RHEUMATOID ARTHRITIS

COMPLETE TOPIC COVERED

LAST SECOND MEDICINE

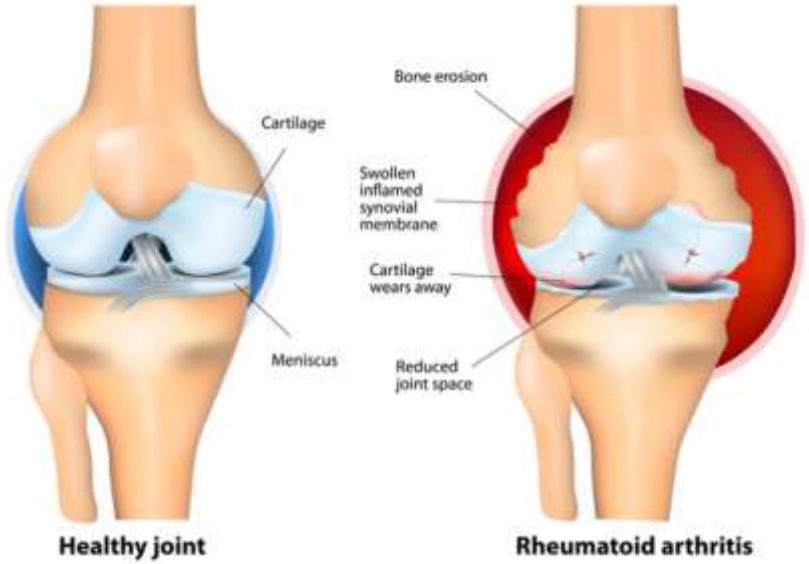
CHRONIC SYSTEMIC INFLAMMATORY DISEASE

- **Synovitis** of multiple joints
- Symmetrical, deforming, peripheral polyarthritis
- Prevalence is ~1%
- Increased incidence & disease severity in smokers
- Female : Male , 2:1
- Peak age - 5th and 6th decade
- Cardiovascular disease risk - 2–3 fold

PATHOPHYSIOLOGY

PATHOPHYSIOLOGY

- Pathogenesis - Genetic and Environmental factors
- **Genetic**
  - 12 -15% monozygotic *compared with* 3% dizygotic twins
  - First degree relatives - Increased frequency
  - HLA DR-4 & HLA DR-1 linked disease
- **Environmental**
  - Triggers autoimmunity
  - Cigarette smoking - More severe disease & Reduced responsiveness to treatment
- Remission during pregnancy



