SLE and pregnancy

Dr Barbara Thompson
Case

- 28yr old Sri Lankan arrived in UK as University student in 2009.

PMHx 2003 – nephrotic syndrome
  Minimal change on renal biopsy
  Immunology negative
  Steroid responsive

- 2004 – 2006: lost to follow up
May 2006: nephrotic syndrome, butterfly rash, ANA positive
Renal biopsy: Class I Lupus nephritis
Initial Rx just steroids - poor response

Aug 2006: microscopic haematuria
Six monthly pulses IV Cyclophosphamide (Aug 06 – Feb 07)
--- then MMF

2009 – arrived in UK

March 2010: see at Lister Nephrology
On 5mg Prednisolone, MMF 500mg bd, Losartan 50mg/day

- No Sx of disease activity
- Dipstix 2+haematuria, 3+proteinuria
- BP 134/86
- Creatinine 54umol/l
- Urine PCR 87 (1,4g proteinuria/day last in Sri Lanka)
- Ds DNA 41 ; Complements normal

- From 2nd OPA, attended with her husband – keen on pregnancy
• Issues surrounding Fertility / conception

• Issues relating to best timing for pregnancy
  • Age
  • Stability of SLE and Lupus nephritis
  • Safe Immunosuppression for pregnancy

• Risks to maternal health - disease flare, PET

• Fetal outcomes and risks
Issues surrounding Fertility / conception

- Fertility and Menstrual pattern?
- Contraception?
- Any previous miscarriages?
- Anti-phospholipid antibodies?
- Previous CYP exposure
- If not fertile – could she consider IVF Rx?
Menstrual cycle

- Regular 28 day cycle – normal

“Most reports agree that fertility is preserved in the absence of advanced renal insufficiency (i.e., creatinine ≥ 3mg/dL/ 244 umol/l) and with no previous therapy with cytotoxic alkylating agents”.

- Menstruation usually returns within one year of stopping CYP

- If amenorrhea/oligomenorrhea
  AND
  two FSH levels (at least one month apart) in menopausal range associated with low estradiol levels

  --- strongly suggestive of ovarian failure.
Contraception

Using condoms

Suitable alternatives:

a) Progesterone only pills (murine models - no effect on SLE activity)

b) Depo Progesterone injections quarterly x 2 yrs (osteoporosis risk)

c) IUD (experience limited) – ok if single partner and only Pred IS

d) low dose oestrogen containing OCP – SELENA Trials

“Safety of Estrogen in Lupus Erythematosus: National Assessment”
Double blind randomised controlled trial of OCP vs placebo x 12 months

Excluded if they had moderate or high levels of anticardiolipin antibodies, lupus anticoagulant, or a history of thrombosis

CONCLUSION:
Low dose oestrogen containing OCP not associated with increased risk of flares
Original Article
A Trial of Contraceptive Methods in Women with Systemic Lupus Erythematosus  Jorge Sánchez-Guerrero

Single-blind clinical trial x 12 months: 162 women with SLE, randomly assigned to combined oral contraceptives / a progestin-only pill / copper IUD (n=54/group)

CONCLUSION:
Global disease activity, maximum SLE DAI score, incidence of flares, time to first flare, and incidence of adverse events were similar among women with systemic lupus erythematosus, irrespective of the type of contraceptive they were using.

All thromboses occurred in patients with APL Ab’s – consider avoiding in these patients!
Contraception conclusion

a) Progesterone only pills

b) Depo Progesterone injections x 2 yrs (osteoporosis risk)

c) low dose oestrogen containing OCP ok

   NOT if: nephrotic and hypercoagulable positive anti-Phospholipid Ab’s previous history of thrombosis

d) IUD (experience limited) – ok if single partner and only Pred immunesuppression
Our patient: previous Miscarriages?
Possible Anti-phospholipid Syndrome?

