Xenoestrogens and Their Effect on Fertility

Fertility, Pregnancy Health and Outcomes

Dr. Gina Sirchio-Lotus DC, CCN
- La Grange Institute of Health
  - Chicago, IL
  - Owner, practicing 11 years
  - Specializing in:
    - Functional medicine & orthomolecular nutrition: chronic illness, auto-immune, athletes, pre-postnatal conditions, specific diet need nutrition
    - [www.lgihealth.com](http://www.lgihealth.com)
    - dsirchio@gmail.com
    - IG drsirchiolotus

About Me...
- Producer of and Educator within the Postgraduate Program:
  - **THE WOMEN’S HEALTH SERIES** (next series begins March 10, 2017 at Palmer College in Davenport, IA)
  - IG & FB @womenshealthseries
- Author and Co-Owner of The Nourish Series: Prenatal Nutrition
  - [www.thenourisheseries.com](http://www.thenourisheseries.com)
- BIRTHFIT Regional Director of BIRTHFIT Chicago
  - [www.birthfitchicago.com](http://www.birthfitchicago.com)
  - IG & FB BIRTHFIT Chicago

About Me...
- Married to Tom
- Mom of 4

The Women’s Health Series
- Interdisciplinary 9 weekend course covering the female reproductive window beginning with pre-conceptive health through fully recovered postpartum
- Preconception, prenatal and baby nutrition, fertility, infertility (Eastern & Western medical approaches), pregnancy, chiropractic care during pregnancy & labor, infant adjusting, childbirth (various practitioners, settings, birth events), postpartum, pelvic floor issues, healing, rehab, breastfeeding, emotional issues, auto-immune diseases, return to sport/athletics, cardiac health and more...
- Each weekend taught by specialists to the topic at hand.
- Information, diagnosis, testing, treatment options, plans and relevant clinical pearls each session.
- Designed to be utilized immediately with current patient base in a variety of professional office settings (hospital, private clinic, birth center, home visits, etc.)

Why Interdisciplinary?
Today’s Goals

- Define xenoestrogens
- List common xenoestrogens
- Learn of the common fertility issues that have been linked to these chemicals
- Learn of the possible pregnancy issues that have been linked to these chemicals
- Define detoxification pathways in the body that may help or be harmed
- Provide tools to aid the body in removing some of this toxic burden

Xenoestrogens

- A type of hormone that mimics estrogen (estradiol specifically, 17-ß-estradiol known as E2)
- Chemical compounds that can be synthetic or natural

Xenoestrogens: Endocrine Disruptors

- This has a scary impact
- Mimicking the body’s natural estrogen can have severe implications
- Are lipophilic and can remain in adipose tissue for a long time
- The large additions of industrial and agricultural chemicals has caused increasing concerns as these are major changes made over the last 70 years
- We are seeing changes both in human individuals as well as human and wildlife populations
- The scope is effects is wide and broadreaching

Xenoestrogens

- Thought to cause harm in 2 ways
  1. Mimic the natural estrogens, be picked up by receptors in the body and elevate the amounts of circulating hormones
  2. Be similar enough to be picked up by the receptor but then have the action of blocking the receptor, impeding the body’s ability to use it’s own estrogens.

Estrogen Receptor locations

- Estrogen signaling occurs through both genomic and nongenomic mechanisms.
- Published online 2014 Oct 23. doi: 10.1155/2014/615917
- PMCID: PMC4226184
- Estrogen Signaling in Metabolic Inflammation
- Rosário Monteiro, 1 , * Diana Teixeira, 1 and Conceição Calhau 1
Estrogens

- Travel via bloodstream to the receptors throughout the tissues.
- Affect the bone formation and density, reproductive functions, and cardiovascular health.
- Their actions with the receptors throughout the body vary.
- Estrogenic receptors are found in bone, muscle, brain, vaginal, gastrointestinal, bladder, skin, uterine, liver, blood vessel and heart tissues.
- Responsible for the development of female sex characteristics.

Estrogens

- The actions of estrogen are mediated by the estrogen receptor (ER), a dimeric nuclear protein that binds to DNA and controls gene expression. Like other steroid hormones, estrogen enters passively into the cell where it binds to and activates the estrogen receptor.
- Estrogen passes easily into all cells and binds to the ER inside the cell.

Is there a BLOCK?

- Consider the effects of higher than necessary circulating levels- where is the ‘block’?

