FSRH The Faculty of Sexual & Reproductive Healthcare

FSRH Guideline

Sexual and Reproductive Health for Individuals with Inflammatory Bowel Disease

October 2016 | FSRH

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ABBREVIATIONS USED

AFRR	adjusted fertility rate ratio
BMD	bone mineral density
BNF	British National Formulary
BSG	British Society of Gastroenterology
CD	Crohn's disease
CEU	Clinical Effectiveness Unit
CHC	combined hormonal contraception
CI	confidence interval
COC	combined oral contraception
DMPA	depot medroxyprogesterone acetate
ECCO	European Crohn's and Colitis Organisation
FSRH	Faculty of Sexual & Reproductive Healthcare
GI	gastrointestinal
IBD	inflammatory bowel disease
IPAA	ileal pouch-anal anastomosis
IUD	intrauterine device
LARC	long-acting reversible contraception
LNG-IUS	levonorgestrel-releasing intrauterine system
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Care Excellence
OR	odds ratio
POP	progestogen-only pill
PSC	primary sclerosing cholangitis
RR	relative risk
SPC	Summary of Product Characteristics
SRH	sexual and reproductive health
TNF-α	tumour necrosis factor alpha
UC	ulcerative colitis
UKMEC	UK Medical Eligibility for Contraceptive Use
VTE	venous thromboembolism

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GRADING OF RECOMMENDATIONS

A Evidence based on randomised controlled trials

B Evidence based on other robust experimental or observational studies

C Evidence is limited but the advice relies on expert opinion and has the endorsement of respected authorities

✓ Good Practice Point where no evidence exists but where best practice is based on the clinical experience of the expert group

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✓	Managed clinical care pathways should be developed locally to promote integrated working between different service providers to ensure that the SRH needs of individuals with IBD are met.

3. IBD and Fertility

C	Health professionals should be aware of the possible effects of some IBD medication on sperm quality and quantity and the potential impact on male fertility.
✓	The risk of subfertility following reconstructive surgery should be discussed with women with IBD and their partners.

4. IBD and Pregnancy

B	Women with IBD should be advised to plan to conceive when the disease is well controlled.
✓	Appropriate referral for pre-pregnancy counselling should be available for men and women in order to optimise their IBD management prior to conception.
C	There is controversy regarding the most appropriate mode of delivery (caesarean section or vaginal) following ileal pouch-anal anastomosis surgery. Women should be guided in their decision by the advice of the obstetric and gastrointestinal specialists in charge of their care.
C	If either partner is taking methotrexate, pregnancy should be prevented by use of effective contraception during and for at least 3 months after treatment.
C	If either partner is taking mycophenolate mofetil, pregnancy should be prevented by use of effective contraception during and for at least 6 weeks (women) or 3 months (men) after treatment has ended.
C	The British National Formulary advises that pregnancy should be prevented by use of effective contraception for women treated with tumour necrosis factor alpha (TNF-α) inhibitors (e.g. infliximab, adalimumab) and for 6 months after treatment has ended. Consideration for use during pregnancy requires specialist advice.

✓	Health professionals should check current National Institute for Health and Care Excellence, British Society for Gastroenterology, and European Crohn's and Colitis Organisation guidelines and the Summary of Product Characteristics for each medication for specific advice on use while trying to conceive and while pregnant or breastfeeding. The decision to discontinue any treatment requires expert clinical judgement, balancing the risks of stopping the drug against the risks associated with continuing.
✓	Health professionals should consider ectopic pregnancy in their differential diagnosis of abdominal pain and gastrointestinal symptoms in sexually active women with IBD.

5. IBD and Contraceptive Choice

B	Women can be informed that a causal association between combined oral contraception (COC) use and onset or exacerbation of IBD has not been established.
✓	Women should be advised that the efficacy of oral contraception is unlikely to be reduced by large bowel disease but may be reduced in women with Crohn's disease who have small bowel disease and malabsorption.
C	Health professionals should consider the impact of IBD-associated conditions (e.g. venous thromboembolism, primary sclerosing cholangitis and osteoporosis) as well as other medical conditions when prescribing contraception to women with IBD.
✓	Health professionals should check whether any prescribed medications for rectal or genital administration contain constituents that could reduce the efficacy of condoms.
✓	Women with IBD should stop COC at least 4 weeks before major elective surgery and alternative contraception should be provided. Advice regarding recommencing COC should be given individually.
B	Previous pelvic or abdominal surgery in women with IBD could affect the safety and success of laparoscopic sterilisation.
✓	Women with IBD considering sterilisation – and their partners – should be counselled about alternative methods of contraception including long-acting reversible contraception and vasectomy.

6. IBD, Sexual Function and Psychosexual Health

✓	Health professionals should provide an opportunity for individuals with IBD and their partners to discuss issues relating to sexuality, body image and mental well-being, and know where to refer locally when appropriate.

FSRH The Faculty of Sexual & Reproductive Healthcare

FSRH Guideline (October 2016)
Sexual and Reproductive Health for Individuals with Inflammatory Bowel Disease

(Revision due by October 2021)

1. PURPOSE AND SCOPE

This guideline provides information on sexual and reproductive health (SRH) for individuals with inflammatory bowel disease (IBD). It is intended for use by health professionals working in SRH, general practice and obstetric and gynaecological settings. Recommendations are based on available evidence and consensus opinion of experts. They should be used to guide clinical practice but are not intended to serve alone as a standard of care or to replace the application of clinical judgement in individual cases. For comprehensive advice on the management of patients with IBD, readers should refer to the guidelines from the British Society for Gastroenterology (BSG).[1] Irritable bowel syndrome is a separate condition that is outside the scope of this guideline. A key to the Grading of Recommendations – based on levels of evidence – is provided on page 2 of this document. Details of the methods used by the Clinical Effectiveness Unit (CEU) in developing this guideline and a list of contributors are outlined in Appendix 1.

