

Lupus And Female Issues: From Puberty through Menopause

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

Amber R. Cooper, MD, MSCI

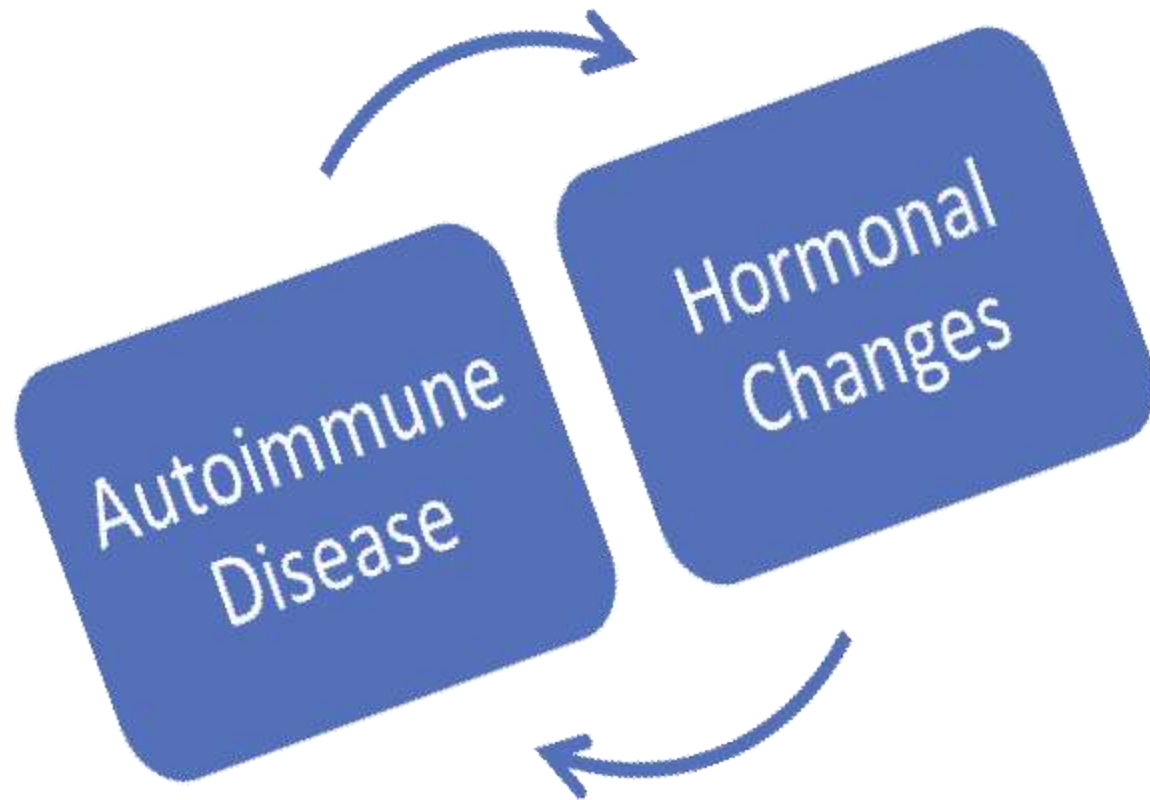
Disclosures

- 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



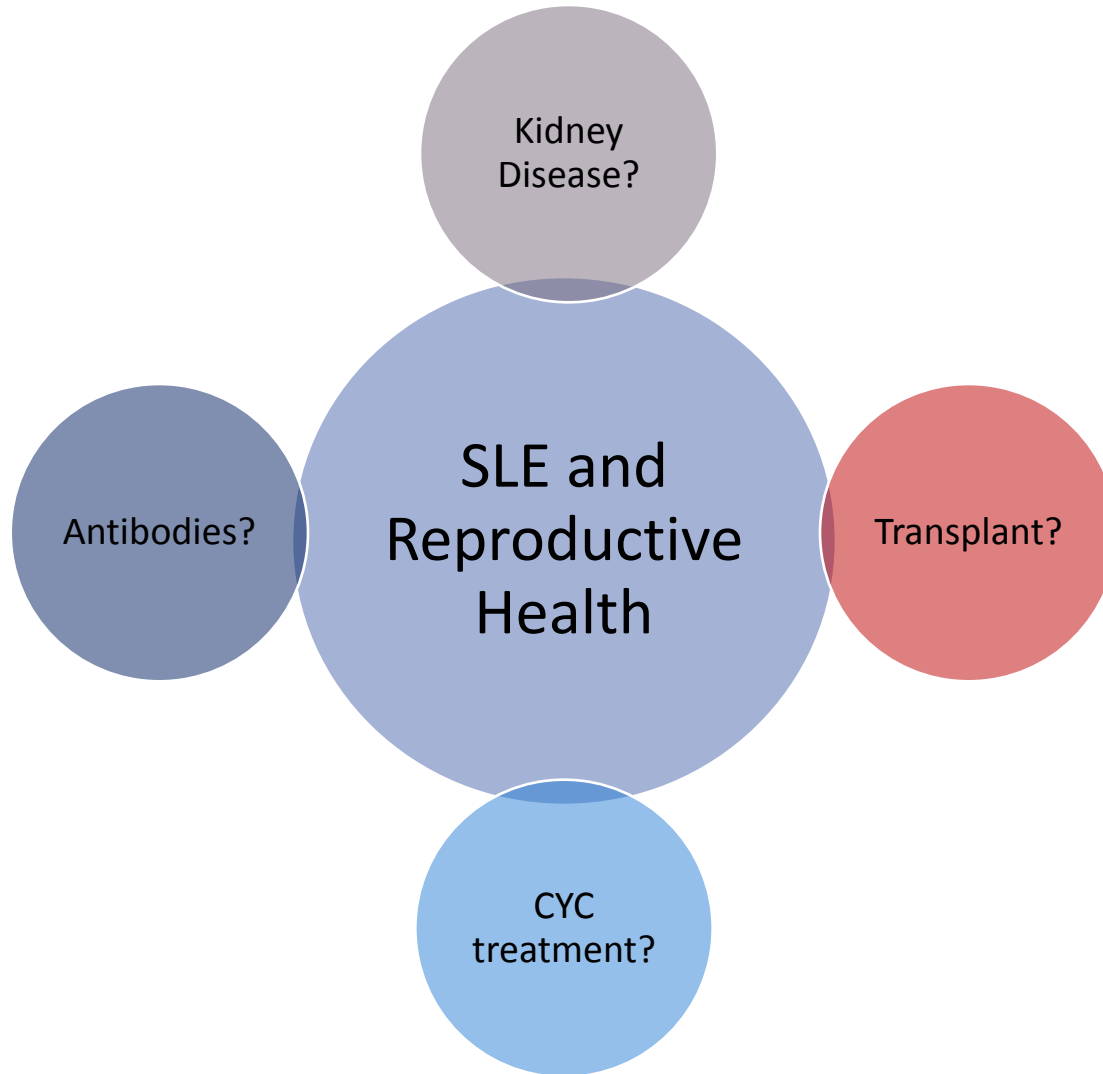
SLE specific women's reproductive health issues

- 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



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 (?TNF α 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

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

Clinical State	Serum FSH Level	Fertility	Menses
Normal	Normal	Normal	Regular
Occult	Normal	Reduced	Regular
Biochemical	Elevated	Reduced	Regular
Overt	Elevated	Reduced	Irregular or absent

Cooper AR, Covington SN, Nelson, LM. Primary ovarian insufficiency (POI). In: Santoro N, et. Al. ed. Amenorrhea: A Case-based clinical guide. Humana Press, c2011.