• Definition of APS: “arterial or venous thrombosis or specific pregnancy complications in women with laboratory evidence of antibodies to proteins bound to anionic phospholipids”

• No miscarriages; no previous pregnancies

• No Anti-phospholipid Ab’s:
  - Negative Lupus anticoagulant
  - IgM and IgG anti cardiolipin negative
  - Antibodies to β2-glycoprotein-I (NA)

• No history of previous thromboses: venous/arterial
Hypothetically: what if positive Anti-phospholipid Ab’s?

- No miscarriages; no previous pregnancies
- No history of previous thromboses: venous/arterial
- A positive Anti-phospholipid Ab’s:

TREATMENT:
- low dose Aspirin 75mg/day till 34 - 36 weeks then heparin (unfractionated UF / LMW)
- NB post partum UF heparin* /LMW Heparin / warfarin* for 6 weeks

* Ok with breastfeeding
Hypothetically: what if positive Anti-phospholipid Ab’s?

With increasing severity of pregnancy complications: previous PET, multiple miscarriages, IUGR, previous pregnancy loss
Or significant previous thromboses

TREATMENT OPTIONS:
- low dose Aspirin 75mg/day till 36 weeks
- AND unfractionated UF or LMW (dose ranges:

<table>
<thead>
<tr>
<th>Dose Ranges UF</th>
<th>low: 5000 u 12 hourly</th>
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<tr>
<td></td>
<td>high: dosing aiming at APTT in mid target range</td>
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</table>

<table>
<thead>
<tr>
<th>Dose range LMW</th>
<th>40mg Clexane daily (adjusted for extremes of BW)</th>
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<tbody>
<tr>
<td></td>
<td>40 mg 12hourly</td>
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<tr>
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<td>1mg/kg every 12hourly</td>
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</table>

- NB post partum UF heparin* /LMW Heparin / warfarin* for 6 weeks
Previous CYP exposure

6 Monthly pulses 0.5 – 1g /m² (BSA = 1.36 m² )
    ---- 6 x 1g doses ( 0.68g – 1.360g)

Two determinants of susceptibility to infertility:
1) Age at which exposed
2) Total Dose

CYP impairs fertility by damaging ovarian follicles, impairing follicular maturation and/or depleting primordial follicles.
- Temporary amenorrhoea will result when maturing follicles destroyed.
- Permanent amenorrhoea or premature ovarian failure (POF) if all primordial follicles destroyed.
Age is NB

Review of 84 women who were menstruating prior to IV Cyclophosphamide:
chronic amenorrhea developed in:
- 0% younger than 26 yrs of age
- 70% (14/20 women) over age of 35 yrs

Huong et al. J Rheumatol. 2002 Dec;29(12):2571-6
Total dose NB

Course of oral CYP – higher total dose
eg 150mg/day x 30 days = 4.5 g

IV Course: 15mg/kg pulses (1g) every 3 weeks
ie after 12 weeks = 4.0g

Transient and permanent amenorrhea are both more common in patients treated with ORAL CYP: *
- oral CYP (37% and 28% respectively)
  vs
- IV CYP (20% and 13% respectively)

Cumulative dose of the cytotoxic drug is a key factor. The total dose of cyclophosphamide needed to induce amenorrhoea

20.4 g at the age of 20 yrs
9.3 g at the age of 30 yrs
5.2 g at the age of 40 yrs
SLE and IVF Rx ? – risky

Ovulation induction (OI): clomiphene / gonadotropins, dosing according to indication:

(i) Anovulation or empirical Rx unexplained infertility – (single follicle)
   low dose clomiphene (50–100 mg x 5 days) / gonadotropins (50–100 U/day)

(ii) for intrauterine insemination: (two or three follicles needed)
   clomiphene or gonadotropins in low/medium doses (100mg clomiphene/ 75–150U gonadotropins)

(iii) IVF with embryo transfer (IVF-ET): (large number of follicles)
   – controlled ovarian hyperstimulation, gonadotropins in high doses (100–450 U/day)

34–36 h before echo-guided retrieval, given hCG - oocytes final maturation
- early activation of coagulation cascade, fibrinolysis, increase in VEGF (risk of OHSS).

