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# Comprehensive reproductive healthcare for women with immune-mediated inflammatory diseases: Addressing rheumatoid arthritis, spondyloarthritis and inflammatory bowel disease through life's stages

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ABSTRACT

Immuno-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis, spondyloarthritis, and inflammatory bowel disease are characterised by pathophysiological mechanisms wherein the immune system erroneously targets the body's own tissues. This review explores the heightened vulnerability of women with IMIDs, influenced by hormonal modulators like estrogen and progesterone. The challenges this poses are multifaceted, encompassing the impact of active disease and medical treatments throughout life stages, including family planning, fertility, and menopause. From the perspectives of rheumatologists and gastroenterologists, we review current management strategies and underscore the need for a multidisciplinary and life-cycle approach to healthcare for women with IMIDs.

## 1. Introduction

In the spectrum of IMIDs, rheumatoid arthritis (RA), spondyloarthritis (SpA), and inflammatory bowel disease (IBD) stand out due to their shared characteristics and interconnected pathophysiological mechanisms. These conditions, rooted in inflammation, often manifest because of the body's immune system mistakenly targeting its own tissue. While each pathology has its unique clinical presentation – RA affecting the joints, SpA targeting the spine, and IBD impacting the digestive tract – they all share commonalities [1–3]. These include a potential genetic predisposition, overlapping symptomatology, and the challenge of diagnosis due to non-specific symptoms [4–7].

IMIDs display a notable gender disparity in their incidence, with women being more frequently affected than men [2,4,5,8–10]. This increased susceptibility in women has been the subject of extensive research and speculation. Hormonal differences, particularly the roles of estrogen and progesterone, are believed to influence immune responses. Estrogen, for instance, has been shown to enhance the immune response under certain conditions, while progesterone can exert immunosuppressive effects [5,11–14]. These hormones, which undergo cyclical variations throughout the menstrual cycle and significant changes during life events like pregnancy and menopause, might modulate the immune system in ways that predispose women to a higher risk of developing IMIDs [15]. Studies have shown that women exhibit stronger humoral and cellular immune responses than males. While this can enhance pathogen clearance, it may also contribute to immune-pathogenic effects and a higher predisposition to autoimmunity due to hyper immune responses [16].

Additionally, genetic factors and the X chromosome might play a role in modulating immune reactions [5,11,12]. The X chromosome is a reservoir of several immune-related genes such as CD40 ligand, chemokine receptor CXCR3, and IL-9 receptor, among others [12]. These genes are instrumental in orchestrating various aspects of the immune response, and their overexpressi2on can influence immune activities in a sex-dependent manner [12].

Furthermore, the phenomenon of X chromosome inactivation in females, a mechanism to avoid the double dosage of X chromosome-derived proteins, is not absolute. Approximately 15% of the genes on the X chromosome escape this inactivation, leading to their overexpression [12]. This is thought to contribute to the heightened immune responses observed in females, providing a genetic basis for the observed sex differences in immune reactions [12].

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Caring for women with immune-mediated inflammatory diseases requires a nuanced approach that diverges from standard health management. Rheumatologists, gastroenterologists, and associated clinicians are often tasked with guiding their patients through complex decisions related to contraception, pregnancy, lactation, assisted reproduction technologies (ARTs), fertility preservation, and hormone replacement therapy (HRT). Collaborative efforts with experts in obstetrics-gynaecology, maternal-fetal medicine, reproductive endocrinology, and infertility are essential [17,18]. The challenges are multifaceted, with concerns about the implications of active disease and ongoing medication throughout a woman's life. This complexity can sometimes lead to clinical inertia, a term discussed by Nelson-Piercy and colleagues, referring to the failure to initiate or escalate treatment despite evidence of active disease. This phenomenon can lead to suboptimal management of a patient's condition, resulting in an increased risk of adverse health outcomes [19].

This review aims to perform a multidisciplinary analysis of the unique needs, expectations, and challenges that women with conditions such as RA, SpA, and IBD face at various life stages. It seeks to discern and compare diversities and similarities in these conditions through the combined expertise of rheumatology and gastroenterology. The review will focus on family planning, fertility, and menopause management, and will highlight medications commonly used in both fields. It will also briefly touch upon pregnancy and breastfeeding topics, referencing the most up-to-date guidelines that thoroughly examined these subjects in prior studies. The objective is to increase awareness of the unmet needs of female patients and to enhance understanding within the medical community, which is essential in ameliorating the standard of care for women with IMIDs.

## 2. Fertility

Fertility is defined as the ability to achieve a clinical pregnancy, whilst fecundity encompasses the capacity to have a live birth, including gamete production, fertilisation, and carrying a pregnancy to term [20–22]. IMIDs often manifest during a woman's reproductive years, presenting unique challenges for those considering starting a family [6,23]. The relationship between disease conditions and fertility is a complex interplay balancing disease activity, health factors, medical interventions, and personal decisions.

Although the occurrence of RA in women of childbearing age is relatively low, a notable 30–40% of female RA patients face an elongated time to pregnancy (TTP), a factor influenced by both the disease activity and its treatments [5]. As highlighted by Smeele and colleagues, a TTP exceeding 12 months is categorised as subfertility. In the general population, subfertility stands at a median of 9%, but it jumps to 25–42% for RA patients [24]. Furthermore, women with psoriatic arthritis and axial SpA (axSpA) also exhibit an extended TTP [1,25]. The underlying reasons for these disparities remain somewhat elusive but are crucial for fertility discussions with patients [1].

