage of a perianal abscess may be safely performed during pregnancy (8) and is the most effective treatment, in association with antibiotherapy.

Delivery

Although vaginal delivery has been reported as being impaired by high serum prostaglandin concentrations or disturbances in the neurological control of smooth muscle (4, 22), caesarean section is not systematically recommended for pregnant women suffering from IBD. Vaginal delivery is considered safe and effective in most situations. Nevertheless, in addition to recognized indications such as fetal malposition, fetal hypoxia or maternal narrow pelvis, caesarean delivery is recommended in two IBD-associated conditions. The first is a previous history of ileoanal anastomosis (8, 11, 13, 15, 16), in order to prevent perineal lacerations during delivery resulting in long-term incontinence. The second is an active perineal disease (4, 5, 8, 11-13, 15, 16), which contraindicates vaginal delivery because of the risk of rectovaginal fistule (up to 18% (4)).

For these reasons, the incidence of caesarean section ranges from 20.9 to 41.4% (5, 20-22) in the IBD population, compared to 15 to 27% (5, 20-22) in a control population.

Breastfeeding

The frequency of breastfeeding in IBD mothers varies in reported studies. According to two studies, babies born after a diagnosis of maternal IBD are less often breastfed than babies born before diagnosis (45% vs 66% (14), a mean of 58% (28)). Other studies, however, showed similar frequency and duration of breastfeeding in women with IBD compared to the general population (82.1% and 22 weeks versus 81.5% and 21 weeks respectively (29)). When breastfeeding is not initiated, reasons mentioned by women include personal choice, but also fear of disease relapse, fear of a drug interaction or the physician's recommendations (28).

There exists no clear evidence that breastfeeding constitutes a risk factor for relapse of IBD in new mothers (29) unless associated with discontinuation of treatment (OR = 2.33 (28)) (28, 29). Indeed, meta-analysis (30) supported the hypothesis that breastfeeding may even provide protection for the baby against the development of Crohn's disease and ulcerative colitis, with odds ratios of 0.26-0.79 and 0.38-0.81 respectively. In multivariate analysis, absence of breastfeeding had been identified as early as 1989 as a predisposing factor for the development of Crohn's disease, possibly due to hypothetical immunological protection conferred by breast milk (31).

Nevertheless, women must be warned of the risk of passage of certain drugs into maternal milk (Table 3). *Quinolones* are not contraindicated during breastfeeding because they do not pass into the mother's milk (2). In contrast, *metronidazole* and *loperamide*, found to be present at high levels in breast milk, should be avoided (2). *Prednisone* is considered the safest corticosteroid in breastfeeding, but at doses higher than 20 mg a waiting period of 4 hours between dose and breastfeeding is recommended to minimize the baby's exposure (2). *Sulfasalazine* and *mesalazine* are considered safe. Metabolism of these molecules occurs in breast glandular tissue, as suggested by evidence of high concentrations of inactive metabolites and low concentrations of drugs themselves in breast milk analysis (32). However, rare cases of severe diarrhea induced by breast milk exposure have been reported (2, 32). Sulfasalazine has also been suspected of inducing kernicterus, but this has been dismissed (2). Until recently, women receiving azathioprine were discouraged from breastfeeding because of the possible risk of bone marrow suppression and infection. Recent trials (2, 33, 34), including a prospective study (33), demonstrated that breastfeeding is safe despite this treatment. Indeed, breast milk analysis showed undetectable levels of azathioprine's active metabolite (6MP) (2). Moreover, children breastfed by mothers on azathioprine were able to receive the usual vaccinations without decreasing their immunity. Finally, these children may suffer from "classical" childhood diseases (varicella, stomatitis, laryngitis, tonsillitis, otis media, scarlet fever, conjunctivitis, gastroenteritis, etc.) at frequencies and a hospitalization rate comparable to that of children not exposed to the drug (33). In contrast, breastfeeding is contraindicated during treatment by *cyclosporine*, *methotrexate* and *thalidomide* because of their high rate of excretion in breast milk and the risk of severe side effects for the baby (2). Finally, concerning *new biologic therapies (anti-TNF antibodies)*, large retrospective and prospective human studies are still lacking. However, data collected thus far seem to indicate that breastfeeding is safe under these therapies. Indeed, their concentration is very low (2, 35) or even undetectable (26, 36) in breast milk. Moreover, they are theoretically inactivated by digestive enzymes in the gastrointestinal tract of newborns (2).