PATHOPHYSIOLOGY

Synovial cell hyperplasia & Endothelial cell activation

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Uncontrolled Inflammation

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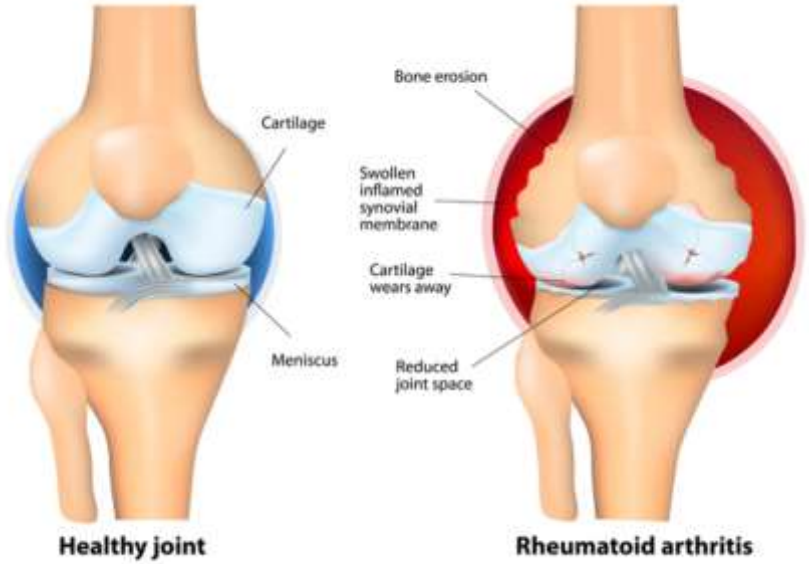
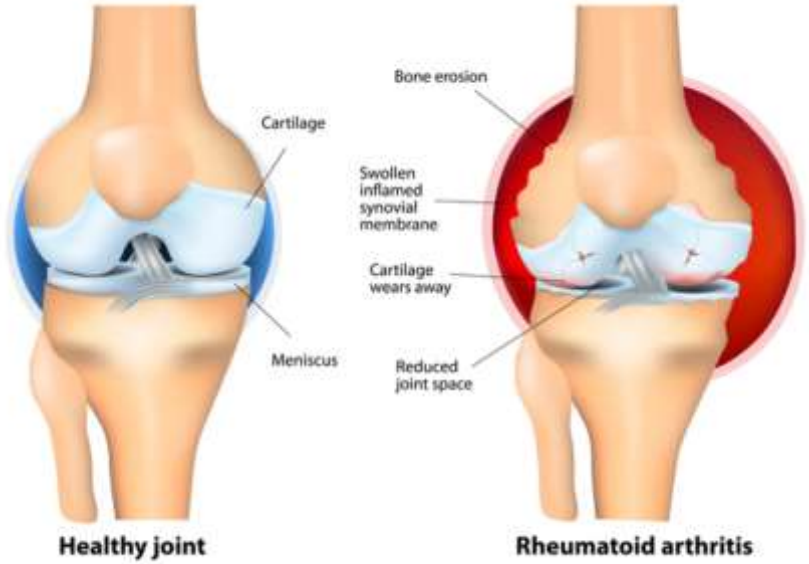
Cartilage & Bone destruction



PATHOPHYSIOLOGY

- **Cells Actively involved in Inflammation**

  CD4 T cells, mononuclear phagocytes, fibroblasts, osteoclasts, and neutrophils



Cytokines, chemokines, & mediators
- Tumor necrosis factor alpha (TNF-α)
- Interleukin (IL)- IL-1, IL-6, IL-8
- Transforming growth factor beta (TGF-ß)
- Fibroblast growth factor (FGF)
- Platelet-derived growth factor (PDGF)

↓

Pannus Formation due to proliferation of synovium → Tissue Destruction

DISEASE **PRESENTATION**

DISEASE PRESENTATION

Common

- Symmetrical
- Swollen, painful, and stiff
- Small joints
- Hands, wrists and feet, worse in the morning
- This can fluctuate and larger joints may become involved.

DISEASE PRESENTATION

Less Common

I. Sudden onset, widespread arthritis, early morning stiffness & pitting oedema - Common in elderly

II. **Palindromic RA**

- Recurring mono/polyarthritis
- Lasting hours or days
- Presage RA, SLE, Whipple's or Behcet's disease
- Remissions complete, leaving no radiological mark

DISEASE PRESENTATION

Less Common

III. Persistent monoarthritis

IV. Systemic illness with extra-articular symptoms with few joint problems initially

V. Polymyalgic onset—Proximal muscle stiffness mimicking polymyalgia rheumatica

VI. Recurrent soft tissue problems
    - Frozen shoulder
    - Carpal tunnel syndrome
    - de Quervain's tenosynovitis

SIGNS - ARTICULAR

- Early

- Swollen and tender joints with damage
- MCP, PIP, wrist, or MTP joints
- Symmetrical
- Erythema – unusual, and presence suggests co-exisiting sepsis
- Tenosynovitis or Bursitis

SIGNS - ARTICULAR

- Late

- Joint damage and deformities - in uncontrolled long-standing disease
  - Ulnar deviation and subluxation of the wrist and fingers
  - Boutonniere and swan-neck deformities of fingers
  - Z-deformity of thumbs
  - Dorsal subluxation of the ulna **>>>** rupture of 4th and 5thextensor tendons
  - Foot changes are similar

