Why Focus on Survivorship?

- Rapidly growing population
- Increasing patient and community expectations for good quality of life
- Increased funding of survivorship research
  - NIH investment in survivorship
    - $38,000,000 Fiscal 2001
    - $46,000,000 Fiscal 2004

What has contributed to this remarkable progress?

- Earlier detection
- New and more effective therapies often including multimodal and multi-agent combinations
- More effective adjuvant and/or maintenance therapies
- Better supportive care
- Growing attention to long-term surveillance
Survivors Needs
Lance Armstrong Foundation LIVESTRONG™ Poll n=1020

- **Secondary Health Problems**
  - 53% - secondary health problems
    - 54% - deal with chronic pain
    - 33% - infertility
- **Non-Medical Support**
  - 49% - non-medical cancer needs were unmet
  - 53% - practical and emotional consequences of cancer are often harder than medical issues
- **Emotional Support**
  - 70% - dealt with depression
  - 78% - did not seek professional services
- **Relationships**
  - 58% - dealt with loss of sexual desire and/or sexual function

Cancer Survivorship is an International Agenda

- **CDC Report 2004**
  - Enhance surveillance, identify ongoing health concerns
  - Educate survivors and general public about value of long-term follow up care
  - Establish clinical practice guidelines for survivorship
  - Establish multidisciplinary teams of health care providers for survivors
- **Lance Armstrong Foundation**
  - Funding source
  - Centers of Excellence
- **NCI**
  - Office of Cancer Survivorship
  - Comprehensive Cancer Center requirements

Why do Patients Need Long-Term Follow-Up?

- Chronic side effects of chemotherapy
- Late effects of
  - radiation therapy
  - surgery
- Risk of secondary cancers
- Other long-term health issues
Survivorship and QOL Concerns

- Cancer Screening
  - Ovarian cancer screening
  - Colon screening
- General Health Maintenance
  - Pap smears
  - Bone health
  - Cardiovascular concerns
- Reproductive Health Concerns
  - Pregnancy
  - Fertility
  - Sexuality
- Life Management
  - Diet
  - Exercise
  - Sleep management
  - Stress management
  - Time management

Breast Cancer-Related Complaints

- Anatomical sequelae from surgical intervention
- Sequelae from adjunctive therapy
  - Chemotherapy
  - Radiation changes
- Maintenance therapies
  - Hormonal manipulation
  - Immune modulators
  - Cytostatic medications

Effect of Treatment: Other Surgeries

- Cosmetic
  - Cosmesis may not always be satisfactory
  - Nipples?
- Prophylactic
  - Bilateral Salpingo-oophorectomy adversely affects sexual functioning
    - Early loss of estrogen has serious medical concerns
      - Prophylactic mastectomy
      - Fear of bilaterality
      - Fear of another primary

Major Concerns for Gynecology Survivorship

- Menopausal Hot Flashes
- Genital Syndrome of Menopause
- Sexual Complaints
- Fertility
- Other:
  - Cognitive and Sleep Disturbances
  - Musculoskeletal Changes
  - Bone

Menopausal Roadblocks

- Literature suggests that the adaptation after BC diagnosis is more difficult for younger women.
- Standardized measures of depression and QOL for younger women show greater changes in mood and poorer emotional functioning.
- Reproductive health effects of adjuvant therapy that specifically affect younger women:
  - Infertility
  - Early menopause
Hot Flashes

- Hot Flashes/Flushes:
  - sudden, transient sensations of warmth to intense heat with a range of physiologic and emotional responses (flushing, perspiration, palpitations, anxiety, embarrassment, irritation, disruption of activities especially sleep) maybe associated with a chill

- Frequency not necessarily related to reported severity → evaluation of hot flashes should include **frequency and patients’ subjective experience**

- 10-15% of women have frequent debilitating hot flashes lasting 1-5 minutes

1. Couzi et al. 1995

Highest frequency
  - in first 2 years of menopause
  - decline thereafter
  - Some persist for 10 years

- Study of women across nations (SWAN) study
  - ethnicity may play role

- Surgical menopause is more severe

- Severe hot flashes in 59% of BC patients
  - severity associated with younger age at diagnosis and with tamoxifen use

