Women with axSpA: Navigating the childbearing years

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Why is axSpA of particular relevance to women?

Prevalence

- A substantial proportion of patients with r-axSpA are female (33%)[1–3]
- Twice as many women have nr-axSpA than men (67 vs 33%)[1]

Delayed diagnosis

- Mean delay in axSpA diagnosis: 8.8 years (95% CI 7.4–10.1) for women vs 6.5 years (95% CI 5.6–7.4) for men (p=0.01)[4]

Disease burden

- Women have a higher disease burden than men[5]

Poor treatment response

- Compared with men, women with r-axSpA have a lower response rate to TNFi therapy (1-year follow-up: women 43%, men 62%, p=0.004)[5,6]

axSpA, axial spondyloarthritis; CI, confidence interval; nr-axSpA, non-radiographic axial spondyloarthritis; r-axSpA, radiographic axial spondyloarthritis; TNFi, tumour necrosis factor inhibitor.

1. Boonen A, et al. *Semin Arthritis Rheum.* 2015;44:556–62; 2. Wright GC, et al. *Semin Arthritis Rheum.* 2020;50:687–94; 3. Kiltz U, et al. *Arthritis Care Res (Hoboken).* 2012;64:1415–22; 4. Jovaní V, et al. *J Rheumatol.* 2017;44:174–83; 5. van der Horst-Bruinsma IE, et al. *Ann Rheum Dis.* 2013;72:1221–4; 6. Rusman T, et al. *Ann Rheumatic Dis.* 2017;76:354–5.

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Pharmacological treatment of axSpA

1 First-line treatment

- **NSAIDs** are equally effective and strongly recommended
  - Use two full-strength **NSAIDs** before advancing to a biologic
- **csDMARDs** and **oral glucocorticoids** are not recommended

2 Second-line treatment

- Adding a **TNFi** is strongly recommended
  - No preferred **TNFi** except for uveitis or IBD *(or pregnancy wish?)*
- **Methotrexate** is not recommended in combination with a **TNF**

3 Third-line treatment

- In primary **TNFi** non-responders:
  - Switch to an **IL17i** is strongly recommended
  - Switch to **tofacitinib** is conditionally recommended
- In secondary **TNFi** non-responders:
  - Switch to an alternate **TNFi** is conditionally recommended

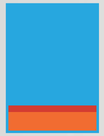
axSpA, axial spondyloarthritis; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; IBD, inflammatory bowel disease; IL17i, interleukin 17 inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; TNFi, tumour necrosis factor inhibitor.

Ward MM, et al. *Arthritis Rheumatol.* 2019;71:1599–613.

Key issues for women of childbearing age with axSpA

Prevalence

- The percentage of **women of childbearing age with** axSpA is estimated to be **~15–20%** of the total axSpA population[1]



Symptom onset

- **Symptoms of axSpA usually start between 15–30 years of age** and there is often a delay to diagnosis[2]

Adverse outcomes relating to pregnancy and birth

Time to pregnancy in RMD may exceed 12 months for many patients, related to:[3]

- Age
- Nulliparity
- Disease activity
- NSAID and prednisolone use

In a study of 388 deliveries among women with axSpA and 1,082 controls, **women with axSpA had a higher prevalence for several adverse birth outcomes**:[2]

- Emergency and elective caesarean section
- Preterm delivery
- Small for gestational age

Results suggested an influence by both disease severity and comorbidities

axSpA, axial spondyloarthritis; NSAID, non-steroidal anti-inflammatory drug; RMD, rheumatic musculoskeletal disease.

1. Taylor P, et al. *EMJ Rheumatol.* 2018;51:2–7; 2. Jakobsson G, et al. *Ann Rheum Dis.* 2016;75:1838–42; 3. Brouwer J, et al. *Ann Rheum Dis.* 2015;74:1836–41.