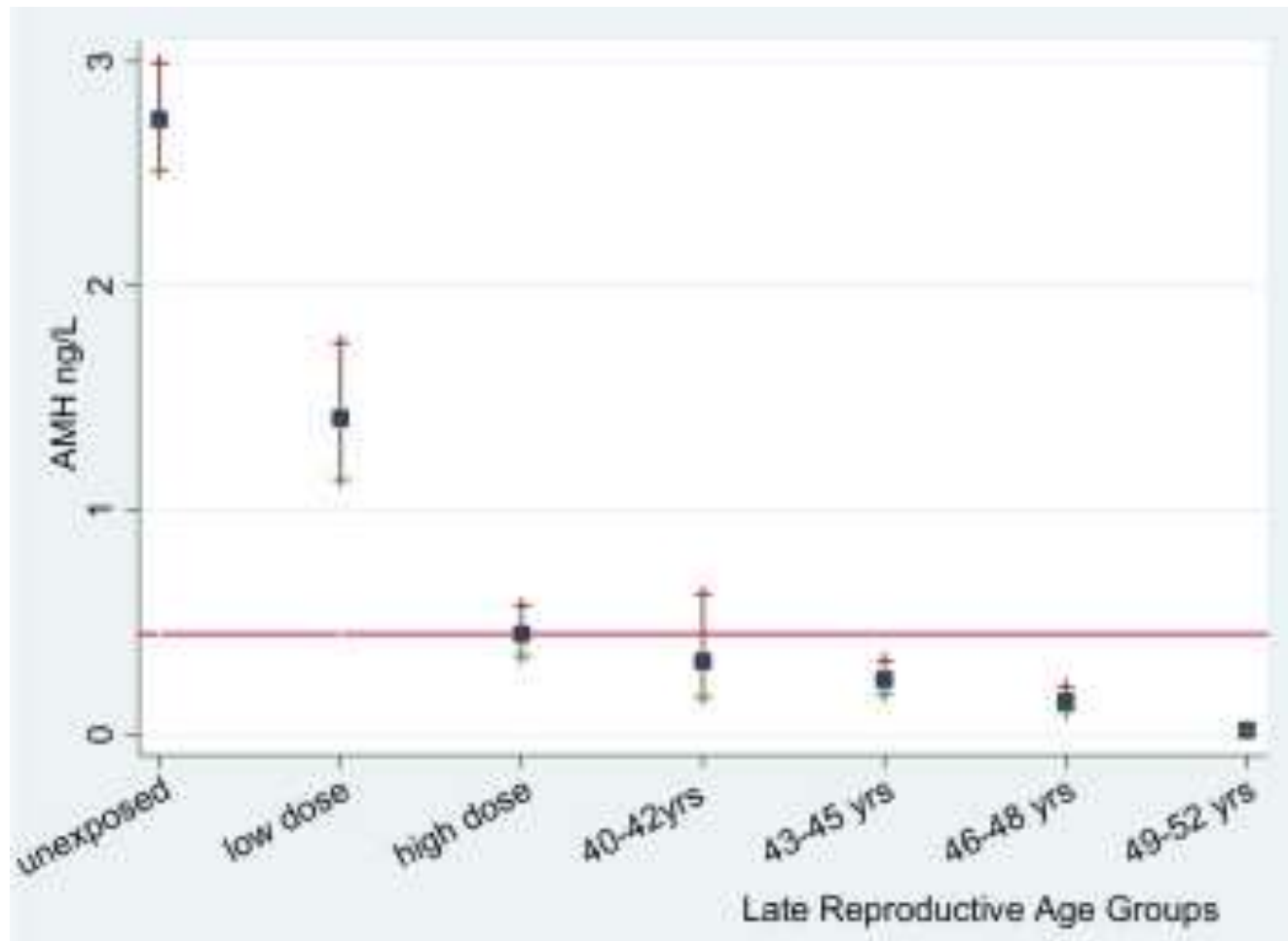
Nelson LM. Clinical practice. Primary ovarian insufficiency. N Engl J Med 2009;360:606-14.

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



Gracia et al. Fertil Steril 2012.

