SGS SEATTLE GYNECOLOGIC SOCIETY

Environmental Toxins and Women's Health

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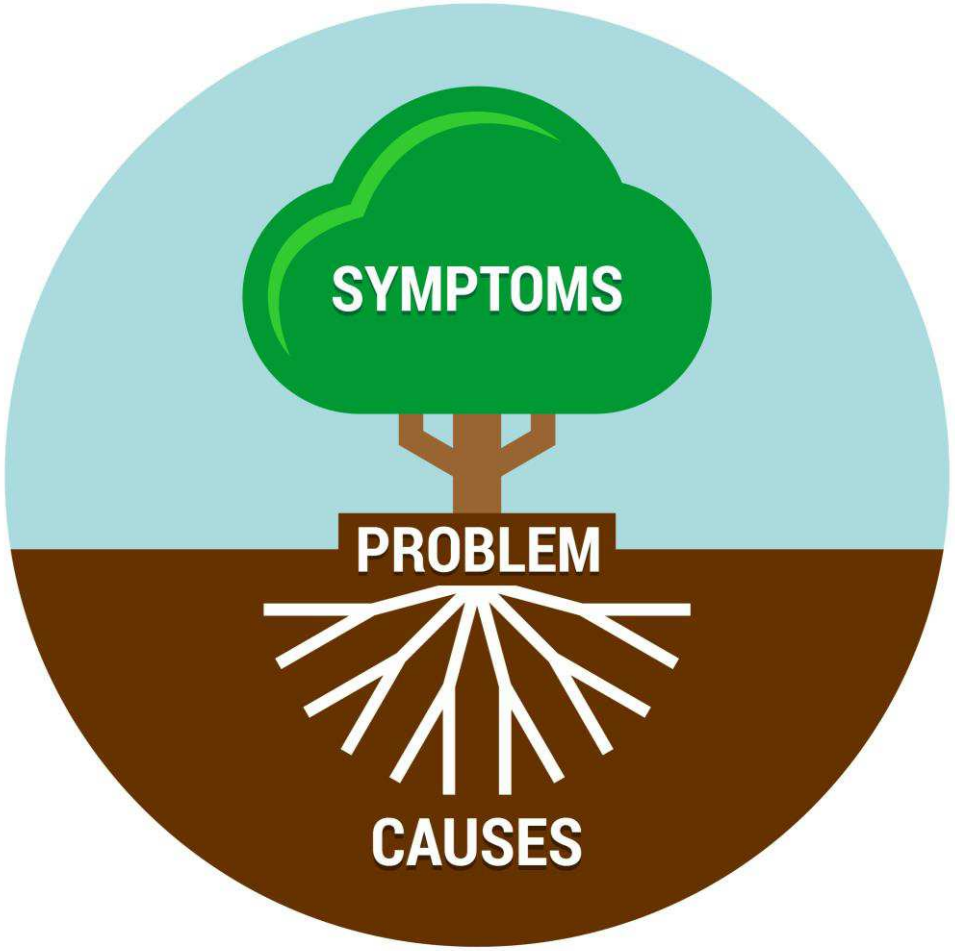
January 17, 2018

Is this our Future?

https://play.google.com/store/tv/show/The_Handmaid_s_Tale?id=vEQdsO-JmQW4Kl1UO2MImg

Exposures

- Easy to Counsel Patients About
  - Tobacco
  - Alcohol
  - Caffeine
  - Marijuana
- Not So Easy to Counsel Patients About But We Should
  - Pesticides
  - BPA
  - Phthalates
- Take Away: Awareness and Action



Association vs. Causality

Association between toxins and health exists

Causality is tough to prove

- Strength of association
- Consistency among studies
- Dose response
- Biologic plausibility
- Specificity of association (other confounding factors and bias)
- Temporal association (recall)