Normal puberty onset

- **HYPOTHALAMIC-PITUITARY-GONADAL AXIS**
- Rise in the pulsed output from the hypothalamus of Gonadotropin releasing hormone (GnRH). **HYPOTHALAMUS**
- This leads to increased levels of leutinizing hormone (LH) and follicle stimulating hormone (FSH) to be released from the anterior pituitary. **PITUITARY**
- These directly impact the ovaries and the ovaries begin releasing estrodial (E2). **GONAD**

Xenoestrogen

- If this foreign compound binds to the ER in a target tissue, it can create the effect (breast development, thickening of endometrium, onset of puberty).
- Creating this actions WITHOUT being initiated by the brain creates the problems
  - ***Blood levels of LOW GnRH while observing puberty onset is one marker of precocious puberty caused by exogenous hormonal impact. ***
- Hence the term, ENDOCRINE DISRUPTOR
HPG axis

- Allows for 3 access points of where development can be affected.
- If the brain (hypothalamus) is not directing the development and instead growth of tissues is due to direct actions of xenoestrogens upon receptors in the tissues...
  - Improper synthesis of estrogen
  - Faulty metabolism of estrogen
  - Interfering with binding of estrogen to ERs
  - Tissue growth and response to exogenous estrogens

Xenoestrogens: Where are they coming from?

Xeno-invasions environmental

- Atrazine - crops, Xmas trees, lawns, golf courses...
- Bisphenol A (BPA)-plastics, lined cans.
- Bisphenol S (BPS)- often used to replace BPA...
- DDT- pesticide until 1972, still found in environment
- Dioxins- from combustion and also bleaching of wood/paper (and their waterways). Also in tampons.
- Endosulfan- insecticide on many foods. Also found in water runoff
- PBBS- added to plastics to resist burning. Not made since 1976, still found in water & soil
- PCB's- used as insulating liquids and coolants. Stopped in 1979 but found in soil, water..
- Phthalates- plasticizers. High molecular weights in plastic items, low molecular weight in perfumes, lotions and control-release Meds.
- Zeranol- anabolic growth hormone for livestock. Continues in US and Canada. Europe discontinued

Xeno-invasion: Phytoestrogens

- Primarily soy, legumes of all kinds, whole grain cereals and some seeds.
- Hmm...Standard American Diet??
- Many galactulogues...
- Oats, flax, soy, sesame, lentils, red clover, ginseng, anise, fennel, yams, rice, fenugreek, mung beans, kudzu, mint, alfalfa...

Xeno-invasion: Mycoestrogens

- Produced in fungi
- Often fungi growing on cereals
- Moldy grains, especially in silos

Xeno-invasion: Medicines

- Ethinylestradiol (EE)
  - Most common ingredient in BCP, patch, NuvaRing
  - Also utilized in HRT

Xeno-invasions: Personal Products

- Lotions: parabens & phthalates
- Sunscreen: 4-MBC
- Perfumes: phthalates
- Cosmetics: phthalates & parabens
- It is estimated that women are exposed to more than 140 chemicals before they leave their house in the morning.

Xeno-invasion: Metalloestrogens

- Metal ions bind to the receptors and can act as agonists
- Concerns this agonistic activity will be another breast cancer risk-causing agent
- Aluminium, antimony, arsenite, barium, cadmium, chromium (Cr(II)), cobalt, copper, lead, mercury, nickel, selenite, tin and vanadate.
  - Metalloestrogens: an emerging class of inorganic xenoestrogens with potential to add to the oestrogenic burden of the human breast. Darbre PD1.

Xenoestrogens + Estrogens=???

Phytoestrogens- genistein (soy)

- "Environmentally relevant doses of genistein have significant negative impacts on ovarian differentiation, estrous cyclicity, and fertility in the rodent model..."
  - Circulating levels of genistein in the neonate, apart from dose and route, predict future adverse female reproductive outcomes. Jefferson WN1, Williams CJ.
Xenoestrogens - all sources

- Xenoestrogens, which accumulate in the body throughout life, are believed to increase breast cancer risk, especially in cases of prenatal and prepuberal exposure
- Exogenous hormonal regulation in breast cancer cells by phytosterogens and endocrine disruptors.

Xenoestrogens - environmental

- The role of environmental estrogens and autoimmunity.
- Chighizola C1, Meroni PL.