Certain treatments, such as nonsteroidal anti-inflammatory drugs (NSAIDs) during the pre-conceptional period and daily glucocorticoid doses surpassing 7.5 mg, are associated with a prolonged TTP [1]. Yet, some treatments, like methotrexate (MTX), seemingly do not influence TTP or the ovarian reserve [1].

Persistent inflammation characteristic of IMIDs can disrupt the hypothalamic-pituitary-ovarian axis, leading to irregular hormone secretion [26]. To manage fertility, consistent monitoring of the hypothalamic-pituitary-ovarian axis and potential utilisation of ARTs can prove beneficial [26].

Fears around motherhood contributes to a reduced family size among patients with IMIDs. Notably, 17% of women with IBD choose voluntary childlessness, in contrast to the 6% observed in the general population [27]. Such decisions are often influenced by concerns related about fertility, potential pregnancy complications, fear of disease transmission to offspring, and pathology-related psychological burden [18,21,28]. Similarly, nearly 40% of patients with RA have expressed a desire for a larger family but are affected by worries regarding the health of their children and their own parenting abilities. These concerns could be proactively addressed through preconception counselling. In fact, nearly 60% of patients who underwent counselling reported it had a positive influence on their family planning decisions [29].

Active disease can impair fertility through mechanisms involving inflammation of the fallopian tubes and a likely reduction in ovarian reserve [6]. The mechanism(s) involved in the diminished ovarian reserve in women with Crohn's disease (CD) is still debated. Biochemical analysis, like measuring basal Follicle Stimulating Hormone (FSH), estradiol, anti-Müllerian hormone levels, and ultrasound imaging for antral follicular count are methods used to evaluate ovarian reserve [10]. In particular, anti-Müllerian hormone levels have been shown to be a good indicator of ovarian reserve and can be a marker of fertility that appears to be influenced by age, but also by disease activity and possibly, type of medication [30].

In the context of IBD, surgical interventions can significantly affect fertility, especially in cases of ulcerative colitis (UC) [6]. Patients with UC who have not undergone surgery tend to have fertility rates comparable to the general population [31]. However, women who have an ileal pouch-anal anastomosis (IPAA) face a higher risk of infertility due to tubal scarring and dysfunction from adhesions [6,32]. Given these risks, it is recommended that patients receive personalized early fertility consultations and consider fertility preservation methods, such as oocyte or embryo freezing [33].

Fertility preservation options should be considered for all IMID patients at risk for fertility loss, which include [26]:

- Gonadotropin-releasing hormone analogues. Their use, although rare, has been reported to reduce the incidence of premature ovarian failure in IMID patients who are treated with potentially gonadotoxic drugs, such as cyclophosphamide. Yet, the efficacy of gonadotropin-releasing hormone agonists as a fertility preservation strategy in terms of post-treatment chance of pregnancy is still debated.
- Oocyte or embryo freezing. Oocyte vitrification for cryopreservation and future use is currently the most effective method for fertility preservation. This option should be contemplated in all patients of childbearing age who are at risk for a reduction in their reproductive potential.
- Ovarian tissue freezing for auto transplantation. This strategy does not require any prior ovarian stimulation and can be beneficial especially for patients of prepubertal age or those facing imminent gonadotoxic treatment. However, it is important to acknowledge that this is not a standard practice in the management of these patients. This is partly due to challenges in promptly accessing to such services and the fact that gonadotoxic therapy is now reserved for a limited number of patients with extremely severe disease.

For patients with IBD who may require surgery with a potential impact on reproductive organs, the options of oocyte or embryo freezing, and ovarian tissue freezing become particularly important.

Across the spectrum of these conditions, adopting a proactive stance towards fertility management is essential. This encompasses regular monitoring, medication adjustments, and contemplating alternative or ARTs when required [23,24]. After ceasing medication, consistent monitoring, and the introduction of alternative treatments compatible with pregnancy become crucial. If conception remains elusive after 6–12 months, seeking a gynaecologist's expertise and investigating the couple's fertility becomes prudent [21,34]. Moreover, patient education and counselling are pivotal, ensuring women are comprehensively informed about their options and potential hurdles [35].

Whilst IMIDs can pose fertility challenges, they are not insurmountable barriers. With informed guidance and a collaborative approach involving rheumatologists, gastroenterologists, and reproductive specialists, women can adeptly navigate these challenges and

make enlightened decisions about their reproductive journeys [8,23,33].

### 2.1. Assisted reproduction technologies (ARTs)

When couples face infertility, women with IMIDs may be directed to ARTs. ARTs commonly involve in vitro fertilisation (IVF) and embryo transfer as its main techniques [36]. As more women with IMIDs turn to ARTs, two primary counselling challenges arise: first, the potential impact of ARTs, particularly hormonal stimulation, on their underlying disease; and second, how the disease itself (taking into account factors like autoantibodies, chronic inflammation, and medications) influences the efficacy of ARTs in facilitating pregnancy [36].