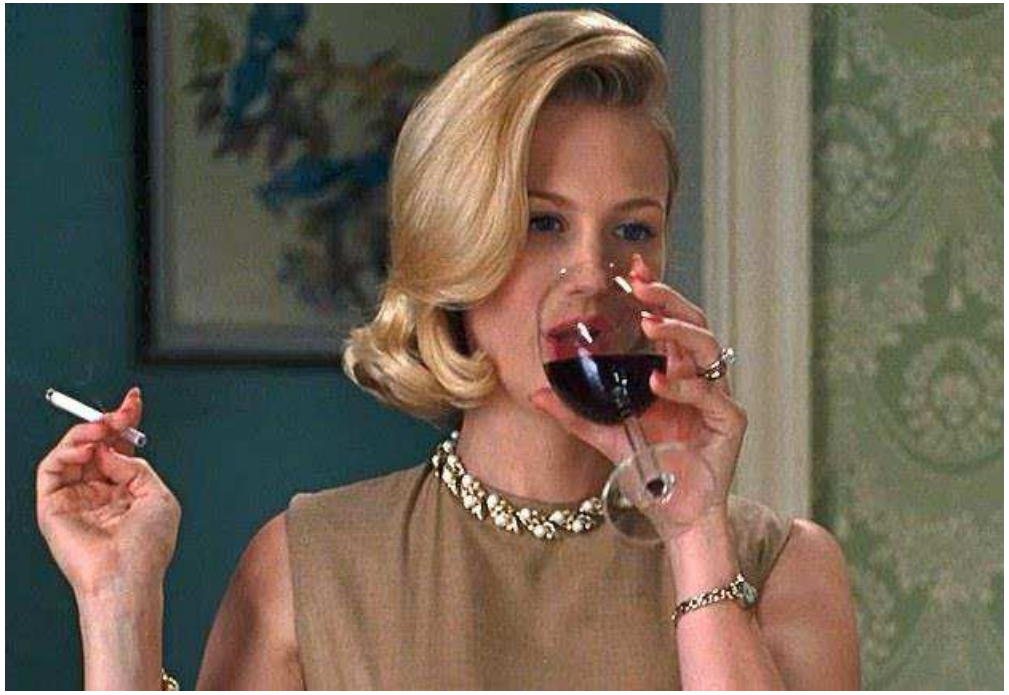
https://envisioningtheamericandream.files.wordpress.com/2014/01/smoking-pregnancy-drs.jpg

Tobacco

- Smoking decreases fertility
  - 60% increase in infertility OR 1.60 (95% CI 1.34-1.91) (Augood et al. Hum Reprod 1998)
- Smoking decreases success with IVF
  - 28% lower LBR with IVF (Lintsen et al. 2005)
- Smoking: miscarriage and other OB complications
  - 25% higher risk of miscarriage with active smoking in pregnancy OR 1.23 (95%CI 1.16-1.30) (Pineles et al. 2014)

Alcohol

- Menstrual irregularity, DOR, and early menopause, very common
- Alcohol and birth defects Feldman **2012**
- Alcohol and infertility
  - 2+ drinks per day OR 1.59 95%CI (1.09-2.31) Eggert et al. 2004
- Alcohol lowers IVF success
  - 21% lower LBR if couple drinks 4+/week OR 0.79 (95% CI 0.66-0.96) Rossi et al. 2011
- Alcohol increased risk of miscarriage in couples doing IVF Klonoff-Cohen 2003



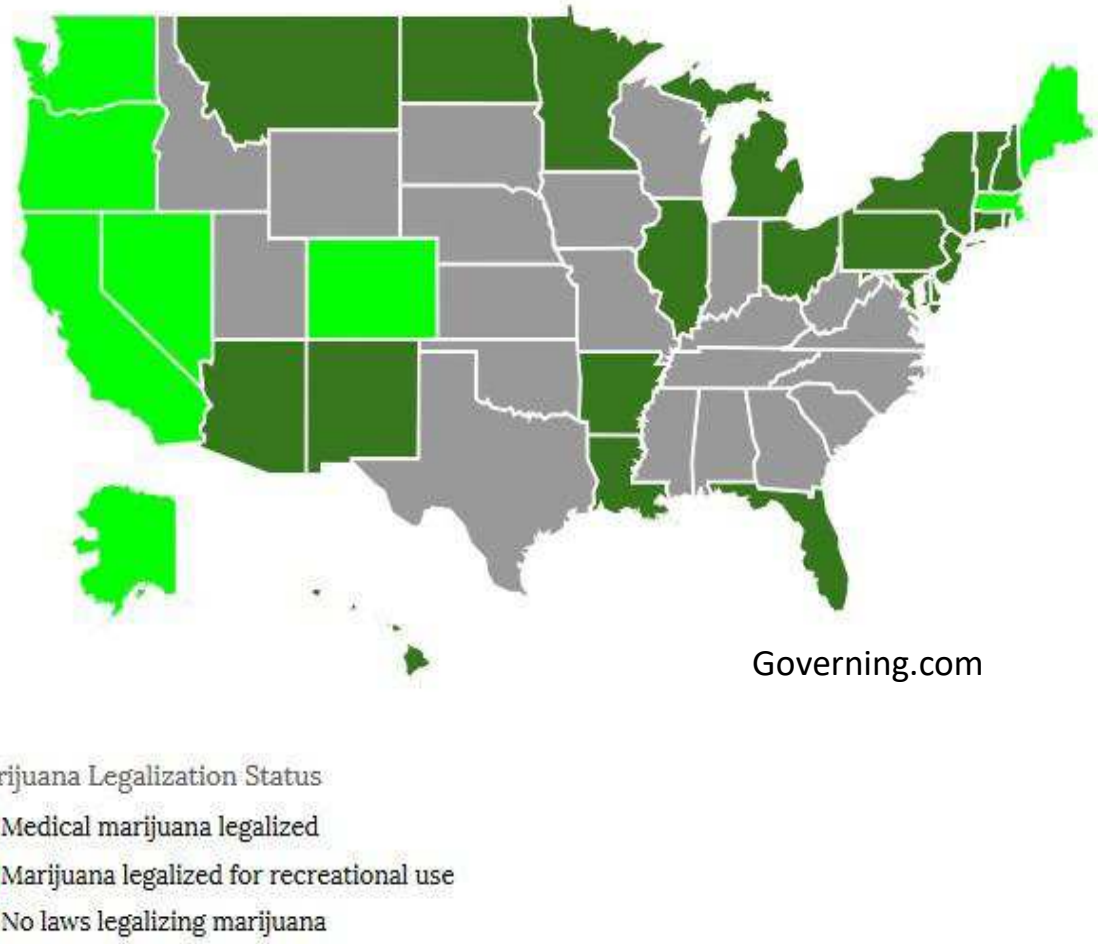
https://s-i.huffpost.com/gen/2417116/images/o-50S-HOUSEWIFE-facebook.jpg