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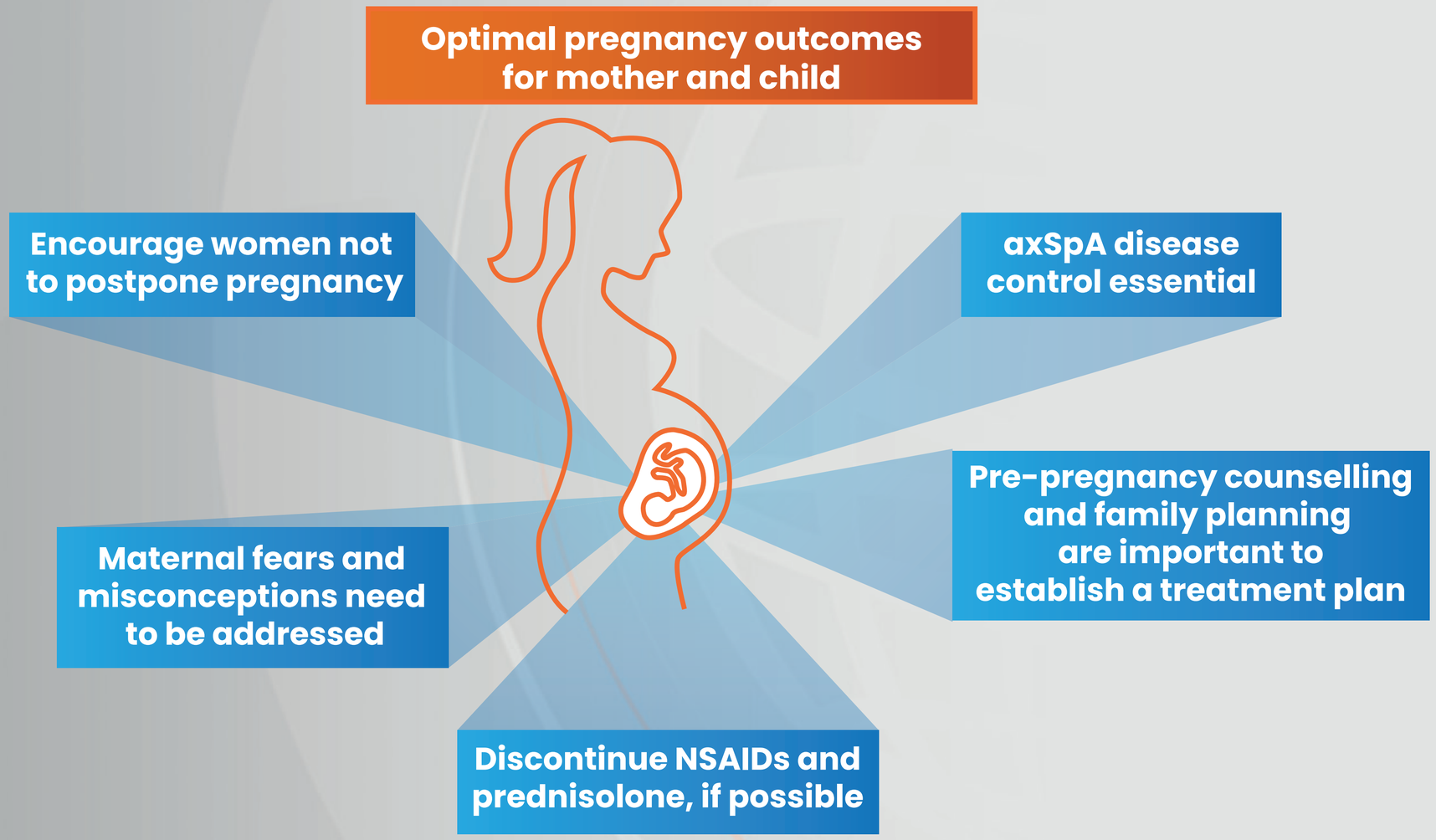
Important considerations for women expressing a pregnancy wish



axSpA, axial spondyloarthritis; NSAIDs, non-steroidal anti-inflammatory drugs.

Taylor P, et al. *EMJ Rheumatol*. 2018;51:2–7.