Hormonal treatments may increase the risk of thrombotic events, especially in patients with persistently positive antiphospholipid antibodies (aPL), and may trigger ovarian hyperstimulation syndrome, a potentially fatal condition. Employing a reduced hormone dosage might mitigate this risk [21]. Consequently, a personalized approach to ARTs, which includes an in-depth discussion of risks and preventive strategies, is essential for optimal outcomes [17]. In RA, ARTs do not typically affect the disease, but the chances of a live birth post-ARTs are notably lower than in women without RA [21]. A comprehensive study from Denmark indicated better outcomes with blastocyst stage transfers and pre-embryo transfer administration of glucocorticoids. However, intracytoplasmic sperm injection resulted in marginally lower live birth rates compared to IVF [37].

While IBD medications do not compromise the success of egg freezing or ARTs, ARTs success rates in IBD patients might not align with those of the general population [10,38,39]. Women with CD should consider starting ARTs prior to any CD-related surgery. For women with UC using ARTs, the risk of preterm birth surges 5-fold, underscoring the need for enhanced antenatal monitoring in this group [10].

### 2.2. Sexual health

Sexual health is defined by the World Health Organization as a state of physical, emotional, mental, and social well-being in relation to sexuality, and it is not merely the absence of disease or dysfunction [20,22,40,41]. This definition underscores the importance of viewing sexual health as a fundamental aspect of quality of life (QoL) [40]. However, discussions on sexual health are often encumbered by barriers such as patient embarrassment, clinician hesitancy, and time constraints. It is important to foster an environment that encourages open, sensitive communication between patients and clinicians [42].

For IMID patients, the physical challenges – like fatigue, musculoskeletal pain, joint stiffness, intestinal discomfort, presence of stoma, irregular bowel movements or direct involvement of the genital tract – can directly affect sexual activity [26,42]. These can undermine self-confidence and mental well-being, often leading to a decreased frequency of intercourse [26]. One third of patients with RA reported a decrease in the frequency of sexual intercourse following their diagnosis, primarily due to pain associated with the disease or a lack of sexual desire [1]. Similarly, patients with IBD, especially reproductive-aged women, face significant challenges related to sexual health. Active disease symptoms, such as diarrhoea, pain, and perianal disease, impact feelings of sexual attractiveness and desire, leading to discomfort during intercourse [40].

Furthermore, IBD can negatively influence sexual health in various ways, considering surgeries and post-surgery condition, medications, and changes in energy level, libido, mood, and body image [22]. Notably, while all IMIDs exert an influence on sexual health, the data suggests that females with IBD experience a more pronounced negative impact on various facets of their sexuality in comparison to their male counterparts [40].

Given these complexities, it is imperative in clinical management for women with IMIDs to incorporate evaluations and counselling focused on psychological well-being and sexual health [41]. Such a multidisciplinary approach should involve not only rheumatologists or gastroenterologists but also psychologists, sexologists, and gynaecologists to address these issues holistically [42]. Clinicians should receive specific training to effectively discuss sexual health and manage sexual dysfunction as part of routine care [42]. A comprehensive assessment of sexual function should include metrics related to intercourse frequency, sexual desire, arousal, orgasm, and overall satisfaction. Additionally, the evaluation of vaginal lubrication in women remains a crucial component of this assessment [34]. Screening for sexual dysfunction should be systematic, using validated questionnaires prior to consultations to identify sexual health issues efficiently and discreetly [42].

### 2.3. Menstrual period management

Menstrual-related hormonal fluctuations have a profound impact on gastrointestinal symptoms, especially in women with UC. Many report cyclical menstrual-related symptoms, including diarrhoea and abdominal pain [22]. Over half of the women with IBD have reported symptom exacerbation during their menstrual periods [8]. Studies support this, indicating that women with UC are twice as likely to experience diarrhoea during menstruation as compared to healthy controls [22].

In adolescents with IBD, disease management can influence the onset of menstruation. Poorly controlled disease can delay menarche due to factors like being underweight, nutritional deficits, or the effects of medications, like corticosteroids [8]. Furthermore, hormonal changes during the menstrual cycle can exacerbate IBD symptoms. For instance, patients with CD often report an increase in diarrhoea prior to and during menstruation, while those with UC experience this primarily during their periods [8].

Additionally, dysmenorrhea, or pain during the menstrual period, has been noted in more than half adolescents with RA, and 72% of women of fertile age experience moderate to severe menstrual pain [43]. Heavy menstrual bleeding is reported by 38% of adult women and 52% of adolescents with RA, contributing to a reduced QoL [43].

There is a notable association between IMIDs and endometriosis – a disease of fertile age characterised by pain and infertility due to ectopic endometrial cells – which often goes undiagnosed due to symptom heterogeneity and the normalisation of menstrual pain. Consequently, women with IMIDs should be considered at high risk for endometriosis, especially when a severe dysmenorrhea is reported [43].

The pathogenetic mechanism underlying menstrual disorders in IMID patients may involve the interplay between sex hormones and the immune system. Some patients have successfully used oral contraceptive pills to manage menstruation-related arthritis flares, with a steady low-estrogen pill helping to prevent monthly flares associated to menstruation [44].

Healthcare professionals should acknowledge these menstrual-related symptom fluctuations and offer informed guidance. Counselling patients about expected symptom variations during the menstrual cycle, not only can improve their overall QoL, but it can also prevent them from mistakenly interpreting these variations as worsening of their underlying disease [8].