Costa and Colia. Treating infertility in autoimmune patients. Rheumatology 2008;47

Embryo transfer – then progesterone to support pregnancy
Infertility Rx in SLE

OVULATION INDUCTION AND IVF IN SLE AND APL
GUBALLA et al. ARTHRITIS & RHEUMATISM Vol. 43, No. 3, March 2000, pp 550–556

Nineteen women who underwent 68 cycles of OI/IVF
3/7 SLE patients had lupus nephritis
10 APS
2 high-titer APL antibody but did not meet diagnostic criteria for SLE or primary APS.

Results:
68 ART stimulation attempts resulted in 12 pregnancies (18%) that lasted 20 or more weeks
14 live births: 5/10 primary APS; 5/7 with SLE, and 0/2 aPL alone
Three women with SLE underwent OI but chose IVF with a surrogate carrier.

Four OI/IVF cycles (25%) in SLE patients resulted in increased lupus activity and 2 (13%) in OHSS
One patient with primary APS who was given heparin during multiple cycles developed osteopenia.
No thrombosis occurred.
Issues relating to best timing for pregnancy

- Age – weighs in her favour
- Stability of SLE and Lupus nephritis
- Safe Immunosuppression for pregnancy
- Other drug adjustments for pregnancy
Stability of SLE and Lupus nephritis

Definition of Active LN:

• Presence of proteinuria > 0.5 g/day and/or active urinary sediment with or without an elevation in serum creatinine (Cr).

vs

• Quiescent lupus nephritis: proteinuria < 0.5 mg/day and inactive urinary sediment

_Lupus_. 2009 April ; 18(4): 342–347
Stability of SLE and Lupus nephritis

Mar 2010 – Feb 2011:
• ongoing 2 + microhaematuria,
• Rising urine PCR 87 – 391 by Feb 2011; Alb 40 - 35
• ds DNA : 41 – 54 – 86 – 87 iu
• Complement: C3 & C4 normal
• Creatinine preserved : 54umol/l

Jan 2011 Renal Biopsy: Class 4 LN
- well preserved interstitium – no inflammation or fibrosis
- Tuft adhesions, focal hyalinosis – previous proliferative disease/healed crescents
- More recent active proliferation in > 50% tufts

ie need for increased immunesuppression (no crescents/ necrosis)
Review of suitable Immunosuppression

- **Steroids**
  - Methylpred / Pred metabolised by placenta – exposure limited
  - rarely adrenal insufficiency (3%) / thymic hypoplasia
  - Aim keep dose < 20 mg: increase maternal risk PET and gestational DM in SLE pregnancy

- **Aza**
  - Rare reports of foetal myelotoxicity
  - EDTA Registry (1992)- no increased risk > 500 infants
• **Chloroquine / Hydroxychloroquine** – OK
  - Both cross the placenta and also present in breast milk
  - advised to continue in pregnancy
  - cessation of hydroxychloroquine - increased disease activity, lupus flares, and preterm birth


• **NSAIDs** – AVOID
  - avoid in 2nd and 3rd trimesters: premature closure of ductus arteriosus
  - avoid even in the 1st trimester:


  - concern also as can interfere with implantation after conception
**MMF (C) – AVOID**
- Teratogenic at < half-Rx doses in animal studies
- Roche 2006: data on 199 pregnancies
  birth defect in 10/119 ( > 8.4% )


**Cyclophosphamide: AVOID**
- teratogenic in 1\(^{st}\) and early 2nd trimesters
- if used in 3\(^{rd}\) trimester (for severe lupus nephritis, not responding to high dose steroids and other immunosuppressive drugs - IUD


**Cyclosporine – OK**
- see slightly more IUGR, HT
- can be used with AZA for lupus nephritis activity in pregnancy
Rituximab

- Animal studies - adverse effects;
  no well controlled studies

IgG molecules are known to cross the placenta (rituximab is an engineered IgG molecule) and rituximab has been detected in the serum of infants exposed in utero.