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

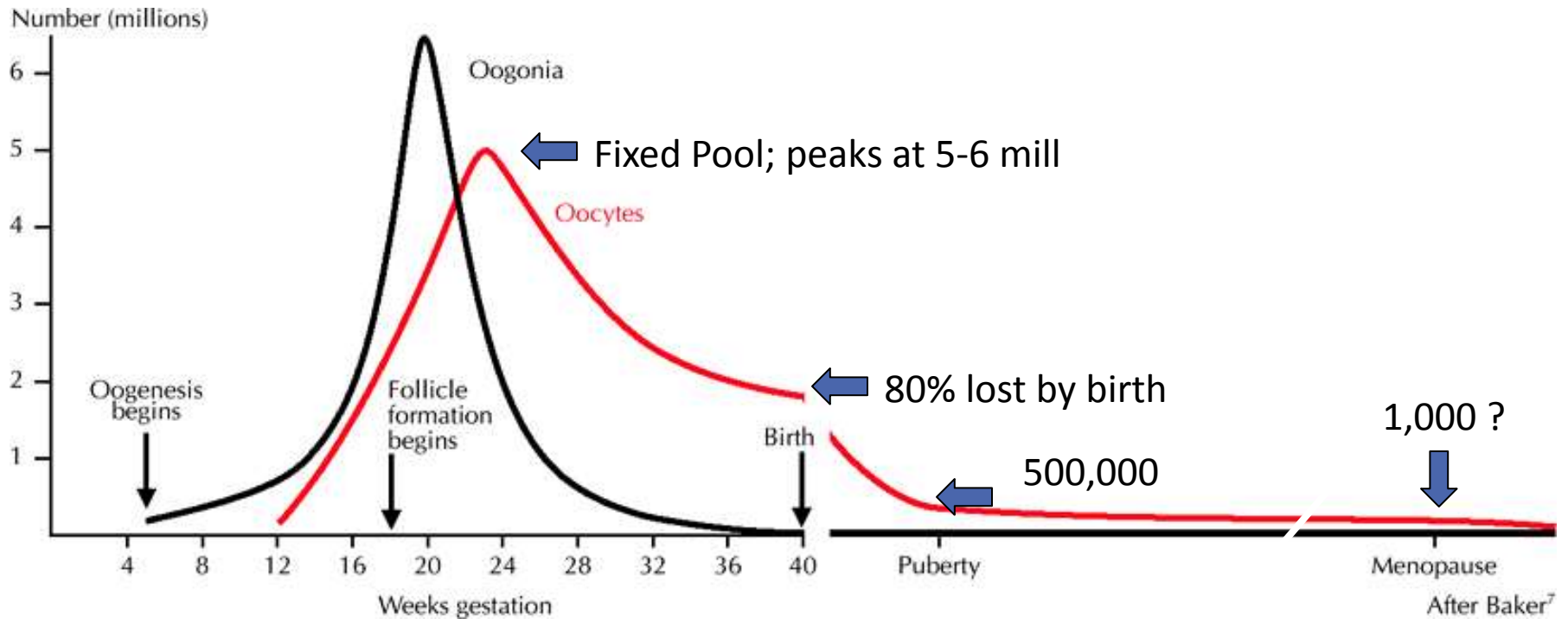
- Sperm banking
- Testicular sperm extraction and banking
- Testicular tissue freezing

- Females

- Embryo banking
- Oocyte banking **
- Ovarian tissue banking
- GnRH agonist therapy
- Pelvic shielding, ovarian transposition