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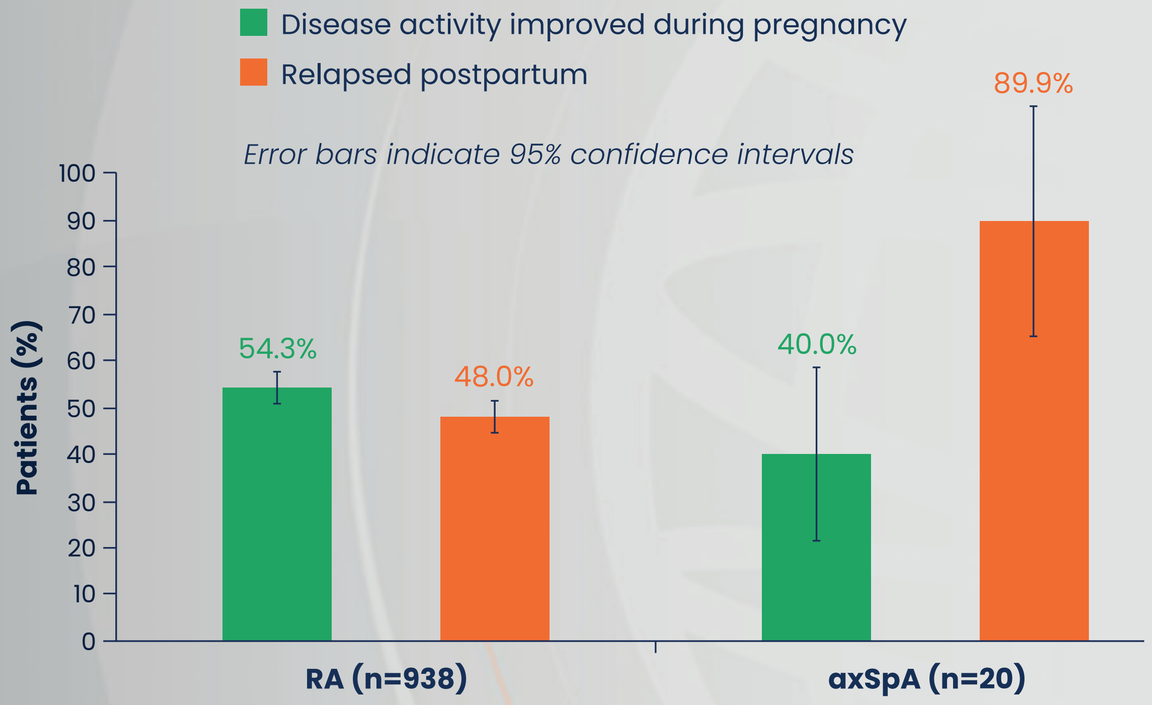
Does inflammatory arthritis improve during pregnancy?



- **Systematic literature review and meta-analysis of prospective studies using validated disease activity scores**
- **Patients with axSpA were less likely to improve during pregnancy and far more likely to relapse postpartum than patients with RA**

axSpA, axial spondyloarthritis; RA, rheumatoid arthritis.

Jethwa H, et al. *Arthritis Rheumatol.* 2016;68 (Suppl. 10):Abstr. 1517.