B-Cell lymphocytopenia lasting <6 months may occur in exposed infants.
Review of other medications: anti-hypertensives

BP goal: ≤ 140/90, to protect the mother (not 120/80)

STOP: ACE-I, ARB
- 1st trimester exposure – concern re CNS and CVS malformations


- 2nd and 3rd Trimester: ACE-I cross placenta, interfere with fetal renal hemodynamics

SAFE: Methyldopa, Hydralazine, Labetolol
   Long acting Nifedipine (30 – 90 – 120mg/day) from week 20 onwards

AVOID: loop diuretics
   can continue BFZ if on it longterm
STOP: Statins; bisphosphonates
- omeprazole not harmful

- Start folate
- Aspirin 75mg from 12th/14th week – PET prophylaxis
Maternal Risk re pregnancy

- Risk of SLE activity / flare
  - risk of flare of Lupus nephritis
- Worsening proteinuria
- Risk of pre-eclampsia
- Risk of loss of GFR
- Risks in anti-phospholipid syndrome: venous and arterial thromboses
- Post partum period - remains a risk for flare for several months
Risk of SLE flare

Controversy re effect of pregnancy on the course of SLE per se:
- Hopkins lupus pregnancy group (1991), Ruiz-Irastorza (1996) – both prospective studies found increased rate of flare

• Specific to Lupus nephritis
  --- agreement that a worsening of activity in most studies
  - associated with increased risk of fetal loss
  - if history of lupus nephritis: 20 – 30 % risk of relapse

“TRUE arthritis flares are less common during pregnancy, while renal and hematologic flares are more common”


Hopins Lupus Pregnancy Center: Ten Key Issues in Management
Risk of SLE or lupus nephritis flare

Frequency of exacerbation / or persistently active disease complicating pregnancy, varies with the state of disease activity at conception:

7 - 33 % if remission for at least six months pre–conception
61- 67% if active disease at the time of conception

7.25 fold increased in risk of flare if recently active disease (Clowse et al)
Patients with preexisting hypertension, proteinuria, and azotemia are at increased risk

RECOMMENDATION: with lupus nephritis - delay pregnancy until disease inactive for at least six months !!
Maternal and Fetal Outcomes in Pregnant Patients with Active Lupus Nephritis


To determine the impact of lupus nephritis disease activity on maternal and fetal outcomes in pregnant SLE patients

Comparing incidence of maternal complications in SLE pregnancies without renal involvement (n=47) vs pregnancies with active lupus nephritis (n=23) vs quiescent lupus nephritis* (n=20):

- incidence of maternal Cx : 11% vs 57% p<0.001 (*vs 35%)

Active lupus nephritis vs no lupus nephritis
- more likely to deliver preterm: (median of 34 vs. 40 weeks, respectively (p=0.002)
- more likely to suffer fetal loss (35% vs 9%, p=0.031)

No stat significant diff between group with inactive LN and no renal involvement.
When is rising proteinuria significant

Moroni et al AJKD 2002 and Wagner et al Lupus 2009 defined: worsening proteinuria for purposes of defining a flare of Lupus:

increase of 2g/day if baseline proteinuria was <3.5 g/day
or
doubling of proteinuria in patients who previously had a nephrotic range proteinuria
Risk of pre-eclampsia

- Occurs in 13% - 35% patients with SLE
- Occurs in up to 66% patients with Lupus nephritis

More likely in anti-PLS, preexisting thrombocytopenia, prior PET, combination SLE and DM

Difficulty distinguishing PET and SLE flare:
  - active urinary sediment with RBC vs proteinuria alone in PET
  - low complement, high ds DNA in SLE vs normal/increased Compl in PET
  - thrombocytopenia in SLE vs low plat, abn LFT and high urate in PET
Risk of loss of GFR

“If worsening RF due to Lupus nephritis in pregnancy, 25% have continued damage after pregnancy, despite aggressive treatment”

( Clowse et al )
Fetal / neonatal / infant outcomes: definitions

Fetal loss:
- spontaneous abortion/ therapeutic abortion – before 20 weeks
- still birth: fetal loss after 20 weeks

