

Issues in Treating Rheumatologic Disease in Women of Child Bearing Age

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PGY2

Case 1

- **41F, married 1 child (9y)**

- **HPI**

- 6 month history of pallindromic rheumatism
- AM stiffness ~45min
- ++ fatigue
- 2 visits to ER with pleuritic CP → “Normal” CXR
- Ø Rash, Ø alopecia, Ø mouth ulcers, Ø photosensitivity;
Ø psychosis; Ø Raynaud's

- **PMH**

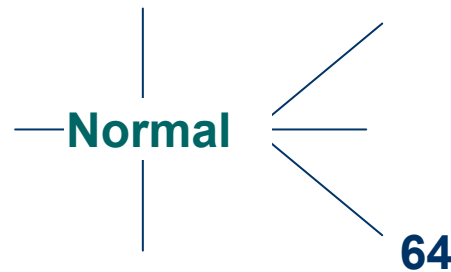
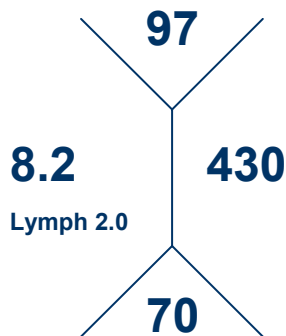
- fibroids
- G₂T₁P₀A₁L₁

Case 1

● O/E

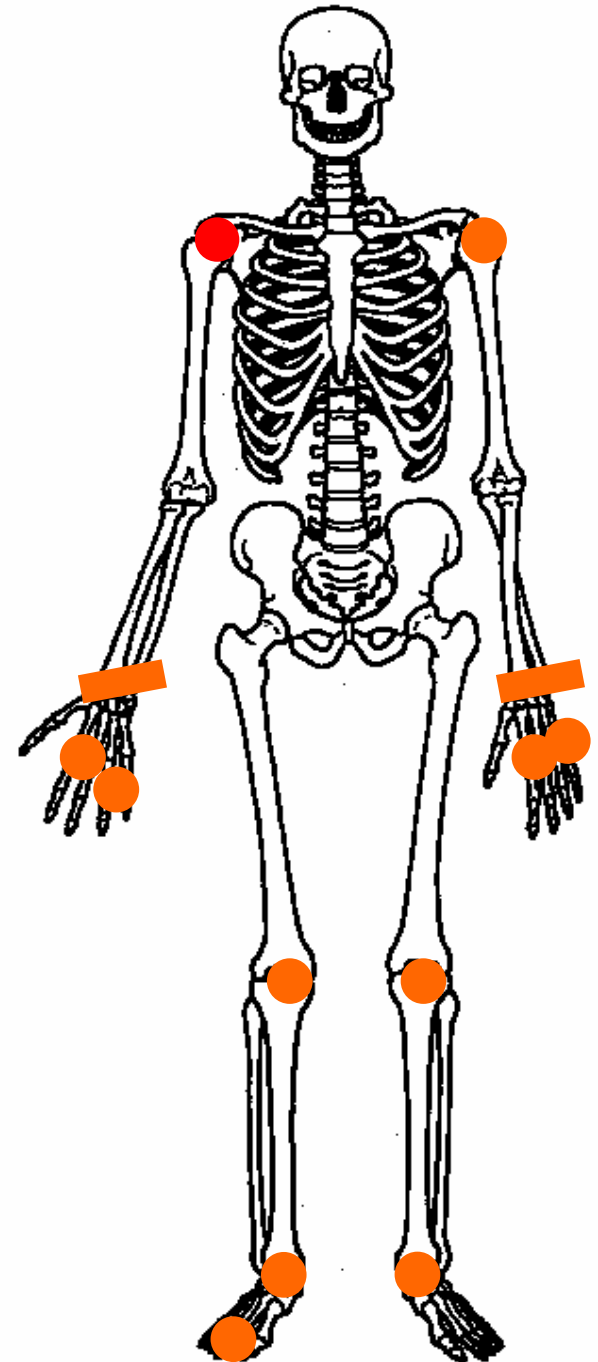
- 11 Effused joints
- Stress Pain at wrists
- No nodules
- Remainder of exam N