Female patients

Fixed Oocyte Pool

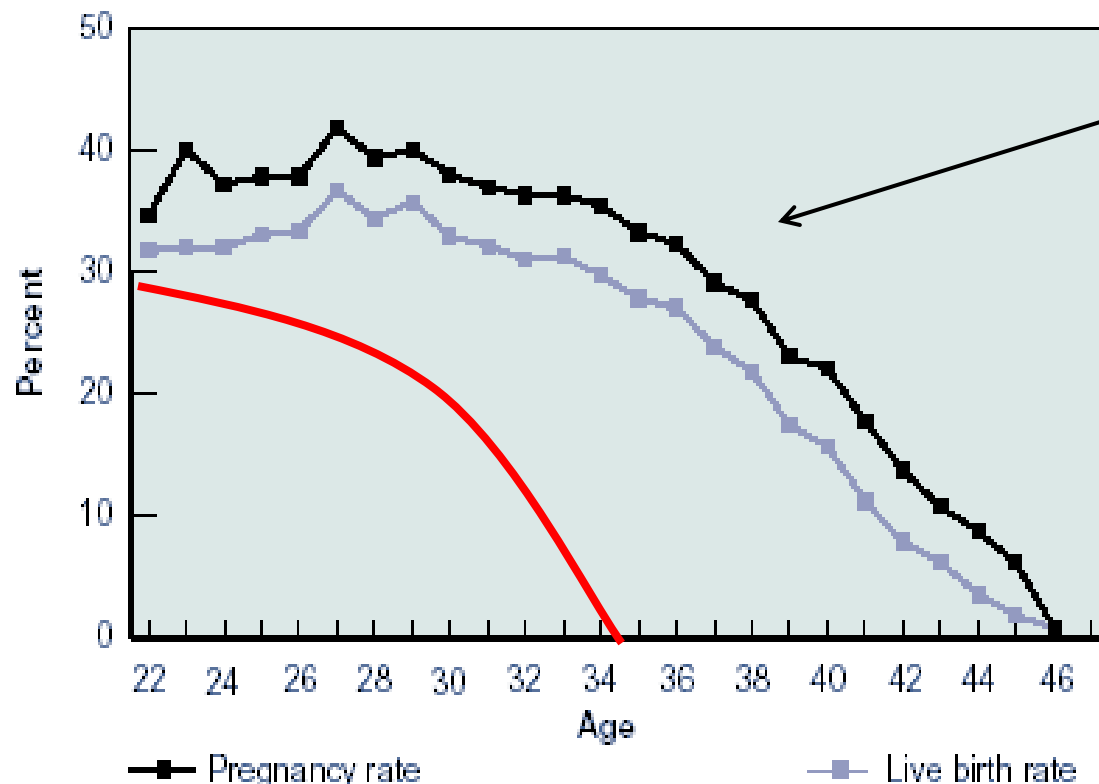


Adapted from Speroff. *Clinical Gynecologic Endocrinology and Infertility*. 7th ed.

Age has ALWAYS mattered: IVF Pregnancy Rates Decline with Age

Figure 10

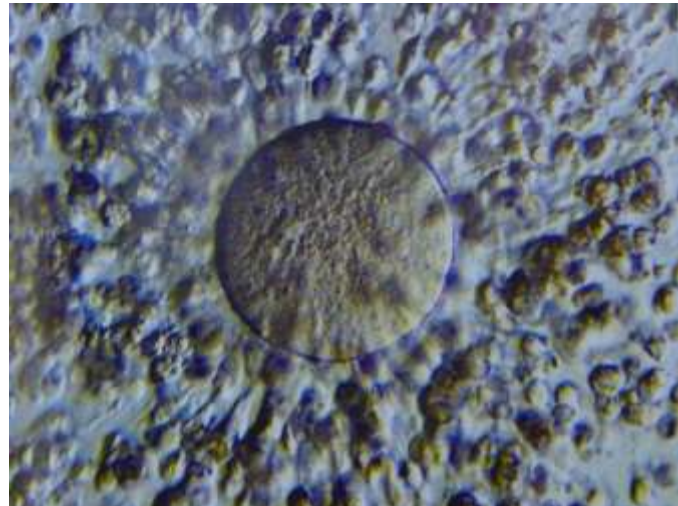
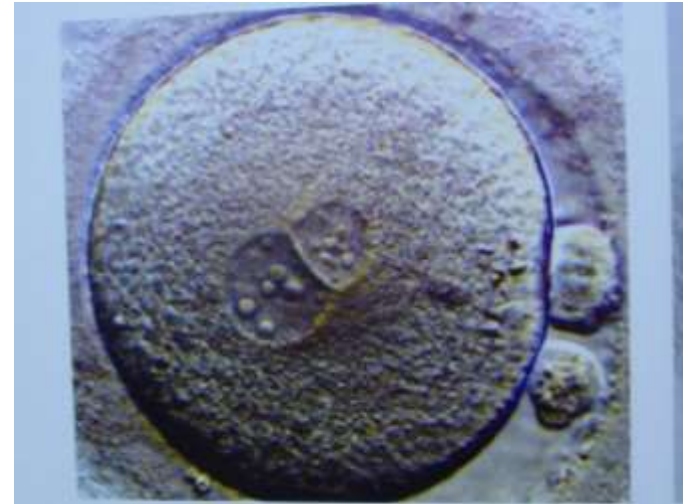
Pregnancy and Live Birth Rates for ART Cycles Using Fresh, Nondonor Eggs or Embryos, by Age of Woman, 1999



