Management of Crohn's disease in pregnancy

Crohn's disease is a chronic inflammatory bowel disease commonly diagnosed during the reproductive years. Disease management involves advocating conception during periods of stable clinical remission and continuing safe medications throughout pregnancy to achieve optimal maternal and fetal outcomes.

Crohn's disease is a type of chronic inflammatory bowel disease frequently diagnosed during the reproductive years. In this context, young women with inflammatory bowel disease and clinicians involved in their care are commonly faced with several important medical decisions that can profoundly impact both mother and baby. The condition of inflammatory bowel disease has been associated with increased risks for adverse pregnancy outcomes that appear to be more pronounced during periods of active disease. Uncontrolled inflammation at conception and inflammatory bowel disease flares during pregnancy have been associated with increased rates of fetal loss, preterm delivery and low birth weight, among other unfavourable outcomes, as described in several epidemiological studies spanning three decades (Baiocco and Korelitz, 1984; Fedorkow et al, 1989; Fonager et al, 1998; Riis et al, 2006; Norgard et al, 2007; Stephansson et al, 2010). Thus, conception should generally be advocated during periods of stable clinical remission, with maintenance of disease control throughout the course of pregnancy (Broms et al, 2014).

Prenatal counselling to address disease outcomes and pharmacotherapeutic options during pregnancy is clinically warranted for patients of childbearing potential who have inflammatory bowel disease. This should be pursued early, as approximately 40% of pregnancies worldwide are unintended (Sedgh et al, 2014), leading to inadvertent fetal exposure to medications, particularly during the critical period of organogenesis in the first trimester. Anticipatory identification of the safest management strategies is crucial; potential risks of uncontrolled disease activity must be weighed against possible side effects of medication(s).

Relationship of Crohn's disease and pregnancy

Patients who conceive during periods of stable Crohn's disease remission are more likely to remain in remission throughout pregnancy (Khosla et al, 1984). Approximately one-third of patients will relapse during pregnancy, similar to non-pregnancy states (Pedersen et al, 2013). Patients with Crohn's disease who conceive with active rather than quiescent inflammatory bowel disease are more likely to experience active disease during pregnancy (risk ratio=2.0, 95% confidence interval=1.2–3.4, P=0.006). This meta-analysis by Abhyankar et al (2013) demonstrated that in 46% of patients with active Crohn's disease continued with active disease, while 23% who became pregnant in remission appeared to relapse.

A Danish population-based cohort study comparing active Crohn's disease (low-medium/high activity; n=71) with inactive Crohn's disease (n=86) during pregnancy demonstrated that the risk of preterm births increased over threefold (crude risk ratio=3.4, 95% confidence interval=1.1–10.6) with moderate-to-high Crohn's disease activity relative to inactive Crohn's disease. Increased risks of low birth weight and congenital abnormalities were not detected (Norgard et al, 2007). A cross-sectional, population-based, retrospective cohort study found that births to patients with Crohn's disease were significantly more likely to be preterm (odds ratio=2.3, 95% confidence interval=1.4–3.8, P<0.0025), small for gestational age (adjusted odds ratio=2.3, 95% confidence interval=1.3–3.9, P<0.001) and of low birth weight (odds ratio=3.6, 95% confidence interval=2.2–5.9, P<0.001), while congenital malformations in births to patients with Crohn's disease (reported 3.4%) appeared similar to the general population (Dominitz et al, 2002). The spontaneous abortion rate appears increased after a diagnosis of inflammatory bowel disease (6.5% *vs* 13%, P=0.005), although the elective abortion rate may not be significantly different (Riis et al, 2006). A prospective, multicentre, case-control study of pregnant women with inflammatory bowel disease (n=332; Crohn's disease=145, ulcerative colitis=187) demonstrated no significant difference in frequency of preterm delivery, birth weight or congenital abnormalities for patients with Crohn's disease or ulcerative colitis compared to controls who did not have inflammatory bowel disease (Bortoli et al, 2011).