Caffeine

- Menstrual irregularity, ovulation dysfunction, male fertility
- Caffeine does not impact female fertility (Wesselink 2016)
- Caffeine does not decrease success with IVF
  - Caffeine intake during IVF (Gormack Hum Reprod 2015)
  - Caffeine intake <200mg/day pre-IVF (Abadia Hum Reprod 2017)
- Caffeine increases Miscarriage Risk
  - >200 mg caffeine daily in pregnancy higher risk of miscarriage OR 1.48 (95% CI 1.03-2.13) (Hahn 2015)
  - >2 daily caffeinated beverages in the preconception window increased miscarriage risk Women OR 1.74 (95%CI 1.07-2.81) Men OR 1.73 (95% CI 1.10-2.72) (Buck Louis 2016)

Marijuana

- In 2014, 4.2 Million Americans endorsed cannabis dependence, 5.4% pregnant women use
- In women, marijuana disrupts the HPO-axis regulation, ovarian hormonal production, menstrual cycle regularity and fertility (Brents 2016)
- Marijuana use associated with decreased success with IVF – fewer eggs, fewer embryos, lower birth weight babies (Klonoff-Cohen 2006)



Governing.com

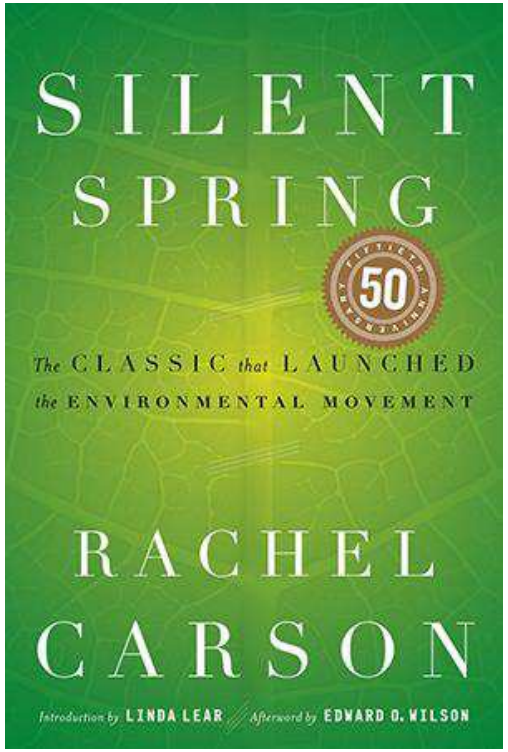
Silent Spring
by Rachel Carson

Published in a series in the New Yorker in the summer of **1962**, read and commented on by JFK, instant best seller

Warned against the environmental and health impact of industrial chemicals

Launched the environmental movement

Died in **1964** before the true appreciation of the book and her warnings were appreciated



http://www.rachelcarson.org/graphics/books/SilentSpring50_300.png

Endocrine Disrupting Chemicals (EDCs)

- Definition: Exogenous chemical that interferes with hormonal action
- Examples
  - DDT (and other pesticides)
  - DES
  - BPA
  - Phthalates
- Outline
  - EDCs impact on health
  - Pathophysiology
  - Legislation
  - What you can do now

Pesticides - DDT

- 1,1,1-trichloro-2,2'bis(p-chorophenyl) ethane
- History
  - 1874 first synthesized
  - 1939 WWII pesticide protect soldiers from malaria
  - 1945 commercial widespread use, credited for eradicating malaria in the US
  - 1950s studies showing reproductive impact in animals
  - 1960s most widely used pesticide in the US
  - 1972 DDT restricted or banned in most developed countries
- DDT's chemical stability and lipophilic nature – accumulates and persists
- Associated with endometrial cancer, breast cancer and Type II Diabetes