Treatment Pearls

- Medications
  - Anti-hypertensives
  - SSRI
  - Venlafaxine
  - Paroxetine (FDA approved)

- HT Alternatives
  - Nutritional counseling
  - Exercise
  - Environmental changes
  - Rhythmic breathing
  - Menopausal PJ/Chillow/Sheets
  - Supplements
  - Integrative medicine
    - Acupuncture
    - Maitake
    - Yoga
Other ongoing trials
- AI have surpassed tamoxifen in treatment for recurrent breast cancer
- Same maybe for early breast disease
- Support AI use for Breast Cancer patients

Will need good treatments for FSD, atrophic vaginitis, bone health and menopausal hot flashes

Introduction
- 25% of new cases present before the menopause and 15% before the age of 45. Younger age is associated with decreased social and emotional function
- Up to 90% BC survivors are suffering in silence. 20 years from diagnosis 29% report sexual problems attributable to having had BC
- FSD leads to changes in
  - Compliance, Marital discord and Poor overall health
- Sexuality is ignored and unaddressed
- Few studies have rigorously addressed sexual dysfunction most are retrospective studies


Urogenital and Vaginal Changes

- Dryness
- Vaginal irritation
- Malodorous discharge
- Sensitive vulva
- Thinning of vaginal rugae

- Urgency
- Frequency
- Urinary stress incontinence
- Increased risk for UTI
- Fecal incontinence maybe caused by decreased estrogen levels and neuromuscular dysfunction
  - The anorectum has abundant estrogen receptors
Breast cancer survivors can possibly use minimally absorbed local vaginal estrogen products like
- vaginal estrogen ring
- vaginal estradiol tablets

With very little systemic escape

Consider following estradiol levels, tailor the treatment regime.

Cellular Shift Changes

<table>
<thead>
<tr>
<th></th>
<th>Premenopausal</th>
<th>Post menopausal</th>
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</thead>
<tbody>
<tr>
<td>Superficial</td>
<td>15%</td>
<td>1%</td>
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<tr>
<td>Intermediate</td>
<td>80%</td>
<td>60%</td>
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<tr>
<td>Parabasal</td>
<td>5%</td>
<td>39%</td>
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</tbody>
</table>

Breast Cancer and Sexual Function

50% to 90% of breast cancer survivors complain of some form of FSD
- “Yes I am thankful to be alive, but I am dead down there”
- “Breast cancer treatment contributed to the deterioration of my excellent marriage”
- “They never told me I would feel like this.....”

- Most common FSD: vaginal dryness with painful intercourse
- Changes in self-esteem are very troublesome
- Prophylactic surgeries adversely affects sexual functioning
- Topical estrogen may not be associated with increased risk of breast cancer recurrence
  
AV Before & After Local Estrogen Therapy

Goals of Treatment

- Relieve symptoms
- Reverse anatomical changes
- Improve sexual function and quality of life

Lubricants

Moisturizers
Hormonal Options: Estrogens

- Systemic Hormonal
  - Tablets
  - Patches
  - Gels/Lotions
    - Estracort
    - Estrace
  - Creams
    - Crestor

- Vaginal Hormonal
  - Cream
    - Estrace® (micronized 17β-estradiol)
    - Femarin® (conjugated equine estrogens)
  - Ring
    - Estrin® (micronized 17β-estradiol)
    - Femring® (systemic)
  - Tablet
    - Vagifem® (17β estradiol)

Minimally Absorbed Local Vaginal Topical Estrogens

<table>
<thead>
<tr>
<th>Composition</th>
<th>Dosing</th>
</tr>
</thead>
</table>
| Vaginal Cream 17β Estradiol cream | Initial: 2-4 g 1-2 wk  
 Maintenance: 1 g/d (0.1 mg active ingredient/g) |
| Conjugated estrogens   | (Formally conjugated equine estrogens) |
| Vaginal ring 17β estradiol | Initial: 2 mg  
 Maintains 17β-estradiol for 90 days |
| Vaginal tablet Estradiol hemihydrate | Initial dose: 1 tab q/day for 14 days  
 Maintenance 1 tab qd  
 Tablet 1 tab 0.5 mg estradiol hemihydrate, equivalent to 1 mg of estradiol |

Effects of Local Estrogen

- Improve sensory perception
- Increase central and peripheral nerve transmission
- Increase lubrication
- Reduce pH
- Increase peripheral blood flow
- Augment capacity to develop muscle tension
- Increase vibratory sensation
- Increase vaginal vault relaxation
- Increase vaginal vault size
- Increase tissue elasticity
- Increase vaginal collagen content


Many Users Claim Vaginal Estrogen Interrupts Routine and Requires Privacy

81% ensure they have privacy before applying vaginal estrogen therapy.