This Clinical Guideline updates the 2009 edition. A summary of the changes to previous guideline can be found in Appendix 2.

2. BACKGROUND

2.1 What is inflammatory bowel disease (IBD)?

C	As IBD usually presents during the reproductive years, health professionals should consider SRH issues in their management of affected individuals.

IBD is estimated to affect approximately 1 in 250 people in the UK.[2] IBD refers predominantly to two distinct conditions: ulcerative colitis (UC) and Crohn's disease (CD).

Ulcerative colitis involves the large bowel only and is characterised by diffuse inflammation of the superficial mucosal layer, which bleeds readily. The whole colon is affected (pancolitis) in up to 20% of patients,[3] whilst in 30% of those affected, disease is confined to the rectum (proctitis).

Crohn's disease can affect the entire gastrointestinal (GI) tract and clinical symptoms generally reflect the site or pattern of the disease (inflammatory, fistulating or stricturing).[1] It is characterised by patchy, transmural inflammation that can lead to fibrosis and bowel obstruction, or to sinus tract and fistula formation involving adjacent organs.

The exact aetiology of IBD is unknown, although it is thought to be caused by both genetic and environmental factors.[1] Diagnosis can occur at any age, but is most common between the ages of 10 and 40 years. Because IBD usually presents in the reproductive years, health professionals should be aware of SRH issues in affected individuals and should discuss these issues where appropriate.

2.2 Extra-intestinal manifestations and associated conditions

IBD may also be associated with extra-intestinal manifestations such as hepatobiliary disease, venous thromboembolism (VTE) and osteoporosis/osteopenia.

2.2.1 Hepatobiliary disease

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterised by fibro-obliterative inflammation of the hepatic bile ducts leading to progressive cirrhosis and hepatic failure.[4]

2.2.2 Venous thromboembolism[5–9]

It is generally accepted that there is an association between IBD and VTE, although the exact prevalence is unclear due to differences in methodologies. The mechanisms underlying the apparent thrombotic tendency in IBD are not fully understood. Several theories have been postulated but no clear consensus has emerged as to whether the risk is related to the disease itself or to related factors such as immobilisation or surgery. There is no evidence of an association with genetic thrombophilias.

2.2.3 Osteopenia and Osteoporosis

Osteopenia and osteoporosis are more common in patients with IBD than in the general population, particularly amongst those with CD. The aetiology remains unclear but factors such as age, gender, duration of disease, corticosteroid use, reduced physical activity, smoking, bowel resection and disease activity may influence the degree of risk.[10,11] Hormone replacement therapy is no longer recommended to be used solely for osteoporosis in women because of the cardiovascular and breast cancer risks. Detailed guidance on IBD and osteoporosis is available from the BSG.[10]

2.3 Treatment of IBD

Managed clinical care pathways should be developed locally to promote integrated working between different service providers to ensure that the SRH needs of individuals with IBD are met.

Medical management of IBD is tailored to the site, severity and activity of disease. Treatments aim to reduce or prevent recurrence of inflammation using aminosalicylates, corticosteroids, immunosuppressant agents (commonly azathioprine, mercaptopurine, methotrexate and ciclosporin) and tumour necrosis factor alpha (TNF-α) inhibitors (e.g. infliximab, adalimumab). Antibiotics such as metronidazole, ciprofloxacin and rifaximin may be used in certain circumstances.

Medication alone is often insufficient; around 20% of individuals with UC and roughly 60–75% of those with CD will require surgery to manage their condition.[12,13] Surgery for IBD may be performed as an emergency procedure for toxic megacolon, perforation, haemorrhage or acute failure of medical treatment. Elective surgery may also be necessary for chronic failure of medical treatment, complications such as fistulae and stricture, or colorectal cancer. UC can be cured by removal of the large intestine; however for CD, surgery can only improve symptoms. The traditional operation for UC is panproctocolectomy, where all of the colon and rectum is removed, leaving the patient with a permanent ileostomy. In the last 35 years, restorative proctocolectomy [colectomy and ileal pouch-anal anastomosis (IPAA)] has been developed, where all of the colon and rectum is removed and the small bowel is fashioned into a reservoir that is anastomosed to the anal canal. For individuals with CD, the nature of surgery will depend on the distribution of the disease and the type of complications that arise; any part of the small bowel, colon or rectum may require excision. Patients with either UC or CD may require temporary or permanent stoma formation.

In addition to medication and surgery, information and support groups, nurse specialists and counselling have been shown to complement physician-led treatment.[14–19]

3. IBD AND FERTILITY

3.1 Does IBD affect fertility?

Fertility rates amongst women with IBD are generally similar to those of the general population.[20] The National Institute for Health and Care Excellence (NICE), the European Crohn's and Colitis Organisation (ECCO) and recent literature reviews have concluded that women with CD may have slightly decreased fertility, especially when their disease is active or if they have adhesions from surgery. They also found that women with UC have the same fertility rate as women without UC, but following pelvic surgery – such as a proctocolectomy or an IPAA – the risk of infertility may increase as much as three-fold.[19–31]

A recent large UK database study including 9639 women with IBD calculated the overall fertility rates of women with IBD, CD and UC compared with the general population. It found a marginally decreased fertility rate amongst women with CD versus women without CD [adjusted fertility rate ratio (AFRR) 0.88, 95% confidence interval (95% CI) 0.83–0.92] but statistically insignificant results for women with UC (AFRR 0.99, 95% CI 0.94–1.04). Disease activity played a significant role; in the 9-month period following disease flare-ups, women with IBD had a significantly lower fertility rate than women without IBD (AFRR 0.70, 95% CI 0.59–0.82).[32]

One systematic review by Tavernier *et al.* (2013). included studies that considered voluntary childlessness as well as those that examined involuntary infertility.[33] The authors found that overall, the majority of studies investigating fertility in women with IBD showed no difference in involuntary fertility rates between women with CD or UC and controls. However, most studies analysing women with CD found an increase in voluntary childlessness amongst that group.