Endocrine Society Scientific Statement on EDC 2015

Image from http://diethylstilbestrol.umwblogs.org/side-effects/

DES (diethylstilbestrol)

- History
  - One of the best studied EDCs
  - Potent synthetic nonsteroidal estrogen taken by pregnant women from 1940s-1971 to prevent miscarriage and other OB complications
  - Doses varied from 5mg/day to as high as 40,000 mg/day
- 1953 study showed it ineffective in treatment
- Associated with 40X increased risk of vaginal clear cell carcinoma in daughters of women exposed in pregnancy and other issues like genital malformations and other cancers in both DES daughters and sons

BPA Bisphenol A

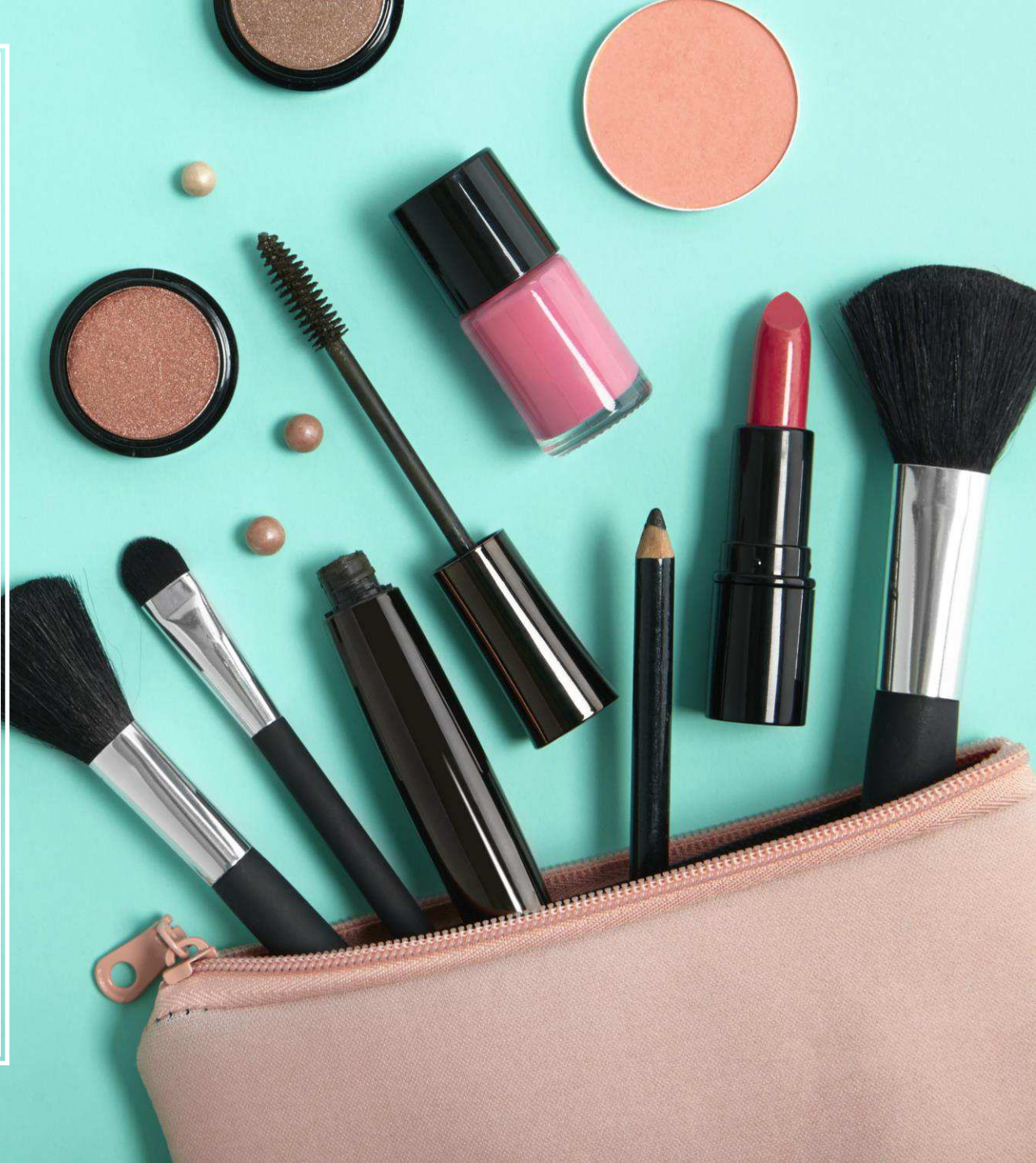
- History
  - 1891 synthesized
  - 1936 founds to be estrogenic and used as hormonal therapy until replaced by DES
  - 1950s epoxy resin in plastics
- Found in
  - Food packaging (canned food, beverage bottles)
  - Toys
  - Printed receipts and tickets
- 15 billion pounds produced in 2013
- 93% of American have BPA in urine (Calafat 2008)
- Safe levels are not agreed upon
  - US EPA says 50 µg/kg/d
  - European Agency 4 µg/kg/d

