Female Disorders

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Disclosure
Devaki Lindsey Berkson, MA, CNS, DACBN, CAN, ND, is owner of Berkson Health in Austin, TX. She is employed at the Wiseman Family Practice Clinic in Austin, TX and the Integrations Health Center Tulsa, OK. Conflict of interest was resolved through peer review of slide content.

Professional Education Services Group staff have no financial interest or relationships to disclose.

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Learning Objectives

• At the conclusion of this activity, the participant will be able to:
  – Discuss nutritional and hormonal correlates to fibrocystic disease
  – Review the new theory and treatment of endometriosis
  – Discuss the emerging clinical applications of 2-methoxyestradiol, progesterone and specific nutraceuticals for these conditions.

Fibrocystic Breast Disease (FBD)

• Synonyms: Fibrocystic Breast Disease, Cystic Diseases, Cystic Mastalgia, Cystic Hyperplasia, Fibrocystic Mastopathy, Chronic Cystic Mastitis, Mammary Dysplasia, Proliferative Diseases of the breast
• Fibrocystic Mastosis (FCM) - fibrosis (thickening and scarring) of epithelial, cystic, cellular alterations
• Basic Cell Issues: * Growth out of control, *Inflammation
• Basic Causes: Hormonal Imbalance, Nutrient Deficiencies, Circulation (lymph/liver), Disinsulinism

Structure

• NORMAL: 12 large milk ducts emerge from the breast at the nipple.
• The ducts branch down from the nipple ending in GLANDS.
• The amount of glandular tissue fluctuates with hormonal activity and time of menstruation.
• This fluctuation depends on hormones (thyroid, estrogen and progesterone and also insulin), inflammation, nutrients like iodine, lymph flow, cellular energy (glucose/insulin function)
Affected Structures – ducts, glands, stroma

- The tissue in between the *ducts and *glands is (fat and fibrous tissue), which makes up most of breast volume and is called *stroma.
- **ABNORMALITIES:** proliferation (growth out of control – more estrogen than progesterone, more ER alpha to ER beta), too little thyroid hormone, excess prolactin, deficiency of iodine, deficiency of vitamins like B6, disinsulinism, excess localized fat, build up of cytokines (molecules of pain and inflammation) from various sources (caffeinated type molecules, food reactivities, endocrine disrupting chemicals like plastics in perfume, poor clearance of hormones)
- Takes place in *ducts, *glands and *stroma.

Definition

- Most common **benign** condition of the breast (gland/ductal/stroma).
- Inflammation of the breast and cell changes.
- Benign fibrocystic breast conditions with **proliferative epithelial cell elements** have been associated with increased risk of subsequent breast cancer, especially if accompanied by **atypical cellular** changes.


Proliferative changes

- Growth out of control: Increase in rapidly dividing cells.
- Cell change: Hyperplasia is the term used when the cells are no longer normal.
- 2 types of hyperplasia: typical hyperplasia (H – most common) and **atypical hyperplasia** (AH – less common), are no longer normal, are atypical.
- Typical 2Xs more BC risk than women without it. **Atypical 4-5Xs increased BC.**
- Women with **atypical hyperplasia**—in one study—had 29% increased risk of developing breast cancer within 25 years. **Atypical biopsy — TAKE ACTION.**
- Hyperplasia doesn’t usually cause a lump that can be felt, but can cause changes that are seen on a **MAMMOGRAM or BIOPSY.**


Atypical Hyperplasia: Specific Recommendations

- MONITOR MORE CLOSELY BY WOMAN HERSELF AND TESTING. Yearly mammogram [7], ultra sound, nipple aspiration, shower self-exams.
- Have a clinical breast exam every 6 to 12 months
- Screening with breast MRI yearly – contrast (mesas)
- Standard of care: Tamoxifen/Raloxifene to lower the risk of developing breast cancer, but functional protocols are effective alternatives (iodine, progesterone, thyroid balancing, insulin sensitizing [Berberine, Metformin] thiamine, hormonal, Liver boosting ie lipotropic factors or hepatic detoxes, etc.)

FBD Incidence Common – 2/3 of US Women

- Estimations and through autopsy studies — over 50-55% of women have signs of fibrocystic breasts and 90% have some cellular changes associated with the condition. (Though some women have no pain.)
- Pain on mammograms, physical touch love making, laying on chest ie at gym, sports.
- Incidence related to age 20% menstruating years, 30%-50% premenopausal years
- Now with HRT occurring in older women on HT. In the Women’s Health Initiative Studies, incidence was increased 1.7 fold in menopausal hormone therapy users.

Risk Factors

- High social class, nulliparity (less estradiol) and progesterone exposure
- Low body mass index [although BMI is associated with increased risk of breast cancer, increasing BMI was not associated with benign pathologies.]
- Progesterin exposure in menopause. In post-menopausal women receiving estrogens + progesterone for > 8 years, the prevalence of benign breast lesions is increased. Synthetic hormones high potential for adversely affect breast tissue.
  - Birth Control Pills,
  - Synthetic HT.
- In the Women’s Health Initiative study, the use of estrogen plus progesterin was associated with a 7% increase in the risk of benign proliferative breast disease.
- Synthetic thyroid replacement long-term while also iodine insufficient.