Table 3. — **Medical treatment and breastfeeding in women suffering from IBD**
(References : see text)

	Passage in breast milk	*Breastfeeding authorized*	*Precaution*
Quinolones	No	Yes	–
Metronidazole	Yes	No	
Loperamide	Yes	No	
Corticosteroids			
Prednisone	Yes	Yes	If dose > 20 mg, wait 4 h between dose and breastfeeding
Bethamethasone	?	?	
Dexamethasone	?	?	
Budesonide	?	?	
Sulfasalazine and mesalazine	+/- (inactive metabolites > drug)	Yes	
Azathioprine	No	Yes	–
Cyclosporine	Yes	No	
Methotrexate	Yes	No	
Thalidomide	Yes	No	
Anti-TNF antibodies	Very low	?	Data lacking, seem safe according to first reports

And what about men ?

As essential actors in conception, men suffering from IBD are concerned with some specific questions mainly focusing on fertility and possible drug toxicity.

Fertility

As mentioned above, fertility is not affected by IBD itself (7), except for a possible deteriorated self-image associated with the status of chronic disease. Fifteen percent of men suffering from IBD report fertility problems and 29.9% report erectile dysfunction (37), but this has not been confirmed by objective data (semen analysis and International Index for Erectile Function test).

However, instead of the normal "milky" appearance, some patients have reported a "watery" aspect in semen which corresponds to oligo- or a-zoospermia. This abnormality, first reported in 1981, is a consequence of sulfasalazine treatment (6, 7-9, 11, 12, 13, 38, 39, 40-42) and has a 60% incidence (12, 13) ; it is completely reversible two to three months after arrest of treatment (6, 8, 9, 12, 13, 38, 40-42). This suggests direct toxicity toward spermatozoid maturation (42). It is therefore important to inform patients about this possible side-effect of sulfasalazine and to reassure them about the reversible nature of this abnormality. Oligo- and a-zoospermia have never been reported to date with infliximab (43) or azathioprine (6, 24, 44, 45). A decrease in the motility of spermatozoids has been observed with infliximab (43), but whether this is of clinical relevance remains to be determined. One study of azathioprine involving 23 patients confirmed that the density, morphology and motility of spermatozoids and the volume of ejaculate were similar to standard levels (44). Another study (46), however, showed a delay in achieving conception which exceeded one year for men on azathioprine, suggesting that this drug could affect male fertility. We also observed one case of azoospermia secondary to azathioprine treatment, but this was reversible after treatment arrest *(personal unpublished data)*.

Erection and ejaculation dysfunctions are rarely reported by men suffering from IBD, and mostly consist of post-operative complications [impotence or retrograde ejaculation after proctocolectomy (13, 18) reported with an incidence of 1.5% (18)].

Conception and drugs

As already mentioned, methotrexate and thalidomide are contraindicated for men wishing to procreate, and must be stopped three to four months before conception. For azathioprine, most studies show no clear evidence of chromosomal abnormalities (8, 17, 45) or negative pregnancy outcome (46). However, one study which included 13 patients reported an increase in miscarriages and infant malformations for couples in which the man was being treated with azathioprine, compared to those who had stopped it before conception (47).

More anecdotally, one case of penile eczema was reported secondary to contact hypersensitivity to azathioprine present in vaginal secretions of a woman suffering from IBD and treated with this medication (48).

Conclusion

IBD is compatible with parenthood. Nevertheless, it is crucial that gastroenterologists in charge of patients be aware of possible problems resulting either from the disease itself or from its treatment. The main recommendation to be given to future parents with IBD is to delay conception if the disease is not fully controlled, or if one of the partners is undergoing IBD treatment which may have possible detrimental side-effects.

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