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A retrospective cohort study (1995–2002, 461 pregnant women with inflammatory bowel disease, 493 pregnant women who did not have inflammatory bowel disease) found that women with inflammatory bowel disease (Crohn's disease=154) were more likely to have an adverse conception outcome (odds ratio=1.65, 95% confidence interval=1.09–2.48), adverse pregnancy outcome (odds ratio=1.54, 95% confidence interval=1.00–2.38) or pregnancy complication (odds ratio=1.78, 95% confidence interval=1.13–2.81). No statistically significant difference in adverse newborn outcomes (e.g. newborn seizure, neonatal intensive care unit admission or infant mortality) was detected between groups. There was no appreciable difference in rate of congenital abnormalities between children born to mothers with and without inflammatory bowel disease, nor was there a difference in rate of congenital abnormalities when comparing patients with Crohn's disease and those with ulcerative colitis. Independent predictors of adverse outcomes included inflammatory bowel disease diagnosis, history of inflammatory bowel disease-related surgery and non-Caucasian ethnicity. Medical treatment and inflammatory bowel disease severity did not appear to predict outcomes in this cohort (Mahadevan et al, 2007a).

Management of disease flares during pregnancy

Treating Crohn's disease flares in pregnancy is similar to non-pregnancy states. Stool samples should be checked to exclude infections including *Clostridium difficile* and cytomegalovirus. If possible, metronidazole should be avoided in the first trimester because of the risk of teratogenicity. Abdominopelvic imaging without radiation (i.e. magnetic resonance imaging, without gadolinium in first trimester; abdominal ultrasound to assess for abscess) is preferred.

Endoscopic and surgical interventions

Endoscopic evaluation of disease activity may be warranted during pregnancy. Procedural indications are largely similar to the non-pregnant state, although procedures should be deferred to the second trimester if possible. Unsedated flexible sigmoidoscopy with distal colonic biopsies should be considered if endoscopy is necessary. Experience with colonoscopy in pregnancy is limited, but it appears relatively safe and should be reserved for strong clinical indications (Cappell et al, 1996; ASGE Standard of Practice Committee et al, 2012). If colonoscopy is required, propofol sedation with obstetric involvement and close fetal monitoring is recommended. Left lateral patient positioning with creation of a pelvic tilt (placing pillow underneath right hip) helps to minimize vascular compression by the gravid uterus. Polyethylene glycol solution is a low-risk option for oral bowel lavage (ASGE Standard of Practice Committee et al, 2012).

Indications for emergent surgery are similar for pregnancy and non-pregnancy states and include perforation, obstruction, abscess and haemorrhage. Surgical interventions carry high maternal and fetal morbidity so should be limited and preferably performed in the late second or third trimesters if possible. Delivery may be an option for serious illness occurring in the late gestational weeks, as continued disease may pose greater fetal risk than surgery (Van Assche et al, 2010).

Mode of delivery

Vaginal delivery is generally possible in patients with Crohn's disease with the exceptions of those with active perianal disease and possibly after ileoanal anastomosis. While inactive perianal disease may allow for vaginal delivery without complexity, caesarean section delivery appears to be more common than vaginal delivery after Crohn's disease diagnosis (8.1% *vs* 28.7% of pregnancies after diagnosis) (Riis et al, 2006). A retrospective cohort analysis (1998–2009) using a large population database revealed that caesarean section delivery rates were significantly higher in patients with Crohn's disease (both with (83.1%) and without (42.8%) perianal disease) compared to patients without Crohn's disease (both with (38.9%) and without (25.6%) perianal disease, $P<0.001$). Rates of fourth-degree perineal lacerations were similar in patients with Crohn's disease without perianal disease and healthy controls (1.4% *vs* 1.3%) but increased significantly in those with perianal Crohn's disease involvement (12.3%, $P<0.001$). Crohn's disease and fourth-degree laceration were not independently associated (Hatch et al, 2014).

In a retrospective study by Cheng et al (2014), the risk of symptomatic perianal Crohn's disease recurrence (within 5 years of delivery) among women with established perianal Crohn's disease ($n=61$; 18% with vaginal delivery, 82% with caesarean section delivery, three patients with active perianal disease during pregnancy, $n=61$ non-pregnant Crohn's disease controls) did not appear significantly different between vaginal birth or caesarean section delivery groups. Additionally, no significant difference in the rate of perianal surgery was observed when comparing Crohn's disease patients by delivery method or by pregnancy state (pregnant *vs* non-pregnant state) (Cheng et al, 2014).

The presence of an ileal pouch-anal anastomosis in a patient with Crohn's disease is a relative indication for surgical delivery (Van Assche et al, 2010; van der Woude et al, 2014), particularly with non-compliant, rigid perineal anatomy. Vaginal delivery after ileal pouch-anal anastomosis has been successfully reported (Hahnloser et al, 2004). Factors including length of labour, multiple births and birth weight did not appear to compromise postpartum pouch function over an average follow-up of 2.4 years (Juhasz et al, 1995). Thus, in the absence of active perianal/fistulizing disease, active rectal involvement, or a post-surgical state that may warrant caesarean section, the delivery mode for a patient with Crohn's disease should generally be dictated by obstetric indication (Van Assche et al, 2010; Hatch et al, 2014).