Pathophysiology

- Hormonal basis – estrogen (ER alpha): Estrogens have been implicated as a causative factor for fibrocystic disease (and breast cancer). One of the most common treatments in allopathic medicine for fibrocystic disease is birth control pills for suppression in the ovaries to lower systemic circulating level of estrogen. But exposing women to more progesterins.
- Root cause: Estrogen sensitivity/balance – Estrogen in ratio to progesterone (and/or progesterone resistance), estrogen receptor imbalance, thyroid, prolatin, nutrients
- Clearance: Locally: Hormonal accumulations/poor drainage in breast due to inflammation and/or iodine deficiency or inflammation
- Clearance: Liver/Gut: And/or poor hepatic estrogen metabolism; Gut – some studies link constipation (poor GI clearance) with abnormal breast cells
- Trauma is not causal factor (but for mastalgia can be)
- Drainage

In breast 3 estrogen receptors

- Two distinct classical estrogen receptors that bind estrogens.
- Estrogen receptor alpha (ER-α) and Estrogen receptor beta (ER-β).
- A third, non-classical estrogen receptor, transmembrane receptor; GPR30 Katzenellenbogen

Estrogen Balance

- ER alpha – promote growth (potential oncogene)
- ER beta – controls growth (oncogene suppressor)
- GPR30 — promotes growth

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ER beta (the good estrogen dominance)

Anti-proliferative

- More than 15 years have passed since the discovery of the second estrogen receptor, estrogen receptor beta (ERβ). It is now evident that ERβ alone works to inhibit breast cancer cells. In fact, ERβ is expressed in the majority of breast tumors although in lower levels than in the normal mammary gland.
- ERβ is expressed in breast cancer infiltrating lymphocytes, fibroblasts and endothelial cells, all known to influence tumor growth.
- By compensating for hormonal and IR beta in breast cancer cell lines, several researchers have investigated its function with respect to proliferation and tumor growth.
- It appears that ERβ antagonizes the function of IR α.
- Male estrogens (male estrogens) have a weak affinity for breast cancer cells whereas numerous epidemiological studies indicate a breast cancer risk reduction by dietary phytoestrogens. It is known that hormone treatment does not reduce the risk of breast cancer in men. In contrast, contraindication of breast cancer risk in men is well-documented in both laboratory studies and in clinical trials. It appears that breast cancer risk in men is associated with a lifelong exposure to phyto-estrogen.

What turns on ER beta? - Estriol

- Estrone (E1) and estradiol (E2) preferentially bind to and activate ER-α, thereby explaining the proliferative effects of these two estrogens.
- E3, estriol, in contrast, binds to and activates ER-β.
- The binding of estrogen hormones to ER-α promotes breast cell proliferation, which can exacerbate benign breast disease and also existing breast cancer.
- Conversely, the binding and activation of ER-β attenuates breast cell proliferation and thus may slow the development of a benign breast disease and cancer and the development of tumors.

Estriol

- GPR30 regulates breast cell growth
- ER alpha turns GPR30 on, increasing risk of proliferation of breast cells and breast cancer cells
- E3, acts as an antagonist of GPR30, though it has a much lower affinity for GPR30 than E2, and reduces proliferation
- E3 acts as a GPR30 antagonist protecting breast cell growth.
- How to get estriol?
  - Estriol Replacement
  - Natural Boosters of ER beta? Rhubarb, okra

Estriol acts as a GPR30 antagonist in estrogen receptor-negative breast cancer cells.
Endocrine Disruptors

- Many carcinogenic toxins, including bisphenol A (BPA) and polychlorinated biphenyl's (PCB's), promote the growth of breast cancer cells by functioning as agonists of GPR30.
- E3, on the other hand, acts as an antagonist of GPR30 – estriol helps offset endocrine disruption!
- Involvement of activating ERK1/2 through G protein coupled receptor 30 and estrogen receptor α/β in low doses of bisphenol A promoting growth of Sertoli TM4 cells.

ER beta - Estriol

- Because of its differing effects on ER alpha and ER beta, we would expect that estriol would be less likely to induce proliferative (potential cancerous growth) changes in breast tissue and to be associated with a reduced risk of breast disease and breast cancer.
- Giving estradiol replacement without estriol, is asking for trouble.

SOY – food ER beta rebooster

- We examined possible relationships between plasma genistein and daidzein concentrations and risk of breast disease in women, in a breast self-examination trial in Shanghai, China, diagnosed with breast cancer (n = 196) or a benign breast condition (n = 304), and 1,002 age-matched controls with no known breast disease.
- Isoflavone concentrations were inversely associated with risk of:
  - Non-proliferative
  - Proliferative benign fibrocystic conditions,
  - As well as with breast cancer.
- Women in the highest quartile of plasma genistein were less likely to have breast cancer or benign conditions compared with women in the lowest quartile.
Rhubarb Extract – herb ER beta reboorder

- A dry extract from the roots of rhapontic rhubarb (extract Rheum rhaponticum (L.); has been commercially available in Germany for over two decades to treat menopausal symptoms. However, the molecular basis of its clinical effectiveness remains obscure.
- This article reviews the in vitro and in vivo data of its estrogenic actions.
- Rhubarb exerts SERM-like activity by boosting ER beta:
  - Slight ER beta binding and,
  - Recruiting co-factors.
  - Net large increase of ER beta signaling


Treatment of menopausal symptoms by an extract from the roots of rhapontic rhubarb: the role of estrogen receptors

Vollmer G
Hormonal Pathophysiology – E/P

- Excess ER alpha: estrogen in ratio to progesterone
- Excess ER alpha dominance – alcohol, fat cells, less clearance liver gut
  - Progesterone deficiency
  - Shortened luteal phase (corpus luteum insufficiency, anovulatory)
  - Women with progesterone deficiency vary 5-fold risk of postmenopausal breast cancer.
- Higher ER alpha linked to higher prolactin
- Benign breast disease often treated in Europe with progesterone cream applied directly to the breast