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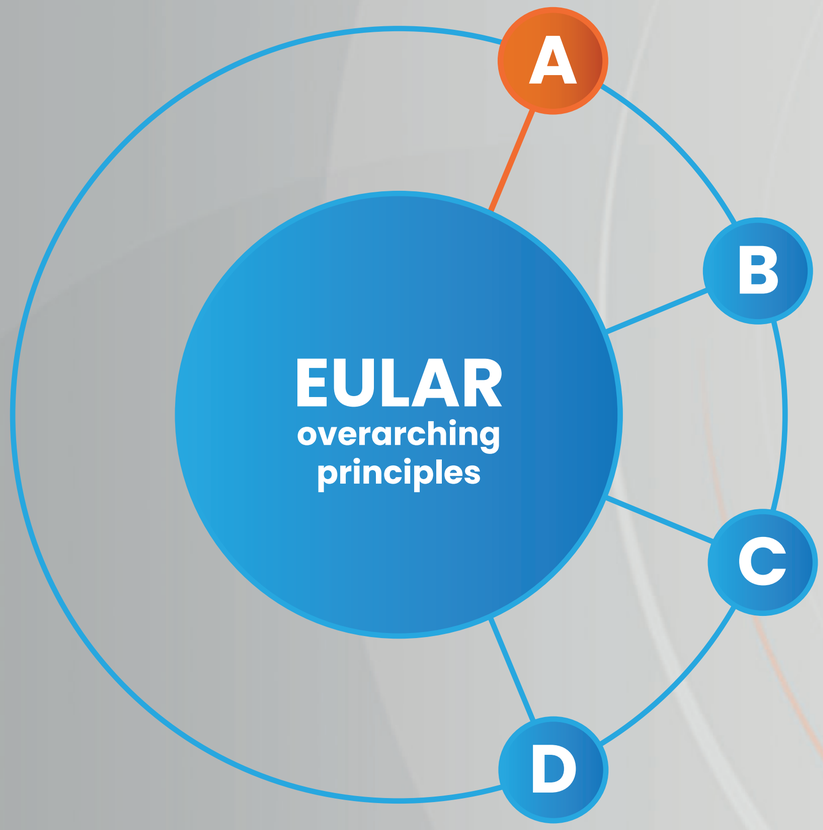
Use of antirheumatic drugs before pregnancy, and during pregnancy and lactation



Family planning should be addressed in each patient of reproductive age and adjustment of therapy considered before a planned pregnancy

axSpA, axial spondyloarthritis; EULAR, European League Against Rheumatism.
Götestam Skorpen C, et al. *Ann Rheum Dis.* 2016;75:795–810.

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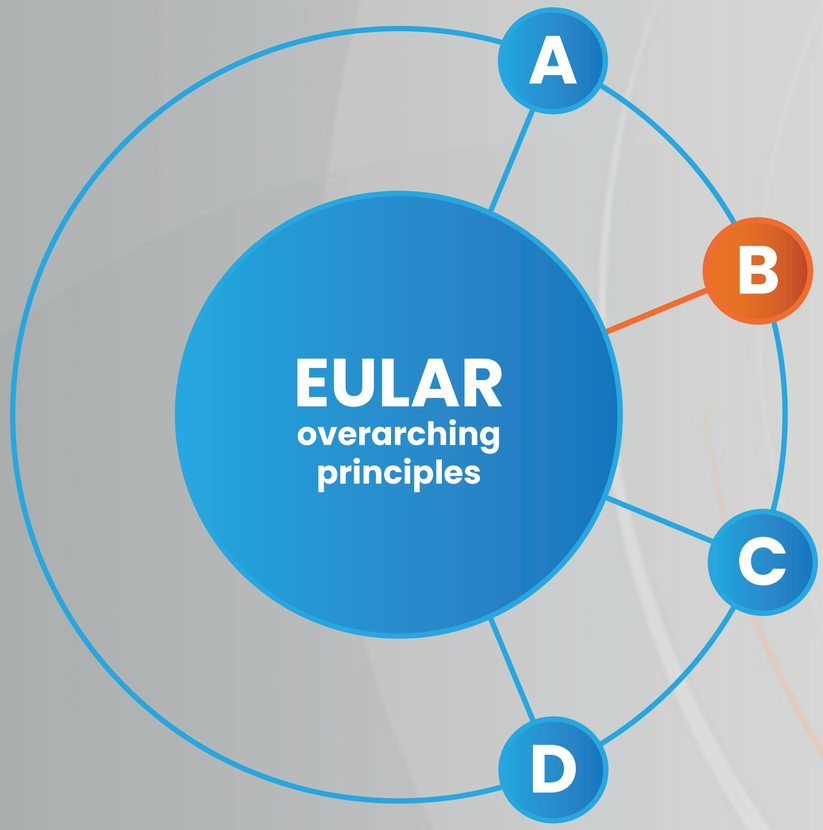
Use of antirheumatic drugs before pregnancy, and during pregnancy and lactation



Treatment of women with axSpA before/during pregnancy and lactation should aim to prevent or suppress disease activity in the mother and expose the fetus/child to no harm

axSpA, axial spondyloarthritis; EULAR, European League Against Rheumatism.

