Lupus And Female Issues: From Puberty through Menopause

A look at lupus through the eyes of a reproductive endocrinologist and infertility specialist...

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Disclosures

• No financial disclosures or conflicts of interest
Objectives

• Discuss SLE and reproductive health
• Discuss the effects of rheumatologic disease and therapies on gonadal function
• Discuss options for fertility preservation
• Increase awareness
Autoimmune disease and the ovary
SLE specific women’s reproductive health issues

• Frequently diagnosis is during childbearing years
• Increased risk of pregnancy complications (mom and baby)
• Increased risk of subfertility and infertility
• Increased chance of early menopause
• Fertility preservation options
• Contraception options
• Breastfeeding concerns
SLE and pregnancy

Part 1
SLE and Ovarian/Pregnancy Health

- Kidney Disease?
- Antibodies?
- CYC treatment?
- Transplant?
Increased risk to pregnancy

- Presence or more severe renal disease
- Hypertension (especially uncontrolled)
- Previous thrombosis
- Presence of antibodies
  - Antiphospholipid antibodies
  - Anti-Ro/Anti-La (SSA and SSB)
- Restrictive lung disease, heart failure, chronic renal failure, stroke in last 6mo
- Recent severe flare in last 6 months
Risks in pregnancy

• **Mom**
  • Exacerbation
    • Pregnancy
    • Postpartum
  • Thrombosis (clot)
  • Hypertension
  • Hemorrhage
  • C-section

• **Baby**
  • Growth restriction
  • Preterm Birth
  • Neonatal lupus
  • Fetal loss
Meds in pregnancy (examples)

• Higher risk of fetal harm
  • Mycophenolate mofetil, azathioprine, cyclophosphamide, methotrexate, leflunomide, warfarin (1st trimester), ACEI/ARBs

• Selective use (discuss individual risk w/MD)
  • NSAIDs (avoid around conception and 3rd trimester), Glucocorticoids, ?azathioprine, cyclosporine, ?TNF antagonists

• Likely minimal risk
  • NSAIDs (other times), hydroxychloroquine, aspirin, sulfasalazine (w folic acid)

• Unknown
  • Biologics (?TNFα antagonists)

** These categories are for discussion purposes only and may change at any time-discuss with MD!!!
Pearls prior to pregnancy in SLE

• Ideally SLE quiet and renal disease in remission at least 6 months
• Consider preconceptual counseling and pregnancy care by MFM (high risk OB)
• Pulmonary hypertension only absolute contraindication to pregnancy due to risk
Menstrual function and SLE

Part 2
Menstrual Function

• Menstrual irregularities are common in women with SLE
  • May be related to systemic inflammation
  • May be related to ongoing therapy
  • May be related to past therapy

• *Remember*-continued menses after treatment does not imply normal fertility
Contraception

- Low dose estrogen-progestin OCP probably safe in mild, well-controlled SLE (individualized decision, discuss with MD!!)
  - May want to avoid if previous clot, uncontrolled hypertension, antiphospholipid antibodies, stroke, heart disease, nephrotic syndrome, ?smoker

- Progestin only likely safe—but more side effects and timing issues

- May consider longer acting options which are often progestin only

- ** Pregnancy may be a bigger risk than the contraception!
Menopause

• Increased risk of premature menopause depending on past therapies
• Menopause may correlate with decreased SLE symptoms
• Menopause issues:
  • Osteoporosis-risks also go up with steroids
  • Heart disease-risks also go up with steroids
  • Hormone replacement therapies
    • Risk benefit ratio-individualize therapy
    • May want to avoid if previous clot or antiphospholipid antibodies
Autoimmune Disease, Cytotoxic Therapies, & Fertility Preservation

Part 3
Cytotoxic Therapies and Reproduction

- Increased survival and decreased morbidity

- Quality of life issues
  - Loss of femininity/masculinity
  - Psychosocial distress
  - Fertility potential

- Age
  - Associations with disease and fertility
  - Delayed childbearing

SEER statistics. 2010-2011.
Treatment effects on fertility

• May be temporary

• The majority of past studies focus on the risk of POF/POI or azoospermia
  • ASCO guidelines- *Permanent amenorrhea risk med categories*

• Many women have diminished ovarian reserve despite normal menses

• Best estimates-risk of infertility (limited data; most in cancer)
  • 40-80% in females
  • 30-75% in males
  • Depends on age, cancer/disease site, treatment type and dose and pretreatment fertility

### Phenotypes of Ovarian Insufficiency

<table>
<thead>
<tr>
<th>Clinical State</th>
<th>Serum FSH Level</th>
<th>Fertility</th>
<th>Menses</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
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<td>Normal</td>
<td>Regular</td>
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<td>Occult</td>
<td>Normal</td>
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<td>Regular</td>
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<td>Biochemical</td>
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<td>Regular</td>
</tr>
<tr>
<td>Overt</td>
<td>Elevated</td>
<td>Reduced</td>
<td>Irregular or absent</td>
</tr>
</tbody>
</table>


Measuring ‘Ovarian Reserve’

• Term coined to predict oocyte yield and outcomes in IVF; Individualize therapies

• Serum assays
  • FSH, Estradiol, Inhibin B
  • Anti-Müllerian Hormone (AMH)

• US measurements
  • Antral follicle count (AFC)
  • Ovarian volume

AMH in cancer survivors: Dose-dependent decline

Is it the disease or the therapies?
Does ovarian dysfunction predict autoimmune disease?