Endocrine Society Scientific Statement on EDC 2015

Phthalates

- Replaced camphor and castor oil as plasticizer used to make plastic more flexible in the 1920s and 1930s
- Found in many products like
  - food packaging
  - medical supplies (IV tubing)
  - Polyvinyl chloride plastics (PVC pipes)
  - beauty products
- Estimated **18** billion pounds produced per year
- 95% of pregnant women have phathlates in their system (Berman 2009)

Endocrine Society Scientific Statement on EDC 2015



EDCs and women's health
Where to start?

- Studies show link between environmental factors and disease
  - Twin studies
- Accidental high level exposure of humans to EDCs show toxicity
- Associations between toxins and disease investigated in animal models to show causation

Seveso Disaster

- July 10, 1976 - Chemical plant explosion and largest exposure to dioxin to date covering 7 square miles and population of about 100,000 people
- Aftermath
  - Within days thousands of animal died (up to 80,000 slaughtered after exposure)
  - People were evacuated after showing skin effects, hospitalized for respiratory distress
- Policy Change
  - Lead to new policies on exposures
  - EU industrial safety regulations are called the Seveso Directive
- Studies on EDCs and health

http://www.toxipedia.org/download/attachments/9353/Seveso.chem.jpg?version=1&modificationDate=1238498605000&api=v2

Health Impact of EDCs: Cancer

- 1996 Seveso Women's Health Study (Warner 2011)
  - HR 1.80 (95% CI 1.29-2.52) all cancers, most common breast and thyroid
  - Dose response
- BPA induces breast cancer cell proliferation (Xu F et al. 2017)
- Phthalates and thyroid function (Calsolaso et al. 2017)

Health Impact EDCs: Obesity, Diabetes, CV Health

- 1996 Seveso Women's Study (Warner 2013)
  - Higher risk of metabolic syndrome in girls exposed <12 years old OR 2.03 (95% CI 1.25-3.30)
- NHANES cross-sectional, 2747 American adults
  Carwile et al. Envrion Res 2011
  - Adjusting for age, race, sex, urinary creatinine, smoking and education level, odds of obesity increased by 36-69% by BPA levels
- Animal models (Miyawaki et al. 2007)
  - Increased exposure to BPA in prenatal period in mice shows increased obesity in offspring

EDC and Endometriosis

- Endometriosis affects 6-10% reproductive age women
- Pathophysiology: ovarian steroidogenesis, immunological dysfunction, role of EDCs
- WREN study (Upson et al Environ Res 2014)

  340 women age 18-49 in Western WA

  Adjusted for age, year of samples, and creatinine concentrations – dose response levels of phthalates associated with higher risk of endometriosis OR 1.3 (95%CI 1.1-1.7) P=0.012

Health Impact of EDCs: Reproduction

- The female reproductive system is especially vulnerable
  - Anatomical malformations (DES)
  - Disrupted puberty (phthalates)
  - Dysfunctional folliculogenesis leading to ovulation dysfunction, PCOS, infertility, diminished ovarian reserve (BPA, DDT, phthalates)
- Male reproduction
  - Anatomic malformations (DES)
  - Disrupted puberty (BPA and phthalates)
  - Sperm production and function (BPA and phthalates)