On average, takes 1 min, 30 secs to apply.

25% apply in bedroom 68% apply in the bathroom

21% apply in morning 11% early evening 61% at night

Dislikes with Current VVA Therapies

<table>
<thead>
<tr>
<th>Dislike</th>
<th>OTC Rx</th>
<th>K-Y Vagisil</th>
<th>Astroglide</th>
<th>K-Y Silk</th>
<th>E Replens</th>
<th>Estrace</th>
<th>Premarin</th>
<th>Vagifem</th>
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<tr>
<td>It's messy</td>
<td>48%</td>
<td>40%</td>
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<td>Not enough relief for VVA symp</td>
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<td>Safety for long term use</td>
<td>41%</td>
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Putting WHI Risks Into Perspective

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk</th>
<th>EPT Absolute Risk (number per 10,000 women)</th>
<th>EPT Absolute Risk (number per 10,000 women)</th>
<th>ET Relative Risk</th>
<th>ET Absolute Risk (number per 10,000 women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>1.29</td>
<td>7 more</td>
<td>0.91</td>
<td>5 less</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.41</td>
<td>8 more</td>
<td>1.39</td>
<td>12 more</td>
<td></td>
</tr>
<tr>
<td>VTE</td>
<td>2.11</td>
<td>18 more</td>
<td>1.33</td>
<td>7 more</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1.26</td>
<td>8 more</td>
<td>0.77</td>
<td>7 less</td>
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</table>

Comparative Risk of Breast Cancer in RCT of Hormone Therapy and Statin Therapy


VVA and Sexual Function

- Cross-sectional, population-based study of 1,480 sexually active, postmenopausal women
- 57% had vulvovaginal atrophy
- 55% had female sexual dysfunction
- Women with sexual dysfunction ~4X more likely to also have vulvovaginal atrophy

Conclusion: Reducing symptoms of one condition may also relieve symptoms of the other

Kendall et. al. cautions that vaginal estradiol is contraindicated in postmenopausal women on adjuvant aromatase inhibitors1.

Labrie et. al. demonstrate that even small doses of vaginal preparations

- Vagifem 25 μg; Premarin Vaginal Cream result in significant systemic absorption through estrogen naïve vaginas(2).

Naessen et al showed that 7.5 μg/24h could improve the lipid profile and bone density without affecting the endometrium3-5.


UK study of 7 women on AI.
Serum E2, FSH, LH measured at baseline the 2, 4 7-10 and 12 weeks later.
Specific assay for postmenopausal LOW levels
Serum levels rose from baseline of <5pmol/l consistent with AI therapy to a mean of 72 pmol/l at 2 weeks, by week 4 this had decreased to <35 pmol/l in the majority of women.

Conclusion: Vagifem significantly raises systemic estradiol levels at least in the short term. This may reverse the estradiol suppression achieved by AI in women with Breast Cancer and is contraindicated.
Current Overview of the Management of Urological Atrophy in Women with Breast Cancer


Table 1. Estrogen Preparations and Maximum Annual Delivered Dose

<table>
<thead>
<tr>
<th>Product name</th>
<th>Mode of administration</th>
<th>Typical regimen</th>
<th>Nominal daily dose (mg)</th>
<th>Maximum annual delivered dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal estrool</td>
<td>Tablet</td>
<td>1 tablet daily</td>
<td>100</td>
<td>1000</td>
</tr>
<tr>
<td>Estrool</td>
<td>Capsule</td>
<td>1 capsule daily</td>
<td>50</td>
<td>500</td>
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<tr>
<td>Estriol</td>
<td>Gel</td>
<td>1 g qd</td>
<td>1000</td>
<td>10000</td>
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<tr>
<td>Estradiol ^</td>
<td>Cream</td>
<td>1 g nightly</td>
<td>500</td>
<td>5000</td>
</tr>
<tr>
<td>Estradiol ^</td>
<td>Tablets</td>
<td>1 tablet daily</td>
<td>100</td>
<td>1000</td>
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</table>