- Xenoestrogen exposure showing immunotoxic effects and may be a cause of the increasing frequency of auto-immune diseases

Estrogen Dominance

- PMS
- Acne
- Ruddy complexion
- Hot flashes
- Mood swings
- Irritability
- Changes in hair (texture, thinning)

- Fibroids
- Polyps
- Adenomyosis
- Polycystic Ovarian Syndrome (PCOS)
- Ovarian Cysts
- Endometriosis
- Irregular Cycle
- Amenorrhea
- Dysmenorrhea
- Oligomenorrhea
- Menorrhagia

Estrogen Dominance

- High levels of xenoestrogens in patients with low-grade endometrial stromal sarcoma--report of two cases.
- Reich O1, Regauer S, Scharf S.

- High levels of xenoestrogens may be a risk factor for tumor progression in those with estrogen sensitive tumors


Fibroids

- Abnormal growth
- Benign
- Possibility of many locations
- May physically be an obstruction to fertility or implantation
- Made from muscle tissue
Polyps
- Growths, mostly benign but have a chance to become malignant
- Made of endometrial lining

Andenomyosis
- Endometrial tissue invading the uterine wall
- Tx options to control the tissue affected by hormones.
- BCP, IUD, ablation, hysterectomy

PCOS
- Hyperinsulinemia causes ovarian dysfunction by affecting hormone receptors.

How related to Xenoestrogens
- Is it possible that the xenoestrogens (which have a higher affinity for the ER than body produced estrogens) are blocking the receptors?
- The body isn’t able to use its estrogen, resulting in higher circulating levels
- Yet, the androgens are left running the show...

PCOS
- A true “syndrome” – collection of symptoms
- Elevated Anti-Muellerian Hormone
- High levels of androgens
- Decreased insulin sensitivity (not always related in these cases to obesity)
- Oxidative stress due to mitochondrial dysfunction
  - Of note: oxidative stress can also CAUSE decreased insulin sensitivity and increased levels of androgens

PCOS
- One of the most common endocrine disorders for women during this reproductive window
- 1958 termed Stein-Leventhal syndrome
- Sometimes named hyperandrogenic anovulation (HA)
- Most recently, most commonly referred to as PCOS
- Overall, underdiagnosed & misdiagnosed.
PCOS- testing

- Body mass index (BMI)
- Fasting lipid panel
- 2-h glucose challenge test
- Thyroid panel

PCOS- 4 TYPES

- Non-classic ovulatory PCOS (regular menstrual cycles, hyperandrogenism, and polycystic ovaries)
- Non-classic mild or normoandrogenic PCOS (chronic anovulation, normal androgens, and polycystic ovaries)

SO, THEN, IS PCOS...
UNDERDIAGNOSED?
OVERDIAGNOSED?
MISDIAGNOSED?

Yes
No

National Institutes of Health Criteria
(2 criteria)

- Hyperandrogenism
- Menstrual Irregularity

Androgen Excess -
PCOS Society Criteria
(2 criteria)

- Hyperandrogenism
- Menstrual Irregularity or Polycystic Ovaries on Ultrasonography

Rotterdam Criteria
(2 out of 3 criteria)

- Hyperandrogenism
- Menstrual Irregularity
- Polycystic Ovaries on Ultrasonography

6 MONTHS of lifestyle changes – (diet and exercise) increased insulin sensitivity by 70%!
Also decreased anovulation
Fertility

Hindered Fertility

- Terrific term coined by Randine Lewis
- Hormones may be out of range***
- Hormone timing may be at fault***
- Receptors can be altered or inadequate in number***
- Tissues may be too inflamed to function properly***

Infertility

- Definition is the inability to become pregnant within 1 year of unprotected sex - with careful timing
- Absence of physical reproductive structures***
- Amenorrhea that has become menopause***
- NOT everyone that struggles with pregnancy is ‘INFERTILE’

For pregnancy to occur:

- A woman’s body must release a healthy egg during ovulation***
- The man’s sperm must fertilize this egg
- The newly fertilized egg needs to embed in the uterine lining and grow***

Optimizing Fertility

- Consider all of the avenues that must be functioning
- Hormones: amount, timing, coordination***
- Receptors/Tissues: responsive, no inflammatory cascade***
- Structures: organs, glands- present, correct in size, structure & function, no obstructive scar tissues, polyps, congenital malformations***

-***May be effected by excessive or inhibited estrogen levels
Baseline Menses

Tanner Stages of Puberty

Did your patient develop within the norm?

Prenat Dev.

- Environmental pollutants and lifestyle factors induce oxidative stress and poor prenatal development.

- Al-Gubory KH1.
- Xenoestrogens and poor lifestyle factors (smoking, obesity..) generate an over abundance of reactive oxygen species (ROS). This increase in OXIDATIVE STRESS overwhelms the protective anti-oxidants and causes cellular damage at the macromolecular level.

