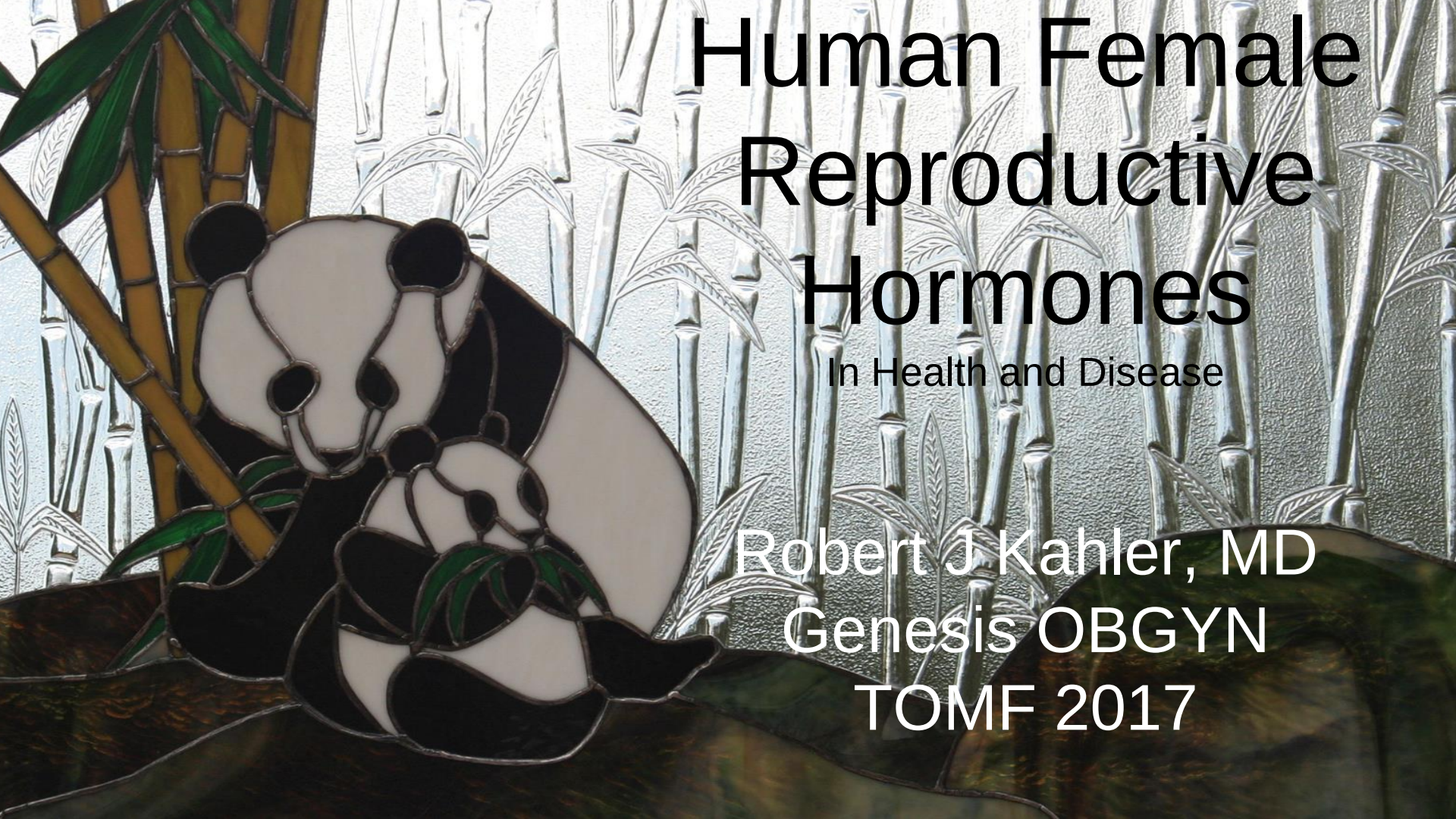

Human Female Reproductive Hormones

In Health and Disease

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Genesis OBGYN

TOMF 2017

We are not alone

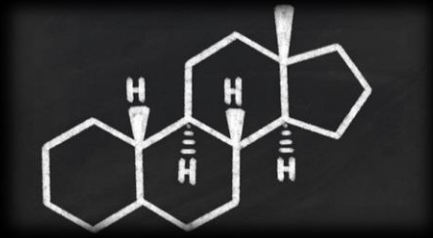
- 2016: 1st evidence of menstruation in a rodent!
  - Not to be confused with estrous cycles in domesticated animals
  - Spiny mouse Acomys cahirinus 8 day cycle with 3 day menses
  - Joins 78 other higher order primates
  - 4 bat species
  - Elephant shrew (actually not a rodent)
  - That’s <2% of all mammals