Local Estrogen Therapy and Risk of Breast Cancer Recurrence among Hormone Treated Patients: A Nested Case Control Study


**Design**
- Impact of vaginal estrogen on recurrence risk was evaluated among 917 women with BC recurrence (cases) who were compared to women with BC in remission (controls)
- Matched for age and initial endocrine treatment
- Rate of vaginal estrogen use was low (<3%)
- Most frequent local estrogen: cream and tablets

**Results**
- Rate of concomitant vaginal estrogen use with endocrine therapy was similar with cases and controls (2.1% versus 2.8% respectively) suggesting that concomitant use is not associated with an increased risk of recurrence (RR 0.97)
- The rate of sequential use of vaginal estrogen following completion of endocrine therapy was also similar (0.25 in cases and controls) suggesting there was no increased risk in the risk of recurrence

Dew et al: Conclusions

- **Cohort:** N=1472
  - HRT: 542 (23%)
  - Local vaginal estrogens: 69 (4.7%)
  - Tablets, cream
- **Diagnosis to treatment:** 5.25 years (0-20 years)
- **Median time of use:** 1 year
- **Deaths:** 11.5% entire population
  - 6% local vaginal estrogen users
- **Study was underpowered for definitive data outcomes**
- Topical vaginal estrogen usage appears not to increase risk of recurrent breast cancer

Important New Studies

Goldfarb et al (SABC 2012) n=26
- BC Stage 1-3 on AI; 10mcg 17β-estradiol
- Median change in estradiol from baseline to wk 12 was 0.2 with a range from -3.0 to 14.6
- Only 5/26 (19%) had sporadic elevation in E2 outside menopausal range
- Clinical significance of the systemic E2 absorption is unknown and warrants further study
- Impression:
  - Elevations in E2 are rare and brief, data does not support the routine monitoring of E2 levels
  - Improvements in sexual function is not associated with an elevation of E2 levels

Melisko et al (SABC 2012) N=29
- Vaginal Testosterone 1% 0.5g qd (15) Vs. Estring 2mg (14) in BC pt on AI
- Preliminary data.
  - Both effective at tx vaginal dryness
  - Neither have met criteria for stopping
  - Median and mostly transient elevations of E2 have occurred, more often and only persistent in the Test arm
  - Accrual continues

- Postmenopausal women with ER(+) or at high risk for BC who were taking an AI or a SERM. (Estring VS 25mcg-17β estradiol tablets) on VE for 90 days
  - VE Ring: E2 levels pre insertion and 12 weeks post insertion were significantly greater than controls (p<0.001)
  - VE Tablets: E2 levels pre insertion were NOT significantly different than controls (p=0.48) and post insertion levels were 76 pmol/L higher than pre insertion
  - Preliminary levels for pt on VE tablets were not elevated compared with those of controls suggesting that E2 elevations with this preparation may not be continuously sustained

Low Dose Vaginal Estrogen Treatment

Breast cancer survivors may possibly use minimally absorbed local vaginal estrogens products like the ring (Estring ®) and tablets (Vagifem ®) and Conjugated Equine Estrogen (Premarin Vaginal Cream) ® Estradiol cream (estrace ®)
- with very little systemic escape. OFF LABEL!

Kendal et al (2006): increased E2 level in BC patients on Vagifem ®

Surgical oncologists, medical oncologists, gynecologists and patients will often disagree about safety

NAMS and OBGYN advocate personalized and individualized plans

Formulate management plan
- Monitor estradiol levels
- Evaluate abnormal bleeding
- Try alternatives first
- Know your personal comfort zone
Topical Testosterone for Breast Cancer Patients with Vaginal Atrophy Related to Aromatase Inhibitors: A Phase II Study.

Abstract Purpose. Controversy exists about whether vaginal estrogens interfere with the efficacy of aromatase inhibitors (AIs) in breast cancer patients. With the greater incidence of vaginal dryness in patients on AIs, it is safe and effective hormone therapy is necessary. We hypothesized that vaginal testosterone cream could safely treat vaginal atrophy in women on AIs.