Estrogen Balance - Progesterone

- Progesterone down regulates ER alpha and increases expression of functional ER beta that mediates estradiol up-regulation.
- Progesterone helps keep balance of estrogens
- Progesterone keeps E Goldilocks “just right”

Progesterone blocks estrogen-induced DNA synthesis through the inhibition of replication licensing.
Estrogen clearance - gut

- The relation between epithelial dysplasia in nipple aspirates of breast fluid and frequency of bowel movements was studied in 1,481 white women.
- 0% in > than one bowel movement.
- 5% of women having one ONLY bowel movement per day had abnormal dysplastic cells in breast fluid.
- 10% of women having < than one bowel movement a day had dysplasia.
- 20% of women having two or fewer bowel movements per week had dysplastic changes. Petrakis and King U of California
- Reproduced. Breast cancer study found link with constipation and consistency to risk of BC. 123 breast cancer cases among 7,702 women from the US NHANES I Epidemiologic Follow-up Study.

Estrogen Clearance

- Gut
- Liver
- Iodine
- Lymph – circulation/exercise
- Nutrients – like vitamin B6

Disinsulinism

- Women with benign proliferative breast disease are at increased risk for developing breast cancer.
- Evidence suggests that accumulation of adipose tissue can influence breast cancer development via hyperinsulinemia, increased estrogen, and/or inflammation.
- Women's Health Initiative. We evaluated serologic markers from these pathways in a case-control study of postmenopausal women nested within the WHI.
- N = 667 women who developed BPRD during follow-up, and they were matched to 1,321 controls.
- Among nonusers of hormone therapy, fasting serum insulin was associated with a statistically significant increase in risk of BPRD, and with estradiol, and CRP.
- These associations not observed if on HT: estrogen alone or estrogen plus progestin hormone therapy. Our results indicate that serum levels of estradiol, insulin, CRP are independent risk factors for BPRD and suggest are associated with the early breast cancer development.

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Iodine

- Studies from nearly 40 years ago show that iodine deficiency in rats produces the exact precancerous changes seen in humans—dysplasia and hyperplasia.
- As iodine depletion continues, more atypical changes demonstrated in rat breast tissue.
- There is a wider spectrum of structural alterations that are associated with the older breast, with sodium perchlorate as the blocking agent. Noticeable calcospherite deposition, intralobular fibrosis, and cystic changes resembling human fibrocystic disease.
- In 52-week-old rats, breasts exhibited atypical lobules cytologically, papillomatosis, sclerosing adenosis, calcifications, and a lobular transformation of a histologically dysplastic type.


Iodine

- Concentrates and 'traps' 30-50 times iodine in blood into the breast
- Activates thyroid in breast
- Rinses out excess estrogen, moves lymph
- Bromide and Chlorine compete with this
- Typical Diet Threatens Iodine: Sodas, brominated refined flour and chlorine block the uptake of iodine into the breast.
- An adequate iodine level is necessary for the development and maintenance of normal breast architecture. Iodine deficiency causes atypical tissue and physiologic changes in both breast and thyroid. Milk from lactating breasts contains four times amount in thyroid to protect baby.


Iodine Increases Breast Cell Sensitivity to Estrogen

- In an iodine-deficient state, research has shown that ovarian estrogen production increases while estrogen receptors in the breast increase their sensitivity to estrogens.

Iodine

- Iodine has also been shown to be extremely effective in treating and preventing fibrocystic breasts in humans.
- Iodine has been the most researched mineral in treating FBD.
- Dr. Bernard Eskin, the world’s foremost researcher on iodine and the breast, writes, “In all these studies, termination of dietary iodine restriction…results in a variable modest return toward the normal (breast) structure.”
- Iodine supplementation shrinks nodules cysts in iodine storage tissues (and in other iodine reserves, thyroid and ovary.)
- Thyroid replacement in face of iodine deficiency promotes more atypia.
- Any atypia, add iodine replacement to protocol. But monitor thyroid function.


Human Trials

- 233 women with FIBs + Lugol’s iodine (95% iodide and 5% iodine) orally for 2 yrs. 5-10 drops/day.
- 56 women in double-blind trial diatomic elemental iodine 6 months.
- 65% improvement in experimental vs. 3% in placebo.
- Side effects of iodine: acne, nausea, diarrhea, hair thinning, skin rash, headache, transient mastalgia. Due to side effects, consider iodine when other nutraceuticals were not effective.
- Hypothyroidism in 3% of patients, Hyperthyroidism in 1% of patients.

Iodine supplements relieve painful, swollen breasts. Family Practice News 1986(Dec 1):16(23):

Iodine – Breast Pain (mastalgia)

- A U.S. National Institutes of Health fact sheet of 2011 reported on a randomized, double-blind, placebo-controlled clinical trial performed on 111 women affected by fibrosis and having a history of breast pain.
- Daily doses of iodine led to decrease in breast pain, tenderness and nodularity.
- It was emphasized that large doses of iodine should only be used under the guidance of a physician.

"Iodine: Fact Sheet for Health Professionals". NIH. Retrieved 2015-02-07
Iodine — Atypia

- Rats given certain carcinogens will develop breast cancer.
- When iodine is given along with the carcinogens, tumor formation is blocked. (Same study with oxytocin, HD)
- These studies indicate that iodine has the ability to block cancer progression in the breast tissue.


Mol Cell Endocrinol. 2005 May 31;236(1-2):49-57. Inhibition of N-methyl-N-nitrosourea-induced mammary carcinogenesis by molecular iodine (I2) but not by iodide (I-) treatment evidence that I2 prevents cancer promotion.