Prematurity: birth before 37 weeks gestation

IUGR/ fetal growth restriction: < 10th percentile for age
Risks for fetal loss: spontaneous abortion and still birth approximately 20%

- hypertension
- active lupus
- lupus nephritis
- hypocomplementemia, elevated anti-DNA *
- aPL
- thrombocytopenia

Cortes et al 103 pregnancies:

Multiple regression analysis: fetal loss significantly associated with:
“Hypertension at conception, C3 hypocomplementaemia, anti- B2 glycoprotein 1 Abs, previous lupus nephritis for still births”
Fetal / neonatal / infant risks: Fetal loss -

2002: Cotes- Hernandez et al: Outcomes of 103 SLE pregnancies

- 66% live births
- 8% therapeutic abortion
- 12% still birth
- 14% spont abortion

20/103 pregnancies born to lupus nephritis pt's: (-1 therapeutic abortion)
- 8/19 (42%) live births
- 5/19 (26%) spont abortion
- 6/19 (32%) still birth

2008: LUMINA study: rate fetal loss & still births 45% (included abortions)

Antiphospholipid antibodies in SLE pregnancies:

present in 30 – 40%

A review of 10 studies: 554 women with SLE found:
- fetal loss was more common if aPL positive (38 – 59%) vs negative (16 – 20%)
- LA positive (36% versus 13%), or aCL (39 % versus 18 %)


Pregnancy related complications related to APS:
- late fetal death (≥ 10 weeks gestation)
- Early, severe preeclampsia / eclampsia
- fetal growth restriction
- recurrent pregnancy loss
- pregnancy-related maternal thrombosis (art/venous)
Anti Ro/La antibodies in SLE

- Passively transferred – can cause neonatal lupus in approximately 1 - 2 % such pregnancies
- The most serious complication CHB in the neonate
- Other Tx: subacute cutaneous lesions, less often other cardiac abnormalities, hepatobiliary disease, and thrombocytopenia

- Neonatal lupus accounts for 90 - 95 % of CHB Most mothers of babies with neonatal lupus do not have lupus or other autoimmune disease and are asymptomatic at the time, although they may develop such a disorder in the future.
Neonatal outcomes / risks

2002: Cotes- Hernandez et al: Outcomes of 103 SLE pregnancies

- Mean gestational age at delivery: 37 weeks (range: 24 – 41)
- Prematurity in 28% (lupus activity and HT strongest predictors)
- Mean birthweight 2162g (range 800g – 4100g)
- IUGR in 35% (9.4 – 35%)
- 80% vaginal delivery; 20% Caesarian section
Neonatal outcomes / risks

2002: Cotes- Hernandez et al: Outcomes of 103 SLE pregnancies

- Mean gestational age at delivery: 37 weeks (range: 24 – 41)
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- 80% vaginal delivery; 20% Caesarian section

Increased risk of adverse pregnancy outcomes for hospitalisation of women with lupus during pregnancy: a nationwide population-based study.

1010 SLE pregnancies CW 5050 randomly selected pregnant women

LBW: 14.9% vs 7.2% --- SLE: 2.23 times more likely
Preterm birth: 14.4% vs 8.5% --- SLE: 1.89 times more likely
SGA: 28.5% vs 17.5% --- SLE: 1.87 times more likely
Neonatal outcomes: if full term, without obstetric complications?

28 full-term neonates of SLE mothers vs control group of 66 full-term babies of age and parity matched controls:
Statistically significant differences:
  - birth weight (2,775 vs. 3,263 g - \( p < 0.05 \))
  - SGA frequency (25\% vs. 4.5\% - \( p < 0.05 \))

Re effect of maternal auto-antibodies on neonates
ANA tested in 17 neonates in lupus group: 10 neonates positive anti-dsDNA at birth and became negative at 6 - 12 months age.
Anti-Ro/SS-A and anti-La/SS-B Abs in 5 and 3 neonates, respectively
  - none developed CHB or neonatal Lupus
Thrombocytopenia (plats < 100) in 7 SLE mums: 5 neonates thrombocytopenia (< 150)
  - spontaneous recovery within 2 weeks