Little evidence is available on the impact of IBD on male fertility. Tavernier *et al*.(2013) identified three studies involving a total of 493 men with CD. These studies showed a decrease in fertility for men with CD, but did not take into account voluntary childlessness. One study found no difference in fecundability between men with IBD and controls, indicating that the reduction in fertility may have had a voluntary component. The two studies investigating fertility rates in men with UC found no reduction in fertility.[33]

3.2 What is the effect of IBD treatment on fertility?

3.2.1 Medication

C	Health professionals should be aware of the possible effects of some IBD medication on sperm quality and quantity, and the potential impact on male fertility.

Little evidence was found to suggest that medications used in the treatment of IBD have a long-term effect on female fertility. With regard to the effect of IBD treatment on men, sulfasalazine has been shown to cause reversible impairment of sperm count and motility.[21,25,34–36] There is limited evidence demonstrating that methotrexate and infliximab impact on male fertility.[37] The Summary of Product Characteristics (SPC) for methotrexate states that it affects spermatogenesis],[38] but findings are mixed and any effect of methotrexate on fertility is reversible.[34,35]

3.2.2 Surgery

✓	The risk of subfertility following reconstructive surgery should be discussed with women with IBD and their partners.

There is evidence to suggest that women may experience subfertility following IBD reconstructive surgery.[27–30,34] Because IPAA is a relatively recent development, this operation has been extensively studied, whereas few data are available for most other operations. A meta-analysis found that IPAA increased the risk of infertility three-fold compared with medical management, although it was unable to identify any patient or procedural factors that consistently affected risk.[29] A systematic review concluded that women's fertility was reduced after restorative proctocolectomy and postulated that this may be partly due to obstruction of the Fallopian tubes and ovaries from pelvic adhesions.[28]

A recent large study using data from a UK general practice database found that the AFRR for women with IBD who had not had surgery was 0.95 (95% CI 0.91–0.99) compared with women without IBD. Fertility rates were lower for women who had had intestinal resection surgery (AFRR 0.84, 95% CI 0.77–0.92). Fertility rates for women who had undergone pouch surgery were lower still (AFRR 0.48, 95% CI 0.23–0.99).[32]

The effects of surgery on male fertility are less well studied. Potential complications of reconstructive surgery, such as retrograde ejaculation or erectile dysfunction, could theoretically make conception more problematic.

4. IBD AND PREGNANCY

B	Women with IBD should be advised to plan to conceive when the disease is well controlled.
✓	Appropriate referral for pre-pregnancy counselling should be available for men and women in order to optimise their IBD management prior to conception.

The Crohn's and Colitis UK information sheet on pregnancy in IBD states that the children of individuals with IBD have a slightly increased risk of developing IBD, although factors other than a genetic predisposition are required to trigger IBD. The risk is estimated at about 2% if one parent has IBD and over 30% if both do.[39]

Ideally, women should be encouraged to plan to conceive when the disease is controlled and they are well nourished. They should be encouraged to continue with their maintenance medication and to take folic acid supplementation.[1] The standard preconception dose of 400 µg folic acid daily is usually adequate, but a higher dose may be required, for example in women taking sulfasalazine (which may affect folate absorption) or women who have malabsorption following small bowel resection.

4.1 What is the effect of pregnancy on IBD?

Review of the available evidence suggests that most women with mild or inactive disease at the time of conception have no worsening of the disease during pregnancy and relapse is no more likely during pregnancy. Conversely, women whose disease is active at the time of conception are more likely to have active disease during pregnancy.[21,25,34,40–42] The BSG advises that women with IBD who wish to conceive should be counselled to do so while their disease is inactive.[1]

There is mixed evidence in the literature regarding the long-term effect of pregnancy on IBD. Two prospective cohort studies[43,44] suggested that pregnancy may reduce subsequent IBD disease activity and there is some evidence that surgical intervention for CD decreases after pregnancy.[10,44] However, two small studies found no change in CD disease activity after pregnancy.[45,46]

4.2 What is the effect of IBD on pregnancy outcomes?

The evidence in relation to pregnancy outcomes for women with IBD is often conflicting and mainly limited to observational studies, which are vulnerable to bias and confounding factors.

4.2.1 Miscarriages

Two retrospective case-control studies found no increase in early pregnancy loss amongst women with IBD.[31,47] However, a recent retrospective case-control study found that in post-IBD-diagnosis pregnancies, miscarriages were significantly more likely than in pre-diagnosis pregnancies.[48] A large Japanese retrospective cohort study found a significantly greater risk of miscarriages after a

diagnosis of CD than prior to diagnosis, but not after a diagnosis of UC. Other small observational studies reported significantly increased risk of miscarriages associated with active CD[49,50] or UC[51] at the time of conception.