Iodine Deficiency Consequences

- Causes estrogen production to increase.
- Increased sensitivity of breast tissue to estrogen and estrogenic pollutants.
- Increase risk of abnormal tissue changes in breast and thyroid including cancer.
- Increased exposure to environmental estrogens (plastics, pesticides, meat, dairy, cosmetics, etc.) it is no wonder that hormone-sensitive disease is on the rise.
- In vivo research links corrections of iodine deficiency with resultant changes back to normal breast tissue.
- Clinical experience shows the same positive results with human patients.
- Atypia, cysts, pain. Caution though!

Iodine – BRAC gene abnormalities

- The combination of iodine/iodide (ie Lugol’s solution) has been shown to positively alter gene expression in estrogen-responsive breast cancer cells.
- BRAC: They found that iodine down-regulated abnormal BRAC gene activity.
- TAMOXIFEN: The same researchers report that iodine/iodide therapy “…could enhance the efficacy of Tamoxifen therapy…thus preventing or slowing the development of Tamoxifen resistance.” So can say.
- This is a very important study showing that iodine can favorably influence the gene expression in breast cancer.


Iodine - Estriol

- Iodine promotes estrogen metabolism to estriol
- And thus ER beta signaling
- Studies of the breasts of ERbeta knock out mice (BERKO) reveal abnormal epithelial growth, overexpression of Ki67 and severe cystic breast disease as mice age.


Estrogen receptor beta in the breast: role in estrogen responsiveness and development of breast cancer.

Iodine – Normalizes Prolactin

- Iodine is required to make T3 and T4.
- Deficiency in T3 and/or T4, then hypothalamus secretes TRH (Thyrotropin-releasing hormone) which releases TSH (Thyroid-stimulating hormone) and prolactin. Pain, lumpiness, feeling poorly.
- Iodine supplementation is like a natural Danazol.


Causes of Prolactinemia – no cause in 1/3 of cases

- Pituitary tumors (prolactinomas).
- Hypothyroidism (underactive thyroid) and/or iodine deficiency or inhibitors.
- Medicines given for depression, psychosis, and high blood pressure i.e. risperidone and women are more sensitive to this effect than males, SSRIs, MAD-L, some tricyclics, etc.
- Herbs, including fenugreek, fennel seeds, and red clover.
- Irritation of the chest wall (from surgical scars, shingles, or even a too-tight bra), Stress or exercise (usually excessive or extreme), excess melatonin.
- B6 deficiency: Pyridoxine hydrochloride (B6) acts like a functional dopamine agonist effective for lowering prolactin and raising dopamine, but less effective than drugs like bromocriptine. And promotes longer ER alpha signaling.
Thyroid

- Rule out thyroid conditions.
- The evidence of association between thyroid disorders and benign and malignant breast diseases is increasing.
- Increased frequency of benign breast conditions in patients with nodular thyroid disease (NTD) and Hashimoto's thyroiditis (HT).
- Taking thyroid replacement without adequate iodine replacement.

*J Endocrinol Invest. 2015 Apr 1. The prevalence of benign breast diseases in patients with nodular goiter and Hashimoto's thyroiditis*

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FBD and Thyroid

- 71 women with nodular thyroid disease, 95 women with Hashimoto's thyroid disease and 72 healthy people as a control group.
- Benign breast diseases were detected in 54.9% of patients with thyroid disease, in 47.4% of those with Hashimoto's, and 29.2% of control group.
- Cysts - most frequent pathology among benign breast diseases; fibrocystic changes, mixed lesions, benign solid mass, ductal ectasia, and complex cyst followed it.

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Thyroid Treatment - *Hypothyroidism*

- Desiccated thyroid = subjective and objective improvement in 286 women with fibrocystic changes who had evidence of hypothyroidism.

Thyroid Treatment - *Euthyroidism*

- 19 women were evaluated for breast pain and nodularity associated with fibrocystic disease.
- Rapid pain relief occurred in 73 of the patients, with total relief in 47 percent after daily treatment with 0.1 mg of levothyroxine.
- Softening of breast tissue and decreased nodularity occurred within 3 months in many patients.
- 3 patients had elevated levels of serum prolactin before treatment, with dramatic pain relief and normalization of prolactin levels after treatment.


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Methylxanthines – Coffee, Tea, Chocolate

- Methylxanthines through dietary sources associated with the etiologic development.
- Complete abstention from methylxanthine consumption resulted in complete resolution of the disease in 82.5% and significant improvement in 15% of those studied.
- Thus 97.5% showed clinical benefit from total methylxanthine abstention.
- The results of a clinical questionnaire answered by 500 women consuming methylxanthines, one half of whom had fibrocystic breast disease, suggest that women with fibrocystic disease may have a genetic predisposition of sensitivity to caffeinated substances.


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Methylxanthines Clinical Trials

- **Strict avoidance** for 6 months in 65-88%.
- Less improvement if modest reduction.
- Women 45 years or older needed longer strict avoidance for up to 1 year.
- Treatment and 6-yr follow-up of 500 women.
- When women stay off, FCD goes away.
- When add back in, recurs. NOT VERY DOABLE.

Vitamin B6 — Breast Pain

- Uncontrolled trial, 100 mg Pyridoxine for 3 month 50% reduction in premenstrual breast pain in 289 women with cyclic mastalgia.
- Mechanism –
  - Duration of signaling time of ER alpha
  - Prevents excess prolactin
  - Breast protector as well as PMS protector


Cyclical breast pain—some observations and the difficulties in treatment

Thiamine (Vitamin B1)

- Case report of woman with FCD due to high alcohol intake had remission of nodules large and small after 3 weeks of B1.
- 2 Case reports 100 mg B1 TID.