BPA-fertility

- Has similar actions as DES
- In vivo studies in experimental animals have demonstrated adverse effects of BPA on the onset of puberty, estrus cyclicity, growth and differentiation of the mammary gland and various other reproductive tract targets
- It is also known that BPA has adverse affects on the maturing oocyte.
- BPA shows evidence of reducing follicular count in the ovarian antral follicle count (AFC). As urine levels of BPA increase, the AFC decreases.

Published online 2013 Oct 4. doi: 10.1016/j.reprotox.2013.09.008
PMCID: PMC4385127
PMID: N0HMSID: NIHMS671465
The Association of Bisphenol A Urinary Concentrations with Antral Follicle Counts and Other Measures of Ovarian Reserve in Women Undergoing Infertility Treatments. 0
Irene Scuteri, MD,*, a Kristen W Smith, PhD, MPH,b Irene Dimitriadis, MD,a,1 Shelley Ehrlich, MD, MPH,b,2 Paige L Williams, PhD, c Antonia M Calafat, PhD,d and Russ Hauser, MD, ScD, MPH,a,b

BPA-fertility cont’d

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BPA - fertility in those with PCOS

- Increased BPA in urine again led to decreased AFC in women with PCOS.
- Bisphenol A and Ovarian Reserve among Infertile Women with Polycystic Ovarian Syndrome.
- Zhou W1, Fang F2, Zhu W3, Chen ZJ4,5,6,7, Du Y8,9, Zhang J10

BPA - DOES cross the placenta

- Has epigenetic influence upon psychomotor, cognition and obesity.
- Maternal exposure setting up complications for next generation
- Published online 2012 Mar 14. doi: 10.1210/er.2011-1050
- PMCID: PMC3365860
- Hormones and Endocrine-Disturbing Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses
- Laura N. Vandenberg, corresponding author Theo Colborn, Tyrone B. Hayes, Jerrold J. Heindel, David R. Jacobs, Jr., Duk-Hee Lee, Toshi Shioda, Ana M. Soto, Frederick S. vom Saal, Wade V. Welshons, R. Thomas Zoeller, and John Peterson Myers, corresponding author

Xenoestrogens affecting pregnancy

- diethylstilbestrol (DES)- hallmark example of this interaction. Devastating results with birth defects
- Most notoriously affecting the reproductive systems in both genders
- The babies directly exposed to the DES had developmental deformities within the reproductive systems IN ADDITION to their children.

Xenoestrogens in fetal life

- Xenoestrogen effect seen consistently within rodent models
- Xenoestrogens affecting receptors
  - hypothesis is that they affect the tissue directly: setting up increased risk within the tissues of breast, uterine, ovarian CA
- *Reprod Toxicol*. Author manuscript; available in PMC 2016 Jul 1.
  - Published online 2014 Sep 30. doi: 10.1016/j.reprotox.2014.09.012
  - PMCID: PMC4379137
  - NHRMSID: NRHIR56319394
  - Estrogens in the wrong place at the wrong time: fetal BPA exposure and mammary cancer
  - Tasie Paulose,* Lucia Speroni,* Carlos Sonnenschein,* and Ana M Soto

Xenoestrogens during pregnancy

- PCB’s leading to low birth weight
- Phthalates may affect placental development
- *Front Biosci (Elite Ed)*. Author manuscript; available in PMC 2011 Mar 8.
  - Published in final edited form as:  *Front Biosci (Elite Ed)*. 2011 Jan 1; 3: 690–700.
  - Published online 2011 Jan 1.
  - PMCID: PMC3050574
  - NHRMSID: NRHIR5274441
  - ENDOCRINE DISRUPTORS, ENVIRONMENTAL OXYGEN, EPIGENETICS AND PREGNANCY
  - Jared C. Robins,1 Carmen J. Marat,2 James F. Pidbury,3 and Surendra S. Sharma3

Xenoestrogens affecting pregnancy

- PCB’s leading to low birth weight
- Phthalates may affect placental development
The lessons learned from 40 years of DES research are that the female fetus is susceptible to environmentally induced reproductive abnormalities, that gonadal organogenesis is sensitive to synthetic hormones during a critical fetal exposure window, that reproductive diseases may not appear until decades after exposures, and that many female reproductive disorders may co-occur.

...oocytes are the longest-lived, nonregenerating cells in the body and are subject to a lifetime of environmental exposures that are difficult to quantify.