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Inflammatory bowel disease-related obstetric complications

Patients with inflammatory bowel disease appear more susceptible to maternal and pregnancy-related complications relative to the general population. An analysis of obstetric hospitalization outcomes using the 2005 US Nationwide Inpatient Sample (4.21 million deliveries; Crohn's disease: *n*=2372, ulcerative colitis: *n*=1368) found increased risks of caesarean section delivery (adjusted odds ratio=1.72, 95% confidence interval=1.44–2.04), protein-calorie malnutrition (adjusted odds ratio=20.0, 95% confidence interval=8.8–45.4), venous thromboembolism (adjusted odds ratio=6.12, 95% confidence interval=2.91–12.9), and blood transfusions (adjusted odds ratio=2.82, 95% confidence interval=1.51–5.26) in the population with Crohn's disease relative to pregnant controls without inflammatory bowel disease (Nguyen et al, 2009). A population-based cohort study reviewing Swedish Medical Birth, Patient, and Prescribed Drug Registers (2006–9; Crohn's disease: *n*=787, ulcerative colitis: *n*=1209, controls: *n*=10 773) reported an increased risk of emergent caesarean section in patients with Crohn's disease (adjusted odds ratio=1.50, 95% confidence interval=1.17–1.92), particularly for those with flaring Crohn's disease (Broms et al, 2012). Antepartum haemorrhage was more frequently seen in patients with Crohn's disease (adjusted odds ratio=1.66, 95% confidence interval=1.12–2.45), with the highest risk among those with inactive disease (Broms et al, 2012). Bowel resection rates (average number 0.52 *vs* 0.66) and stenosis development (37% *vs* 52%) appear similar in pregnant and non-pregnant patients with Crohn's disease (Riis et al, 2006).

Crohn's disease medications in pregnancy and lactation

Table 1 presents medications for Crohn's disease and drug safety recommendations in pregnancy and lactation. These are described in greater detail in subsequent sections.

Recognizing the effects of pharmacotherapy on fetal development is an important aspect of providing care to patients with inflammatory bowel disease who are pregnant or of childbearing potential. The US Food and Drug Administration had previously categorized medications for use during pregnancy and lactation based on potential fetal risk by letter (A, B, C, D, X). In December 2014, the Food and Drug Administration published the Pregnancy and Lactation Labeling Rule requiring changes to the content and format of prescription drug labelling information (effective 30 June 2015).

Guidelines generally advocate that pharmacotherapy for Crohn's disease (except methotrexate) should continue during pregnancy because medication benefits often outweigh the risks of uncontrolled disease (Van Assche et al, 2010). Effective inflammatory bowel disease control during the preconception and pregnancy periods is essential, as active disease at the time of conception and disease flares during pregnancy have been associated with adverse pregnancy outcomes and fetal complications as described above. In a study of 207 conceptions in 113 patients with inflammatory bowel disease, inflammatory bowel disease drug therapy was not associated with negative pregnancy outcomes (Moskovitz et al, 2004).

A national UK study using a mother–child linked dataset (1990–2010) of 1703 singleton children born to mothers (aged 15–45 years) with inflammatory bowel disease (384 811 children born to mothers without inflammatory bowel disease) found no increased risk of major congenital anomalies related to maternal inflammatory bowel disease or its medical therapy during pregnancy (prevalence 2.7% and 2.8% respectively, 1.9% in children born to women with Crohn's disease). The adjusted odds ratio of a major congenital anomaly associated with medications in children born to women with inflammatory bowel disease was 0.82 (95% confidence interval=0.42–1.61) for 5-aminosalicylates, 0.48 (95% confidence interval=0.15–1.50) for corticosteroids and 1.27 (95% confidence interval=0.48–3.39) for azathioprine/6-mercaptopurine (Ban et al, 2014). A 6-year population-based study of 105 patients with Crohn's disease found that 52% used medications during pregnancy, with 95% in disease remission. Women taking pharmacotherapy for Crohn's disease showed no increased risk of preterm delivery (prevalence odds ratio=0.71, 95% confidence interval=0.18–2.79), caesarean section (prevalence odds ratio=1.40, 95% confidence interval=0.63–3.08) or congenital malformations (prevalence odds ratio=0.60, 95% confidence interval=0.10–3.76)(Julsgaard et al, 2014).