Methods. Twenty-one postmenopausal breast cancer patients on AIs with symptoms of vaginal atrophy were treated with testosterone cream applied to the vaginal epithelium daily for 28 days. Ten women received a dose of 300 μg, 10 received 150 μg, and one was not evaluable.

Results. Estradiol levels remained suppressed after treatment to <8 pg/mL. Mean total symptom scores improved from 2.0 to 0.7 after treatment (p < .001) and remained improved 1 month thereafter (p = .002). Dyspareunia (p = .0014) and vaginal dryness (p < .001) improved. The median vaginal pH decreased from 5.5 to 5.0 (p = .028). The median maturation index rose from 20% to 40% (p < .001). Although improvement in total symptom score was similar for both doses (-1.3 for 300 μg, -0.8 for 150 μg; p = .37), only the 300-μg dose was associated with improved pH and maturation values.

Conclusions. A 4-week course of vaginal testosterone was associated with improved signs and symptoms of vaginal atrophy related to AI therapy without increasing estradiol or testosterone levels. Longer-term trials are warranted.

Intravaginal DHEA (Vaginorm/Prasterone ®)

- Labrie et al. Menopause vol 16 no 5 907-922

- One ovule of DHEA 0.0%, 0.5%, 1.0% or 1.8%
- 7 days vaginal PH was significantly decreased
- Serum Estradiol and Testosterone remained within normal postmenopausal values at all DHEA values
- DHEA permits rapid effects for local beneficial effects against vaginal atrophy, without changes in estradiol thus avoiding the increased risk of breast cancer associated with the current intravaginal or systemic estrogenic formulations
Ospemifene (Osphena)

- First and Only oral non estrogen for the treatment of moderate to severe dyspareunia a symptom of VVA due to menopause
- 2010 RCT Stage III: SERM ospemifene
  - Quatrix Inc/ Shionogi Inc.
  - 827 women randomized either 30, 60 mg or placebo for 12 weeks
  - 60 mg was shown to be effective, well tolerated for vaginal dryness and dyspareunia
  - No proliferative effect on endometrium
  - Side effect: 8 % hot flashes
    - 0.7% severe in 60mg group
    - one participant (0.4%) in the 60 mg group discontinued because of hot flashes.

- Interesting: Ospemifene and 4-hydroxyospemifene effectively prevent and treat breast cancer in Mtag.TG Transgenic Mouse.

TSEC ( AKA STEAR) pair a selective estrogen receptor modulator (SERM) with 1 or more estrogens to provide clinical results based on their blend of tissue selective activities.  APPROVED AS DUOVIV ® STAY TUNED!!!

- The ideal TSEC maintains the positive benefits of estrogens on vasomotor symptoms, vulvar/vaginal atrophy (VVA) and bone without stimulatory effects on the uterus and breast
- The first TSEC in clinical development pairs Bazedoxifene (BZA) a SERM with a unique endometrial profile with conjugated estrogens.

Neogyn ® Vulvar Soothing Cream

- Cutaneous Lysate of cultured fetal fibroblasts
- More than 100 cytokines, growth factors, inflammatory interleukins IL-1RA, IL-4 and IL-10.
- In clinical studies improvement in symptoms of atrophy as well as for vulvar pain disorders (vulvodynia, lichen sclerosus)
- Don’t forget the VUVLA
**Treatment Tools**

- Lifestyle modification
- Diet/exercise
- Modify medications
- Structured sexual tasks
- Vibrators/dilators
- Sexual enhancers/accessories
- Moisuturizers/lubricants
- Behavioral techniques
- Mindfulness
- Therapy
- Relaxation exercises
- Acupuncture

**Pharmacological Agents**

- Hormones
  - Estradiol
  - Testosterone
- PDE5 inhibitors
- Local Treatment for atrophy
- BZA/CEE
- Osphefene
- Estriol
- Tibolone
- Bremelanotide
- Lybryo/Lybridos
- Femprox
- Flibanserin

