Endometriosis Diagnosis & Treatment: A call to action

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www.cert.ucsd.edu

Disclosures

- Consulting
  - Sumitomo Pharma
  - Pfizer
- Research Funding:
  - Krupp foundation (PI)
  - NIH RO1 (Co-I) and R44 (Co-I)

Learning Objectives

- Be aware of common endometriosis symptoms – it's not just dysmenorrhea
- Understand surgical, imaging *and* rational for clinical diagnosis of endometriosis
- Become more comfortable with the use of FDA approved endometriosis treatments
- Understand limitations in current endometriosis care consider strategies to overcome them

Endometriosis

Presence of endometrial tissue outside the uterus…

Resulting in a chronic, estrogen dependent, inflammatory disease

Surgical Treatment of Endometriosis

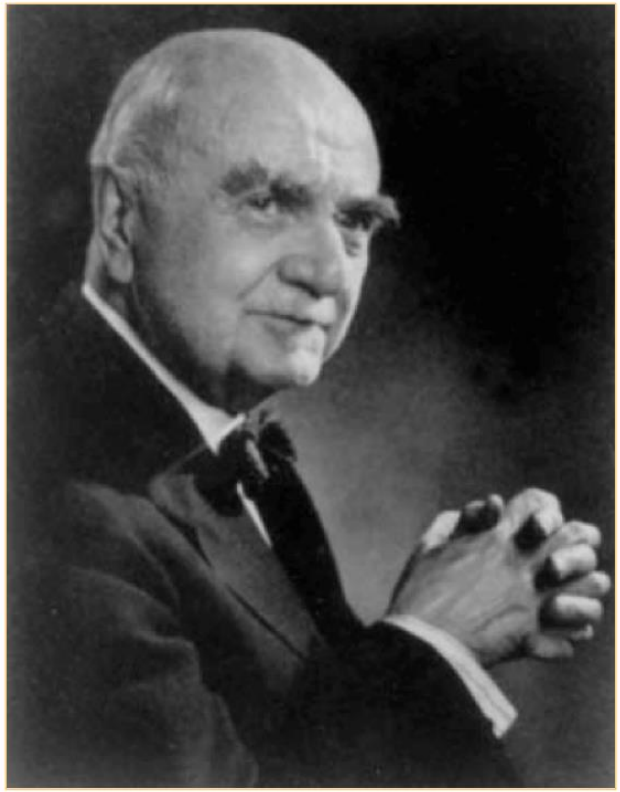
1860 von Rokitansky

1895 von Recklinghausen

Fist reference to endometriosis was by von Rokitansky and termed adenomyoma
The earliest description of the lesion called endometriosis was by von Recklinghausen

Clinical Ob/Gyn Vol 9. No. 2 June 1960.

Surgical Treatment of Endometriosis



1897 Thomas Cullen

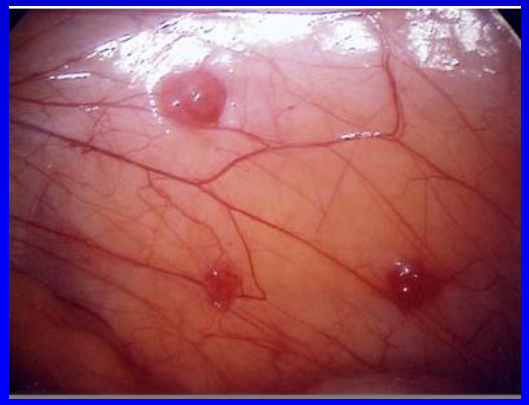
1921 John Sampson

Cullen was first American to discuss differences between endometriosis and adenomyosis
Sampson's studies led to current understanding. First to describe chocolate cysts of ovary

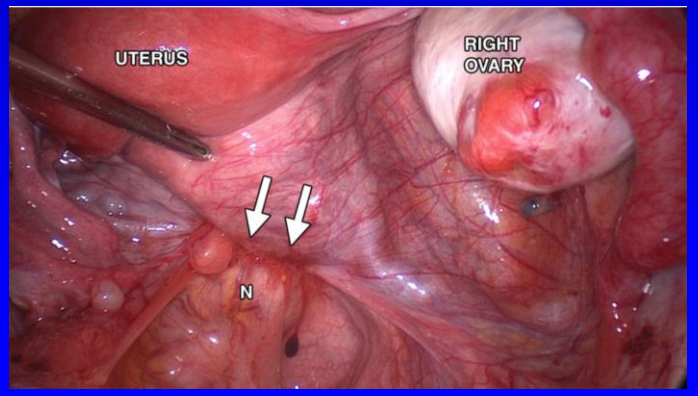
Endometriosis – Contemporary Concepts in Clinical Management. Rob Schenken, Lippincott 1989.