The PIANO (Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes) Registry is a prospective, US national multi-site study that has enrolled over 1000 pregnant patients with inflammatory bowel disease to determine whether in-utero medication exposure to thiopurines (azathioprine/6-mercaptopurine) +/- biologic agents (infliximab, adalimumab, certolizumab, natalizumab) adversely influences various outcomes (i.e. rates of pregnancy and newborn adverse outcomes, congenital anomalies, newborn growth). Maternal medication exposure, inflammatory bowel disease duration, disease activity, and pregnancy/post-partum complications have been recorded. Cohort data have been collected throughout pregnancy, at delivery and every 4 months during the children's first year of life to assess growth and developmental milestones.

Interim analysis of 896 completed pregnancies found that 43% of patients with Crohn's disease were exposed to biologics. Inactive disease during pregnancy was seen in 80–90% of patients with Crohn's disease, who were more likely to have inactive disease at the beginning of pregnancy compared to postpartum. After adjusting for underlying inflammatory bowel disease, most adverse events, including congenital abnormalities and spontaneous abortions, did not appear to occur at significantly elevated rates compared to general populations (US/community-based). However, rates of caesarean section delivery and neonatal intensive care unit stays were

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Table 1. Medications for Crohn's disease and drug safety recommendations in pregnancy and lactation

Medication		FDA safety category*	Pregnancy recommendations	Lactation recommendations	Other considerations
Aminosalicylates (sulfasalazine, some formulations of mesalamine)		B	Appear low risk for continued use during pregnancy	Appear low risk for continued use during nursing, sulfasalazine metabolite (sulfapyridine) negligibly secreted in breast milk	Aminosalicylates not recommended or FDA-approved for treatment of Crohn's disease, folic acid supplementation (2 g/day) is recommended with sulfasalazine
Mesalamine (Asacol HD, olsalazine)	Asacol HD	C	Dibutyl phthalate coating linked to congenital malformation of male urogenital tract		
	Olsalazine	C	High doses linked with fetal toxicity in rats; not proven in humans	High doses linked with growth retardation in lactating rats; caution advised when administered to nursing mothers	
Anti-tumour necrosis factor (TNF)-alpha agents	Infliximab, adalimumab	B	No apparent increased risk of adverse pregnancy outcomes, IgG1 antibody with increased transplacental transfer in late second and third trimesters, consider stopping infliximab at 30–32 weeks gestation with drug resumption post-partum, consider stopping adalimumab at 36–38 weeks gestation with drug resumption post-partum	Appear low risk for continued use during nursing	Not recommended to switch anti-TNF agents solely because of pregnancy, particularly with maternal disease remission, increased risk of neonatal infections when combined with thiopurines, avoid live virus vaccines† for the first 6 months in infants exposed to infliximab or adalimumab in utero with detectable serum levels
	Certolizumab	B	No apparent increased risk of adverse pregnancy outcomes, PEGylated Fab' antibody fragment lacking Fc portion; minimal passive transplacental antibody transfer throughout trimesters, continue drug throughout pregnancy	Compatible with breastfeeding; drug not detected in breast milk	Low drug levels detected in neonatal cord blood at delivery despite high maternal serum drug levels
Anti-integrin agents	Natalizumab	C	Monoclonal IgG4 antibody against α4 integrin with limited pregnancy data to date	Lactation safety unknown; limited by inadequate available data	
	Vedolizumab	C	Gut-selective IgG1 monoclonal antibody against $\alpha4\beta7$ with presumed increased transplacental transfer in late second and third trimesters, limited pregnancy data to date	Lactation safety unknown; limited by inadequate available data	
Antibiotics	Metronidazole	B	Appears low risk for short-term use in pregnancy	Detected in breast milk, lactation safety uncertain; not routinely recommended given unclear long-term exposure effects	
	Ciprofloxacin	C	Associated with cartilage damage and arthropathy in animal models; not reproduced in humans	Lactation safety uncertain	
	Rifaximin	C	Pregnancy safety unknown; limited by inadequate available data	Lactation safety unknown; limited by inadequate available data	
Steroids (corticosteroids, budesonide)		C	Possible association with cleft lip/palate, high doses may predispose to intrauterine infection and premature delivery	Drug concentration in breast milk appears low, although lactation data are limited	Prednisone, prednisolone and methylprednisolone are drugs of choice
Thiopurines (azathioprine, 6-mercaptopurine)		D	Appear low risk for continued use in pregnancy, no increased risk of poor pregnancy outcomes in IBD, may increase preterm birth risk in women with disease flares	Appear low risk for continued use in lactation, minimal drug transfer to newborn; low peak drug levels detected 4 hours after ingestion	Avoid thiopurine initiation in pregnancy because of risk of pancreatitis
Other (methotrexate, thalidomide)		X	Contraindicated for use during pregnancy	Contraindicated for use during lactation	Discontinue medication >3 months before conception