Vitamin E

- Vitamin found beneficial in double-blind trial of 105 women and in uncontrolled 600 IG/day or placebo 3 months, 43% symptoms with E and 23% in placebo.


NEJM 1965, 272:1080-1081

But clinically has not been consistently reproducible.
FCB Dietary Factors

- Diets high in fiber and soy products have also been associated with reduced risk, (but a randomized trial showed increased cell division in lobular mammary epithelium after soy protein supplementation so it’s whole food, NOT protein powders or isolated isoflavones).
- Consumption of green vegetables has been inversely associated specifically with risk of proliferative benign breast disease.
- Results from studies of total fat are inconsistent. In one study, high daily intake of energy (especially saturated fat) was reported to be positively associated with benign epithelial cell proliferative disease.

Topical NSAIDs Mastalgia

- An open, non-randomized, comparative study of topical (NSA) gel versus OEP was carried out over a period of one year.
- 50 female patients attending the outpatient department, with moderate to severe breast pain, were given 1 of the 2 agents, alternatively, after selection.
- Results showed that out of 25 patients treated with OEP, 64% had a clinically significant response after 3 months of treatment, compared with 92% with topical NSAIDs. Only one patient (4%) had side effects with OEP, while no patient had side effects with topical NSAIDs.
- This study has shown topical NSAIDs to be safe, effective, rapid and acceptable mode of treatment for cyclical and non-cyclical mastalgia.
- NSAIDs now shown to be anti-progestins NOT A GOOD IDEA.

Topicals

- DMSO + iodine – iodinated DMSP: Concentration of 6.2 milligrams/Lugol’s/drop, 2-4 drops per breast daily
- Frankincense
- Rosemary/Sage
- METFORMIN 100MG/ML APPLIED ONE TO TWO TIMES A DAY RUBBED WELL INTO AXILLA AREA
**Inflammation – Frankincense**

- Boswellia-based cream for prevention of adjuvant radiotherapy skin damage in mammary carcinoma: a randomized placebo controlled trial.
- Boswellia acids are pentacyclic triterpenes extracted from the resins of the tropical tree Boswellia serrata with strong anti-inflammatory properties.
- The acute skin reactions from radiation, are inflammatory in nature.
- These findings indicate that the use of a boswellia-based cream is effective in reducing the use of topical corticosteroids and is able to reduce the grade of erythema and the skin superficial symptoms, being well tolerated by the patients.

Clinical evaluation of safety and efficacy of

**Rosemary/Sage Essential Oil**

- One study in particular observed an inverse relationship between consumption of Mediterranean herbs such as rosemary, sage, parsley, and oregano with lung cancer.
- One agent in particular, carnosol, has been evaluated for anti-cancer property in prostate, breast, skin, leukemia, and colon cancer with promising results. These studies have provided evidence that carnosol targets multiple deregulated pathways associated with inflammation and cancer.
- This mini-review reports on the pre-clinical - as a cancer chemoprevention and anti-cancer agent.


**Progesterone Mastodynia (not hardness or cysts)**

- 80 regularly menstruating women with mastodynia.
- One group received 4 grams of vaginal cream containing 2.5% natural progesterone for six cycles from day 19 to day 25 of the cycle. (Each gram will have 25 mg of progesterone. So 4 grams = 100 mg of progesterone) The other group was similarly treated with placebo.
- Both subjective reporting clinical examination (daily) revealed a significant 50% reduction in breast pain in 64.9% of subjects receiving progesterone and 22.2% of subjects receiving placebo. No change on nodularity or adverse side-effects.


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Functional Medicine Treatment

- In-depth thyroid check
- Fragments or and/or stress
- Soy, alcohol
- Avoid refined - methylxanthines
- Pyridoxine hydrochloride 50 mg/bid
- Thiamin 100 mg/bid
- B complex once a day = intrinsic factor
- Boost B1kets (maltol, xylitol, T)
- Inulin only or temporarily
- Spontaneous factors (methionine, choline, inositol assist hepatic detoxification)
- Vitamin D 1,000 IU/daily - Vitamin E mixed tocopherols 600 IU/daily
- B1 test alergies and avoid (irritantatory contribution)
- Improve IR
- If cutting raw works for hardening and pain, consider topical meftinol

Endometriosis - Definition

- Chronic abdomen with endometrial tissue at sites outside the uterus.
- One of most common causes of infertility and chronic pelvic pain.
- DISEASE OF INFLAMMATION and acting like AUTO-IMMUNE DISEASE.
- Dumb white blood cells that cause havoc. Immune system needs to be made more intelligent.
- The most striking aspect of endometriosis is its dependence on estrogen for growth, similar to that seen in eutopic (right place) endometrium.
- Estrogen drives it, but different receptors, different actions and with failure and insinuation of conventional care and understanding diverse pathophysiology's emphasizes functional interventions.

Progestosterone resistance in endometriosis: link to failure to metabolize estradiol.

Endometriosis Incidence

- Its incidence is estimated to be as high as 30% in patients with infertility and 45%-90% in patients with chronic pelvic pain.
- Endometriosis causes infertility via impairing the tubal anatomy or function, sperm-egg link, decreasing egg quality, embryo quality, and the rate of implantation.
- Subgroups, such as women undergoing laparoscopy for fertility investigations or hysterectomy, show a higher prevalence.
- Similar to other common chronic diseases, like diabetes mellitus and asthma, it’s possibly inherited in a polygenic manner and has a complex and multifactorial etiology. IN ANY WOMAN WITH A HISTORY OF IT, EVEN FIXED SURGERY, EVALUATE HER FOR CHRONIC INFLAMMATION, and IMMUNE FUNCTION.
- Heritable disease with environmental triggers [diemis].
  - There is a sevenfold increase in the incidence of endometriosis in relatives of women with this disease compared with disease-free women.
  - And higher (clinically) in parents with toxic job exposures.