**Treatment Paradigm**

- Alternative Medicine
- Structured Sexual Tasks
- Treat Systemic Illnesses
- Evaluate medications
- Patient and Partner Education
- Pain management
- Sexual Pharmacology
- Sexual Devices
- Behavioral Modification
- Mindfulness
A Tale of Recovery

Flibanserin

- Novel, non-hormonal therapy that works on key sexual pathways in the brain
- Over 10,000 women studied in trials to date
- Once daily pill taken at bedtime
- Demonstrated efficacy on measurements of desire, distress and satisfying sexual events (SSEs)
- Well tolerated safety profile. Most common side effects – dizziness, nausea, fatigue and somnolence
- Flibanserin acquired by Sprout Pharmaceuticals from Boehringer Ingelheim
- Re-submission to FDA with 14 new trials and a validation study scheduled for 2013

Flibanserin: Structure
Mechanism of ACTION

- Serotonin may have a role in HSDD by acting as a sexual satiety signal.
- Serotonergic agents (e.g. SSRIs) inhibit desire, arousal, and orgasm.
- Flibanserin is a 5-HT1A receptor agonist which could have pro-sexual effects.
- Stimulating the serotonin 5-HT2A receptor has been associated with decreased sexual behavior (male rodents).
- Flibanserin is a 5-HT2A antagonist which might have pro-sexual effects.

**FLIBANSERIN’ S MECHANISM OF ACTION**


**Pivotal Study Endpoints**

**Primary Endpoints**
- Change from baseline to the final visit period in the monthly frequency of Satisfying Sexual Events (SSEs)
- Desire score as measured by eDiary (511.71 and .75) or FSFI-d (511.147 and .130)

**Secondary Endpoints**
- Female Sexual Function Index (FSFI) desire items (511.71 and .75)
- Female Sexual Distress Scale-Revised total score and Item 13 (FSDS item 13)

**Other Endpoints**
- Female Sexual Function Index (FSFI) total score
- Patient Global Impression (PGI) of improvement
- Patient benefit evaluation responder endpoint
- Diary Distress
- Diary Desire day

**CHANGE FROM BASELINE FOR SATISFYING SEXUAL EVENTS (SSE) – STUDY 511.147**


Consistent Efficacy: 4 different US Phase III Clinical Trials*

Data on file Sprout Pharmaceuticals.

*Somnolence, fatigue, or sedation in phase III placebo controlled trials (%)

** p = 0.0002; ** p < 0.0001 difference between placebo and flibanserin
Flibanserin
Summary & Conclusions
- Consistently demonstrated safety and efficacy
- Large scale trials in more than 10,000 women
- Fourteen new trials and one validation study
- Only compound for FSD in Phase III clinical study
- To be re-submitted to FDA in 2013

Femprox
- RCT Stage III trial of topical alprostadil 0.4% cream with a skin penetration enhancer (DDAIP) an ester of N, N dimethylalanine and dodecanol
- 900 mg dose showed statistically significant and clinically relevant improvements in primary and secondary efficacy outcomes
  - Primary endpoint: arousal success (yes to #3 of Female Sexual encounter profile)
  - Secondary endpoints: FSFI and Global Assessment Questionnaire and Sexual Distress Scale.

Lybrido and Lybridos
- Lybrido combines testosterone with a phosphodiesterase inhibitor (PDE5 inhibitor)
- Lybrido is designed for women with HSDD and low motivation, relatively insensitive system for sexual cues.
- Testosterone is believed to improve desire, whereas the PDE5 inhibitor works to increase genital sensitivity.
- Administered sublingually, the time of peak concentration of the PDE5 inhibitor coincides with the 4-hour delay in behavioral effect of the testosterone.
- Lybridos combines testosterone with a 5HT(1A) agonist (buspirone).
- Designed for women with HSDD who have sexual inhibition.
- Testosterone increases sexual motivation and buspirone counters the sexual inhibition.
- Administration of Lybridos is sublingual and the timeframe for the pharmacological effects of the buspirone coincide with the behavioral window for testosterone administration.3,4
Bremelanotide

- Melanocortin receptor 4 agonist (MCR4 agonist) for treatment of HSDD and/or FSAD.
- Was initially delivered as a nasal spray and Phase II - adverse effects on BP.
- The drug reformulated in a lower dose for SQ injection.
- Phase IIb study is completed in premenopausal women with HSDD and or FSAD.