● Ix



U/A – neg

X-ray hands → Normal



Case 1

- **Inflammatory Arthritis**

- RA
- SLE

- **Initiated Rx with Plaquenil while awaiting serology/further Ix**

- 1. Is it safe to become pregnant on Plaquenil?*
- 2. What other treatment options are safe in pregnancy?*
- 3. Can I breast feed?*

Case 2

- **18F college student**

- **HPI**

- Presented to ER with pleuritic CP + dyspnea
- Hx of pericarditis 1 month before; Rx with ASA by cardiology
- Malar rash x 1.5 yrs
- Raynaud's x 3 months
- Ø Oral ulcers, Ø other rash; Ø alopecia; Ø arthritis; Ø psychosis/Sz;

- **PMH**

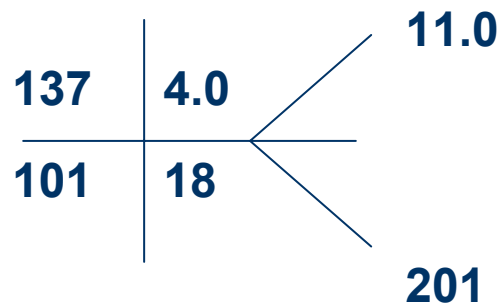
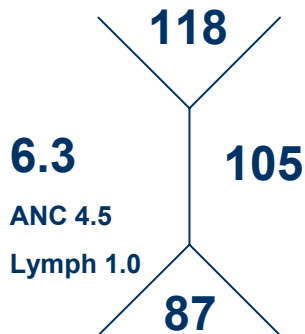
- Nil

Case 2

• O/E

- ++ Accessory muscle use
- Marked ↓B/S to bases R>L
- No clinical signs of tamponade
- Ø Rash, Ø active joints; Ø oral ulcers;

• Ix



- **U/A:** +RBC,+ RBC casts
- CXR:** mod bilateral effusions
- ECHO:** Marked RV strain, moderate effusion
- CT Thorax** → no PE

Case 2

- **Presumptive diagnosis of SLE**
 - (serositis, malar rash, cytopenia, nephritis)
- **Initiation of corticosteroids**
 - (methylprednisolone 1g IV x 3d)
- **Serositis responded very well with resolution of dyspnea**
- **Renal impairment worsened**
- **Decision to initiate cyclophosphamide Rx**

Case 2

- 1. Will I be able to have children?***
- 2. Would the answer be different if I was 35yo?***
- 3. Is there anything that can be done to preserve fertility?***

Outline

- **Describe the interaction of pregnancy and rheumatoid arthritis**
- **Discuss the safety of rheumatologic drugs in pregnancy and breast feeding**
- **Describe the effects of cytotoxic therapy on fertility**
- **Review current methods of fertility preservation**

Immunology of Pregnancy

- **Fetus is a hemi-allograft**
- **Immunological changes must occur at maternal fetal interface to prevent “rejection”**
 - Cytokines: Th1(predominant) → Th2(predominant)
 - ↑ Complement : Estrogen mediated hepatic synthesis
 - ↑ TNF α receptors → thus ↑ binding of circulating TNF α and antagonism of IL-1

Rheumatoid Arthritis in Pregnancy

- **70-80% of women with RA experience an improvement in arthritis during pregnancy**
- **Starts early T1 and lasts through immediate post partum period**
- **The degree of improvement in RA during pregnancy related to degree of HLA disparity between fetus and mother**
- **90% of patients flare in the post-partum period (~3mo)**

Rheumatoid Arthritis in Pregnancy

● Pregnancy outcomes

- Kaplan *et al* (1965) case control study
 - Slight increased risk of spontaneous abortion
- Morris W (1969) and Ostensen M (1983)
 - No difference in fetal loss or fetal morbidity in patients with rheumatoid arthritis

Kaplan *et al* Rheumatoid arthritis and pregnancy. Clin Obstet Gynecol 1965;8:286

Morris W. Pregnancy in rheumatoid arthritis and systemic lupus erythematosus. Aust NZ J Obstet Gynecol. 1969; 9:136