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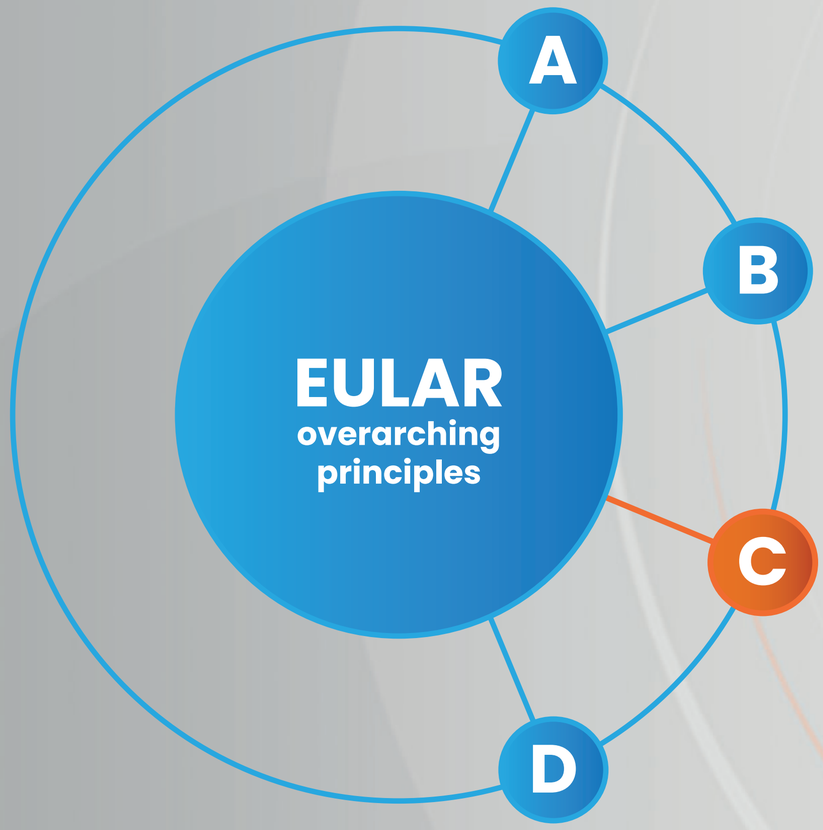
Use of antirheumatic drugs before pregnancy, and during pregnancy and lactation



The risk of drug therapy for the child should be weighed against the risk that untreated maternal disease represents for the patient and the fetus or child