Breastfeeding - Low Milk Supply

- Hypoplasia / Insufficient Glandular Tissue
- Not enough growth of glandular breast tissue to make adequate milk
- Able to be traced to puberty growth patterns
- Often late onset menarche and compare to Tanner scale

Reduce Intake & Exposure

- Commercial Meat & Dairy: can have extremely elevated levels of xenoestrogens if the animals have been treated with growth hormones and other anabolic estrogenic hormones
- Sprayed, Non-Organic Produce: can have a few different forms of xenoestrogens
- Tap Water: This varies on location and water source.
- Beauty Products: Phthalates, parabens and some metals
- Soft Plastics: Think of tupperware, take out containers, straws, coffee lids...

Reduce Intake & Exposure

- Artificial Sweeteners, Additives and MSG: Affect hormone levels of insulin, cortisol, the receptors in the cells- all skewing how estrogen can be utilized
- Soy Protein / Soy Protein Isolates: Isoflavones from soy show some benefit in post-menopausal women, prior to that can bring excess levels of phytoestrogens
- Dryer Sheets: The components that allow your clothes to end up feeling extra soft and fluffy are chemical xenoestrogens
- BCP/HRT: Contains Ethinylestradiol (EE)
- Disposable menstrual pads/tampons: dioxins left from bleaching

WHAT DO WE DO?

- Reduce intake/exposure
- Dietary modification
- Biotransformation/Detoxification
- Elimination

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PMCID: PMC4086418
NIHMSID: NIHMS608305

Female reproductive disorders: the roles of endocrine-disrupting compounds and developmental timing

- D. Andrew Crain, Ph.D., a Sarah J. Janssen, M.D., Ph.D., M.P.H., b Thea M. Edwards, Ph.D., c Jerrold Heindel, Ph.D., d Shuk-mei Ho, Ph.D., e Patricia Hunt, Ph.D., f Taisen Iguchi, Ph.D., g Anders Jodal, M.D., h John A. McLaughlin, Ph.D., i Jackie Schwartz, M.P.H., j Niels Skakkebaek, M.D., k Ana M. Soto, M.D., l Shanna Swan, Ph.D., m Patricia Hunt, Ph.D., n Thea M. Edwards, Ph.D., o Linda C. Giudice, M.D., Ph.D., and Louis J. Guillette, Jr., Ph.D., d
Read labels

Biotransformation/Detoxification

...in the Liver...

Biotransformation/Detoxification

Calcium D-Glucarate

- Use of SERMs: Selective Estrogen Receptor Modulators: If a SERM is in the estrogen receptor, there is no room for estrogen and it can’t attach to the cell. (These can be selective enough to upregulate estrogenic effects in desirable areas such as bone, but to decrease effects in breast and uterine tissue...)

- Published online 2016 Aug 16. doi: 10.4184/asj.2016.10.4.787
- PMCID: PMC4995266
- Selective Estrogen Receptor Modulators
- Ki-Chan Ancorresponding author

- Published online 2013 Nov 12. doi: 10.1080/10937404.2013.842523
- PMCID: PMC3856475
- Sucralose, A Synthetic Organochlorine Sweetener: Overview of Biological Issues
- Susan S. Schiffman1 and Kristina I. Rother2

- This form helps the liver to break down steroid based hormones such as estrogen.

- Calcium D-Glucarate is a patented form of D-glucaric acid complexed with calcium.
- Glucaric Acid found in the body and in many fruits and vegetables
Indole 3-carbonyl (I3C)

- The 2-hydroxy pathway results in beneficial, or “good,” estrogen metabolites.
- The bad estrogen metabolism pathway is the 16-hydroxy pathway. Estrogen broken down in this pathway results in metabolites responsible for many of estrogen’s undesirable actions, including weight gain and an increased risk of breast and other gynecological cancers.

Diindolylmethane (DIM)

- DIM is produced naturally in the gut by the breakdown of I3C.

Elimination

- Constipation is extremely common
- Lack of water intake
- Poor fiber intake
- Poor fat intake
- Poor microbiome balance
- Medication use
- Lack of consistent exercise
- Progesterone of pregnancy
- Baby’s position further along in pregnancy

Decreasing Intestinal Transit Time

- 5+ cups of veggies/day
- Eliminate bananas
- Probiotics
- Walk daily; 20-30 minutes to pink cheeks (minimum)
- Abdominal massage
- Acupuncture
- Aloe juice
- Increase fat intake
- Brans (psyllium, apple, oat…to name a few…)
- Position of toilet
- Getting enough time to use the bathroom
- Position of toilet
- Getting enough time to use the bathroom