Ostensen M *et al* A prospective clinical study of the effect of pregnancy on rheumatoid arthritis and ankylosing spondylitis. Arthritis Rheum 1983; 26:1155

Rheumatoid Arthritis in Pregnancy

● Pregnancy outcomes

– Bowden *et al* (2000)

- 133 pregnant F with RA or undifferentiated inflammatory arthritis
- Case control study
- 5(4%) admission to hospital for HTN, Ø pre-eclampsia, Ø fetal or maternal mortality

	Arthritis	Control	P value
Birth Weight	3.3kg	3.5kg	0.004

Treatment of RA in Pregnancy

A	Controlled studies show no risk Adequate, well controlled studies in pregnant women, no harm
B	No evidence of risk in humans Animal studies do but human do not, or inadequate human studies with negative animal
C	Risk cannot be ruled out Human studies lacking and animal studies show risk or negative Potential benefits justify potential risks
D	Positive evidence of risk Investigational or post marketing data shows risk to fetus Potential benefit may outweigh risk
X	Contraindicated in pregnancy Studies in animals or humans, investigational or post marketing reports have shown fetal risk which clear outweighs any benefit

Treatment of RA in Pregnancy

1. NSAIDs

- Crosses placenta
- No reports of teratogenic effects (Ostensen & Ostensen 1996)
- Use in 2nd and 3rd trimester can increase rate of **premature closure of ductus arteriosus** → **pulmonary hypertension**, interfere with uterine contraction and parturition
- Cox-2 can interfere with embryo implantation

General Recommendation to avoid use of NSAIDs during pregnancy (C/D)

DMARD's in Pregnancy

2. Antimalarial Drugs

- 3.3% congenital abnormalities
- Levy *et al* (1991)
 - 24 women, 27 pregnancies expose to C or HC
 - 14 live births, 6 TA, 4 SA, 3 still births
 - 7 fetal losses occurred in patients with active lupus, but 1 stillbirth + 1 SA in RA patients

Risk factor C. Risk may exist, but benefit likely outweighs it

DMARD's in Pregnancy

3. Glucocorticoids

- Crosses placenta
- Park-Wyllie et al
 - Case control; 184 F on prednisone, 188 control
 - No statistical difference in rate of major anomalies
 - 3.4 fold increase of oral cleft palate
- Increased risk of PROM, PIH, Gestational DM and IUGR

Recommend dose of <10mg/day if required for disease control. (B)

DMARDs in Pregnancy

4. Azathioprine

- Teratogenic in animal studies
- Crosses placenta
- Congenital anomalies, immunosuppression and IUGR

5. Cyclosporine

- Premature births and low birth weight infants
 - Bar *et al* (2001)
 - Meta-analysis
 - No increased risk of teratogenicity

Recommended only if life/organ threatening disease (C/D)

DMARDs in Pregnancy

6. Methotrexate

- Anti-metabolite (folate metabolism)

Contraindicated in pregnancy (X)
May be safe to D/C in T1

- Lewden *et al* (2004)
 - Retrospective review → 28 cases of low dose MTX in T1
 - Normal birth weight
 - 1 child had mild abnormalities (metatarsus varus)

DMARD's in Pregnancy

7. Anti-Tumour Necrosis Factor α agents (etanercept, infliximab)

- Animal studies reveal no evidence of harm
- No human studies

**Recommend use only if “clearly”
needed for disease control (B)**

DMARD's in Pregnancy

8. Leflunomide (Arava)

- Associated with teratogenic and embrolethal effects in animal models at low doses

Contraindicated in pregnancy (X)

- Pregnancy must be excluded prior to initiating treatment; OCP used throughout
- Pregnancy should be avoided after use until plasma levels $<0.02\text{mcg/ml}$ (x2 14days apart)
- May use resin (cholestyramine 8g, TID x 11days) to increase elimination

DMARD's & Breast Feeding

- **Many of same restrictions on medications advised**
- **NSAID's may be used safely**
- **Gold and sulfasalazine should be used cautiously → reports of infant hematologic, hepatic and GI complications**
- **Azathioprine, CsA, Cyclophosphamide should be avoided**