FDA = Food and Drug Administration; Fab' = fragment antigen binding; Ig = immunoglobulin; IBD = inflammatory bowel disease; PEG = polyethylene glycol. *The FDA risk categorization by letter (category A, B, C, D, or X) has transitioned to the Pregnancy and Lactation Labeling Rule that requires changes to the content and format of prescription drug labeling information (effective as of 30 June 2015). †Live virus vaccines (rotavirus, intranasal influenza, bacillus Calmette-Guérin, varicella zoster, measles-mumps-rubella) are contraindicated in the first 6 months of life for infants with in utero exposure to infliximab or adalimumab if serum levels are detectable. Certolizumab concentrations in the infant are thought to be undetectable by the time of rotavirus vaccination (2 months). Treating paediatricians should be made aware of these exposures, and infants should be monitored closely for signs of infection.

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higher in children born to mothers with inflammatory bowel disease. Higher rates of caesarean section delivery and spontaneous abortion were detected in the group taking anti-tumour necrosis factor (anti-TNF) therapies, while a higher preterm birth rate was seen in the combination (thiopurine/biologic) group. Newborns of mothers with Crohn's disease did not demonstrate increased complication rates or adverse effects. No association of drug exposure with congenital anomalies was detected. Thus, maternal inflammatory bowel disease activity may present a greater fetal risk than the use of immunomodulator or biologic therapy (Mahadevan et al, 2012).

Crohn's disease medications

Thiopurines

6-mercaptopurine and azathiopurine

6-mercaptopurine and its prodrug azathioprine (used individually or in conjunction with other inflammatory bowel disease medications) are particularly controversial for use during pregnancy. Birth defects have been reported in animal studies involving higher doses and varied administration routes (e.g. intraperitoneal or subcutaneous) (Polifka and Friedman, 2002). Human studies have identified these agents as low risk in pregnancy and compatible with lactation (minimal transfer). A retrospective, multicentre, Spanish cohort study documented 571 inflammatory bowel disease pregnancies (53% Crohn's disease, 21% with active disease), with 253 pregnancy exposures to immunomodulators (n=187) or anti-TNF agents during or within 6 months of pregnancy (74% immunomodulator monotherapy, 11.5% anti-TNF-agent alone, 14.5% combination therapy, non-exposed control group: n=318). There were no increased risks of poor pregnancy outcomes with immunomodulators. Multivariate analysis showed that thiopurine therapy (odds ratio=0.6, 95% confidence interval=0.4–0.9) was the only predictor of favourable global pregnancy outcome (both favourable pregnancy and neonatal outcomes)(Casanova et al, 2013). The neonatal complication rate was significantly lower in the thiopurine-exposed group compared to the unexposed group (P=0.01). Anti-TNF treatment was not associated with unfavourable global pregnancy outcomes (odds ratio=1.62, 95% confidence interval=0.92–2.87, P=0.09)(Casanova et al, 2013). It is best to avoid thiopurine initiation in pregnancy because of the risk of pancreatitis. Thiopurine exposure may also increase preterm birth risk in women with stable and flaring disease (Broms et al, 2014).

Breastfeeding is possible during azathioprine/6-mercaptopurine therapy with minimal drug transfer to the newborn. A small study of lactating women (n=8) receiving azathioprine (75–200 mg/day) demonstrated variation in drug bioavailability (wide range of milk and plasma drug levels within the first 3 hours post-ingestion); the major part of 6-mercaptopurine excretion in breast milk was seen within the first 4 hours of drug administration (maximum drug concentration detected was 0.008 mg/kg bodyweight/24 h, with the infant dose amounting to <1% of the maternal dose) (Christensen et al, 2008). Infant exposure may be further minimized by breastfeeding with milk produced more than 4 hours after medication ingestion.