SIGNS - ARTICULAR

- Late
  - Atlanto-axial joint subluxation
    - New onset occipital headache
    - Paraesthesia or electric shock are present in the arms

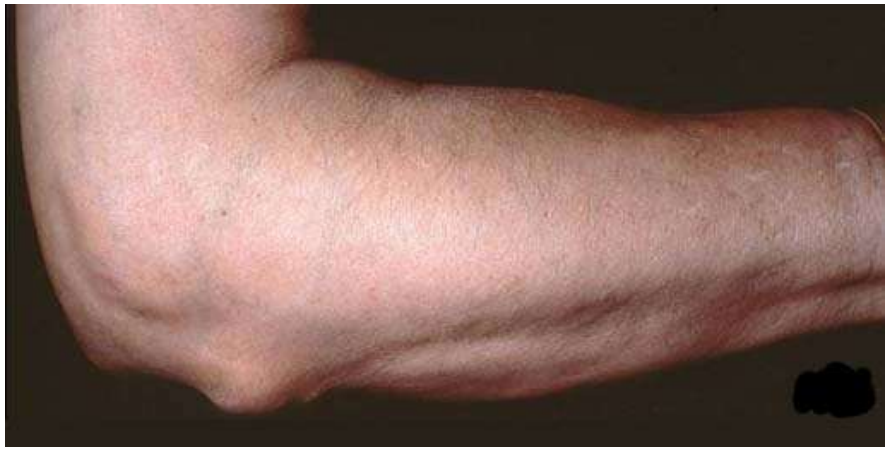
SIGNS – EXTRA ARTICULAR

- Incidence
  - Affect ~40% of RA patients
  - Commoner in patients with long standing

SIGNS – EXTRA ARTICULAR

- Nodules

- Occurs in RF or ACPA positive patients
- Usual site - extensor tendons
- Asymptomatic
- Complicated by ulceration and secondary infection



SIGNS – EXTRA ARTICULAR

- Vasculitis
  - Seropositive patients
  - Present with
    - Systemic features
    - Cutaneous ulceration
    - Skin necrosis
    - Mesenteric, Renal or Coronary artery occlusion

SIGNS – EXTRA ARTICULAR

- Lungs
  - Pleural disease
  - Interstitial fibrosis
  - Bronchiolitis obliterans organizing pneumonia

SIGNS – EXTRA ARTICULAR

- Cardiac
  - IHD

    NSAIDs, glucocorticoids, the effects of inflammatory cytokines on vascular endothelium + conventional risk factors
  - Conduction defects
  - Cardiomyopathy
  - Aortic regurgitation
  - Pericarditis & pericardial effusion

SIGNS – EXTRA ARTICULAR

- Neurological

- Cervical cord compression - Atlanto-axial subluxation
- Carpal tunnel syndrome – From compression by hypertrophied synovium or by joint subluxation
- Tarsal tunnel syndrome
- Peripheral neuropathy and mononeuritis multiplex

SIGNS – EXTRA ARTICULAR

- Lymphatic
  - Splenomegaly - 5% patients
  - Felty's syndrome – 1%
    - RA + splenomegaly + Neutropenia & Thrombocytopenia
  - Localized or Generalized lymphadenopathy in active disease
  - Persistent lymphadenopathy may indicate development of lymphoma

SIGNS – EXTRA ARTICULAR

- Hematological

  - Anemia

    Iron deficiency

    Normocytic anemia with thrombocytosis

SIGNS – EXTRA ARTICULAR

- Eye
  - Keratoconjunctivitis sicca due to secondary Sjogren's syndrome
  - Episcleritis, Scleritis, Scleromalacia
  - Peripheral Keratitis