Case 1 Revisited

1. Is it safe to become pregnant on Plaquenil?

- Most women experience improvement in their disease during pregnancy and may not require on going treatment throughout
- There is no evidence of teratogenicity with anti-malarials

2. What other treatment options are safe in pregnancy?

- Low dose glucocorticoids
- If severe/refractory disease may use azathioprine or cyclosporine or TNF α antagonists

3. Can I breast feed?

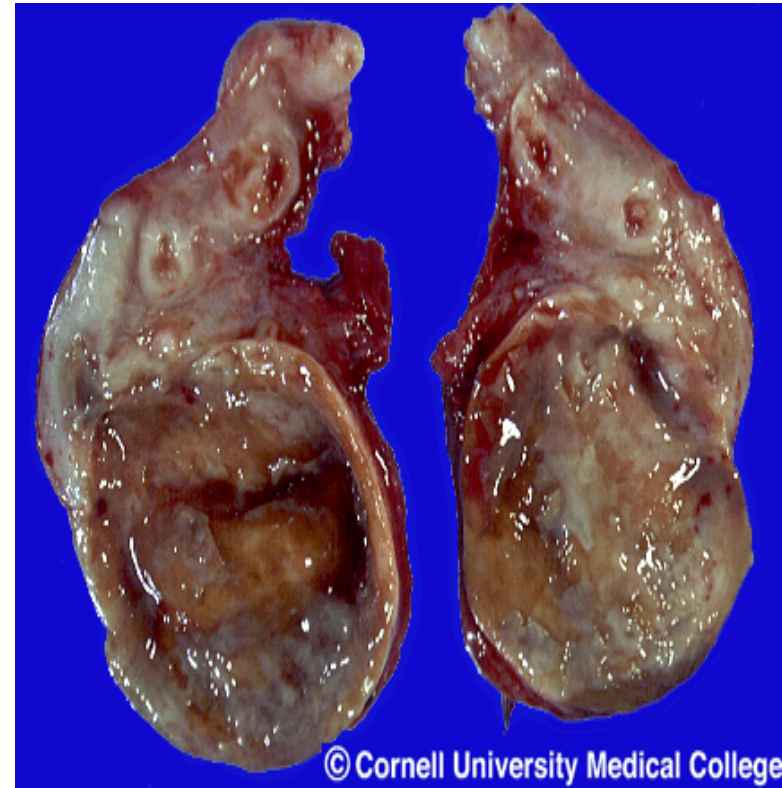
- Safety of medication similar to during pregnancy
- NSAIDs may be safely restarted
- Post partum flare may require re-institution of Rx

Cytotoxic Agents and Fertility

- **Cyclophosphamide major cytotoxic agent used in rheumatic disease**
- **Alkylating agent → Interact chemically with DNA causing inaccurate base pairing and DNA RNA breakage**
- **Largest impact on rapidly dividing cells**
- **Damage to rapidly dividing cells (i.e., GI, BM) is reversible after cytotoxic therapy, the damage to gonadal tissue appears to be irreversible**

Cyclophosphamide and Fertility

- Action on both oocyte and pregranulosa cells in primordial follicles
- Impaired follicular maturation (temporary amenorrhea) + depleted primordial follicles (POF)
- Histological sections show a spectrum of changes
 - Decreased number of follicles
 - Absent follicles
 - Fibrosis



Cyclophosphamide and Fertility

- **Ovarian failure occurs in 13-83% of females treated with cyclophosphamide**
- **Rate varies with concomitant drugs, mode of administration and age**
 - PO > IV (20% vs. 16%, Mok *et al*)

Cyclophosphamide and Fertility

- **Le Thi Hong *et al* (2002)**
 - 84 F receiving IV Cyclophosphamide
 - 56 SLE, 28 Other (Wegener's, vasculitis)
 - 27% of female developed amenorrhea

Table 1. Main characteristics of premenopausal women treated with intravenous cyclophosphamide.