4.2.2 Premature birth and low birthweight

Two meta-analyses[52,53] reported significantly increased incidence of preterm delivery and low birthweight amongst women with IBD. Recent reviews concluded that active disease increases the risks of preterm delivery and low birthweight.[25,34,42,53]

4.2.3 Congenital abnormalities

Some studies have found that the incidence of congenital abnormalities may be increased in IBD pregnancies.[48,52–55] A recent meta-analysis reported an odds ratio (OR) of 1.29 for congenital anomalies (11 studies; 95 % CI 1.05–1.58) for women with IBD, but commented that this result may be unreliable secondary to publication bias.[53]

One large Danish cohort study found no increased risk of women with IBD delivering a living singleton with a congenital abnormality, but did find that women with CD had a moderately increased risk of delivering a child with a major congenital abnormality [relative risk (RR) 1.85, 95% CI 1.06–3.21].[54] One case-control study of 71 women with UC found an increased risk of some specific congenital abnormalities, but no significant increase in the overall risk of congenital abnormalities (OR 1.3, 95% CI 0.9–1.8).[56]

Conversely, a large observational Scandinavian study found no association between UC and overall risk of congenital abnormalities (prevalence OR 1.05, 95% CI 0.84–1.31) or specific congenital abnormalities;[57] a case control study in the USA including 461 pregnant women with IBD found no increase in risk of congenital abnormalities with either UC or CD;[58] a European case-control study including 332 pregnant women with IBD found no increase in risk of congenital abnormalities;[59] and a large Japanese cohort study reported rates of congenital abnormalities amongst pregnant women with IBD that are consistent with those in the general population.[60]

4.2.4 Caesarean section

C There is controversy regarding the most appropriate mode of delivery (caesarean section or vaginal) following IPAA surgery. Women should be guided in their decision by the advice of the obstetric and GI specialists in charge of their care.

A variety of studies have shown increased rates of caesarean section in women with IBD.[28,30,31,41,52,57,58,60–64] A case-control study of 332 pregnant women with IBD and 332 pregnant controls without IBD found that previous intestinal surgery was associated with a higher rate of caesarean section (OR 3.6, 95% CI 1.3–10.2).[59]

Caesarean section may be the best mode of delivery for individuals who have an ileo-anal pouch or perianal CD, as it may minimise the risk of damage to the anal sphincter. However, there does not appear to be agreement as to whether an elective caesarean section should be recommended in such cases, and there is some evidence to suggest that women who have undergone reconstructive surgery can successfully undergo vaginal delivery with few complications.[28,30,31]

4.3 What is the effect of IBD treatment on pregnancy outcomes?

4.3.1 Medication

C	If either partner is taking methotrexate, pregnancy should be prevented by use of effective contraception during and for at least 3 months after treatment.
C	If either partner is taking mycophenolate mofetil, pregnancy should be prevented by use of effective contraception during and for at least 6 weeks (women) or 3 months (men) after treatment has ended.
C	The BNF advises that pregnancy should be prevented by use of effective contraception for women treated with TNF-α inhibitors (e.g. infliximab, adalimumab) and for 6 months after treatment has ended. Consideration for use during pregnancy requires specialist advice.
✓	Health professionals should check current NICE, BSG and ECCO guidelines and the SPC for each medication for specific advice on use while trying to conceive and while pregnant or breastfeeding. The decision to discontinue any treatment requires expert clinical judgement, balancing the risks of stopping the drug against the risks associated with continuing.

The decision to stop, continue or commence any treatment prior to conception, during pregnancy and whilst breastfeeding requires expert clinical judgement based on the balance of risk between stopping the drug versus the risks associated with continuing. Good IBD control prior to and during pregnancy is extremely important. Because drugs such as methotrexate can have a teratogenic effect even if it is the male partner who is taking them, men receiving medication for IBD should also be advised about the effects of certain drugs on pregnancy outcomes.

Current NICE guidelines on CD[21] and UC[20] highlight the lack of good-quality evidence relating to the safety of use of specific drug treatments for IBD during pregnancy and advise that the recommendations given in the British National Formulary (BNF) should be followed. Appendix 3 outlines guidance from the BNF and manufacturers on the use of certain IBD drugs prior to conception and during pregnancy.

The Second European Crohn's and Colitis Organisation (ECCO) consensus paper on reproduction and pregnancy in inflammatory bowel disease[34] and BSG guidelines[1] offer guidance on use of

medications for IBD during pregnancy. Crohn's and Colitis UK produce an information sheet on pregnancy and IBD that covers use of medications during pregnancy.[39] Additional information for healthcare professionals and patient information is available from the UK Teratology Information Service.[65]

A retrospective cohort study found no significant differences in pregnancy outcomes when investigating the effect of aminosalicylates, metronidazole, ciprofloxacin, corticosteroids, 6-mercaptopurine, azathioprine and ciclosporin.[66]

Aminosalicylates: Aminosalicylates have limited placental transfer and a meta-analysis in 2008 of pregnancy outcomes in women exposed to this class of drugs found no statistically significant increase in adverse outcomes. The ORs were 1.16 for congenital abnormalities (95% CI 0.76–1.77, p=0.57), 2.38 for stillbirth (95% CI 0.65–8.72, p=0.32), 1.14 for miscarriage (95% CI 0.65–2.01, p=0.74), 1.35 for preterm delivery (95% CI 0.85–2.13, p=0.26) and 0.93 for low birthweight (95% CI 0.46–1.85, p=0.96).[67]

A 2014 review, ECCO guidelines and BSG guidelines support the view that aminosalicylates are generally considered safe in pregnancy, although it is emphasised that the risk is uncertain above doses of 3 mg/day.[1,34,68] Advice currently given by the BNF and the manufacturers is outlined in Appendix 2. Folate supplementation (5 mg) is recommended for women taking sulphasalazine, which interferes with folic acid absorption.