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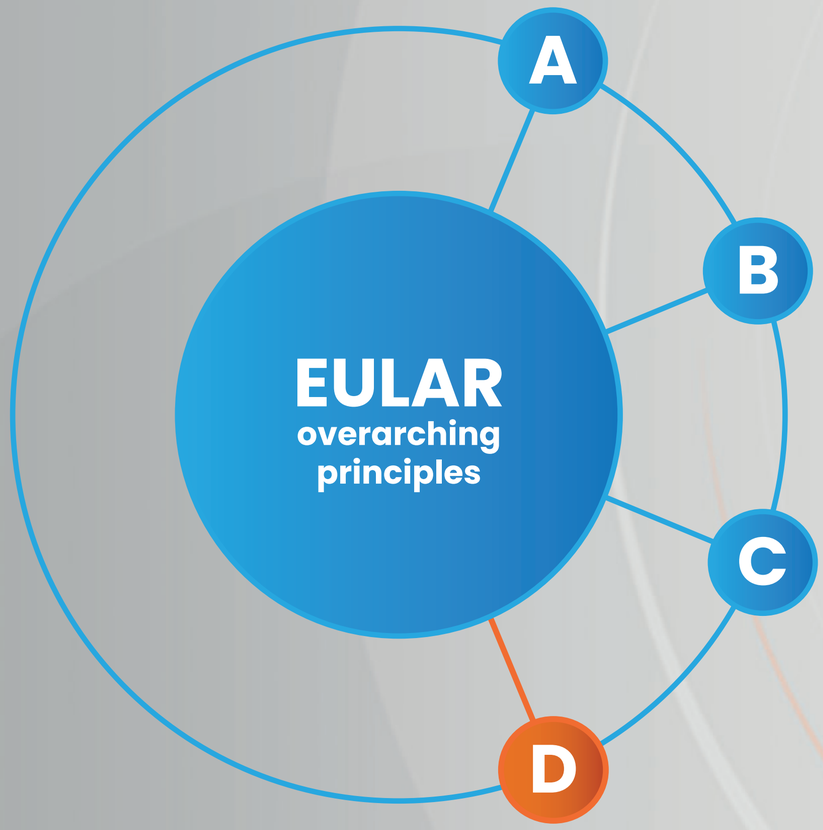
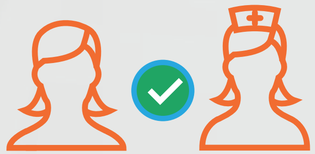
Use of antirheumatic drugs before pregnancy, and during pregnancy and lactation





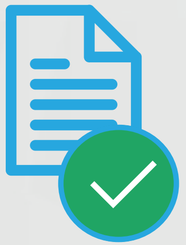
The decision on drug therapy during pregnancy and lactation should be based on agreement between the internist/rheumatologist, gynaecologist/obstetrician and the patient, and including other healthcare providers when appropriate

axSpA, axial spondyloarthritis; EULAR, European League Against Rheumatism.

Götestam Skorpen C, et al. *Ann Rheum Dis.* 2016;75:795–810.

Treatment considerations during pregnancy

- **Discontinue NSAIDs** if possible (and certainly after 32 weeks)



- **Continue TNFi until the gestational week recommended (EULAR and BSR guidance)** and only then discontinue if the patient remains well and pain-free

axSpA, axial spondyloarthritis; BSR, British Society for Rheumatology; EULAR, European League Against Rheumatism; NSAIDs, non-steroidal anti-inflammatory drugs; TNFi; tumour necrosis factor inhibitor.

Götestam Skorpen C, et al. *Ann Rheum Dis.* 2016;75:795–810.

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Treatment considerations during pregnancy

- Bear in mind that there are differences in guidance between biologics within class

- **Discuss/consider discontinuation of TNFi for third trimester** to limit neonatal levels in the case of *actively transported* TNFi

- Explain that in axSpA, **steroids are unlikely to control disease/symptom exacerbation**, but could restart TNFi if required in third trimester

axSpA, axial spondyloarthritis; BSR, British Society for Rheumatology; EULAR, European League Against Rheumatism; NSAIDs, non-steroidal anti-inflammatory drugs; TNFi; tumour necrosis factor inhibitor.

Götestam Skorpen C, et al. *Ann Rheum Dis.* 2016;75:795–810.

Importance of continued TNFi therapy when possible during pregnancy to limit axSpA flares

Of 61 patients with axSpA, 24 were on TNFi therapy and discontinued at the time of positive pregnancy test

- Disease aggravation could be observed in the second trimester
- In patients who restarted TNFi therapy or glucocorticoid treatment, disease activity remained elevated throughout pregnancy: **62.5% of patients**
- Relative risk of flare in patients stopping TNFi therapy: **3.08 (95% CI 1.2–7.9)**

axSpA, axial spondyloarthritis; CI, confidence interval; TNFi, tumour necrosis factor inhibitor.

van den Brandt S, et al. *Arthritis Res Ther.* 2017;19:64.