Results:
1.25 and 1.75 mg SC was effective in decreasing distress, increasing arousal and desire and increasing the number of SSE with robust dose response and consistency of effect across all key endpoints.

Fertility

Do you have any questions concerning infertility and parenthood after cancer?
Many of your cancer patients are at risk for infertility due to treatment.......  

A patient seen in General Gynecology recently said...... I was never given any information concerning infertility and sexuality at any point in my treatment, I think this is malpractice.
Parenthood Options after Cancer

1) Natural Conception

2) Assisted Conception
   - Donor eggs
   - Donor sperm
   - Donor embryos

Third Party Reproduction
   - Surrogacy
     - Gestational versus Traditional
   - Adoption
     - Infant
       - National and International
       - Cancer friendly agencies
     - Embryo

Child free living

Oocyte Cryopreservation
   - No longer considered experiment
   - Improved outcomes with vitrification
     - Rapid freezing with liquid nitrogen and the oocyte is solidified into a glass like structure
     - No evidence of increased neonatal risks
     - Implantation Rates 17%-41%
     - Clinical Pregnancy Rates 36-65%
       - Cobo et al 2010; Rienzi 2010

Embryo Cryopreservation
   - Often considered gold standard
   - Mature oocytes harvested
     - ASRM and SART Guidelines
Invitro Oocyte Maturation
- Experimental
- Attractive to those who need urgent chemotherapy
- Lower implant rates, clinical pregnancy rates and live birth rates versus IVF

Ovarian Tissue Cryopreservation
- Prepubescent girls (6000 cancers girls aged:
- Orthotopic reimplantation in the pelvic cavity
- Heterotopic reimplantation outside
- > 24 live births orthotopic /505 naturally conceived

Surgical Techniques
- Ovarian shielding
- Ovarian transposition
  - Variable success
  - 16-90% reduction
  - Rodriguez et al 2012

Fertility Sparing Surgery
- Simple Oophorectomy for Borderline
- Radical trachelectomy
  - 212 case study. 66% achieved pregnancy, of those who were pregnant, 45% reached full term, 255 delivered between 28-36 weeks, and 5% delivered before 28 weeks
  - Speiser et al 2011

Early Stage Endometrial Cancer
- 45 studies - 391 participants
- Complex atypical hyperplasia or Grade 1 adenocarcinoma treated with progestin
- CAH response (66%)- repro outcome 41.2%
- Grade 1 response (48%)- repro outcome 34.8%
- 117 live births
  - Gunderson et al 2012

Medical Suppression
- GNRH agonists prior to chemo
- Debatable efficacy
Embryo Freezing  Ovarian Suppression  Embryo Freezing
Egg (Oocyte) Freezing  Ovarian Shielding  Egg (Oocyte) Freezing
Ovarian Tissue Freezing  Ovarian Tissue Freezing  Donor Embryos
Ovarian Transposition  Donor Eggs  Surrogacy
Radical Trachelectomy  Adoption  Natural Conception

Using Frozen Embryos
Using Frozen Eggs
Using Frozen Ovarian Tissue

Cycle of Cancer

Attention to Issues!
There are Needs to be Addressed!

OF 635 Japanese breast surgeons, 32% were consulted about sexual issues.1

"Although majority recognized importance of patients' sexuality-related concerns, they did not necessarily think that surgeons had a professional responsibility to deal with them."

"Of 35 specialists in gynecologic/women's cancers, 20% reported they had the time to discuss sexual issues with their patients.2"

With little time for sensitive discussions on sexuality, fertility and intimacy issues, and perceived lack of support once a problem has been identified, it is understandable why physicians do not routinely discuss such issues with their patients."
The Business of Survivorship Medicine

Healing is an Art

Medicine is Science

Healthcare is Business

Preceptorships and consultations are available for you and your institution

Components of Cancer Care

Clinical Excellence

Patient Education And Support

Medical Training and Education

Research

Conclusions

- **ASK**...
  You cannot treat a problem if you do not know that one exists... Menopausal issue, Sexuality and other quality of life concerns are paramount.

- Know your own personal comfort zone and level of expertise

- Get help, get trained and get formalized

- Refer when appropriate
Thank you for your kind attention