Summary

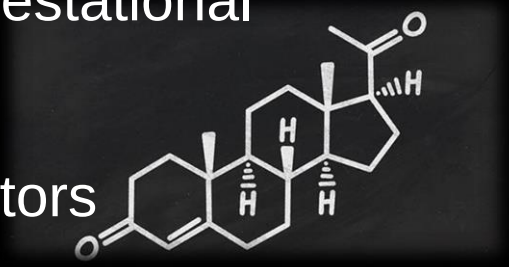
- Understanding Reproductive hormones thru the lifecycle
  - Focus on Estrogen, Progesterone, receptors, and target organs
  - Normal patterns of hormone cycling provide reproductive efficiency.
  - Abnormal patterns may lead to inefficiency and disease
  - Use for menopausal sxs control

Human reproductive hormones

- “Estrogens” (defined here as a molecule that binds to Estrogen Receptors) are found in significant amount and diversity in nature, plastics, etc



- Pro-gest(ation)erone. A vertebrate hormone
  - “Progestin” is the global name for all progestational compounds, natural or synthetic
  - Bind to PRs, ARs and other steroid receptors

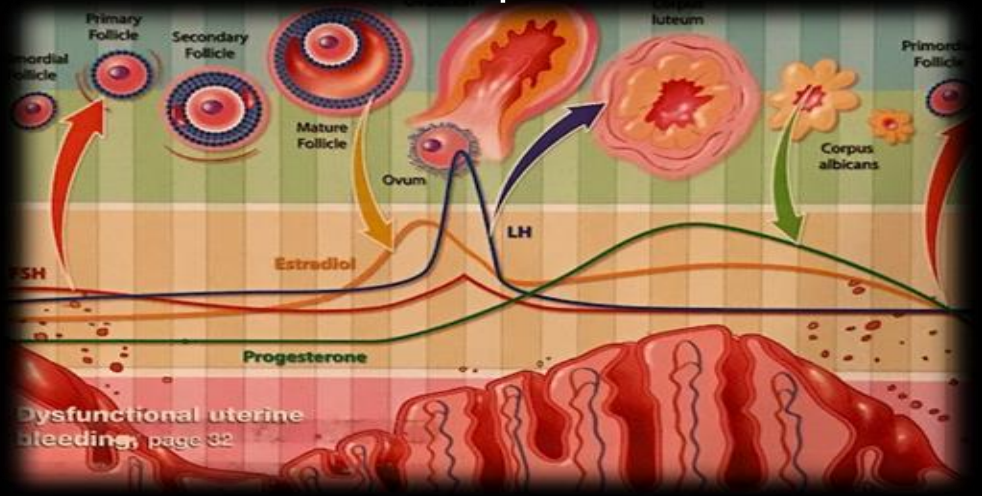


Menarche

- Start this discussion with menarche
- Regulation of cycling hormones takes some time
  - Months to years along with breast and bone growth
  - Irregularity of ovulation
    - Leads to irregular menses
    - Poor but not absent reproductive capability

Reproductive Maturity

- Regular ovulation cycle
  - Start each cycle on cycle day 1: first day of menses
  - FSH already rising due to fall of hormones from the prior failed cycle. Max to about 15 pg/ml
  - Estradiol at its lowest level
    - 60-100pg/ml
  - Progesterone nearly absent



Follicle phase

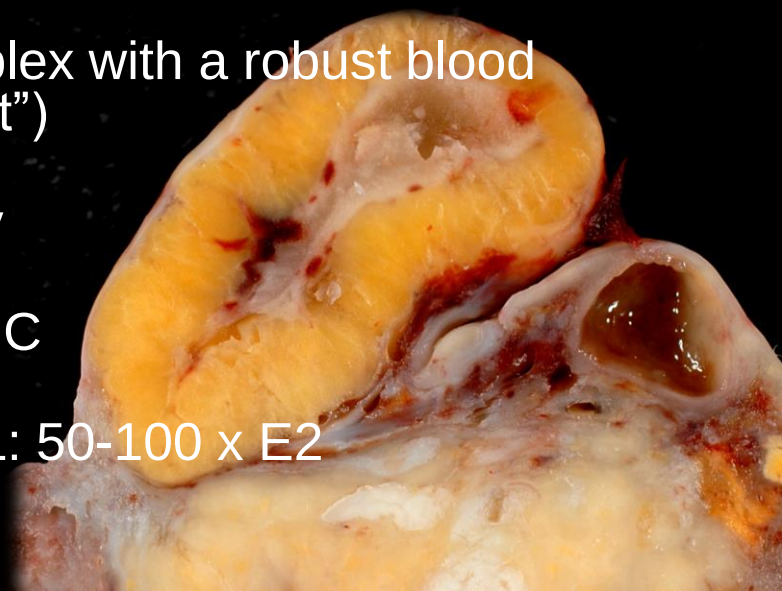
- FSH stimulates many follicles
- Rapid increase in estradiol suppresses FSH to a few pg/ml
- A single (usually) follicle becomes dominant producing more E2
  - up to 400-600pg/ml
  - One ovary (follicle) does all the work while the other(s) is suppressed.
- Ovulation: Release of the egg near CD14