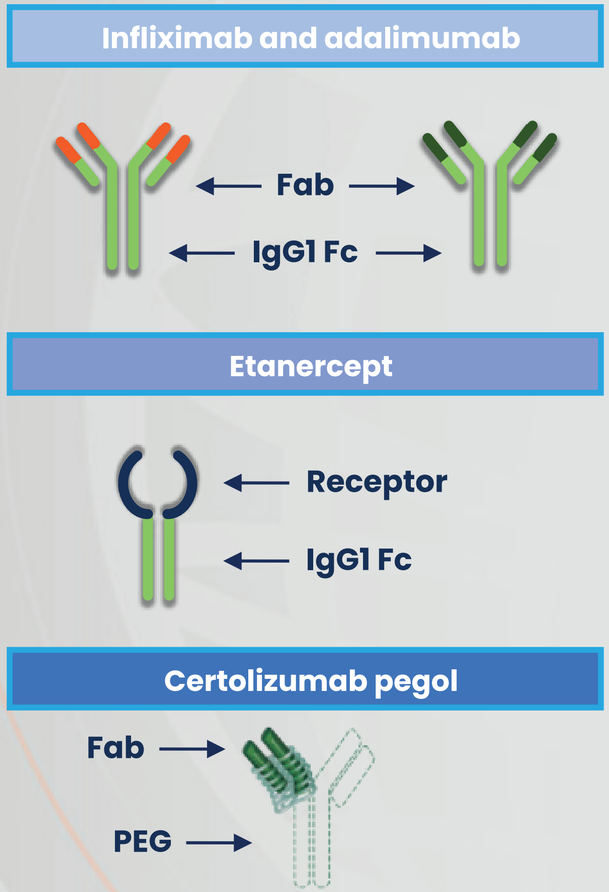
Intrapartum care

- No contraindication to vaginal birth[1]
- No contraindication to regional analgesia or anaesthesia (epidural)[1]
- Discuss positioning in labour with midwife if hip/back stiffness pain/limitation of movement
- Parenteral steroids if >7.5 mg prednisolone for >2 weeks[2]

1. Taylor P, et al. *EMJ Rheumatol.* 2018;51:2–7; 2. National Guideline Alliance (UK). NICE Guideline, No. 121. Appendices. Available at: www.ncbi.nlm.nih.gov/books/NBK546875/ (accessed January 2021).

Important structural differences between the bDMARDs

Drug	Contains Fc domain
Adalimumab[1,2]	✓
Certolizumab pegol[1,2,a]	✗
Etanercept[1,2]	✓
Golimumab[1,2]	✓
Infliximab[1,2]	✓
Ixekizumab[1,2]	✓
Secukinumab[1,2]	✓



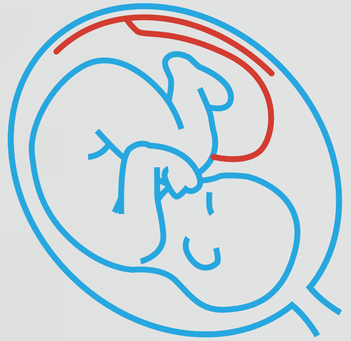
a. Distribution studies have demonstrated that placental and milk transfer of certolizumab pegol to the fetal and neonatal circulation is negligible. In a clinical study in 17 lactating women, minimal transfer of certolizumab pegol from plasma to breast milk was observed.[2,3]

bDMARD, biological disease-modifying anti-rheumatic drug; Fab, fragment antigen binding; Fc, fragment crystallizable; Ig, immunoglobulin; PEG, polyethylene glycol.

1. Van der Horst-Bruinsma I, et al. *EMJ Rheumatol.* 2019;6:41–9;
2. Summaries of product characteristics available from the European Medicines Agency at: www.ema.europa.eu/en (accessed January 2021).

Impact of Fc domain on transplacental transport

Drug	Contains Fc domain	Transplacental transport
Adalimumab[1,2]	✓	✓
Certolizumab pegol[1,2,a]	✗	Negligible
Etanercept[1,2]	✓	✓
Golimumab[1,2]	✓	✓
Infliximab[1,2]	✓	✓
Ixekizumab[1,2]	✓	✓
Secukinumab[1,2]	✓	Limited data



CRIB[3]

- Designed to accurately evaluate placental transfer of certolizumab pegol from mothers to infants
- Minimal/no placental transfer of this biologic during pregnancy

a. Distribution studies have demonstrated that placental and milk transfer of certolizumab pegol to the fetal and neonatal circulation is negligible. In a clinical study in 17 lactating women, minimal transfer of certolizumab pegol from plasma to breast milk was observed.[2,3]

Fc, fragment crystallizable.