## 3. Pregnancy management

RA:

- RA often shows spontaneous remission during pregnancy. Data from a meta-analysis show that, of the 204 pregnancies for which data were available, the percentage of patients experiencing improvement in disease activity scores ranged from 40.4% to 90.0%. Postpartum, a flare in disease activity was observed in 46.7% of cases [45].
- Concerning gestational outcomes, adverse events such as preterm births and low birth weight were observed. Out of 135 pregnancies

**Table 1**
Overview of common medications for RA, SpA, and IBD: recommendations for the use during pregnancy and breastfeeding. Table adapted from [39,69].

| Drug | Pregnancy | | Breastfeeding | |
|---|---|---|---|---|
| | **RA/SpA** | **IBD** | **RA/SpA** | **IBD** |
| Corticosteroids | Compatible | Compatible | Compatible | Compatible |
| Sulfasalazine | Compatible (with folic acid 5 mg/day in first trimester) | Compatible | Compatible (in the healthy full-term infant only) | Compatible |
| Methotrexate | Contraindicated due to teratogenic potential (stop ≥1 month pre-conception) | Contraindicated | Contraindicated due to teratogenic potential | Contraindicated |
| Ciclosporin | Compatible | Compatible, limited data | Compatible | Limited data |
| Tacrolimus | Compatible (suggested monitoring maternal blood pressure, renal function, blood glucose and drug level) | Compatible, limited data | Compatible | Limited data |
| TNF inhibitors | **Chimeric mAb (iv):** If low risk of disease fiare and stopped by 20 weeks, full-term infant can have a normal vaccination schedule*.<br>**Fusion protein (sc):** If low risk of disease fiare and stopped by 32 weeks, full-term infant can have a normal vaccination schedule*.<br>**Fully human mAbs (sc):** If low risk of disease flare and stopped by 28 weeks, full-term infant can have a normal vaccination schedule*.<br>**Humanized pegylated Fab (sc):** compatible for the treatment throughout pregnancy (minimal to no transplacental passage) | Compatible | Compatible | Compatible |
| Anti-IL-12/IL-23 mAb | Compatible, limited data | Compatible, limited data | Compatible, limited data | Compatible, limited data |
| JAK inhibitor | Contraindicated due to the lack of data | Contraindicated | Contraindicated due to the lack of data | Contraindicated |

Fab: fragment antigen-binding region; iv: intravenous; JAK: Janus Kinase; mAb: monoclonal antibody; sc: subcutaneous; TNF: Tumor Necrosis Factor.
* Including both non-live and live attenuated vaccines.

for which postpartum data were available, 23% resulted in premature births, and 22% of babies were small for their gestational age [45].

Psoriatic Arthritis (PsA):

- PsA often sees a change in disease activity postpartum compared to the pregnancy period. A worsening of symptoms can be observed during the second trimester in up to 15–22% of patients with PsA [46,47].
- No significant increases in the risk of gestational diabetes, infants small for gestational age, or low birth weight have been observed. However, evidence suggests a higher risk of pre-eclampsia, elective caesarean section, and preterm birth [47].

axSpA:

- Women with axSpA may maintain stable remission or low disease activity from preconception to one year post-delivery. However, up to half of women can experience a disease flare during the second trimester [48].
- axSpA is associated with an increased risk of preterm birth, infants small for gestational age, preeclampsia, and higher likelihood of caesarean section [49].

Juvenile Idiopathic Arthritis (JIA):

- JIA patients in remission without treatment at the time of conception typically remain stable throughout pregnancy. Flares are commonly observed in patients who withdrew from disease-modifying anti-rheumatic drugs (DMARDs), both conventional synthetic and biologic, at the start of pregnancy, with 100% of flares during pregnancy and 75% of postpartum flares occurring in these patients [50].
- Women with a history of JIA are associated with preterm birth, though not necessarily with poor foetal growth [51]. A study observed that preterm delivery occurred in 20% of the pregnancies, all of which involved patients who experienced a flare during pregnancy [50].

IBD:

- The activity of IBD at the time of conception significantly predicts the likelihood of a flare during pregnancy. For those with active UC, about 45% might experience worsening conditions, as a third of patients with active CD. However, if IBD is in remission at conception, there is an 80% chance that patients will maintain remission throughout pregnancy, with a 20% risk of experiencing a flare-up [10].
- Women with IBD are more likely to experience pregnancy complications such as spontaneous abortion, infants small for gestational age, preterm birth, and labour and delivery complications, compared with the general population. These complications are correlated with the disease's activity [10].

General advice:

- Pregnancy in women with IMIDs can lead to serious maternal and/or foetal adverse outcomes. Pre-pregnancy assessment is crucial to perform an individualised risk stratification and tailor pregnancy management and use of medications, with the aim of minimising the risk of adverse pregnancy outcomes (Table 1) [17].
- It is important to address fertility concerns that may be associated with the disease or its treatment when considering pregnancy. If the patient is over 35 years of age and has not achieved conception within six months, a referral to a gynaecologist for a fertility assessment should be considered [5].
- Collaboration between rheumatologists, gastroenterologists, and obstetrics-gynaecology or maternal-fetal medicine specialists is essential for optimal pregnancy management in women with IMIDs.