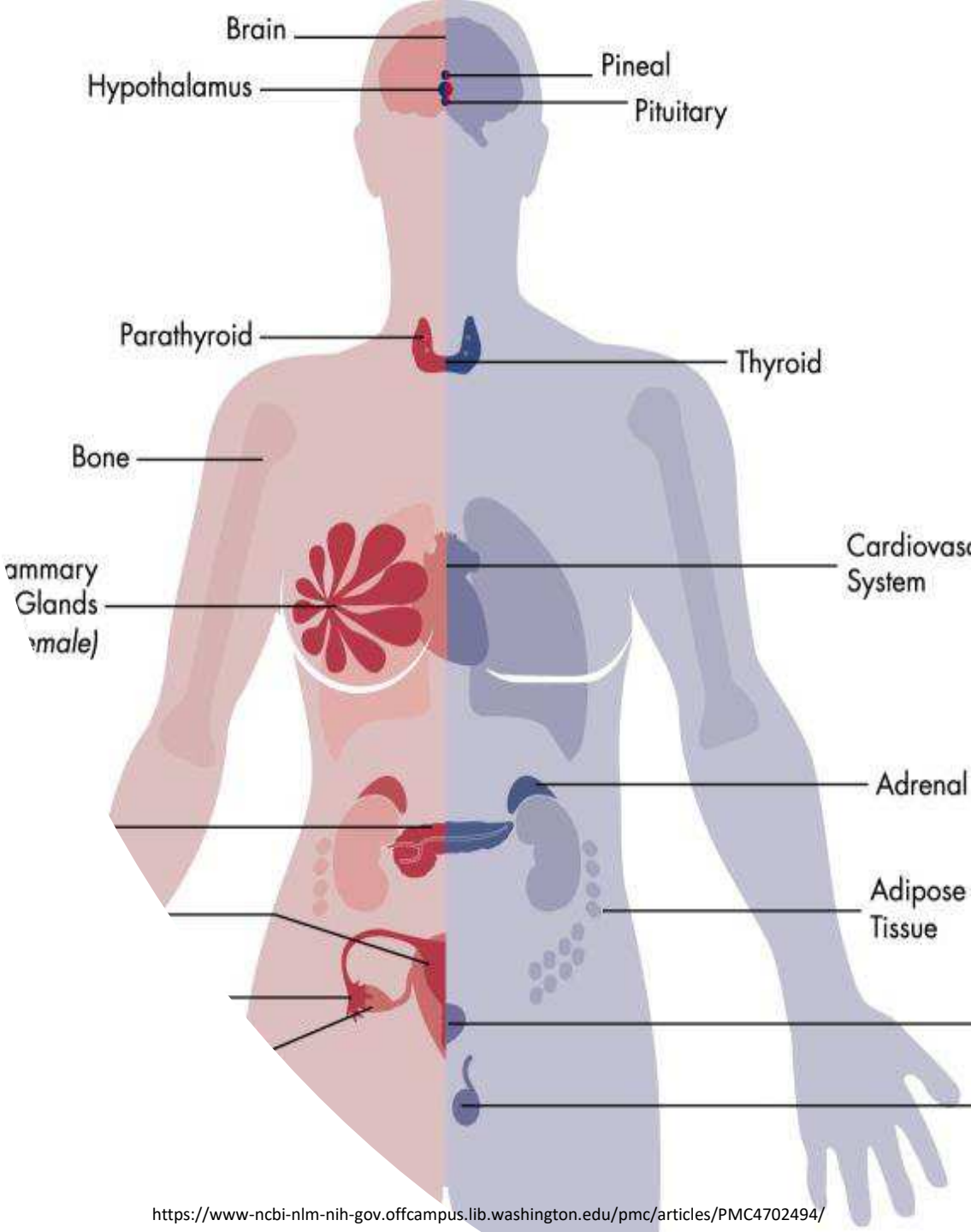
Endocrine Society Scientific Statement on EDC 2015

EDCs and reproduction

- 1996 Seveso Women's Study (Eskenazi et al. 2010)
  - For every 10X increase in EDC concentration in serum 25% increase in time to pregnancy, OR 0.75 (95%CI 0.60-0.95) and a doubling in odds of infertility, OR 1.9 (CI 1.1-3.2)
- BPA and infertility – Lamb et al UCSF 2008
  - BPA levels in follicular fluid and urinary samples on day of egg retrieval associated with lower success with IVF cycle
- BPA and miscarriage – Lathi et al. Stanford 2014
  - Women with high levels of BPA in serum have 83% higher risk of miscarriage (OR 1.83 95%CI 1.14-2.96)

Pathophysiology of disease and EDCs

- Hormonal regulation and EDC disruption
  - Disease: genetic predisposition and environmental factors
- EDC disruption
  - Hormonal communication at receptor level
  - Genetic level with epigenetic effects like methylation, post-translational modifications of histones, and altered microRNA expression
  - transgenerational effects



https://www-ncbi-nlm-nih-gov.offcampus.lib.washington.edu/pmc/articles/PMC4702494/

Transgenerational effects of EDCs

- Animal studies - Anderson et al. 2012
  - Higher levels of BPA in diet of pregnant mice showed both phenotypic changes (altered coat color) and epigenetic changes in the DNA of offspring
- Human studies – Kim et. Al 2013
  - Girls age 10-13 with highest level of BPA in urine showed epigenetic changes in genes associated with immune function
- Epigenetic changes in genes can be passed on to offspring
  - Disease in grandchildren of women who used DES in pregnancy – Titus-Ernstoff 2008

Legislation and Policy

DDT

- 1972 banned from use in US (still used in some areas of the world)

DES

- 1971 banned by FDA for use in pregnant women

BPA

- 2008
  - Canada limited BPA and labeled it a reproductive toxin
  - California banned baby bottles with BPA
  - FDA stated that BPA is safe at current estimated levels
- 2011 FDA banned it from baby bottles and sippy cups
- 2012 FDA states low levels are safe (based on weak evidence)

Phthalates

- Europe has banned >1300 chemicals from beauty products (US 11)
- Last year law passed limiting chemicals in beauty and health products in US: 1938