Episcleritis

Scleritis

Scleromalacia

SIGNS – EXTRA ARTICULAR

- Osteoporosis
- Amyloidosis

  - Rare and present with nephrotic syndrome

WHEN TO SUSPECT **RA**

DIAGNOSIS IS CLINICAL

- ***Suggestive clinical history***
- ***≥1 swollen joint***
- Not better explained by another disease

Investigations are useful in confirming the diagnosis & assessing the disease activity

DIAGNOSTIC CRITERIA

Clinical criteria

I. Number/Size of joint involved
II. Duration of symptoms

Laboratory criteria

I. Serology - Rheumatoid factor or Anti CCP antibodies
II. ESR or CRP

Score - 6 and above is diagnostic

2010 ACR / EULAR Criteria

	Criteria	Score
A	Joint involvement (swelling or tenderness +/- imaging evidence)	
	1 large joint	0
	2–10 large joints	1
	1–3 small joints	2
	4–10 small joints	3
	> 10 joints (at least 1 small joint)	5
B	Serology (at least 1 test result needed)	
	Negative RF and negative anti-CCP	0
	Low +ve RF or low +ve anti-CCP	2
	High +ve RF or high +ve anti-CCP	3
C	Acute phase reactants (at least 1 test result needed)	
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
D	Duration of symptoms	
	<6 weeks	0
	≥6 weeks	1

INVESTIGATIONS

INVESTIGATIONS

- Confirmation of the diagnosis
- Assessing the disease severity
- Monitoring drug safety

LABORATORY - SEROLOGY

- Rheumatoid Factor (RhF)
  - Positive in ~70% cases
  - High titres associated with severe disease, erosions, and extra-articular disease
- Anticyclic citrullinated peptide antibodies (Anti-CCP or ACPA)
  - Highly specific (~98%) with a reasonable sensitivity (70–80%)
  - Predict disease progression

LABORATORY - ACUTE PHASE REACTANTS

- ESR
- C – Reactive Protein (CRP)

- Raised
- Can be normal if only few joints involved

LABORATORY - COMPLETE BLOOD COUNTS (CBC)

- Anaemia of chronic disease & Thrombocytosis in active disease
- Iron deficiency – GI blood loss due to NSAID induced gastropathy
- Leukopenia – Felty's Syndrome