Thiopurines: Two recent meta-analyses relating to use of thiopurines in pregnancy were identified: one demonstrates no significant increase in risk of congenital abnormality (OR 1.45, 95% CI 0.99–2.13) or low birthweight (OR 1.01, 95% CI 0.96–1.06) but suggests an increased risk of premature delivery (OR 1.67, 95% CI 1.26–2.20).[69] The other finds no difference in risk of congenital abnormality amongst women with IBD using thiopurines during pregnancy when compared with IBD controls (RR 1.37, 95% CI 0.92–2.05, p = 0.1).[70]

ECCO guidelines[34] suggests that thiopurines are low risk during pregnancy (limited data on 6-thioguanine) and BSG guidelines[1] recommend that thiopurines are probably safe in pregnancy. Advice currently given by the BNF and the manufacturers is outlined in Appendix 2. The manufacturer of mercaptopurine states that it is potentially teratogenic.

Methotrexate: Methotrexate is teratogenic and is contraindicated in pregnancy. Effective contraception is required during and for at least 3 months after treatment in men or women.[71]

Mycophenolate mofetil: Mycophenolate mofetil is contraindicated in pregnancy. Women are advised to use effective contraception during treatment and for 6 weeks after discontinuation. Female partners of male patients should use effective contraception during treatment and for 3 months after discontinuation.[72]

Tacrolimus: Data relating to use of tacrolimus for management of IBD in pregnancy are extremely limited.

TNF-α inhibitors: There is some evidence that suggests TNF-α inhibitors are low risk in pregnancy.[26] There is, however, transplacental transfer and stopping treatment in the third trimester to limit fetal exposure may be considered.[1,34,42,73] Evidence regarding use of TNF-α inhibitors (e.g. infliximab, adalimumab) in pregnancy is not yet strong enough to exclude adverse effects.[1,34,74–76] The current ECCO and BSG guidelines point out that although intrauterine exposure to infliximab and adalimumab does not appear to increase the risk of adverse pregnancy outcomes and is probably low risk, the long-term effects (for example on the developing immune system) are unknown.[1,34] Advice currently given by the BNF and the manufacturer is outlined in Appendix 2. The manufacturer advises that effective contraception must be used to avoid pregnancy for at least 5 months (adalimumab) and 6 months (infliximab) after the last dose.

Antibiotics: The BNF advises avoiding use of ciprofloxacin in pregnancy due to a risk of arthropathy and avoiding high-dose regimens of metronidazole during pregnancy.[77]

4.3.2 Surgery

Much of the literature on pregnancy and IBD surgery has focused on restorative proctocolectomy. There is no evidence that pregnancy following restorative proctocolectomy is associated with an increase in complications.[28] A prospective cohort study looking at pregnancy and delivery before and after IPAA in the same women found no difference in birthweight, duration of labour, delivery complications, vaginal delivery rates and unplanned Caesarean section.[78] Pregnancy and delivery in patients with a stoma is generally considered safe; however, stoma size may increase during pregnancy.

4.4 Other considerations relating to pregnancy and IBD

✓ Health professionals should consider ectopic pregnancy in their differential diagnosis of abdominal pain and GI symptoms in sexually active women with IBD.

Ectopic pregnancy may present with GI symptoms, as highlighted in the UK enquiry into maternal deaths.[79] Clinicians should consider ectopic pregnancy in the differential diagnosis of abdominal pain and GI symptoms in sexually active women with IBD.

5. IBD AND CONTRACEPTIVE CHOICE

5.1 Does contraception influence IBD?

B Women can be informed that a causal association between COC use and onset or exacerbation of IBD has not been established.

There is no clear consensus on the relationship between contraception and IBD. A meta-analysis found evidence of an association between the use of oral contraception and the development of IBD, in particular CD,[80] while two recent systematic reviews found limited evidence of an association.[81,82] Postmarketing surveillance has recently identified colitis as an adverse event in Evra® combined patch users.[83] Despite these apparent associations, a causal relationship has not been confirmed. There are limited data on combined oral contraception (COC) use and disease severity. A study of women with CD found that COC use did not alter the course of the disease.[84]

5.2 Does IBD affect contraceptive choice?

5.2.1 Medical eligibility

For any individual, the suitability of a contraceptive method may depend on factors such as age, smoking, family history, medical conditions and drug treatment. For individuals with IBD, mobility, malabsorption, surgical treatment, extra-intestinal manifestations of IBD and associated conditions such as osteoporosis may further influence contraceptive choice.

The *UK Medical Eligibility Criteria for Contraceptive Use* (UKMEC) have been developed to provide guidance for health professionals on the suitability of contraceptive methods with specific clinical conditions.[85] Recommendations are based on available evidence and expert opinion, and classify conditions into one of four categories (Table 1). The UKMEC include guideline on IBD and some of its associated medical conditions (Table 2).

Women with IBD who fulfil medical eligibility criteria can use intrauterine contraception (IUC). Although pelvic infection may occur and should be considered in the differential diagnosis of abdominal pain, the risk of pelvic infection is only increased in the 21 days following IUC insertion.[86] Thereafter, the risk of pelvic infection is not increased unless there is exposure to sexually transmitted infections. Studies on pelvic infection and IUC, however, are not specific to women with IBD.

Table 1: Definition of UKMEC categories

UKMEC	Definition of category
Category 1	A condition for which there is no restriction for the use of the method.
Category 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks.
Category 3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other, more appropriate methods are not available or not acceptable.
Category 4	A condition which represents an unacceptable health risk if the method is used.

Table 2: UKMEC summary table for hormonal and intrauterine contraception methods

	Cu- IUD	LNG-IUS	IMP	DMPA	POP	CHC
	I = Initiation, C = Continuation					
Inflammatory bowel disease (including Crohn's disease and ulcerative colitis)	1	1	1	1	2	2

Cu-IUD = Copper intrauterine device; LNG-IUS = Levonorgestrel-releasing intrauterine system; IMP = Progestogen-only implant; DMPA = Progestogen-only injectable: depot medroxyprogesterone acetate; POP = Progestogen-only pill; CHC = Combined hormonal contraception

5.2.2 Absorption of oral contraception

✓ Women should be advised that the efficacy of oral contraception is unlikely to be reduced by large bowel disease but may be reduced in women with CD who have small bowel disease and malabsorption.