Minor physical anomalies are not increased in the offspring of mothers with SLE


13/30 (43%) infants had minor anomalies - general population (14-40%)
- 1/3 women reported alcohol (7), tobacco (4), and illicit drug use (4).
No major anomalies. Facial anomalies - most common MPAs

The relative risk and 95% confidence interval for any MPA were:
2.05 (0.99 to 4.26) for tobacco use
1.95 (0.92 to 4.11) for alcohol use

1.36 (0.165 to 11.23) for maternal disease flare (#2 also illicit drug use)
0.63 (0.27 to 1.47) for prednisone use
0.72 (0.21 to 2.44) for aspirin use.

* unable to calculate RR because illicit drug exposure was not reported in mothers whose infants did not have any MPAs
<table>
<thead>
<tr>
<th>Symptom Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>Constitutional</td>
<td>Fatigue that can be debilitating throughout entire pregnancy</td>
</tr>
<tr>
<td>Skin</td>
<td>Palmar erythema and a facial blush from increased estrogen</td>
</tr>
<tr>
<td>Face</td>
<td>Melasma: ‘Mask of Pregnancy’ A macular, photosensitive hyperpigmented area over cheeks and forehead.</td>
</tr>
<tr>
<td>Hair</td>
<td>Increased hair growth and thickness during pregnancy</td>
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<tr>
<td></td>
<td>• Hair loss in the weeks to months post-partum</td>
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<tr>
<td>Pulmonary</td>
<td>Increased respiratory rate early in pregnancy from progesterone.</td>
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<td></td>
<td>• Dyspnea from enlarging uterus late in pregnancy</td>
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<tr>
<td>Musculoskeletal</td>
<td>Back pain in 2nd and 3rd trimesters</td>
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<tr>
<td></td>
<td>• Relaxin loosens SI joint and symphysis pubis</td>
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<td></td>
<td>• Gravid uterus increases lumbar lordosis</td>
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<tr>
<td></td>
<td>• Joint effusions: noninflammatory in lower extremities</td>
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<tr>
<td>CNS</td>
<td>Headache can be part of normal pregnancy or associated with hypertension.</td>
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<tr>
<td></td>
<td>• Seizures occur in eclampsia</td>
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<tr>
<td></td>
<td>• Cerebral vascular accidents can be caused by preeclampsia or antiphospholipid syndrome</td>
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</tbody>
</table>
What’s normal for pregnancy vs active SLE disease

- Arthralgias are common among pregnant women; worsening fibromyalgia seen – only steroids for true inflammation
- Fall in HCT – dilutional vs haemolytic anaemia of SLE / HELLP
- Mild thrombocythaemia (plat 100) seen in 8% healthy pregnancies. Below 100 – think SLE / HELLP
- Creatinine should fall due to increased GFR – proteinuria that doubles from baseline – concern
- In normal pregnancy complement levels may increase 10–50% in response to increased hepatic protein synthesis
- ESR is unreliable in pregnancy as it increases significantly in normal pregnancy. The CRP may be more useful
Pregnancy probably increases lupus activity

- 50% of women will have measurable SLE activity during pregnancy – mostly mild to moderate, mostly skin, arthritis / Hematologic disease
- 15–30% have very active SLE in pregnancy

- Risk factors for increased lupus activity:
  Active lupus within the 6 months prior to conception
  Multiple flares in the years prior to conception
NB references

Lupus Activity in Pregnancy
- Megan E. B. Clowse, MD, MPH. Associate Professor of Medicine, Division of Rheumatology & Immunology, Duke University Medical Center, Durham, North Carolina

The Hopins Lupus Pregnancy Center: Ten Key Issues in Management
- Michelle Petri, MD, MPH. Division of Rheumatology, Johns Hopkins University School of Medicine
Gonadal suppression using GnRH-a