RADIOLOGY - PLAIN X-RAYS

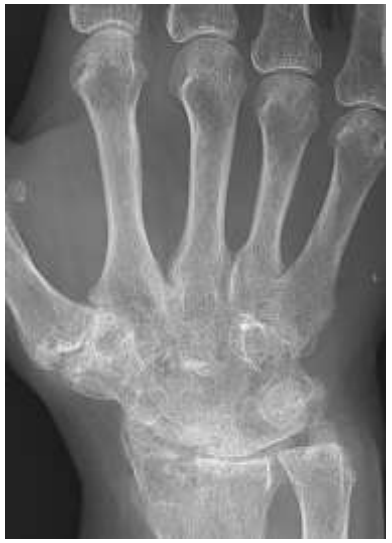
i. Early disease

- Soft tissue swelling, juxta-articular osteopenia and reduced joint space

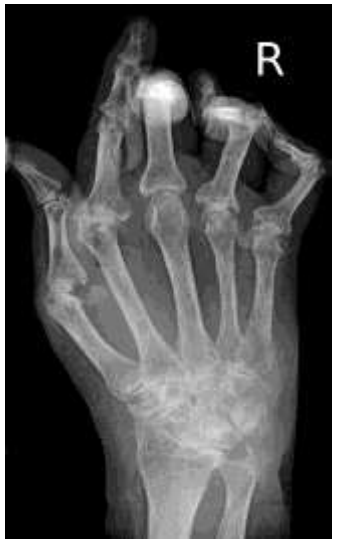
ii. Late disease

- Bony erosions, subluxation, or complete carpal destruction

Carpal ankylosis



Deforming Arthritis



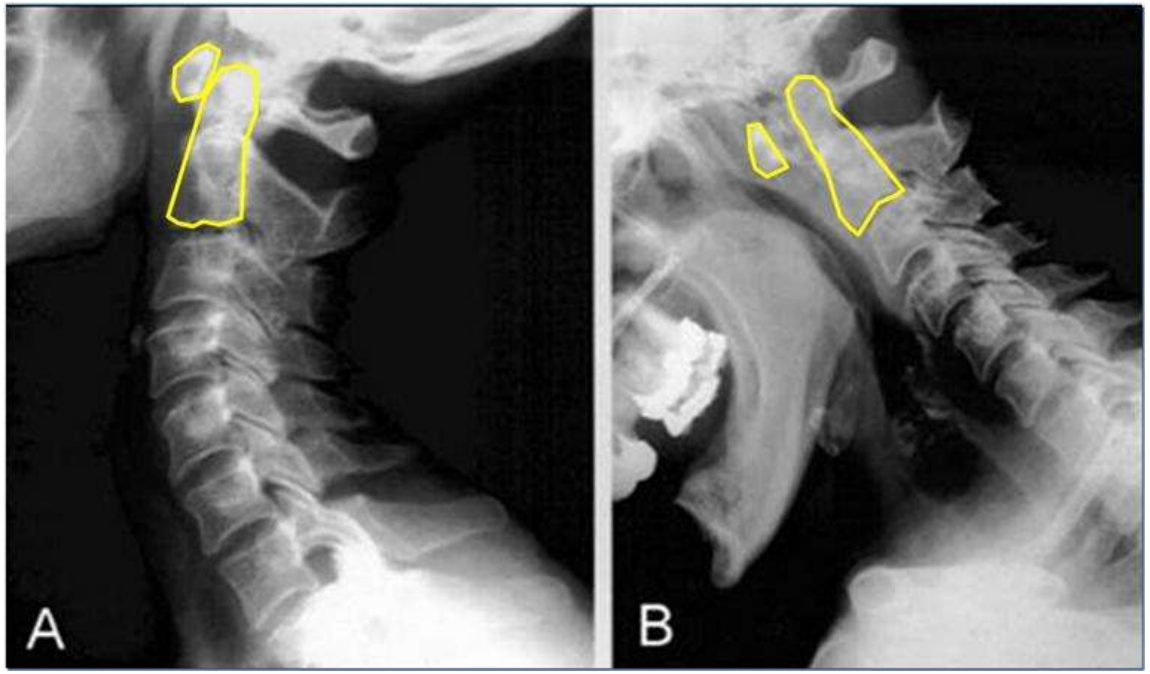
RADIOLOGY

Ultrasound & MRI

- Identify synovitis more accurately especially during acute phase
- Greater sensitivity in detecting bone erosions than conventional X-rays
- Ultrasound helpful in Baker's cyst diagnosis in suspected cases

RADIOLOGY

Patients who are suspected of having atlanto-axial disease should have lateral X-rays taken in flexion and extension, and an MRI



Extension

Flexion

TO MONITOR **DRUG SAFETY**

- **CBC**
- **Urinalysis**
- **Urea & Creatinine**
- **Liver Function Tests**
- **Chest X-Ray**

MANAGEMENT

MANAGEMENT

- Suppress inflammation
- Symptom control
- Preserve joint function
- Prevention of joint damage

As the chief biological event is inflammation with over-production of cytokines

Early use of disease modifying anti-rheumatic drugs (DMARDs) and biological agents improves long-term outcomes

Key Point

MANAGEMENT - DMARDs

- **General**
  - First line drugs
  - Start within 3 months of persistent symptoms
  - Symptomatic benefit in 6 – 12 weeks
  - Combination - Methotrexate, Sulfasalazine, and Hydroxychloroquine
  - Leflunomide is another option

MANAGEMENT - DMARDs

- **General**
  - Side effects

    Immunosuppression, pancytopenia, increased susceptibility to infection & neutropenic sepsis
  - Regular FBC, LFT monitoring necessary