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Internal Endometriosis - Adenomyosis

- Definition: When endometrial tissue which normally lines uterus grows in muscular layer of uterus.
- Incidence: Kunz et al, found a prevalence of adenomyosis in 70% of women with endometriosis, compared with 9% in healthy controls. DES daughters (EXPOSURE TO ENDOCRINE DISRUPTORS IN UTERO – call for GREEN pregnancies).
- Detection of discrete and diffuse patterns of adenomyosis in 54% of young women with infertility and severe dysmenorrhea or menorrhagia.
- Hallmark: SEVERE pain and cramping often premenstrual and mid-cycle.

Symptoms

1/3 of women with endometriosis remain asymptomatic. When they do occur, symptoms typically reflect the area of involvement:

- Dysmenorrhea – significant painful menstruation
- Heavy or irregular bleeding — dysmenorrhea
- Pain pelvic, lower abdominal or back pain
- Dyspareunia – painful intercourse or after sex
- Dizziness
- PMS or menstruation and/or urinary frequency, defecation, exercise, love-making
- Fatigue due to inflammatory component
- FMS in premenstrual, cycles of diarrhea and constipation, or bloating, nausea, and vomiting
- More immune diseases: autoimmunediseases, chronic fatigue, fibromyalgia, asthma, allergies, eczema.18% have ANA antibodies

Type Of Endometriosis

- ABDOMEN - superficial lesions over peritoneal and other serosal membranes that line abdominal cavity
- OVARIAN endometriosis - Endometriotic cysts (endometrioma or chocolate cysts) in which endometriosis foci are surrounded by fibrous capsules
- HOW? Dislocation of primitive endometrial tissue outside the uterine cavity during organogenesis.

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**Diagnosis**

- Laparoscopy is considered the primary diagnostic modality for endometriosis. This is an invasive procedure with an overall sensitivity of 97% but with a specificity of only 77%.
- Ultrasonography - Endometriosis can be assessed by either transvaginal US or endorectal US
- Magnetic resonance imaging (MRI)
- Adenomyosis – only by surgery (lots of missed cases)

**Allopathic Management**

- The dependence of endometriosis on the cyclic production of menstrual hormones is basis for therapy.
- Combination oral contraceptive pills (COCPs)
- Danazol (suppresses E + P pituitary/ovarian axis)
- Progestational agents (progestins)
- Gonadotropin-releasing hormone (GnRH) analogues – stop estrogen/ovulation Zoladex Lupron

**Surgery**

- Semiconservative surgery is indicated mainly for women who have completed childbearing, are too young to undergo surgical menopause, and are delineated by the symptoms, anemia, fatigued, frustrated. Such surgery-cytoreduction of pelvic endometriosis and in some cases hysterectomy.
- Ovarian endometriosis can be removed surgically, because 1/10 of functioning ovarian tissue is all that is needed for hormone production. (Patients who undergo hysterectomy with ovarian conservation have a 6-fold higher rate of recurrence compared to women who undergo oophorectomy)
- Over 95% of patients who undergo abdominal surgery develop adhesions and are almost inevitably part of the body’s healing process. Although most adhesions are asymptomatic, some can cause bowel obstructions, infertility, and chronic pain.
- In a study that reviewed over 18,912 patients who underwent previous open abdominal surgery, 14.3% presented with a bowel obstruction in 2 yrs., with 2.6% of these patients requiring adhesiolysis to relieve the bowel obstruction. Dr. Moorehead – Tulane

Recurrence Rates After Surgery

- Studies show endometriosis recurs at a rate of 20 to 40% within 5 years post conservative surgery.
- A recent follow-up study investigated the recurrence of symptoms after hysterectomy with or without removal of the ovaries.
- In patients who kept their ovaries, a higher proportion of women required further surgery compared with women who had their ovaries removed.
- Removal of ovaries though accompanied by significant side effects.
- With total oophorectomy, no adverse effects of estrogen therapy on endometriosis recurrence have been reported in many studies.

Womenshealth.gov Endometriosis Fact Sheet 2014

Typical History

- Parent's/children's high exposure.
- Thyroid disorders i.e. hypothyroid, Hashimoto's hypothyroid. Causes more severe bleeding.
- Iron deficiency from severe bleeding. Check and treat. Low iron causes more severe bleeding.
- Severe fatigue and obesity.
- Pelvic Pain, Micturition, Dysmenorrhea, Menorrhagia.
- Poor Stress Coping Skills secondary to chronic pain.
- Infertility.
- Problems with immune system. Chronic fatigue syndrome, fibromyalgia syndrome, asthma, allergies, and eczema.
- Chronic fatigue syndrome and is a disease involving pain in the muscles, tendons, and ligaments. Women with endometriosis are very likely to have asthma, allergies, and the skin condition eczema. The researchers surveyed 3,680 women and they had been surgically diagnosed with endometriosis.
- "This study indicates that women with endometriosis may be more likely to have a variety of diseases involving the immune system."