	SLE n = 56	Other Diseases n = 28	Total n = 84
IVCY			
Mean age at onset, yrs (range)	28 ± 9 (13–53)	30 ± 10 (14–50)	29 ± 10 (13–53)
Mean dosage per pulse, g (range)	0.9 ± 0.14 (0.5–1)	0.9 ± 0.12 (0.5–1)	0.9 ± 0.16 (0.5–1)
Mean No. of pulses (range)	12.8 ± 9 (3–42)	13.6 ± 5.3 (6–25)	13 ± 6.3 (3–42)
No. of sustained amenorrhea (%)	13 (23.2)	6 (21.4)	19 (22.6)
No. of pregnant women (%)	13 (23.6)	5 (17.8)	18 (21.6)

Cyclophosphamide and Fertility

● Le Thi Hong *et al* (2002)

- Prolonged amenorrhea related primarily to age of patient
 - <30y 12% POF
 - >30y 39% POF
- Weak association with # pulses. No relation to underlying disease

Table 2. Influence of the age at IVCY initiation on occurrence of sustained amenorrhea after intravenous cyclophosphamide therapy.

Age at IVCY initiation, yrs	< 26	26 to 30	31 to 35	36 to 40	> 40
SLE Systemic lupus erythematosus, n = 56					
≤ 7 pulses	0/5	0/1	0/3	2/4	1/4
≥ 8 pulses	0/8	4/19	1/6	2/3	3/3
Other diseases, n = 28					
≤ 7 pulses	0/1	0/1	0/1	1/1	0/0
≥ 8 pulses	0/8	0/3	0/8	0/0	5/5
Total, n = 84	0/22	4/24	1/18	5/8	9/12

Cyclophosphamide and Fertility

- **Le Thi Houng *et al* (2002)**
 - 18 women (22 pregnancies) occurred during or after treatment with IV cyclophosphamide

Fertility Preservation

1. Pharmacological

- Oral Contraceptive Pills
- GnRH Agonists
- Progesterone
- Apoptotic Inhibitors

2. Surgical Options

- Oocyte and embryo cryopreservation
- Ovarian Transplantation

Oral Contraceptives

a) Chapman and Sutcliffe (1981)

- Hodgkin's Lymphoma treated with MVPP
- Women on concomitant OCP had a larger number of follicles on histological examination post treatment.

b) Whitehead (1983)

- Retrospective review of 44 women receiving MVPP for Hodgkin's Lymphoma; 9 of whom took OCP throughout treatment
- 4/9 amenorrheic post therapy, 3/9 oligomenorrhic
- No significant benefit to OCP for ovarian preservation

The Pill - Oral Contraceptive



Oral Contraceptives

c) Letterie (2004)

- Induction of anovulation for protection of ovaries in rats treated with cyclophosphamide.
- Cyclophosphamide stimulated ovarian follicular development
- The stimulation was independent of hormonal ovarian suppression.
- No protective effects of inducing anovulation

The Pill - Oral Contraceptive



GnRH Agonists

- **GnRH agonists given in a continual, as opposed to cyclical manner, result in suppression of pituitary secretion of LH/FSH.**
- **Without cyclical LH/FSH secretion, ovarian follicular development is halted.**

GnRH Agonists



- **Glode *et al* (1981)**

- Using murine model → GnRH agonist infer protection of male gonads

- **Ataya *et al* (1995)**

- GnRH-a protect ovarian function in Rhesus monkeys receiving cyclophosphamide by decreasing the number of follicles lost.

- **Studies have questions whether these results can be extrapolated as human ovaries have fewer GnRH-a receptors than rats/monkeys.**

GnRH Agonists

- **Blumenfeld *et al* (2000)**

- Cohort study
- 17 F with autoimmune disease undergoing chemotherapy (Cyclophosphamide or chlorambucil)
- Buserelin vs no treatment