- Ovarian dysfunction and subsequent autoimmune disease
  - Primary ovarian insufficiency (POI or POF; 1-2% of population)
  - Higher prevalence of autoimmune disease in POI women than general population
    - Thyroid and adrenal most common
    - Other syndromes
  - Etiologic factor in POI or a consequence?
Or does autoimmune disease lead to ovarian dysfunction?

- Autoimmune disease and subsequent ovarian dysfunction
  - Autoimmune disease severity
  - Therapies
  - Fertility preservation
  - Genetics...
Is it in the inflammation?

• SLE disease alone may decrease ovarian reserve
  • Lawrenz B et al, Lupus 2011

• JSLE patients with regular menstrual cycles show signs of diminished reserve during therapy vs controls
  • Aikawa NE et al, Clin Exp Rheumatol 2012
Or in the cytotoxic medications?

- Often related to cumulative dose
- Age of disease onset and age of therapies
- Timing in relation to pubertal/menarchal status
SLE and ovarian function

• Known effects of cyclophosphamide
  • Longer duration/larger cumulative dose
  • Older age
  • 50% amen 32+ yrs: 8gm/m2
  • 90% amen 32+ yrs: 12gm/m2
    Ioannidis JF. J Rheumatol 2002; 29(10)

• More amenorrhea w longer duration of disease (>5yrs), anti-Ro, anti-U1RNP?

• Less flares if amenorrheic??
  Mok CC. Arthritis Rheum 1999;42(6)
Chemotherapy-like meds

• Often the focus is on alkylating agents
• Others may be synergistic
• Animal studies suggest a dose-dependent loss of primordial follicles with cyclophosphamide doses as low as 20 mg/kg
• We often underestimate gonadotoxicity and do not think about damage to the rest of the ovary (stroma)
Cyclophosphamide

• Target?
  • Rapidly dividing granulosa cells and oocytes
• Most studies use POF/POI as primary outcome
• Prepubertal girls-depends on combo of meds; mixed studies; some show depletion of oocytes
• Don’t forget the boys too…
Other medications of interest

• Methotrexate/Leflunomide
  • ? Some ovarian effect
  • Less data in rheumatic disease patients than in cancer patients

• TNF-α
  • Pivotal role in inflammation
  • Also pivotal role in ovarian function

• Remember-there is a difference between teratogenic and cytotoxic to the ovary in some cases...
GnRH Agonists

• Protecting ovarian function—”a return to the prepubertal state”

• Proposed mechanisms:
  • Central
  • Ovarian receptors
  • Decreasing metabolism and blood flow
  • Upregulation of gonadal protective molecules -prevent apoptosis?
  • ??? Protection of germ line stem cells
Use of GnRH Agonists

• Bottom line: Conflicting data
• Not side effect/risk free

• Animal data supports use
  • Improved pregnancy rates & follicular loss
    Ataya et al. Cancer Res 1985; 45(8); Ataya et al. Reprod Toxicol 1993;7(3)
    Ataya et al. Biol Reprod 1995;52 (primates); Meirow et al. Hum Reprod 2004

• Observational and small controlled studies are mixed

• Much less data in rheumatologic patients
Fertility preservation procedures
Fertility preservation options

• Males
  • Sperm banking
  • Testicular sperm extraction and banking
  • Testicular tissue freezing

• Females
  • Embryo banking
  • Oocyte banking **
  • Ovarian tissue banking
  • GnRH agonist therapy
  • Pelvic shielding, ovarian transposition
Female patients
Fixed Oocyte Pool

Adapted from Speroff. Clinical Gynecologic Endocrinology and Infertility. 7th ed.
Age has ALWAYS mattered: IVF Pregnancy Rates Decline with Age

Decline related to quantity and quality of oocytes
Female Options

• Most popular choices
  
  • **Embryo Banking**
    • **Remains standard of care**
    • Requires sperm
  
  • **Oocyte (EGG) Banking**
    • No longer experimental!!
  
  • Vitrification has improved success
  
  • Financial assistance programs
IVF in cancer/rheumatology patients

• Ovarian Stimulation
  • Gonadotropin Injections
    • +/- Letrozole or tamoxifen
  • Medications to prevent ovulation
  • Monitoring-serum and ultrasound

• Ultrasound guided follicle aspiration
  • Oocyte retrieval

• Fertilization
  • Conventional or ICSI

• Embryo culture and cryopreservation
Oocyte Retrieval
Oocyte Retrieval
IVF in patients who need cytotoxic therapies

• When to start stimulation?
  • Early follicular phase
  • Random-start in follicular or luteal phase
    • Similar results in small series/studies

• Bottom line...can now start ovarian stimulation quickly and immediately!
Ovarian stimulation in cancer/rheumatology patients

• Number of oocytes may be reduced
  • Catabolic state, HPA and HP-gonadal axis may be altered
• Fertilization rates often similar
• Require more medication
• Longer stimulation
• Increased risk of poor response
• ? Oocyte quality issue

Additional risks for autoimmune disease patients

• Thrombosis risk
  • May be ok in certain SLE patients
    • Case series; Elizur SE et al, Rheumatology 2008

• Comorbid conditions

• Risks to offspring

• Future pregnancy
Other options for women

• Ovarian tissue cryopreservation
  • Experimental
  • How to utilize?
  • Requires general anesthesia, surgery, need to remove often part or all of 1 ovary; cortex usually what is frozen
    • Limited duration of implant survival

• Pelvic Shielding
• Ovarian transposition
• GnRH agonists
Other Hot Topics

• Immediate IVF with In Vitro Maturation
  • Increasing use, still investigational

• New medications to protect the ovary

• PGD (pre-implantation genetic diagnosis) on frozen embryos
Thank you!

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