Pathophysiology - Old

Implants, inadequate oxygen, grow, feed, don't die, inflame.
- Retractile Menstruation - Because retraction menstruation occurs in 90% of all women, endometriosis is believed to be caused by molecular defects that favor survival and establishment of endometrial tissues.
- Fetal implants - Dislocation of primitive endometrial tissue outside the uterine cavity during organogenesis.
- Hype supply of intratool - Endometriotic tissue has anomalous biogenesis of C from cholesterol.
- Dysfunctional peritoneal immune cells. Activated but STUMP macrophages - stickiness, inflammation, adhesions damage infertility.
- Angiogenesis, hyperaemia, inflammation.
- Resistance to apoptosis.
- Resistance/Deficiency to end of progesterone. So trying Progesterone replacement but not adequate treatment by itself, too many other factors going on.

An & Curr Menop. 2013, 63(10), 1699-1707. Increased activation of proinflammatory cytokines in fertile women with adult endometriosis.


Womenshealth.gov 2012 Oct; 37(10):1587. 163,500 (p<0.000). Endometriologic origin of endometriosis in women male patients
Pathophysiology – New

- Driven by estrogen dysfunction. Cases of ER beta secondary to methylation issues from EDCs - promotes secondary deficiency/insensitivity of progesterone.
- This means environmental cause of progesterone resistance no matter blood levels.
- This means adding element of DETOX is very helpful.
- Down-regulates ER alpha - deficiency in endometriosis, failure of estrogen to induce PR expression, thus also contributing to secondary PR deficiency and progesterone resistance.
- Lower levels of both isoform receptors of progesterone. Need to give very HIGH replacement of progesterone in 400 to 600 mg level for a while. And with HCG which boosts body’s ability to use it.
- Excess electricity exposure – melatonin deficiency.
- Gluten Sensitivity
- 2-ME deficiency promoting hypoxia and angiogenesis.

Autoimmunity

- Increased propensity to develop autoimmune issues.
- 18% of endometriosis patients have positive ANA levels as body makes antibodies to try to deal with ectopic tissue.
- Be hypervigilant to look for other autoimmune diseases and treat with emphasis on GUT and GUT WALL.
- Endometriosis as a disease fulfills criteria for autoimmune.
- Treat these patients with gluten free diet and immune boosters.

Estrogen Receptor Beta

- ER beta levels in endometriosis are >100 times higher than those in normal endometrial tissue.
- Deficient methylation of the ER beta promoter results in pathological overexpression of ER beta.
- A severely high ER alpha to ER beta ratio in endometriotic stromal cells is associated with suppressed progesterone receptor and increased cyclo-oxygenase-2 levels contributing to progesterone resistance and inflammation.

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Methylation Defects > ER beta Excess > Lower PR > Pain > Inflammation

- A severely high ERβ-to-ERα ratio in endometriotic stromal cells is associated with suppressed progesterone receptor and increased cyclooxygenase-2 levels contributing to progesterone resistance, pain and inflammation.


High ER beta More Pain & Inflammation

- ERβ is the only estrogen receptor expressed in primary placental villus endothelial cells.
- In these cells, ERβ is essential for maintaining optimal cyclooxygenase (COX)2 mRNA levels.
- COX2 expression is severely higher in endometriotic tissue, ERβ is at least in part responsible for high COX2 (prostaglandins, prostacyclins, thromboxanes) = inflammation and pain.


EDCs (endocrine disrupting chemicals)

- PCBs
- Pesticides
- Alter methylation, especially in utero
- Affect ER beta levels in uteri genes and then as woman matures

Front Cell Dev Biol. 2015 Jun 18;3:37 Endocrine disrupters: the new players able to affect the epigenome. Caselli L

Endometriosis - Endocrine Disruptors

- Human and animal exposure to DIOXIN affects levels of the steroid receptors and steroid-responsive gene expression and has an impact on metabolism and serum transport of steroids.
- Endometriotic cells + TCDD = dysfunctional macrophages M2 (adhesion, implantation, and growth of the endometriotic tissue, as opposed to clearance).


J Clin Endocrinol Metab. 2013 Dec;98(12):E1871–9. Increased AKT or MEK1/2 activity influences progesterone receptor levels and localization in endometriosis.

Progesterone Resistance: Kinases

- High ER beta causes high kinases which cause PR.
- Hyperactivity of the kinases (enzymes that transfer phosphate groups) cause dysfunctional PR receptors.

Gut Health/Food Allergy

Gut health

2 methoxyestradiol (2 MEO/ 2MEO)


Melatonin

- 12 mg (two 3 mg time release, two 3 mg fast acting)
- Melatonin has emerged as an important analgesic, antioxidant, and anti-inflammatory agent.
- Melatonin compared with placebo on pain and sleep quality in 40 females (18 to 45 yrs.) were randomized into the placebo (n = 20) or melatonin (10 mg) (n = 20) treatment groups for a period of 8 weeks.
- Melatonin reduced daily pain scores by 39.80% and dysmenorrhea by 38 %.
- Melatonin improved sleep quality, reduced the risk of using an analgesic by 80%.


Melatonin

- Rodent Study
- Melatonin treatment resulted in the regression of endometriotic lesions in oophorectomized rats.
- Higher doses were more effective.

Arch Gynecol Obstet. 2015 Mar;291(3):591-8. The effects of different doses of melatonin treatment on endometrial implants in an oophorectomized rat endometriosis model. Cetinkaya N
Gluten

- 207 patients with severe painful endometriosis; assessed before study and after one year of GF.
- At 12 month follow-up, 158 patients (75%) reported statistically significant change in painful symptoms, 51 patients (25%) reported no improvement of symptoms.
- No patients reported worsening of pain.
- A considerable increase of scores for all domains of physical functioning, general health perception, vitality, social functioning, and mental health was observed in all patients.
- In our experience, painful symptoms of endometriosis decrease after 12 months of gluten free diet.
- Department of Gynecology and Obstetrics, for Targets University, Rome, Italy.