	Buserelin	No treatment
Ovarian Failure	0/8	5/9

GnRH Agonists

- **Cruz et al (1999)**

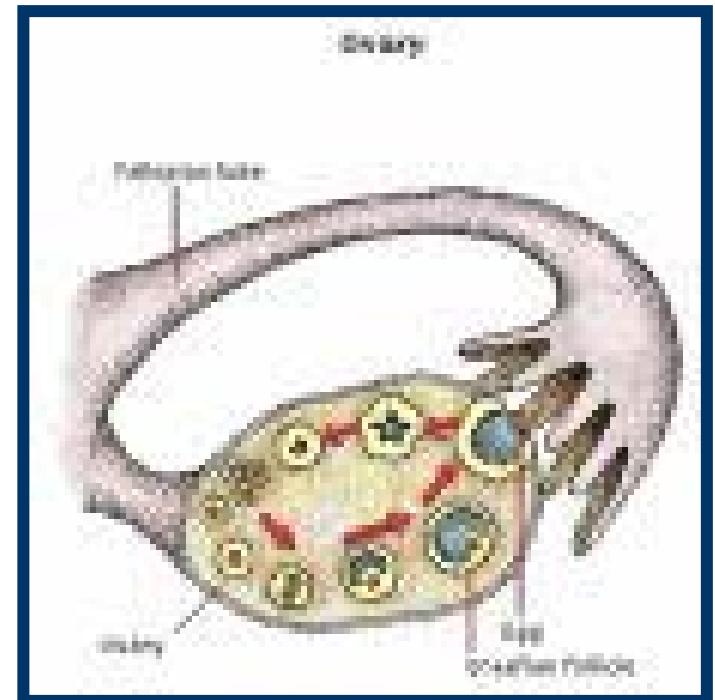
- Double blinded control trial
 - chlormadinone (2mg OD x 21 days) vs. Placebo
- 61F SLE nephritis undergoing IV cyclophosphamide
- ↓LH/FSH, ↑Estradiol in chlormadinone

	Chlormadinone	Placebo
Ovarian Failure	4/31	8/31

Progesterone

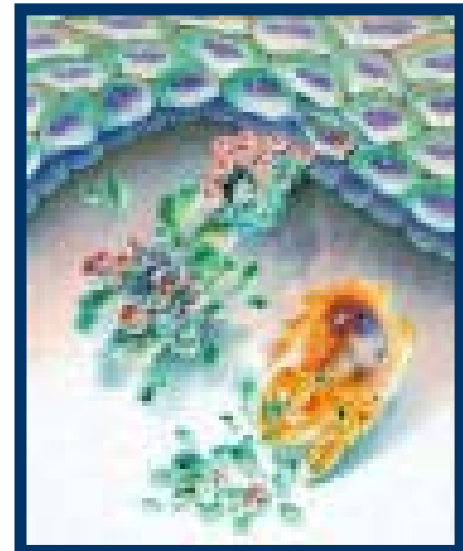
- **Familiari et al (1993)**

- Examined the ultrastructural changes of primordial follicles of females exposed to cytotoxic drugs and progesterone.
- Progesterone unable to protect ovaries from the early follicular atresia and resulting decreased ovarian reserve.



Apoptotic Inhibitors

- Apoptosis is integral to normal germ cell depletion both pre and postnatal.
- Can cytotoxic chemotherapy activate this apoptotic pathway leading to germ cell damage?
- If so, can we selectively stop the activation in germ cells?



Surgical Interventions

5. Cryopreservation

- Preimplantation embryos
- Success rate: 18.6% (deliveries/embryo transfer)
- Requires male partner
- Success with oocyte preservation much lower

6. Ovarian Transplant

- Cryopreservation of intact ovarian tissue
- Very susceptible to damage to premordial tissues during cryopreservation and ischemia during re-implantation
- Falcone et al (2004) → successful transplant in sheep
- September 2004 Belgium, 1st successful human transplant

Summary of techniques

1. GnRH-a

- promising small trials suggest protective benefit of GnRH agonist.

2. Apoptosis Inhibitors

- Potential for future research

3. Embryo and Oocyte cryopreservation

- Increasing success in viable pregnancies
- Fertility solution only.

4. Ovarian Transplant

- Early Successes
- Potential for long term preservation of ovarian function.

Case 2 Revisited

1. Will I be able to have children?

- Rates of ovarian failure low for women <30y (10-15%)
- Viable pregnancies possible after cyclophosphamide treatment
- May have early menopause

2. Would the answer be different if I was 35yo?

- Ovarian failure much higher for women >30 y (39-85%)

3. Is there anything that can be done to preserve fertility?

- GnRH antagonists promising in small studies
- Cryopreservation and Ovarian transplant improving

Questions?