MANAGEMENT - DMARDs

- **Specific Side Effects**

Methotrexate

Pneumonitis (pre treatment CXR necessary)

Oral ulcers

Hepatotoxicity

Teratogenic

Sulfasalazine

Rash

Decreased sperm count

Oral ulcers

GI upset

Leflunomide

Teratogenicity (male and female)

Oral ulcers

Raised BP

Hepatotoxicity

Hydroxychloroquine

Retinopathy

Pre treatment and annual eye screen required

MANAGEMENT - BIOLOGICAL AGENTS

NICE guidance

- Initiated by specialists
- **Indications** - Active disease despite adequate trial of at least 2 DMARDs
- **Pretreatment screening** - TB , hepatitis B, hepatitis C , HIV

MANAGEMENT - BIOLOGICAL AGENTS

TNF – α Inhibitors

- **Infliximab**
- **Etanercept**
- **Adalimumab**
- **Golimumab**
- **Certolizumab pegol**
- Approved by NICE as 1st-line agents

MANAGEMENT - BIOLOGICAL AGENTS

B-cell Depletion

- **Rituximab**
- Used in combination with methotrexate
- Approved by NICE - where DMARDS and a TNF alpha blockers have failed

MANAGEMENT - BIOLOGICAL AGENTS

IL-6 inhibition

- **Tocilizumab**
- Approved by NICE in combination with methotrexate in TNF alpha blocker
- Monitor for hypercholesterolemia

MANAGEMENT - BIOLOGICAL AGENTS

Inhibition of T-cell co-stimulation

- **Abatacept**
- Licensed for active RA in patients not responded to DMARDS or TNF alpha blocker

MANAGEMENT - BIOLOGICAL AGENTS

Side effects

- Serious infections
- Reactivation of TB
  (screen and consider prophylaxis)
- Reactivation hepatitis B
- Worsening heart failure
- Hypersensitivity
- Injection-site reactions and blood disorders
- ANA and reversible SLE-type illness
- Skin cancers - may be more common

MANAGEMENT - STEROIDS

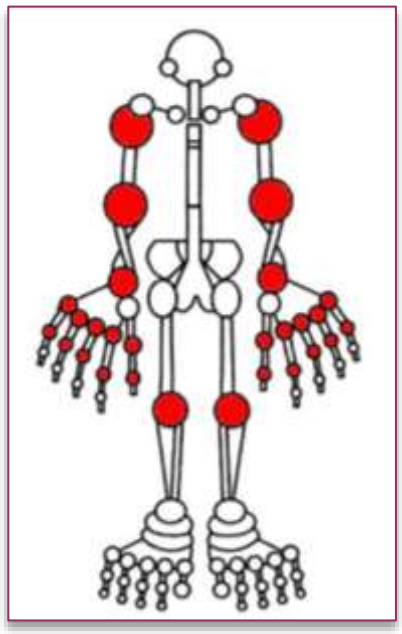
- Steroids rapidly reduce symptoms and inflammation
- Avoid unless appropriately experienced
- Useful for acute exacerbations, e.g., ***IM depot*** methylprednisolone
- ***Intra-articular*** steroids - Rapid but short-term effect
- ***Oral*** steroids (e.g., prednisolone 7.5mg/d) for difficult to control symptoms

MANAGEMENT - ANALGESIA

- **NSAIDs** - Good for symptom relief but no effect on disease progression
- Paracetamol and weak opiates are rarely effective

MANAGEMENT – DISEASE ACTIVITY MONITORING

28-joint
Disease Activity Score
(DAS28)



- Assess disease activity, response to treatment and need for biological therapy
- **Method**
  1. Counting the number of swollen and tender joints in the upper limbs and knees
  2. ESR
  3. Visual analogue scale
     - Scale 0 to 100 - 0 indicates no symptoms and 100 the worst symptoms possible