Advocacy: Professional Statements

UCSF Professional Society Statement Database
https://prhe.ucsf.edu/sites/prhe.ucsf.edu/files/Professional%20Statements%20Database.pdf

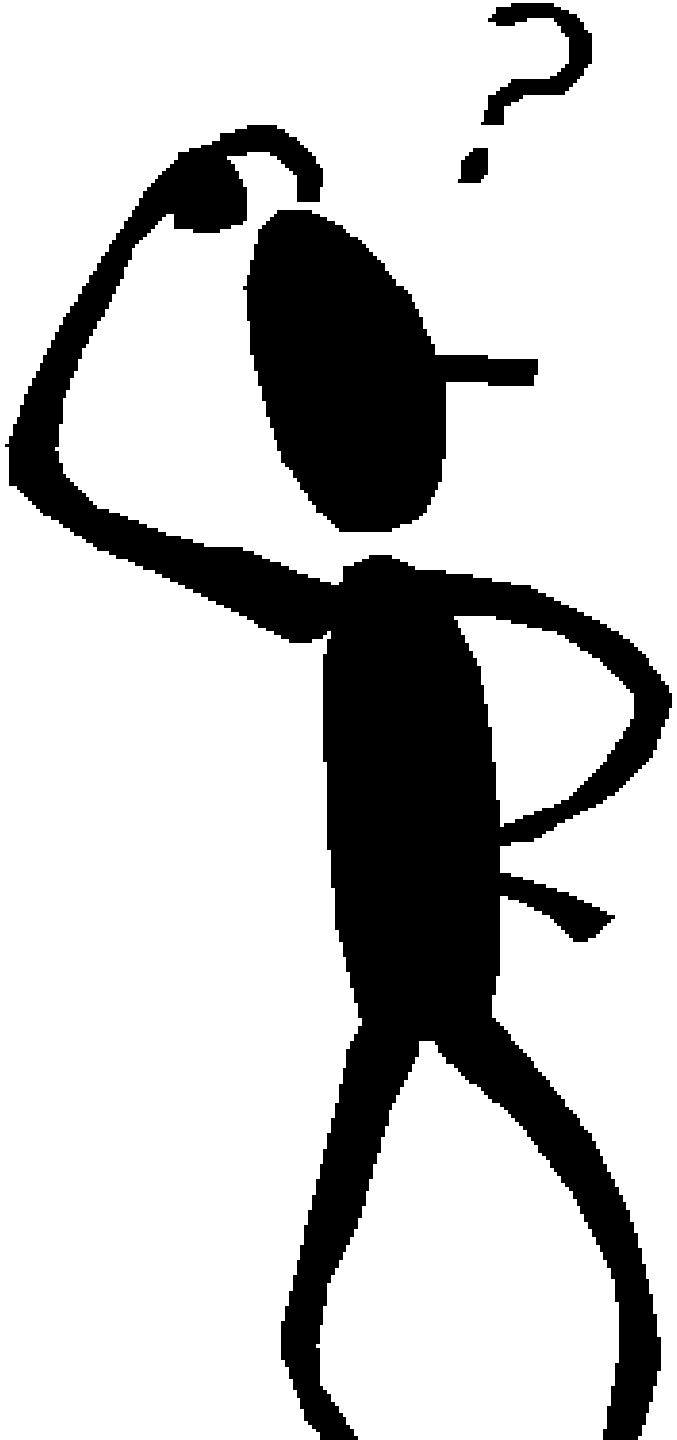
ACOG/ASRM Committee Opinion Fertil Steril 2013;100:931-4

- Robust scientific evidence has emerged over the past 20 years demonstrating that preconception and prenatal exposure to toxic environmental agents can have a profound and lasting effect on reproductive health across the life course
- Evidence based recommendations for preventing exposure must involve policy change
- Action at the individual level can reduce exposure some toxins and informed consumer-purchasing patterns can send a signal to the marketplace to help drive societal change
- The incorporation of the authoritative voice of health care professionals in policy arenas is critical

What can you do?