## 4. Family planning

Consistent evidence shows that family planning promotes healthier behaviours and enhances pregnancy outcomes, reducing misunderstandings related to fertility and pregnancy [27,52]. Conducting a thorough disease evaluation before conception can refine disease management. Notably, in-person preconception care is linked with better medication adherence, increased efforts to quit smoking, fewer disease relapses, and a reduced risk of delivering low birthweight infants [27].

Rheumatologists and gastroenterologists should assess disease activity, adjusting treatments as needed to achieve stable disease

remission before conception, ideally within 6–12 months, using medications that are compatible with the use during pregnancy [21,22]. For patients with rheumatological diseases, preconception counselling can be an opportunity to test for autoantibodies, like aPLs, especially if this is not already documented in the patient's medical history [21].

Gynaecologists and obstetricians typically concentrate on maternal comorbidities such as arterial hypertension and obesity, harmful lifestyle habits like smoking, medication safety, and devising a strategy in case IMIDs exacerbate during pregnancy [21,22]. The multidisciplinary team is also responsible for clarifying any contraindications to pregnancy, be they permanent or temporary [21,33]. It might be prudent to advise delaying pregnancy for patients with a recent onset of the disease, active disease (especially with renal involvement), or recent arterial events like strokes or heart attacks [21]. Due to the heightened risks during pregnancy, patients with IMIDs should be advised against conceiving if they have severe organ involvement, such as pulmonary hypertension or cardiomyopathy, or have experienced conditions like preeclampsia while on treatment [21].

Many women with IMIDs are hesitant to discuss family planning with their healthcare providers. Concerns about the potential impact of pregnancy, disease activity, effects on the unborn child, and the heritability of the disease often intertwine, creating apprehension [8,27,52]. This reluctance is further supported by studies suggesting that women with IMIDs might choose not to have children more often than their healthier peers [24,27,34,39,44].

Given these concerns, it is vital for clinicians to proactively address family planning. Discussions about fertility should be initiated when a patient is considering pregnancy, especially before stopping medications that have maintained their disease in remission [34]. Halting effective treatments in preparation for pregnancy might trigger a disease flare, particularly if conception does not occur promptly [53]. After stopping a medication, regular monitoring and the introduction of pregnancy-compatible alternatives are crucial. If conception does not occur within 6 months, a referral to a gynaecologist for a comprehensive fertility evaluation is recommended [21,34].

### 4.1. Contraception

Effective contraception is an important component of family planning for women with IMIDs, especially when prescribing potentially teratogenic medications such as MTX, mycophenolate mofetil, and cyclophosphamide to women of childbearing age [52]. The effectiveness of a contraceptive method is evaluated based on its use – when it is used consistently and precisely as directed every time – and its typical use effectiveness, which accounts for human error and inconsistencies in use. For this reason, intrauterine devices (IUDs) are generally the preferred contraceptive method for those with IMIDs due to their superior safety and effectiveness profile [21,54]. The American College of Rheumatology has developed an algorithm to guide physicians in selecting appropriate contraceptive measures for women with rheumatic diseases [17]. This involves an initial assessment for the presence of aPL and subsequent patient stratification. Estrogen-containing compounds are contraindicated for patients positive for aPL because of the heightened risk of thrombosis [21].

Accordingly, the Centre for Disease Control and Prevention (CDC) recommends levonorgestrel-IUDs, copper IUDs, and progestin-based contraceptive implants as first-line agents for women with IBD. Depot medroxyprogesterone acetate contraceptives and progestin-only pills are considered second-line agents, while combination estrogen-based oral contraceptive pills, transdermal patches, and vaginal rings are third-line agents [54].

Special considerations are essential when recommending contraceptive methods for women with IBD [8]. The potential failure rates of barrier methods and reports of IBD flares following IUD insertion should be taken into account [8]. Additionally, the interaction between oral contraceptives and concurrent IBD medications must be considered, to

**Table 2**
Overview of different contraceptive methods. Table adapted from [17].

| | Method | RA and SpA considerations | IBD considerations |
|---|---|---|---|
| Hormonal | Progestin IUD[a] | Safe; may decrease menstrual bleeding | CDC recommends as first-line agents |
| | Progestin implant[a] | Limited data, but likely safe | – |
| | Progestin-only pill (daily)[b] | Safe; higher rate of breakthrough bleeding than with combined contraceptives; must take same time every day for efficacy | Preferred to reduce risk of venous thromboembolism. Effectiveness may be reduced in extensive ileal CD and post-multiple abdominal surgeries |
| | Depot medroxyprogesterone acetate (intramuscular injection every 12 weeks)[b] | Safe; exceptions: positive aPL, at high risk for osteoporosis | – |
| | Combined estrogen and progesterone pill (daily)[b] | Safe; exceptions: positive aPL | Potential gastrointestinal symptom improvement: some report worsened symptoms |
| | Transdermal patch (weekly)[b] | Safe; exceptions: positive aPL; serum estrogen levels higher than with pill or vaginal ring | – |
| | Vaginal ring (monthly)[b] | Safe; exceptions: positive aPL | |
| Non-hormonal | Copper IUD[a] | Safe; may increase menstrual bleeding | CDC recommends as first-line agents. Concerns about IBD flares post-insertion, though causality lacks |
| | Diaphragm[c] | Safe | – |
| | Condom[c] | Safe; only form to prevent sexually transmitted diseases | – |
| | Fertility awareness–based methods[c] | Safe; limited efficacy, especially if menses are irregular | – |
| | Spermicide[c] | Safe; use with condoms or diaphragm to improve efficacy | – |

IUD, intrauterine device.
[a] Highly effective.
[b] Effective.
[c] Less effective.

ensure that the absorption of the contraceptive is not compromised [8].