- Leuprolelin, a synthetic gonadotropin-releasing hormone analog (GnRH-a)
- Initially stimulates pituitary release of the gonadotrophins LH, FSH, but then downregulates the GnRH receptors
- results in loss of gonadal stimulation and period of quiescence ie diminishing ovarian function during the period of the toxic treatment; decrease the rate of follicular atresia
Gonadal suppression using GnRH-a

- Give monthly IM Leuprolrelin acetate injections (3.75-mg monthly) during CYP treatment to protect against premature ovarian failure (POF)
Evidence for use

Somers et al. Arthritis Rheum 2005 Sep;52(9):2761-7:
• POF developed in 5% (1/20) women treated with GnRH-a, compared with 30% (6/20) controls, matched by age and cumulative CYC dose.

• A study of 25 women with Lupus and diffuse proliferative glomerulonephritis, who received IV monthly CYC and 3.75 mg IM Leuprolide, all the women regained their menses after their treatment courses; three eventually became pregnant

- a meta-analysis of 9 studies (included 366 women): 3 studies included women with autoimmune disease receiving CYC; 6 studies of women with hematologic malignancy receiving combination chemo

In total, 178 women were treated with GnRHa during chemotherapy,
- 93% of these maintained ovarian function vs 48% of the 188 women not treated with GnRHa
- Among the GnRH a-treated women: 22% achieved pregnancy following treatment compared with 14% of women without GnRHa therapy (summary RR = 1.65, CI 1.03-2.6).
If preserved fertility ---

- For women who remain fertile post - CYP

Reassuringly, there are no reports of increase in foetal abnormalities or abortion rates.
Male fertility

- Reduced sperm count - in relation to total dose of CYP
- Usually reversible within one year's completion of Rx
- Occasionally - particularly after high dose CYP, sterility can be permanent.

Sperm banking prior to therapy is recommended!

- When no sperm are found in ejaculate / if patient unable to ejaculate - sperm recovered by epididymal sperm aspiration or testicular sperm extraction (TESA)

("Suppression of testicular function during chemotherapy with GnRH analogues - not been successful and is not recommended as the main protective measure")
Males: CYP and fetal abnormalities in offspring

CYP can result in some fetal abnormalities, if conceive during treatment.
• spermatogenesis takes 10 weeks and spermatozoa have no DNA repair mechanisms.
• at the cellular level there is evidence of both overt and covert genomic damage and some fetal abnormalities
• risks are quite difficult to assess but ---

Suggest allowing a number of spermatogenic cycles to pass after CYP before choosing to have children.

Males advised to take contraceptive precautions throughout treatment and for 12 months after.
Assessing renal function — what’s normal?

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<tbody>
<tr>
<td>Creat</td>
<td>73</td>
<td>65</td>
<td>51</td>
<td>47</td>
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<tr>
<td>Urea</td>
<td>4.3</td>
<td>3.5</td>
<td>3.3</td>
<td>3.1</td>
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<tr>
<td>Proteinuria up to</td>
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<td>300mg /day</td>
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<td>Albumin falls 5-10g/l</td>
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<td>Serum sodium falls</td>
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<td>by 5meq/l</td>
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<td>Normal serum Bicarb</td>
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<td>18-22mmol/</td>
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‘Hyperfiltration’ of normal pregnancy occurs; maintained until 3rd trimester. Thereafter, transient reduction in GFR.
<table>
<thead>
<tr>
<th>Creatinine Range</th>
<th>Loss GFR during preg</th>
<th>Persistant loss post partum</th>
<th>ESRF</th>
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<tbody>
<tr>
<td>Creat &lt; 125</td>
<td>2%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Creat 125 - 180</td>
<td>40%</td>
<td>20%</td>
<td>2%</td>
</tr>
<tr>
<td>Creat 180 – 220</td>
<td>65%</td>
<td>50%</td>
<td>33%</td>
</tr>
<tr>
<td>Creat &gt; 220</td>
<td>75%</td>
<td>60%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Creatinine > 180: 1 in 3 chance of ESRF within 1 year

Davison’s pooled data