Biologic agents

Anti-TNF agents

Infliximab: Infliximab (human-murine anti-TNF-α antibody with human IgG1 constant region) (Simister, 2003) is actively transported across the placenta in the late second and third trimesters (Mahadevan et al, 2005), thus potentially shielding the fetus from drug exposure during organogenesis. A report from the infliximab safety database assessing pregnancy outcomes in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis revealed that pregnancy outcomes in drug-exposed patients were similar to those expected in the general US population of pregnant women or pregnant women with disease unexposed to infliximab (live births=67%, miscarriages=15%) (Katz et al, 2004).

Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry data collected over 5 years of follow up showed that, among maternal and paternal (i.e. treated male partner) live births, the majority of babies exposed to infliximab during pregnancy were healthy; 90.2% had no reported adverse events, and 92.4% had no birth defects (Lichtenstein et al, 2012).

A European observational study compared pregnancy outcomes in 42 inflammatory bowel disease cases directly exposed to anti-TNF treatment (35 infliximab and seven adalimumab, exposed within 3 months of conception and/or during pregnancy until second trimester), with 23 pregnancies occurring before inflammatory bowel disease diagnosis, 78 pregnancies after inflammatory bowel disease diagnosis and before start of anti-TNF therapy, and 53 pregnancies after inflammatory bowel disease diagnosis with indirect exposure (mother received anti-TNF before pregnancy) to anti-TNF therapy. Direct pregnancy exposure to anti-TNF treatment was not associated with a higher incidence of adverse pregnancy outcomes than inflammatory bowel disease overall (Schnitzler et al, 2011).

Infliximab can be detected in newborns of exposed mothers. Infant serum and cord blood infliximab levels appear greater than maternal drug levels at the time of neonatal birth, and the drug can remain in the infant system for up to 6 months after delivery (Vasiliauskas et al, 2006; Mahadevan et al, 2007b, 2013). Decisions to maintain infliximab dosing through the third trimester must be individualized. Discontinuing infliximab at around 30–32 weeks gestation may be considered to decrease late placental transport to the newborn (Mahadevan et al, 2011).

Adalimumab: Adalimumab is a fully humanized IgG1 monoclonal anti-TNF-α antibody. Limited data exist regarding adalimumab effects on fetal development and pregnancy outcomes. Rates of spontaneous abortions, stillbirths or congenital malformations do not appear increased among patients with drug exposure during

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pregnancy (Jurgens et al, 2010). Adalimumab can be detected in newborns of exposed mothers and can remain in the infant system for up to 4 months after delivery. In a study of 10 pregnant women taking adalimumab, infant serum and cord blood drug levels were greater than maternal levels (Mahadevan et al, 2013). The risks/benefits of continuing adalimumab through the third trimester must be individualized. Discontinuing adalimumab at around 36–38 weeks gestation may be considered to decrease late placental transport to the newborn. Owing to shorter dosing intervals relative to infliximab, stopping earlier may predispose to disease flares (Mahadevan et al, 2011).

Certolizumab pegol: The molecular structure of certolizumab pegol lacks an Fc portion. Its cross-placental transfer varies from that of infliximab and adalimumab. The fragment antigen binding (Fab') fragment appears to passively cross the placenta in low levels during pregnancy, including the first trimester; such transfer is not expected with the IgG1 antibody (Kane and Acquah, 2009). Infant and cord blood certolizumab levels appear to remain low (<2 μg/ml) despite high maternal drug levels at delivery (following maternal treatment dosages during delivery week)(Mahadevan and Abreu, 2009).

Anti-integrin agents

Natalizumab: Natalizumab is a humanized, monoclonal IgG4 antibody against the α4 integrin adhesion molecule (Targan et al, 2007) with limited pregnancy/lactation data. The safety of natalizumab exposure during pregnancy has been scarcely described, and most of the literature has been reported in the multiple sclerosis population. A recent prospective, controlled, observational study investigating accidental first trimester exposure to natalizumab in patients with multiple sclerosis (101 exposed patients with 102 pregnancy outcomes, 78 disease-matched patients unexposed to natalizumab, 97 healthy controls) found no significant difference in premature birth, low birth weight or major malformations among the groups, although it may have been limited by small sample sizes (Ebrahimi et al, 2015). A investigation reporting the safety of natalizumab after first trimester exposure during pregnancy among 164 pregnancies in patients with Crohn's disease (*n*=35) or multiple sclerosis detected no increased risk of adverse birth outcomes or congenital anomalies (Nazareth et al, 2008; Mahadevan et al, 2011).