The decision on the contraceptive method should be a collaborative effort between the multidisciplinary team and the patient. No woman should feel that her diagnosis prevents her from using birth control [52].

All available contraception methods with considerations for IMIDs patients are summarized in Table 2.

### 4.2. Long-term outcomes of offspring born to women with IMIDs

RA:

Studies have shown that children born to mothers with RA do not face an increased risk of major congenital malformations [24]. However, there is an observed association between an increased RA disease activity during pregnancy may lead to lower birth weight in offspring, associated with a greater risk of cardiovascular and metabolic diseases later in life [55].

Additionally, familial trends in RA may be influenced by genetics, possibly due to contributions from multiple genes interacting with environmental factors [56]. While there is an observed association, the absolute risks remain low, and certain associations, such as that between maternal RA and neurodevelopmental disorders in offspring, are still inconclusive [57].

IBD:

Children born to mothers with IBD may exhibit higher faecal calprotectin levels, suggesting potential challenges in establishing optimal intestinal barrier function, possibly due to a diminished immune tolerance to commensal bacteria [6,39]. Selinger and colleagues have highlighted that the genetic risk for offspring to develop CD is 2.7% and UC is 1.6%. Risk increases to 30% when both parents are affected and varies with family history and ethnicity [27,39].

## 5. Menopause

Menopause, a transition marked by the cessation of ovulation and a decline in estrogen levels, typically occurs between the ages of 50 and 52 in industrialised countries, with the perimenopausal transition starting around age 47.5 [58]. The average menopausal age in Caucasian women is approximately 51 years, with menopause before 45 years being recognised as early menopause [35].

The relationship between menopause and IMIDs is of significant interest. Observational studies have shown variable results regarding the impact of menopause on RA. Some suggest that the onset of RA symptoms coincides with menopause, while others indicate that early menopause might be associated with milder RA [35]. Similarly, some studies suggest that women with IBD, particularly CD, might experience menopause slightly earlier than their counterparts without IBD [40]. However, the data on the effect of IBD on menopause and vice versa remain limited and conflicting [8].

A decline in estrogen, the hallmark of menopause, is believed to play a pivotal role in the pathogenesis of RA [59]. Hormone replacement therapy (HRT) has been a topic of interest in the management of postmenopausal symptoms. Current recommendations suggest limiting HRT use in healthy postmenopausal women to the lowest dose that alleviates symptoms for the shortest duration necessary due to associated risks such as stroke and breast cancer [17].

However, for postmenopausal women with rheumatic diseases other than systemic lupus erythematosus and/or without positive aPL who have severe vasomotor symptoms, HRT might be considered like in the general population, in the absence of contraindications [17]. In RA, small randomised controlled trials have shown that HRT appears safe, with no significant effect on RA incidence or severity [60]. Interestingly, estrogen therapy has been shown to decrease synovial nerve fibre neurotrophins in animal models of osteoarthritis, and both estrogen and testosterone can modulate pain perception [60]. In the context of IBD, HRT's role is complex, with some studies suggesting a protective effect against flare-ups in postmenopausal women with IBD, while others indicate an increased risk of developing UC with HRT use [8].

### 5.1. Osteoporosis, sarcopenia, and the risk of falls

Osteoporosis often emerges as a prominent concern among women with IMIDs, not just because of menopause but also potentially presenting in the premenopausal phase. It underscores the importance of early and regular screenings for detecting early bone density loss, allowing for timely interventions to mitigate the risk of fractures and associated morbidity [5,40,61]. Osteoporosis is significantly more common in patients with RA. Studies indicate that osteoporosis occurs twice as often in RA patients compared to those without the condition, with an overall prevalence approaching 30% [5]. The prevalence of osteoporosis in IBD patients varies widely. Some studies report its presence in 2% to 15% of patients, while osteopenia is found in 37% to 39% of cases [40].

Factors such as female gender, postmenopausal status, disease-related inflammation, malabsorption leading to poor absorption of calcium and vitamin D, and avoidance of dairy products have been identified as risk factors associated with IMIDs osteoporosis [5,40]. Moreover, the widespread use of glucocorticoids, a common treatment for RA and IBD, can diminish bone mineral density, thereby compromising bone quality. Glucocorticoids have the dual effect of enhancing bone resorption and inhibiting bone formation. Additionally, these medications impact bone quality by triggering apoptosis in osteocytes and can exacerbate bone weakening by contributing to the loss of muscle mass and function [62,63]. Inflammation and glucocorticoid use can also result in hypogonadism, impacting sex hormone production [62].

Body composition also plays an integral role in bone health. Muscle mass has a strong correlation with bone structure and density, independent of fat measures. The forces exerted by muscles majorly determine the stress experienced by bones, thereby influencing their structure. In RA, muscle loss is a significant contributor to bone loss. Factors like sarcopenia, sarcopenic obesity, and frailty, often present in RA, can lead to bone structure alterations, increased osteoporosis risk, and low bone mineral density [62].