1. Van der Horst-Bruinsma I, et al. *EMJ Rheumatol.* 2019;6:41–9;
2. Summaries of product characteristics available from the European Medicines Agency at: www.ema.europa.eu/en (accessed January 2021).
3. Mariette X, et al. *Ann Rheum Dis.* 2018;77:228–33.

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bDMARD use during pregnancy and lactation

Drug	Contains Fc domain	Transplacental transport	Excreted into breast milk	Use during pregnancy[a]	Use during lactation
Adalimumab[1,2]	✓	✓	✓	✓	✓
Certolizumab pegol[1,2,b]	✗	Negligible	Negligible	✓	✓
Etanercept[1,2]	✓	✓	✓	✓	✗
Golimumab[1,2]	✓	✓	Limited data	✗	✗
Infliximab[1,2]	✓	✓	Limited data	✓	✗
Ixekizumab[1,2]	✓	✓	Limited data	✗	✗
Secukinumab[1,2]	✓	Limited data	Limited data	✗	✗

a. Certolizumab pegol can be used if clinically needed. Adalimumab, etanercept, golimumab and infliximab can be used if clearly needed.[1,2]
b. Distribution studies have demonstrated that placental and milk transfer of certolizumab pegol to the fetal and neonatal circulation is negligible. In a clinical study in 17 lactating women, minimal transfer of certolizumab pegol from plasma to breast milk was observed.[2]

bDMARD, biological disease-modifying anti-rheumatic drug; Fc, fragment crystallizable.

1. Van der Horst-Bruinsma I, et al. *EMJ Rheumatol.* 2019;6:41–9;
2. Summaries of product characteristics available from the European Medicines Agency at: www.ema.europa.eu/en (accessed January 2021).

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Emerging therapies for axSpA

NCT number (acronym)	Drug	Condition (actual/planned enrolment)	Phase	Status
NCT03447704	BCD-085	axSpA (N=228)	III	Active (Jul-20)
NCT04169373 (SELECT AXIS 2)	Upadacitinib	r-axSpA/nr-axSpA (N=690)	III	Recruiting (Dec-20)
NCT03928704 (BE MOBILE 1)	Bimekizumab	nr-axSpA (N=240)	III	Recruiting (Nov-20)
NCT03502616	Tofacitinib	r-axSpA (N=270)	III	Completed (Aug-20)
NCT02985983	Brodalumab	r-axSpA/nr-axSpA (N=159)	III	Completed (Sep-19)
NCT03117270 (TORTUGA)	Filgotinib	axSpA (N=116)	II	Completed (Jul-18)
NCT01786668	Tofacitinib	r-axSpA (N=208)	II	Completed (Mar-15)

axSpA, axial spondyloarthritis; nr-axSpA, non-radiographic axial spondyloarthritis; r-axSpA, radiographic axial spondyloarthritis.
Clinical trials listed by their identifiers at ClinicalTrials.gov (accessed January 2021).

Conclusions

- Important **clinical differences exist between men and women** with axSpA

axSpA, axial spondyloarthritis.

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Conclusions

- Women with axSpA of reproductive age face **unique challenges on their journey to motherhood**, which should be **proactively** addressed

axSpA, axial spondyloarthritis.

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Conclusions

- **Pre-pregnancy counselling** and **family planning** are important for patients and partners to explain risks, overcome fears and establish a treatment plan

Conclusions

- **Disease control** before and during pregnancy is important to achieve optimal outcomes for mother and child

Conclusions

- Open and clear **communication** of the treatment guidelines is required to aid decision-making and ensure patients are fully informed

Conclusions

- Many drugs have an **acceptable benefit–risk profile** in pregnancy and breastfeeding