Vedolizumab: Vedolizumab is a gut-selective IgG1 monoclonal antibody against α4β7 integrin (Sandborn et al, 2013). Recent abstract data from clinical studies in inflammatory bowel disease reported 27 pregnancies (Crohn's disease or ulcerative colitis=25, healthy volunteers=two) after direct (maternal) or indirect (male partner) vedolizumab exposure. Female participants who became pregnant during the study discontinued vedolizumab therapy. Live births (two premature) were reported in 11 of the 24 vedolizumab-treated women. A congenital anomaly (corpus callosum agenesis) was reported in one healthy volunteer (obstetric history of two spontaneous abortions and one ectopic pregnancy) after one vedolizumab dose administered 79 days before the estimated conception date. Nineteen vedolizumab-exposed partner pregnancies resulted in nine live births, two spontaneous abortions, two elective terminations and three undocumented outcomes. An observational pregnancy registry enrolling inflammatory bowel disease patients on vedolizumab therapy is under development to assess long-term drug safety data (Dubinsky et al, 2015). Lactation data related to vedolizumab are currently lacking.

Corticosteroids

Corticosteroids are thought to be safe in pregnancy at doses up to 15 mg/day, with higher doses predisposing to intrauterine infection and premature delivery. Some data suggest that first-trimester fetal exposure to systemic corticosteroids may enhance the risk of oral clefts, although other data have shown no increased risk (Rodriguez-Pinilla and Martinez-Frias, 1998; Park-Wyllie et al, 2000; Hviid and Molgaard-Nielsen, 2011; Bay Bjorn et al, 2014). The rate of major congenital malformations does not appear to be significantly increased (Park-Wyllie et al, 2000; Gur et al, 2004; Bay Bjorn et al, 2014). Owing to higher placental metabolism relative to other formulations, preferred steroids include prednisone, prednisolone and methylprednisolone. Steroid concentrations appear low in breast milk; mothers can generally breastfeed through the medication course (Ostensen and Forger, 2009). Less than 0.1% of the maternal prednisolone dose is secreted into breast milk, correlating to <10% of the infant endogenous cortisol level (American Academy of Pediatrics Committee on Drugs, 2001).

Methotrexate

Methotrexate (an antimetabolite) has teratogenic properties and is contraindicated during pregnancy and lactation.

5-aminosalicylates

5-aminosalicylates (Food and Drug Administration category B) are not Food and Drug Administration-approved or suggested to treat Crohn's disease, although some patients who have Crohn's disease continue on these medications. Mesalamine and sulfasalazine are generally considered low risk for continued use during pregnancy and nursing (Van Assche et al, 2010). Some reports have noted an increased incidence of neural tube defects, cardiovascular defects and oral cleft with use of these agents (Chambers et al, 2006). Others studies have detected no increased risks of congenital anomalies with mesalamine and sulfasalazine (Mogadam et al, 1981; Diav-Citrin et al, 1998; Norgard et al, 2001).

A meta-analysis in pregnant women with inflammatory bowel disease (*n*=2200; 1158=no medication, 642=received 5-aminosalicylates) demonstrated that 5-aminosalicylates did not significantly increase the risks of preterm delivery (odds ratio=1.35), spontaneous abortion (odds ratio=1.14), stillbirth (odds ratio=2.38), low birth weight (odds

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ratio=0.93) or congenital abnormalities (odds ratio=1.16) (Rahimi et al, 2008). Folate synthesis, arrested via dihydrofolate reductase inhibition, is important for neural tube development. Thus, folic acid supplementation (2 mg/day) is recommended with sulfasalazine treatment and appears to decrease the risks of cardiovascular defects and oral clefts associated with folate antagonist therapy during pregnancy (Hernandez-Diaz et al, 2000). The sulfasalazine metabolite, sulfapyridine, is negligibly secreted into breast milk, but aminosalicylates are generally considered safe in lactation (Klotz and Harings-Kaim, 1993; American Academy of Pediatrics Committee on Drugs, 2001).

5-aminosalicylates classified as Food and Drug Administration category C include Asacol HD (dibutyl phthalate (DBP) coating) and olsalazine. DBP-coated medication has been linked with measureable urinary phthalate metabolite levels; fetal exposure to DBP can lead to congenital malformations of the male urogenital tract (Hernandez-Diaz et al, 2013). Olsalazine has been linked with fetal developmental toxicity in pregnant rats (doses 5–20 times greater than the human dose), and there are no adequate, well-controlled studies in pregnant women. Lactation studies in rats have demonstrated growth retardation in pups with high maternal drug doses (5–20 times greater than the human dose). It is unclear whether olsalazine is excreted through human breast milk; caution in nursing is advised.