It is also imperative to account for other conditions and risk factors that might affect bone mineral density in IMID patients. This includes habits like alcohol and tobacco use. Smoking, in particular, directly influences RA pathogenesis and can influence bone density by several mechanisms including inflammation, autoantibody induction, reduced calcium absorption and osteoblast inhibition [62].

The increase in bone fragility puts patients with RA at risk of falls with serious consequences. Impaired mobility, balance, and postural stability due to lower limb joint involvement are factors that increase the risk of falls in RA patients. Aging and environmental factors can heighten the risk of falls and fractures. With advancing age, individuals may experience reduced physical function, impaired vision, and an accumulation of comorbidities and medications. Moreover, patients with IMIDs might develop age-related comorbidities prematurely, and the treatments for these conditions can lead to polypharmacy, that can contribute significantly to falls [62]. Indeed, specific medication classes, such as sedatives, anticholinergics, first-generation antihistamines, antidepressants, antihypertensives, benzodiazepines, and pain medications are known to enhance the risk of falls [62]. Chronic inflammatory processes and the side effects of medications can lead to reduced balance with possible increased risk of falls. Pain medications can be frequently used by IMID patients and, in particular, opioid use in RA can cause side effects such as dizziness, sedation, and impaired balance, which is reported to increase the risk of falls [64]. Patients with RA and IBD who are taking opioids as analgesic treatment should be monitored closely for these side effects and may require additional interventions to prevent falls. Risk of falls can be increased in IBD patients, arising from physiological needs such as frequent or night toileting. The home environment, particularly the safety measures and accessibility, play an important role in preventing fractures. Simple interventions, such as

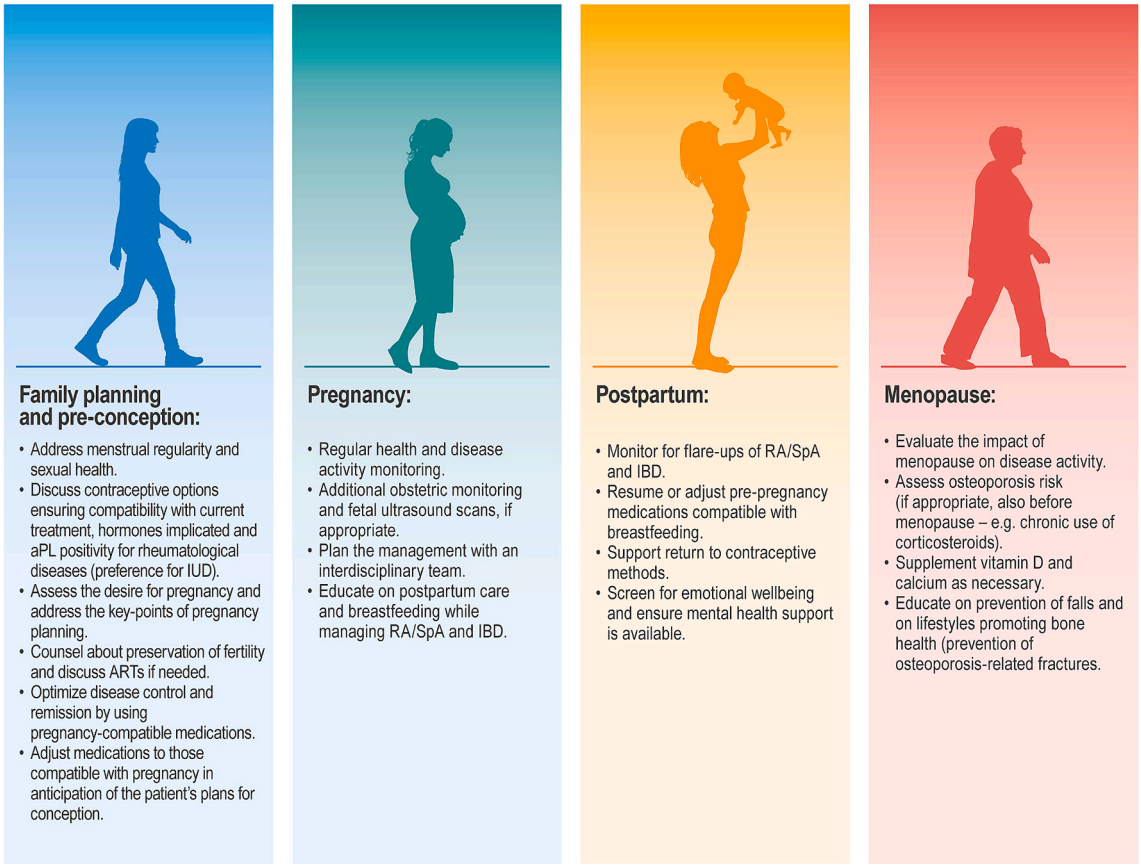


**Fig. 1.** Perspectives on Management of Women's Health in IMIDs throughout the Lifecycle.
Abbreviations: aPL: antiphospholipid antibodies; IUD: intrauterine device; ARTs: assisted reproduction technologies.

enhancing bathroom safety, decluttering living spaces, and installing better lighting, can effectively reduce the number of future falls [62].

Muscle weakness and painful, stiff joints are also significant contributors to fall. Patients with a high burden of joint disease or pain need special attention to prevent the risk of falling. It is also worth noting that increased fat mass can elevate the risk of lower extremity fractures, emphasizing the importance of physical therapy and exercise interventions for patients at high osteoporosis risk [62].