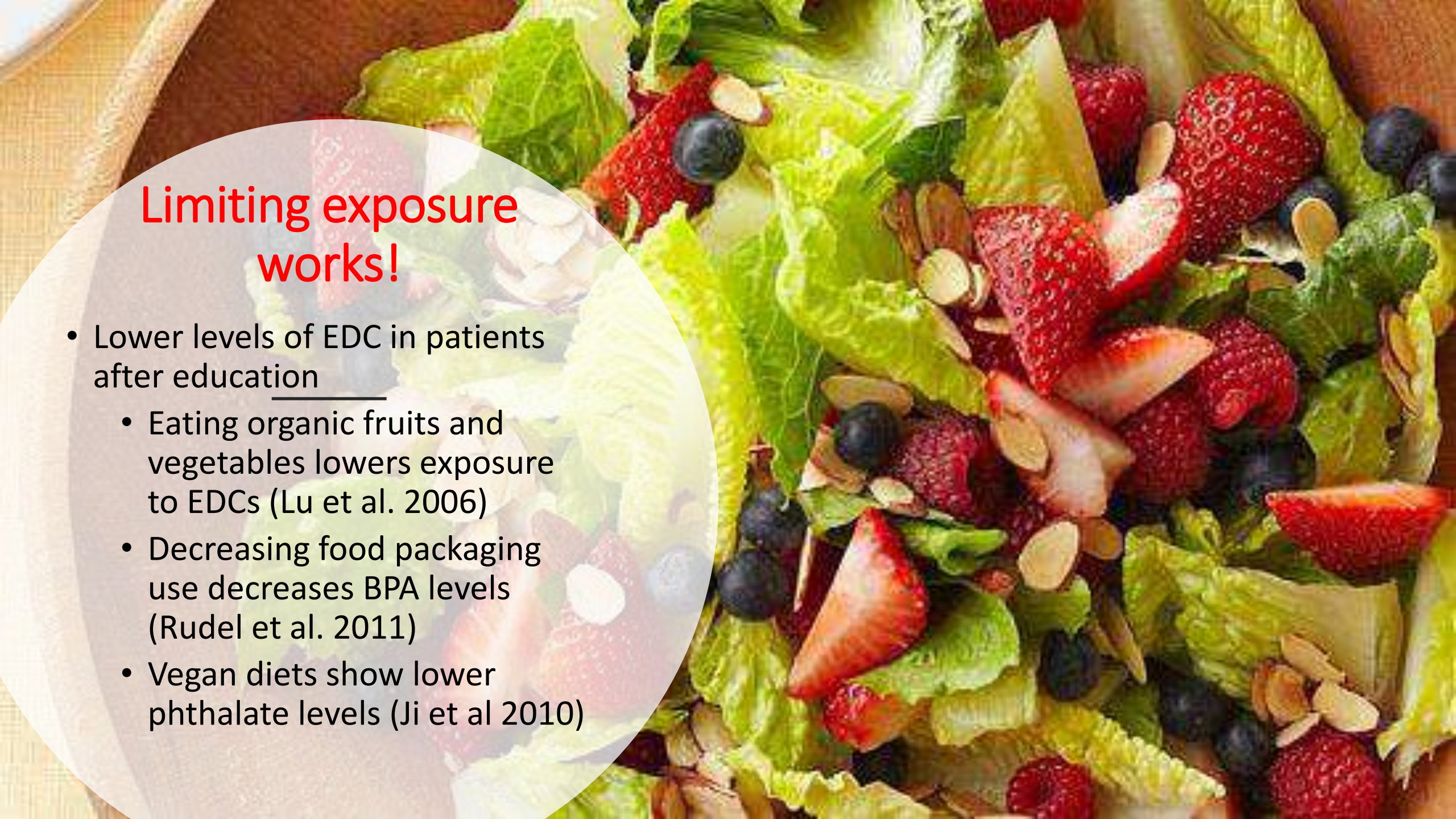
ASRM and ACOG say

- You do not have to be an expert in environmental toxins
- You do not have to read, interpret every study that comes out
- You should
    - Report occupational exposure to the Association of Occupational and Environmental Clinics (http://www.aoec.org/about.htm)
    - Be informed, aware, educate patients – handout for pregnant patients



What you can do: Awareness and Education

- You already discuss smoking, alcohol, marijuana, caffeine
- Educate about environmental toxins
  - Wash fruits and vegetables, try to eat organic (pesticides)
  - Limit processed foods (EDCs in preparation and storage)
  - Switch from plastics to glass or stainless steel in kitchen
    - Water bottles, coffee maker, glass food containers
    - Do not mix Heat, plastic, and food (EDC leak from container into food with heat from microwave, take out containers, dish washer)
  - Check your beauty products
  - Check your household cleaning products (laundry, dish washing, household)



Limiting exposure works!

- Lower levels of EDC in patients after education
  - Eating organic fruits and vegetables lowers exposure to EDCs (Lu et al. 2006)
  - Decreasing food packaging use decreases BPA levels (Rudel et al. 2011)
  - Vegan diets show lower phthalate levels (Ji et al 2010)

Take Away

- Be Aware
- Educate
- It’s ok to say
  - We’re still learning and until we know more, limit exposure

Resources and Questions?
Ask Now or Later

Ask:

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@drlorashahine

Resources:

1. Endocrine Society Statement 2015
2. UCSF Professional Society Statements 2016
3. ACOG/ASRM Joint Committee Opinion 2013
4. EWG https://www.ewg.org
5. Toxipedia https://www.toxipedia.org