Oral contraception may be less reliable in women with IBD who have malabsorption due to severe small bowel disease or resection, or who have vomiting or severe diarrhoea for more than 24 hours. No evidence was identified to suggest any reduction in the efficacy of the combined patch, progestogen-only injectables, progestogen-only implants or intrauterine methods in women with IBD.

5.2.3 Osteoporosis

C Health professionals should consider the impact of IBD-associated conditions (e.g. VTE, PSC and osteoporosis) as well as other medical conditions when prescribing contraception to women with IBD.

Concerns have been raised about the use of the progestogen-only injectable method, depot medroxyprogesterone acetate (DMPA), and its potential effects on bone mineral density (BMD). Several studies, including a systematic review performed for NICE on long-acting reversible contraception (LARC)[87] have concluded that there is conflicting evidence of a link and that any effect may be reversible upon cessation of the method.[88] The Department of Health Medicines

and Healthcare products Regulatory Agency (MHRA)[89] and the Faculty of Sexual & Reproductive Healthcare (FSRH)[88] recommend that:

- In women aged under 18 years, DMPA may be used after all other options have been discussed and considered unsuitable or unacceptable.
- A re-evaluation of the risks and benefits of treatment for all women should be carried out every 2 years in those who wish to continue use.
- For women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered.

As osteoporosis and osteopenia are more common amongst individuals with IBD, women should be assessed for other risk factors and advised about the effect of their disease on BMD. The possible effects of DMPA on BMD should be weighed against the possible benefits (i.e. low risk of thrombosis and the fact that contraceptive efficacy is unaffected by malabsorption or drug interactions). For those women who choose to use DMPA, re-evaluation should occur at least every 2 years as outlined above.

A systematic review[90] exploring combined hormonal contraception (CHC) and bone health concluded that the relationship between COC and BMD is unclear. There are no studies of COC use and BMD or fracture risk in women with IBD. There is no evidence of a clinically significant effect on BMD with the use of the progestogen-only implant.[91,92]

5.3 How might IBD treatment affect contraceptive use?

5.3.1 Medication

✓ Health professionals should check whether any prescribed medications for rectal or genital administration contain constituents that could reduce the efficacy of condoms.

No specific interactions are listed between estrogen or progestogen and the majority of anti-inflammatory and biological medications used to treat IBD. Plasma levels of ciclosporin may be increased by sex steroid hormones.[77] The SPC for ciclosporin[93] indicates that measuring blood levels of ciclosporin is questionable in non-transplant patients because the relationship between blood levels and clinical effect is less well established. Therefore, if drugs are being used concomitantly that are known to increase ciclosporin concentration, frequent assessment of renal function and careful monitoring of ciclosporin side effects may be more appropriate.[93] The SPC for tacrolimus advises that ethinylestradiol and potentially some progestogens may increase serum tacrolimus levels.[94]

FSRH guidance [95] and the BNF advise that the effectiveness of CHC is not reduced by concomitant use of non enzyme-inducing antibiotics (unless the antibiotic causes vomiting or diarrhoea in a woman taking COC).

Information on potential drug interactions with hormonal contraception can be found in separate CEU guidance.[96]

Women with IBD may wish to use barrier methods of contraception (i.e. condoms, cervical caps and diaphragms). However, the typical failure rates make these methods inappropriate for women who are using teratogenic drugs.

There is a theoretical risk that some IBD medications for rectal administration may reduce the efficacy of latex condoms if the product spreads to the genital skin. Whilst no direct evidence of an interaction was found, it is known that the strength of condoms can be reduced by contact with oil- or witepsol-based products. Information on product constituents can be obtained from the package insert or the pharmaceutical company.

5.3.2 Surgery

✓	Women with IBD should stop COC at least 4 weeks before major elective surgery and alternative contraception should be provided. Advice regarding recommencing COC should be given individually.
B	Previous pelvic or abdominal surgery in women with IBD could affect the safety and success of laparoscopic sterilisation.
✓	Women with IBD considering sterilisation – and their partners – should be counselled about alternative methods of contraception including LARC methods and vasectomy.

Major surgery, hospitalisation and immobilisation are all considered risk factors for VTE. The risk of postoperative VTE is higher amongst COC users.[97–99] For individuals undergoing major surgery with prolonged immobilisation, the UKMEC classify CHC use as a Category 4 (the method should not be used).[85] In women with IBD, CHC should be stopped at least 4 weeks before elective major surgery. Counselling and provision of alternative methods is important. Advice regarding recommencing CHC should be given individually.

Women using progestogen-only methods do not appear to be at increased risk of VTE[100] and need not discontinue them prior to surgery. All progestogen-only methods are UKMEC Category 2 for individuals undergoing major surgery with prolonged immobilisation;[85] the copper IUD and barrier methods are Category 1.[85]

Sterilisation can be offered if other options are unsuitable. Previous pelvic or abdominal surgery could affect the safety and success of laparoscopic sterilisation.[101] The Collaborative Review of Sterilisation concluded from a large, prospective, multicentre cohort study that women who had previous abdominal or pelvic surgery were twice as likely to develop complications following laparoscopic sterilisation than women who had no previous surgery (OR 2.0, 95% CI 1.4–2.9).[102] If a sterilisation procedure is planned, it should be undertaken in a setting with an experienced surgeon and other backup support. Alternative methods such as vasectomy and LARC methods may be as effective, if not more so, than sterilisation.[103] Hysteroscopic sterilisation techniques might be a suitable alternative: limited available evidence suggests that hysteroscopic sterilisation is unaffected by previous pelvic surgery.[100] If abdominal surgery is indicated for a woman with IBD who wishes sterilisation, both procedures could be performed at the same time providing the woman has been counselled preoperatively and has given specific consent.