Novel estrogen-related therapies are emerging as potential treatments for bone degradation in the context of chronic inflammation [14]. Tissue-selective estrogen complexes, which combine selective estrogen receptor modulators with estrogens, have shown promise in treating menopausal symptoms and protecting against osteoporosis [14].

### 5.2. Vitamin D

Vitamin D, traditionally associated with bone health, plays a pivotal role in modulating and regulating both innate and adaptive immune responses [65]. Its deficiency has been linked not only to bone disorders such as rickets, osteoporosis, and osteomalacia but also to a spectrum of diseases including cardiovascular diseases, type 2 diabetes, and notably, autoimmune diseases [65]. The active form of vitamin D, 1,25(OH)2D, has profound immunological activities, influencing differentiation, maturation, and cytokine production in immune cells [65].

In the context of RA, vitamin D deficiency could exacerbate synovial inflammation, with studies suggesting a negative correlation between serum vitamin D levels and RA disease activity, disability and QoL [65,66]. Supplementation of vitamin D has been observed to provide pain relief and improve disease activity in some studies. For example, in patients with early RA, vitamin D deficiency was found to be a risk factor for the development of active disease, and vitamin D supplementation resulted in greater pain relief [67]. In IBD, particularly CD, vitamin D modulates gut mucosal immunity and intestinal barrier integrity, with deficiency being associated with increased disease activity [3].

In managing IMIDs, particularly in the context of IBD and osteoporosis, the importance of vitamin D intake cannot be overstated. The British Society of Gastroenterology, as early as the year 2000, recommended evaluating bone density in specific IBD patient groups, such as postmenopausal women, men aged 55 or older, those under corticosteroid treatment, and those diagnosed with a fragility fracture. Alongside general measures like exercise, dietary calcium intake, and reducing alcohol and tobacco consumption, they also advocated for the prevention or treatment of bone loss during corticosteroid treatment. This includes prescribing 800 units of vitamin D daily, making co-treatment with steroids and vitamin D a standard practice [61]. The American Gastroenterological Association guidelines also recommend vitamin D co-treatment while on corticosteroids, especially for patients with proven osteoporosis or those at high risk. The European Crohn's and Colitis Organization (ECCO) guidelines further emphasize adding calcium and vitamin D for patients on corticosteroid treatment if the therapy duration is expected to exceed six weeks [39].

Similarly, EULAR guidelines recommend calcium and vitamin D supplementation if a patient starts the treatment with prednisone (more or equal to 7.5 mg daily) and continues for >3 months [68].

Furthermore, vitamin D interaction with estrogens suggests gender-specific effects, potentially leading to a more potent anti-inflammatory response in women than in men [65]. Given the multifaceted roles of vitamin D in immune regulation and its potential therapeutic implications, it is important for clinicians to not only monitor vitamin D levels but also ensure that patients adhere to recommended intake guidelines, especially when managing IMIDs. In fact, studies have shown that adherence to calcium and vitamin D supplements in postmenopausal

women is around 70%, highlighting the need for consistent patient education and monitoring [61].

## 6. Importance of counselling on reproductive healthcare

IMIDs represent a diverse range of conditions that can profoundly influence a woman's journey through life. From the challenges of adolescence to the transitions of menopause, these diseases can touch every facet of her existence. Counselling, in this context, emerges not merely as a supportive tool but as an essential component of holistic care.

The significance of counselling is multifaceted. Firstly, it offers a platform for comprehensive health management. IMIDs can cast a shadow over a woman's physical, emotional, and mental well-being. Through counselling, women gain a clearer understanding of their condition, empowering them to manage symptoms and make informed health decisions. Particularly important is the domain of reproductive health. Given that many IMIDs can intersect with a woman's reproductive journey, affecting fertility, pregnancy outcomes, and family planning decisions, counselling ensures that women are well-equipped in these areas.

However, the absence of counselling can lead to a myriad of challenges. Without this guiding hand, women might find themselves ensnared by misinformation, leading to misconceptions about their condition and its management. This lack of clarity can result in suboptimal treatment choices, where women might either miss out on effective therapeutic strategies or remain unaware of potential side effects. Beyond the physical aspect, the emotional and psychological strain of living with IMIDs cannot be understated. Without the support structure that counselling provides, feelings of isolation, anxiety, or depression might become unwanted addition to the disease.

As qualitative research emphasises, it is important to not neglect any areas of a woman's health [34,44]. For patients diagnosed during adolescence or early adulthood, counselling serves as an essential tool, facilitating a comprehensive understanding of their condition in relation to their future goals. As they progress into the reproductive years, it helps in addressing concerns related to fertility, the potential interactions between pregnancy and IMIDs, and postpartum considerations. Furthermore, as they transition into menopause and subsequent stages, the complexities of IMIDs may manifest differently or with increased severity. In these phases, continued counselling is important to ensure optimal health management and maintain the QoL. Practice points for managing these aspects are summarized in Fig. 1.

## Declaration of Competing Interest

L.A. and M.P. received an honorarium from Pfizer in connection with the development of this manuscript.

G.P. and I.G. are Pfizer employees.

## Data availability

No data was used for the research described in the article.

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