HCG

- 31 patients with histologically verified endometriomas refractory to therapy received 1 to 2 intramuscular injections of 1500 to 5000 IU HCG per week for a period of 3-12 months.
- All patients had a highly significant reduction of endometriomas related pain and to improvement of disease-related parameters such as sleeplessness, irritability, overall discomfort, depression mood and sexual disfunction.
- Prolonged therapy with HCG for up to 12 months (mean: 4.42 months) did not lead to reduction of the beneficial effect.
- HCG injections lead to significant and clinically relevant reduction in pain intensity and to greatly improved quality of life in women with therapy-refractory endometriomas.
- Division of Perinatal Medicine, Department of OB/GYN, Medical University of Vienna, Vienna, Austria.


Therapeutic Goals (dietary, hormonal, lifestyle)

- GI food allergies and avoid.
- Address gut: digestive enzymes, probiotics, fermented foods, diagnose leaky gut, dysbiosis, SIBO.
- Fx methylation issues
- Consider: Enteral, Progesterone (high-dose), T on individual basis.
- GF; Melotones, HCG injections (3-5 months)
- Topical iodinated isotope over areas of pain.
- Proteolytic enzymes to reduce inflammation.
- Rnatenoid system:
  - Nonhercetable and improve diet.
  - Proteolytic enzymes away from food, Quercitin 1000 mg BID, Taurine 1.5 g BID, green tea, Reaveratrol 1000 mg BID, Chrysin 1000 mg BID, OME 50 mg BID, Vitamin D test and restore Thymou? Cystin?
- Decrease stress, hands on, diet?
Proteolytic Enzymes

- In between meals to reduce inflammation and to promote immune surveillance.
- The study was designed to investigate the role of three proteolytic enzymes viz., chymotrypsin, trypsin and serratiopeptidase on hind paw edema and cotton pellet induced granuloma and their possible interactions with aspirin in albino rats.
- Chymotrypsin, trypsin and serratiopeptidase possess anti-inflammatory activity and exhibit synergistic effect with aspirin in both acute and subacute models of inflammation in rat.
- Avoid amylase.

Indian J Pharm Sci. 2008 Jan-Feb; 70(1): 114–117. Effect of Some Clinically Used Proteolytic Enzymes on Inflammation in Rat


Quercetin

- Anti-oxidant
- Anti-inflammatory
- Anti-bacterial
- Hepatoprotective

Food Chem. 2015 Jul 15;179:305-10. Role of quercetin as an alternative for obesity treatment: you are what you eat!

Hands On – Visceral Manipulation

- 1,392 female patients between the years of 2002 and 2011. Varying degrees of infertility, including occluded fallopian tubes, hormonal dysfunction, and endometriosis. Some women were undergoing in vitro fertilization (IVF).
- All patients underwent whole-body, patient-centered treatments that used a protocol of manual physical therapy, which focused on restoring mobility and motility to structures affecting reproductive function.
- 65.85% rate of clearing occluded fallopian tubes, and 56.64% pregnancy
- Patients with endometriosis experienced a 42.81% pregnancy rate.
- 49.18% normalized follicle stimulating hormone levels, with a 39.34% pregnancy
- 53.5% pregnancy with PCOS
- The manual physical therapy represented an effective, conservative treatment for women diagnosed as infertile due to mechanical causes, independent of the specific etiology.

Endometriosis – Stress

- Elevated stress levels alter hormonal secretions, mood and behavior, sexual disorders and appetite custom.
- Neurogenic mechanisms are described in endometriotic lesions and they affect peripheral and central nervous system of these patients increasing pain sensitivity and stress reactivity.

Turmeric

- Extensively verified that continued oxidative stress and oxidative damage promote chronic inflammation, which, in turn, keeps many chronic diseases progressing.
- Curcuminoids have strong anti-oxidative and anti-inflammatory activities when used as a remedy for the prevention and treatment of chronic diseases.
- The antioxidant properties of curcumin plays a key role in the treatment of chronic inflammation diseases. Molecules. 2015 May 20;20(5):9183-9213. Curcumin, Inflammation, and Chronic Diseases: How Are They Linked?

Green Tea

- Samples from 55 patients (45 with and 10 without endometriosis) of reproductive age with normal menstrual cycles were analyzed. A total of 40 nude mice received single injection proliferative endometrial fragments.
- Treatment with EGCG significantly inhibited cell proliferation, migration and invasion and increased TGF-β1-fibrotic markers.
  - EGCG - approximately 45% of green tea extract 500 to 750 mg
- Epigallocatechin-3-gallate is a potential drug candidate for the treatment and/or prevention of endometriosis

Hum Reprod. 2014 Aug;29(8):1677-87. Antifibrotic properties of epigallocatechin-3-gallate in endometriosis
Resveratrol

- 33 non-pregnant female Sprague-Dawley rats, in which experimental model of endometriosis.
- 4 groups, 3 varying dosages of R, 2 weeks.
- The endometriotic implant volumes, histopathological grade and immunoreactivity to VEGF were significantly reduced and plasma and peritoneal fluid levels of IL-6, IL-8 and TNF-a were significantly decreased in group 1 and group 2 in comparison to group 3 and group 4.
- Resveratrol alone is a potential agent for the treatment of endometriosis and may be an alternative to LA. In contrast, the combination of LA and resveratrol decreased the anti-inflammatory and anti-angiogenic effects of each agent.


Thank you

Questions?

Obtaining CE/CME Credit

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http://pcca.cds.pesgce.com