6 IBD, Sexual Function and Psychosexual Health

Health professionals should provide an opportunity for individuals with IBD and their partners to discuss issues relating to sexuality, body image and mental well-being, and know where to refer locally when appropriate.

Several studies have looked at how IBD affects sexual function and found varying results. One systematic review found that the majority of studies demonstrated impaired sexual function amongst those with IBD, with women more affected than men.[104] It also found that depression was the most consistent negative predictive factor of sexual function. One case-control study did not find higher prevalence of sexual dysfunction in those with IBD versus those without it, but did find that people with active disease were more likely to score within the sexual dysfunction range than those in remission or controls ($p<0.05$).[105]

There are limited data regarding IBD medication and sexual function. A survey of 217 IBD patients found that 37% of patients felt their medication had a negative effect on their libido, and 10% sometimes or frequently skipped medication because of the perceived effect on sexual function.[106]

Studies looking at IBD surgery and sexual function showed mixed results. One small, prospective cohort study found that post-surgery, both men and women experienced improved sexual desire, but only men felt an improvement in sexual function.[107]

Complications that have been noted following IBD surgery include dyspareunia in women and loss of ejaculation and retrograde ejaculation in men.[28,108–110] These problems are associated with pelvic surgery rather than abdominal surgery. However, one systematic review found that although dyspareunia increased after proctocolectomy surgery in women, it did not appear to have a negative impact on overall sexual satisfaction.[28] A prospective study of individuals with UC found that despite around one-third reporting dissatisfaction with their sex life before surgery, the majority

were happy afterwards.[108] The effect of successful surgery on general well-being after a long period of systemic illness presumably contributes to changes in attitude about sexual health.
Some individuals with an ileostomy report that a stoma negatively affects their sex life. Concerns noted include feeling sexually undesirable and anxious about detachment of their stoma.[108] Depression, which is more prevalent amongst those with IBD in comparison to the general population,[111] has been identified as a determinant of low sexual function.[112]

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APPENDICES

Appendix 1 – Development of FSRH Guideline

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None of the individuals participating in the development of these guidelines had competing interests.

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FSRH Clinical Guideline is developed in collaboration with the CEU of FSRH. The CEU Guideline development process employs standard methodology and makes use of systematic literature review and a multidisciplinary group of professionals. Evidence is identified using a systematic literature review and electronic searches are performed for: MEDLINE (1996–2016); EMBASE (1996–2016); PubMed (1996–2016); The Cochrane Library (to 2016) and the US National Guideline Clearing House. The Cochrane Library is searched for relevant systematic reviews, meta-analyses and controlled trials relevant to sexual and reproductive health for individuals with inflammatory bowel disease. Previously existing guidelines from the FSRH (formerly the Faculty of Family Planning and Reproductive Health Care), the Royal College of Obstetricians and Gynaecologists (RCOG), the World Health Organization (WHO) and the British Association for Sexual Health and HIV (BASHH), and reference lists of identified publications, are also searched. Summary evidence tables are available on request from the CEU. The process for the development of CEU Guideline is detailed in the CEU section of the FSRH website (www.fsrh.org). The methods used in the development of this Guideline (CEU Process Manual January 2016) have been accredited by National Institute for Health and Care Excellence (NICE).

Appendix 2 – Summary of Changes to Previous Guideline

IBD and Contraceptive Choice

Previous recommendation	New recommendation
Women using combined hormonal contraception (CHC) should use additional contraception while taking antibiotic courses of less than 3 weeks and for 7 days after the antibiotic has been discontinued.	FSRH guideline[95] and the BNF advise that the effectiveness of CHC is not reduced by concomitant use of non-enzyme-inducing antibiotics (unless the antibiotic causes vomiting or diarrhoea in a woman taking combined oral contraception).

IBD and Pregnancy

Previous recommendation	New recommendation
Effective contraception must be used by women treated with infliximab or adalimumab and for at least 6 or 5 months, respectively, after treatment.	The BNF advises that pregnancy should be prevented by use of effective contraception for women treated with tumour necrosis factor alpha (TNF-α) inhibitors (e.g. infliximab, adalimumab) and for 6 months after treatment has ended. Consideration for use during pregnancy requires specialist advice.
Previously no recommendation given. Mycophenolate mofetil is now used in IBD treatment.	If either partner is taking mycophenolate mofetil, pregnancy should be prevented by use of effective contraception during and for at least 6 weeks (women) or 3 months (men) after treatment has ended.

Appendix 3 – Guidance from the *British National Formulary* and manufacturers on the use of inflammatory bowel disease drugs

Summary of Information from Pharmaceutical Companies and the *British National Formulary* (BNF) [77,113]		
Type of medication/ drug	**BNF and manufacturer guideline in relation to pregnancy**	**BNF and manufacturer guideline regarding breastfeeding**
5-Aminosalicylic acid drugs		
Mesalazine	Negligible placental transfer. Use with caution.	Mesalazine concentration in breast milk is low whereas the metabolite, acetyl-mesalazine, appears in similar or increased concentrations. Hypersensitivity reactions such as diarrhoea cannot be excluded. Caution with use in nursing mothers.
Olsalazine	Experience in pregnant women limited therefore advice is to avoid use unless potential benefits outweigh risks.	Manufacturer advises avoidance.
Balsalazide	Human experience is limited therefore manufacturer advises avoidance.	Manufacturer advises avoidance.
Sulphasalazine	Studies have failed to reveal any teratogenic or icteric hazards. There is a theoretical but unproven risk of neonatal haemolysis. Expectant mothers should be given adequate folate supplements.	Manufacturer advises avoidance.