MANAGEMENT – DISEASE ACTIVITY MONITORING

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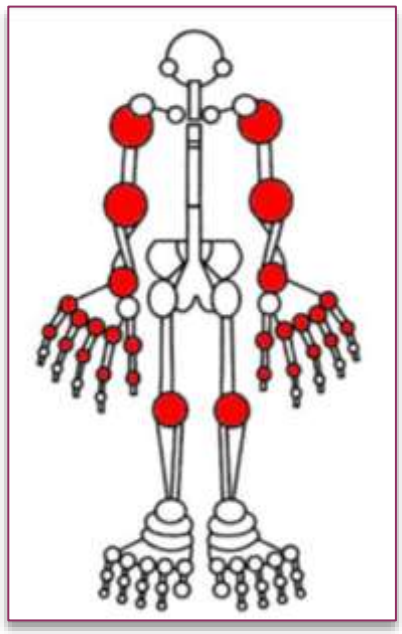

- The higher the value, the more active the disease
- ***'Treat to Target' -*** Treatment should be escalated until satisfactory control is achieved

- **5.1 & Above** - Active disease
- **<3.2** - Low disease activity
- **<2.6** - Remission

(https://www.nras.org.uk/the-das28-score)

MANAGEMENT – OTHER MEASURES

Physiotherapy

Occupational Therapy

- Aids
- Splints

Surgery

- Synovectomy
- Joint replacement
- Excision of metatarsal heads
- Neurosurgery - atlanto-axial subluxation

CVD Prevention

- Manage cardiovascular risk factors
- Smoking cessation

RHEUMATOID ARTHRITIS & **PREGNANCY**

RHEUMATOID ARTHRITIS & **PREGNANCY**

Conception

- Many patients with rheumatoid arthritis go into remission during pregnancy
- Methotrexate should be discontinued for 3 months, &
- Leflunomide discontinued for 24 months before conception

Paracetamol

- Oral analgesic of choice during pregnancy

RHEUMATOID ARTHRITIS IN **PREGNANCY**

NSAIDs & COX-2 Inhibitors	• Can be used from conception to 20 weeks' gestation
Glucocorticoids	• Used to control disease flares • Main *maternal risks* are hypertension, glucose intolerance and osteoporosis
DMARDs	• Sulfasalazine, Hydroxychloroquine and Azathioprine, if needed • **Avoid:** Methotrexate, Leflunomide, Cyclophosphamide, Mycophenolate and Gold

RHEUMATOID ARTHRITIS & **PREGNANCY**

Biological therapy

- Relatively safe during pregnancy
- Theoretical risk is immunosuppression in the neonate
- Certolizumab contraindicated as it cross placenta in negligible amounts

Breastfeeding

- Methotrexate, Leflunomide and Cyclophosphamide are contraindicated

RHEUMATOID ARTHRITIS IN **PREGNANCY - SUMMARY**

- **Conception:** Methotrexate should be discontinued for at least 3 months & Leflunomide discontinued for at least 24 months before trying to conceive
- **Paracetamol** Oral analgesic of choice during pregnancy
- Oral NSAIDs and selective COX-2 inhibitors can be used from conception to 20 weeks' gestation
- Glucocorticoids may be used to control disease flares; the main maternal risks are hypertension, glucose intolerance and osteoporosis.
- DMARDs that may be used: Sulfasalazine, Hydroxychloroquine and Azathioprine if required to control inflammation.
- DMARDs that must be avoided: Methotrexate, Leflunomide, Cyclophosphamide, mycophenolate and gold.
- Biologic therapies: experience is limited but they may be relatively safe during pregnancy. The main theoretical risk is immunosuppression in the neonate, except for certolizumab, which does cross the placenta in negligible amounts.
- Breastfeeding: Methotrexate, Leflunomide and Cyclophosphamide are contraindicated

REFER EARLY TO RHEUMATOLOGIST FOR EXPERT MANAGEMENT