Follicle phase

- Meanwhile, the endometrium is growing: “Proliferative”
- Wall thickens from a few mm after menses to 4-6mm
- Cervical mucous becomes watery and copious, perfect for sperm transport
  - High pH 8 just like semen
  - Provides access for sperm to the upper reproductive tract for the last 4-5 days prior to ovulation

Luteal phase

- Starts with ovulation
  - Some follicle cells travel with the egg looking for sperm
  - The rest transform rapidly into a complex with a robust blood supply: The corpus luteum (not a “cyst”)
    - “Yellow body” known since antiquity
    - Role in fertility deduced in mid 20th C
- High levels of Progesterone from the CL: 50-100 x E2



Luteal phase cervix

- Progesterone
  - Shuts down cervical mucous production and hydration to avoid further sperm transport
    - No fertility after ovulation so no need for further motile foreign bodies roaming around
    - Like trying to swim in the Rillito r.

Luteal phase endometrium

- Decidualization
- Progesterone suppresses estrogen receptors
  - decreases further proliferation
- Endometrium thickens due to fluid production, sugars, etc ready for implantation

Pregnancy and lactation

- Reproductive success!
  - CL (maintained by hCG) required for first trimester until the placenta is large enough to provide enough pregnancy hormones
  - CL then resolves and both ovaries stay suppressed for the rest of pregnancy and through lactation due to Prolactin

Lactation

- Amenorrhea also continues due to hyperprolactinemia of nursing suppressing FSH
  - Low E2: warmth, wakefulness, dyspareunia, etc (familiar?)
- Once Prolactin suppression ends, FSH rises generating a new ovulation cycle and hopefully another pregnancy.
- Given 9mo + a year or two of lactation, starting age 15 and ending age 45, there could be 10 or more pregnancies
- Ovarian and endometrial suppression are normal

Menopause

- Skipping over the “peri”-menopausal transition for now
- Not the absence of eggs but the absence of follicles receptive to FSH: Very low E2 levels
- Defined clinically as > 12 months without spontaneous menses
  - Confusion: Mirena, DMPA, OC
  - Confusion with Ablation, hysterectomy: supracervical hysterectomy, “partial hysterectomy”, etc

So what can go wrong?

- Infertility and bleeding disorders are common
  - Ovulation disorders
  - Physical issues

Think “Ovulation cycle” rather than “Menstrual cycle”

- Everything will make more sense.
- Why call something by its failure?

Why “menstrual cycle”?

- Menses is what we notice physically
- Hidden ovulation
  - No overt human signs of ovulation
  - Keeps the Hunter-gatherers around camp?
  - T shirt studies
    - Maybe signs but we no longer pay attention

Abnormal Uterine Bleeding

- “Ovulation cycle” would make things more clear
  - Oligo- (irregular) ovulation still results in pregnancy or normal (but irregular) menses
  - Anovulation will not result in pregnancy and may lead to irregular menses, hyperplasia, etc

Follicle Stimulating Hormone

- TSH:T4
  - Like getting your kid to do homework. Constant oversight > work output
- FSH:E2
  - Like asking (FSH) your favorite Aunt (follicle) to bake some cookies (ovulation and CL production)
  - Ask politely and she’ll bake them (ovulation and CL production) w/o further oversight

AUB-O

- Think of ovulation as a traffic light
- If the light's malfunctioning, traffic (menses) may go OK or not
  - Expected in adolescence, perimenopause
  - Estrogen may be very low if follicles suppressed (anorexia, xs exercise, "MFO", >PRL, thyroid)
  - Estrogen production and action may continue without progesterone withdrawal (irregular, prolonged, heavy menses, hyperplasia, cancer) (PCOS, thyroid)