Antibiotics

Antibiotics are commonly used to treat infections such as pouchitis or inflammatory bowel disease-related complexities including perianal Crohn's disease and intra-abdominal abscesses. Metronidazole appears safe in pregnancy over the short term. Metronidazole is mutagenic in some bacteria and carcinogenic in mice with long-term use (not seen in humans). No association with preterm birth, low birth weight or congenital anomalies was shown with fetal drug exposure in the first or later trimesters of pregnancy (Koss et al, 2012). Metronidazole can be detected in breast milk. Although immediate neonatal effects are unapparent, effects of long-term exposure are unclear (Passmore et al, 1988), so use during breastfeeding is not recommended (Mottet et al, 2009).

Ciprofloxacin has been associated with joint/cartilage damage in animals (Linseman et al, 1995). Although no clinical studies have been conducted in pregnant women, animal reproduction studies have failed to demonstrate significant arthropathy or musculoskeletal problems following in-utero ciprofloxacin exposure. A prospective observational study of 200 pregnancy exposures to fluoroquinolones (ciprofloxacin=52.5%, 68% first-trimester exposures) during organogenesis reported no increased risks of major congenital malformations or significant musculoskeletal dysfunction among live births (Loebstein et al, 1998). A prospective follow-up study (549 fluoroquinolone-exposed pregnancies, 70 first-trimester ciprofloxacin exposures) found no increased risk of congenital malformations or adverse pregnancy outcomes with exposure (Schaefer et al, 1996). Women with second- or third-trimester ciprofloxacin exposure (n=7) delivered healthy babies (Koul et al, 1995). Lactation safety for ciprofloxacin is uncertain (Mottet et al, 2009).

Rifaximin (non-systemic) has demonstrated efficacy in inducing remission for moderately-to-severely active Crohn's disease (Prantera et al, 2012). Pregnancy/lactation safety profiles are unknown based on limited clinical experience.

Sulfonamides and tetracyclines should be avoided in pregnancy. Sulfonamides can interfere with folate metabolism and appear teratogenic in animals. Tetracycline can retard fetal skeletal development and lead to defective dental enamel with tooth discolouration (Van Assche et al, 2010).

Conclusions

Inflammatory bowel disease management during pregnancy is complex with a multitude of considerations. Preconception counselling is paramount for patients of childbearing age who have inflammatory bowel disease, as the disease and its related treatments can affect both mother and baby. Most non-surgical inflammatory bowel disease patients have normal fertility, although voluntary infertility is often reported among patients with Crohn's disease. Patients who conceive during periods of stable Crohn's disease remission are more likely to remain in remission throughout pregnancy. Crohn's disease relapse rates in pregnancy are comparable to the general inflammatory bowel disease population, and disease flares should be treated similarly. Patients with Crohn's disease appear to have higher rates of caesarean section delivery, adverse birth outcomes such as preterm birth and low birth weight, and maternal/obstetric complications relative to the general population. The rate of congenital anomalies does not appear to be increased in Crohn's disease. Pharmacotherapeutic options should be carefully discussed, and safe medications should generally be continued throughout pregnancy. Knowledge of long-term drug safety with pregnancy and lactation exposure will evolve with the American Pregnancy and Lactation Labeling Rule drug labelling initiative and analysis of national drug registry data. **BJHM**

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KEY POINTS

- Prenatal counselling addressing disease outcomes and pharmacotherapeutic options during pregnancy is clinically warranted for all patients with inflammatory bowel disease who are of childbearing potential.
- Patients who conceive during periods of stable Crohn's disease remission are more likely to remain in remission throughout pregnancy.
- Active disease at conception or during pregnancy can result in increased rates of adverse birth outcomes including fetal loss, preterm delivery and low birth weight.
- Most patients with inflammatory bowel disease, except for those who have undergone ileal pouch-anal anastomosis, maintain normal fertility; patients with Crohn's disease often report voluntary infertility.
- Crohn's disease relapse rates in pregnancy are comparable to those in the general inflammatory bowel disease population, and disease flares should be treated similarly.
- Patients with Crohn's disease experience higher rates of caesarean section delivery, adverse birth outcomes such as preterm birth and low birth weight, and maternal/obstetric complications relative to the general population. The rate of congenital anomalies does not appear to be increased in Crohn's disease.
- Pharmacotherapeutic options should be selected carefully while patients are of reproductive age. Safe medications should generally be continued throughout pregnancy to maintain disease control and to achieve optimal maternal and newborn outcomes.

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