Summary of Information from Pharmaceutical Companies and the *British National Formulary* (BNF) [77,113]		
Type of medication/ drug	**BNF and manufacturer guideline in relation to pregnancy**	**BNF and manufacturer guideline regarding breastfeeding**
Immunosuppressive agents		
Azathioprine Ciclosporin	Little evidence that azathioprine or ciclosporin are teratogenic but some reports of premature birth and low birthweight (particularly in combination with corticosteroids), and some reports of miscarriage following maternal or paternal exposure. Should be used in pregnancy only if benefits outweigh risks.	Manufacturer advises avoidance.
Methotrexate Mercaptopurine	Teratogenic, therefore contraindicated in pregnancy. Manufacturer advises use of effective contraception during treatment and for at least 3 months after treatment if taken by either partner.	Manufacturer advises avoidance.
Tumour necrosis factor alpha (TNF-α) inhibitors		
Infliximab Adalimumab Golimumab Vedolizumab	There is currently limited experience of use of these drugs during pregnancy; therefore it is advised that they are avoided. Manufacturer advises adequate contraception during treatment and at least 5 months after last dose of adalimumab or vedolizumab and 6 months after last dose of infliximab or golimumab.	Breastfeeding should be avoided for at least 6 months after last dose of infliximab or golimumab and at least 5 months after last dose of adalimumab or vedolizumab.
Corticosteroids		
	The benefit of treatment outweighs risk. Betamethasone and dexamethasone cross the placenta readily, whereas 88% of prednisolone is inactivated as it crosses the placenta. Prolonged administration may cause intrauterine growth restriction but no evidence with short-term use.	Systemic effects in infant unlikely with maternal dose of prednisolone up to 40 mg daily. Monitor infant's adrenal function with higher doses. Amount in breast milk too small to be harmful. Benefits outweigh risks.

QUESTIONS FOR CONTINUING PROFESSIONAL DEVELOPMENT

The following multiple choice questions (MCQ) have only one correct answer and have been developed for continuing professional development (CPD). The answers to the questions and information on claiming CPD points can be found in the 'members-only section' of the FSRH website (www.fsrh.org), which is accessible to all Diplomates, Members, Associate Members and Fellows of the FSRH.

1. Women with inflammatory bowel disease (IBD) who are planning a pregnancy should be informed that:

a. Women with IBD are much less fertile than those without IBD
b. Medications for IBD must be stopped prior to conception
c. Active disease at the time of conception is likely to become inactive during pregnancy
d. Active disease during pregnancy is associated with poorer pregnancy outcomes

2. In women with IBD, the effectiveness of oral contraception may be reduced by:

a. Large bowel disease
b. Small bowel disease
c. Both small and large bowel disease
d. None of the above

3. Drugs for IBD that have been shown to reversibly reduce male fertility are:

a. Azathioprine
b. Tacrolimus
c. Sulfasalazine
d. Mycophenolate mofetil

4. Drugs used in IBD that can have a negative effect on folate levels are:

a. Prednisolone
b. Tacrolimus
c. Sulfasalazine
d. Mycophenolate mofetil

5. Women whose partners are taking methotrexate should be advised to use effective contraception for which time period after discontinuation?

a. 6 weeks
b. 3 months
c. 6 months
d. 9 months

6. Women with IBD are more likely to have active disease during pregnancy if:

a. They have no sign of active IBD at the time of conception
b. They have active IBD at the time of conception
c. The diagnosis is made before conception
d. They have had previous abdominal surgery

7. Which of the following *UK Medical Eligibility for Contraceptive Use* (UKMEC) recommendations for a woman with a diagnosis of IBD is correct?

a. Depot medroxyprogesterone acetate: UKMEC 1

b. Levonorgestrel-releasing intrauterine system (LNG-IUS): UKMEC 2

c. Combined oral contraception (COC): UKMEC 3

d. LNG-IUS: UKMEC 3

8. Rectal administration of treatments for IBD may reduce the effectiveness of:

a. COC
b. Progestogen-only pill
c. Non-latex diaphragm
d. Latex condoms

9. The safety and success of laparoscopic sterilisation may be reduced if the woman:

a. Is subsequently diagnosed with IBD
b. Has medically-treated IBD
c. Has had surgery for IBD
d. Has well-controlled IBD but is on no medication

AUDITABLE OUTCOMES

The following auditable outcomes have been suggested by the FSRH Clinical Standards Committee.

1. Women taking methotrexate should be advised about the risks of teratogenicity and avoiding pregnancy for 3 months after ceasing treatment. This should be recorded in the patient record. [Auditable standard 97%]

2. Women requesting sterilisation who have had pelvic or abdominal surgery for inflammatory bowel disease (IBD) should be informed of the higher risk of complications and also the effectiveness of long-acting reversible contraception methods. This should be recorded in the patient record. [Auditable standard 97%]

3. Women with IBS who plan to conceive should be advised that it is best to do so when the disease is well controlled and they are well nourished. This should be documented in the patient record. [Auditable standard 97%]

4. Couples should be advised regarding appropriate referral options for pre-pregnancy counselling that could optimise their disease management prior to conception. This should be documented in the patient records. [Auditable standard 97%]

COMMENTS AND FEEDBACK ON PUBLISHED GUIDELINE

All comments on published guideline can be sent directly to the Clinical Effectiveness Unit (CEU) of the Faculty of Sexual & Reproductive Healthcare (FSRH) via the FSRH website www.fsrh.org.

The CEU may not respond individually to all feedback. However, the CEU will review all comments and provide an anonymised summary of comments and responses, which are reviewed by the Clinical Effectiveness Committee and any necessary amendments made subsequently.

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