AUB-O Rx

- Broken traffic light (anovulation)
  - “Fix the light”: if ovulation is important (fertility)
  - Put a “cop” in the intersection if not
    - Progestin vs OC
      - MPA 20mg (Megace 40mg, Aygestin 5mg) tid or OC tid x 7d then qd x 21d
    - Endometrial sampling and or surgery if pathology is suspected

AUB Hormonal Rx

- OC work by suppressing FSH and substituting EE and P for endogenous hormones: stopping ovulation, regulating cycle, reducing menses, etc. Just like biological norm
- Progestins work by down regulating estrogen receptors
  - episodically (cyclic oral) organizing and sloughing
  - Constant suppression
    - DMPA: suppress endometrium and ovary
    - Mirena: Suppresses endometrium, not ovary

AUB

- Treatment depends on present and future goals
  - 48 G5P5 w/ TL, fibroids and dysmenorrhea treated differently than 18 G0 with hirsutism and weight gain.
  - 25yo attempting pregnancy will be treated differently than 40yo sexually active smoker w/o contraception who desires no pregnancy

AUB physical Rx

- The target tissue may be abnormal or vasculature disturbed
- Common physical issues
  - Polyps (> 10% of women)
  - Fibroids (>40% with increasing age).
    - Location, location, location!
  - Adenomyosis (in 2/3rds of hysterectomies)

AUB

Polyp
Adenomyosis
Leiomyoma
Malignancy & hyperplasia

Submucosal
Other

Coagulopathy
Ovulatory dysfunction
Endometrial
Iatrogenic
Not yet classified

Leiomyoma subclassification system

SM - Submucosal	0	Pedunculated intracavitary
	1	<50% intramural
	2	≥50% intramural
O - Other	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserosal ≥50% intramural
	6	Subserosal <50% intramural
	7	Subserosal pedunculated
	8	Other (specify e.g. cervical, parasitic)

Hybrid leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.

AUB physical Rx

Polypectomy, myomectomy

Ablation

Hysterectomy

Tranexamic acid (Lysteda)

- Maintains already created clot

Perimenopause

- Normal transitional state like adolescence
  - May be abnormal (excessive or endometrial pathology)
  - May need or desire treatment
  - Juggling up to 3 balls at a time
    - Bleeding (heavy, prolonged, irregular, painful
    - Contraception
    - Menopausal symptoms

FSH: (Back to your Aunt)

- As she ages the cookies aren’t quite as good. Maybe she forgot something (follicle but no ovulation), and sometimes no cookies at all (>AUB)
- As she becomes more hard of hearing, you have to talk louder but once she hears you: cookies! (FSH rises higher to stim resistant follicles, often >>20)
- Once deaf (no more receptive follicles), no cookies, no matter how loud you are. (Don’t be surprised initially if suddenly cookies appear)
- No abnormal (or diagnostic) level of FSH, just how it relates

Menopause

- Very low levels (not zero) of E2 and E1 (<20pg/ml)
  - No follicle activity (once produced 60 – 600pg/ml)
  - E2 from aromatization of existing androgens (mostly from adrenal production) in some tissues
    - Adipose cells: Obesity leads to higher circulating E2 levels. Better bones, thicker endometrium
    - Breast cancer cells: AIs can reduce breast CA risk
    - Even this level is symptomatically meaningful for some

Menopause: Anthropology

- Normal adaptive event to post reproductive years (due to public health, etc)
  - Humans and Killer whales
    - Grandmother hypothesis: enhanced reproductive benefit to offspring
  - Only treat menopausal symptoms if needed
- Or
- Estrogen deprivation endocrinopathy
  - Wasting bones, worsening C-V events, etc
  - Treat it as a disease

Symptomatic menopausal treatment

- All ERs will respond in their reproductive age pattern to postmenopausal E2
  - Good for brain, vagina, and bone. C-V if timely.
  - Bad for endometrium
  - SERMs
    - ERs respond selectively depending on tissue
  - Think of ER like a baseball glove: Catch all sorts

Post menopausal Rx

- Think of the target organs that will respond (brain, bone, etc)
- Levels are meaningless (when FDA approved products used) compared with clinical effect. There is no “balance”.
- If using estrogen and her uterus is present
  - Need to suppress estrogen proliferative effect on endometrium w/o negative impact on other tissues
  - Utilize progesterone to down regulate ER and decidualize the endometrium
  - BZA: anti ER