**Decline related
to quantity and
quality of
oocytes**

Female Options

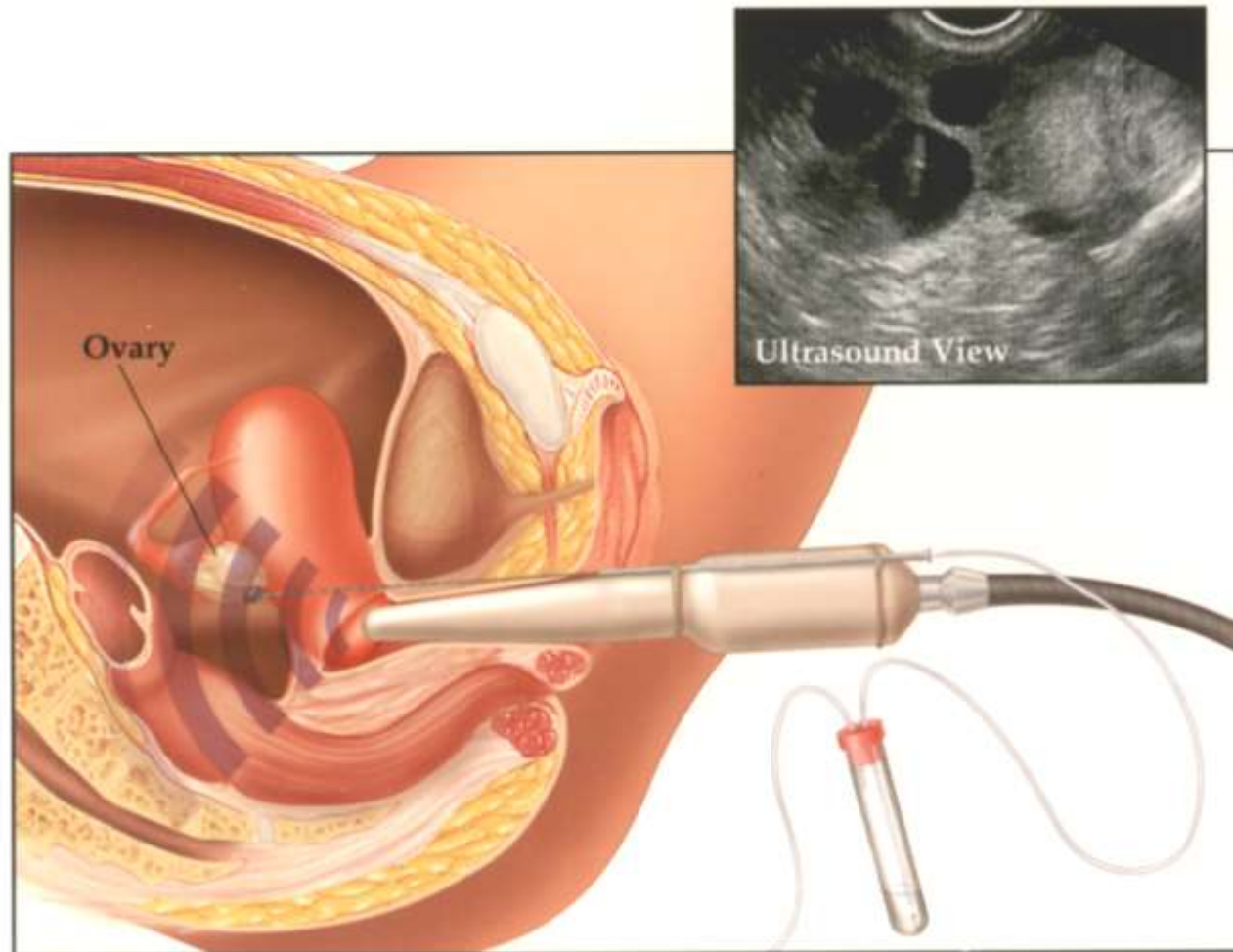
- Most popular choices
 - Embryo Banking
 - ** Remains standard of care **
 - Requires sperm
 - Oocyte (EGG) Banking
 - No longer experimental!!
 - Vitrification has improved success
 - Financial assistance programs



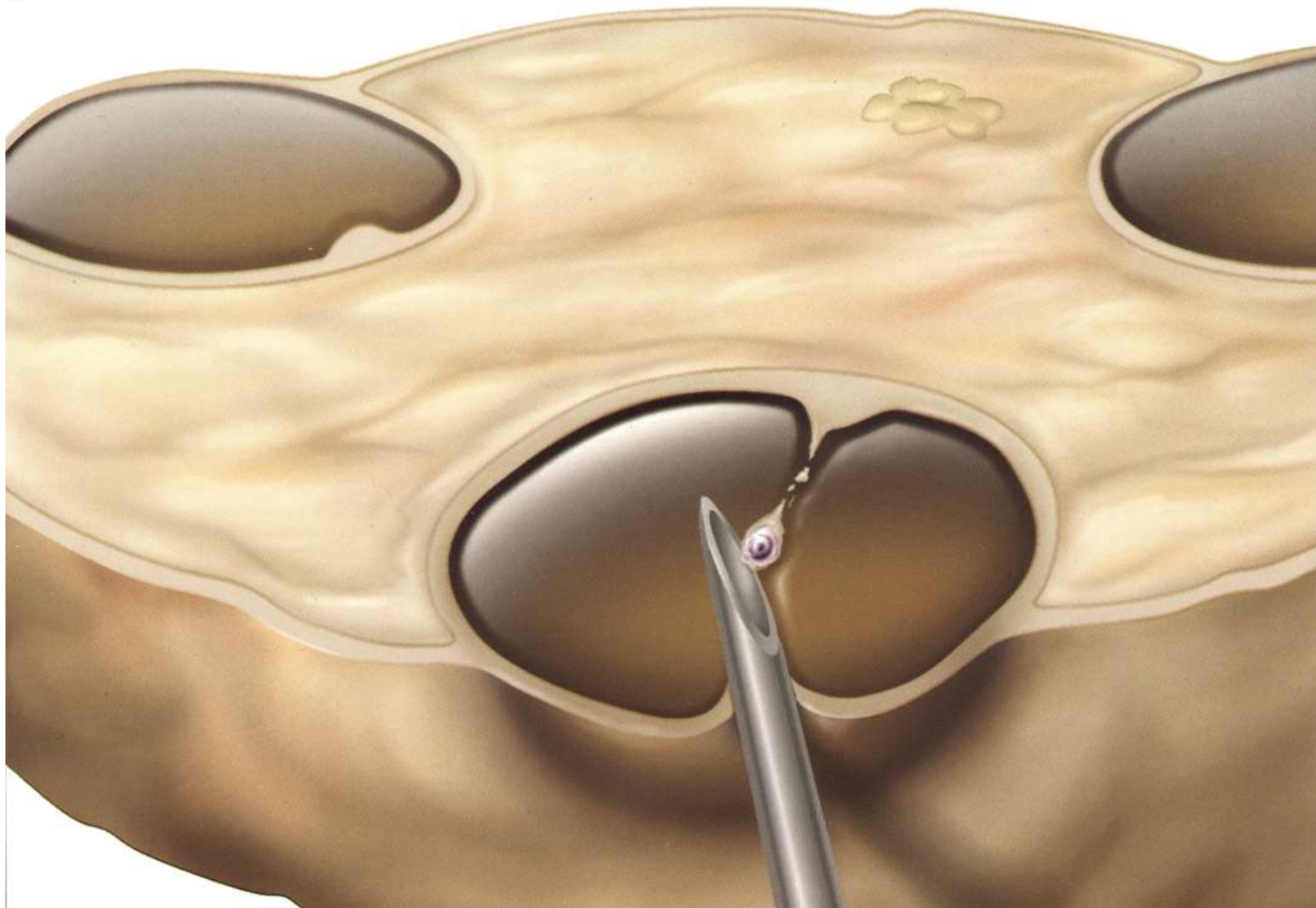
IVF in cancer/rheumatology patients

- 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

Quintero et al. Fertil Steril 2010.; Friedler S et al. Fertil Steril 2012.

Domingo J et al. Fertil Steril 2012. In Press

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!

Amber R. Cooper MD
Vios Fertility Institute

1-866-258-VIOS

info@viosfertility.com