Post menopausal Rx:
Nothing universal about the available therapies

- Vehicle matters
  - Oral ET (eg E2 1mg) not TD (0.05mg) doubles VTE risk
    - 1st pass liver takes out 19/20 of the oral E2 and alters liver production of clotting factors, etc
  - E2 well absorbed thru the vagina
    - Femring 50-100mcg/d for systemic use
    - Estring 7.5mcg/d, Vagifem 3mcg/d
    - Creams: Low systemic level or rival systemic doses

Nothing universal:
The choice of P may matter

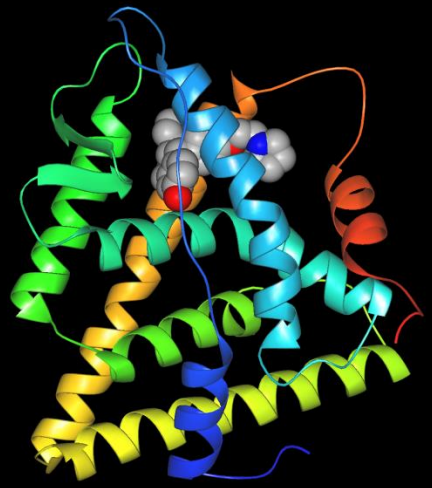
- Progestins: synthetic, $, many doses and effects
- Oral Micronized Progesterone (in peanut oil cap): sleepy (great for most, too much for some)
- Progesterone not universally well absorbed thru skin
    - Don’t use P cream for endometrial protection

Compounded HT

- You are on your own.
- You decide dose, vehicle, combination
  - The Pharmacy won’t do it for you
  - Nor will the FDA

ER

- ER alpha and beta (550 million yrs old)
- ERR: Estrogen related receptor
- GPR30: Non genomic ER in cytoplasm
- Different concentrations in different tissues
  - Helper proteins to add complexity
- Polymorphisms



Menopausal Sxs

- Think of 6 tissues out of the dozens with estrogen receptors
  - Endometrium
  - Brain
  - Vascular
  - Bone
  - Vagina
  - Breast

SERMs

- Tamoxifen
  - Originally and still indicated for ovulation stimulation
  - Antagonist: breast, vagina, brain. Agonist: endometrium, bone, VTE
- Raloxifen (Evista) same as TAM but neutral to endometrium
- Basedoxifene
  - Bone agonist (Europe)
  - Coupled with Premarin (Duavee). Anti-ER in endometrium only
- Ospemifene: Agonist: vagina. Antagonist (mice): endometrium, breast
- RAD1901 (Menopause Jan 2017)
    - Agonist for brain, bone. Antagonist for breast, endometrium

Menopause is the end of estrogen, right?

- Hardly
- Low but not absent E2 due to aromatization
  - Ask anyone starting an AI: HF, bone loss
- Environmental
  - Phytoestrogens
  - Xenoestrogens

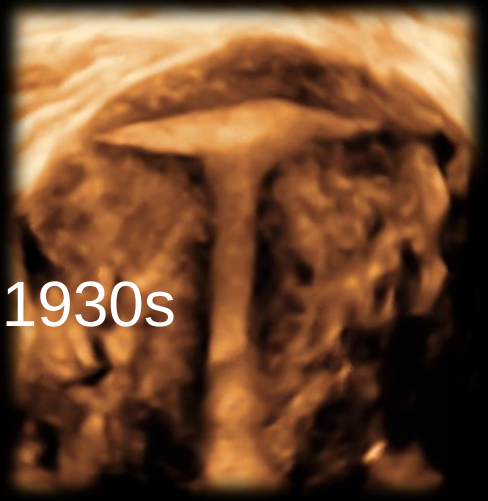
Phytoestrogens

- Soy and other legumes: color flowers: attract bees and attract bacteria to the root: Fix nitrogen to make proteins
  - We didn’t figure this out until WWII
    - Explosives and fertilizer (Succotash)
- Clover: Sheep become infertile when eaten
- Giant fennel: Ancient Greece as OC (extinct)

Xenoestrogens
“Endocrine disruptors”

- Plastics: BPA, PCBs, phthalates
  - Carcinogenic, hormone cycle disruption
  - Also interrupt nitrogen fixation
- DDT
- Mycotoxins from fungi on stored grain, etc

Other estrogens
We are not alone



- BPA initially tested as a synthetic estrogen 1930s
- DES produced as alternative
  - Stopped as prescription in 1971 but produced until 1996
  - Production of 4m tons annually. 1m tons leached into environment annually from waste

What’s the future?

- Evatar: NYTimes 3/30/17
  - Human tissue and hormone model
- SERMs
- Genetics to individualize treatment
- Minimally invasive surgery
- More xenoestrogens