A History of Endometriosis. Ronald Batt, MD, Springer 2011.

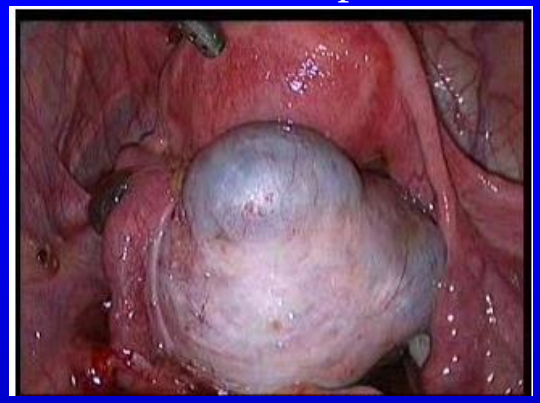
Endometriosis has many different appearances



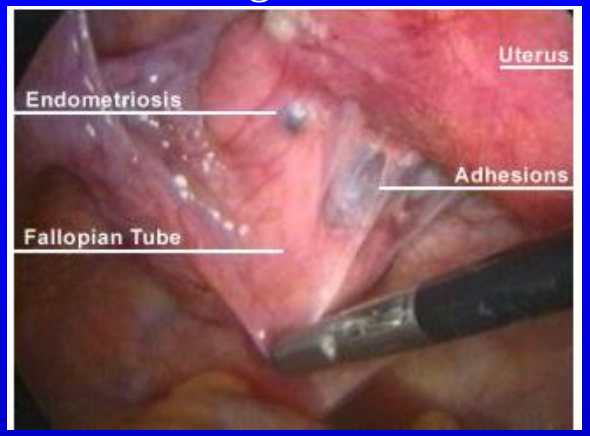
Peritoneal implant



Rectovaginal nodule

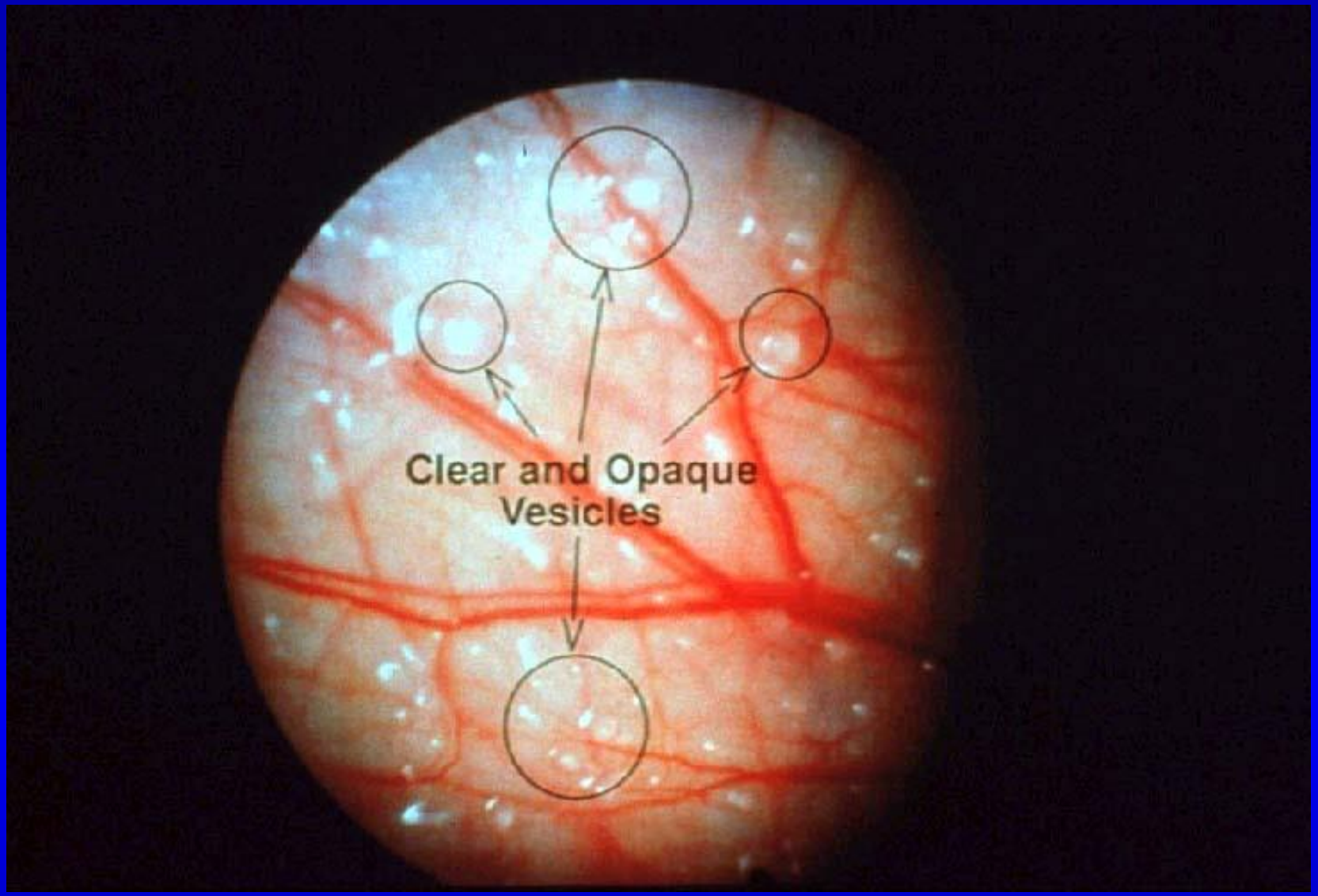


Ovarian endometrioma



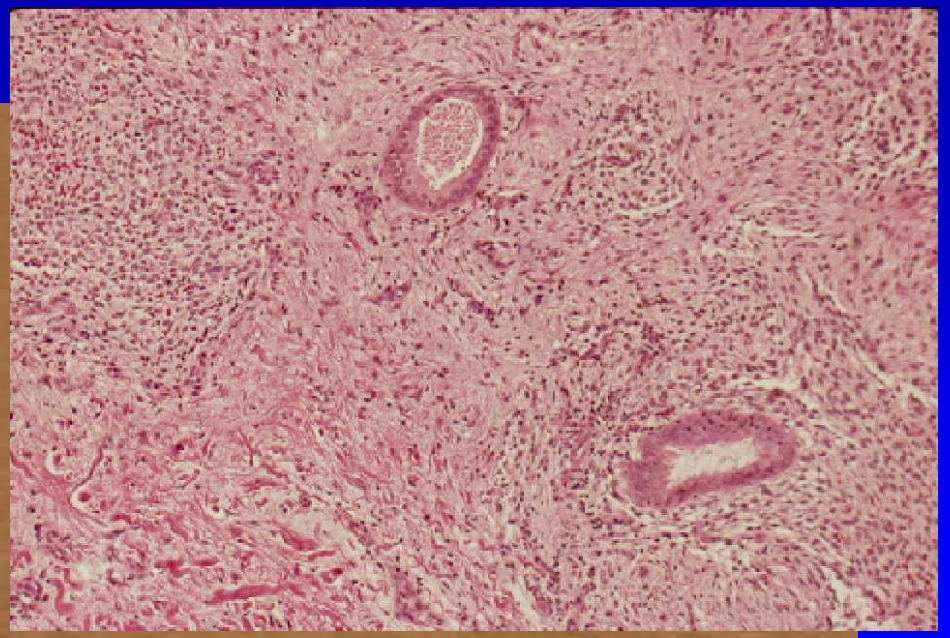
Adhesion

Images from: carolyn-overton.co.uk, endometriosis.in, radiographics.rsna.org, acfs2000.com



White/clear/red lesions 76% Painful

Demco L. *J Am Assoc Gynecol Laparosc*. 1998;5:241-245.


cm
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SPECIMEN
DATE

Etiology: Theories

- **Sampson: "Retrograde Menstruation"**
- **Hematologic Spread**
- **Lymphatic Spread**
- **Coelomic Metaplasia**
- **Genetic Factors**
- **Combination of the Above**

No Single Theory Explains All Cases of Endometriosis

Common endometriosis related problems

- Painful periods (Dysmenorrhea)
- Pain with intercourse (Dyspareunia)
- Non menstrual pelvic pain

- GI/GU symptomatology (bloating, cramping, etc)
- Infertility
- Ovarian endometriosis cyst (Endometrioma)

Others:

- Heart disease?

Ultimately leading to a negative impact on productivity, relationships, family, self esteem, …

Diagnosis

- Laparoscopy with histology is traditional
- Imaging
- Clinical diagnosis of endometriosis
- Biomarkers: *BDNF, miRNA, integrins, etc*

Clinical diagnosis of endometriosis

Call to Action ajog.org

Clinical diagnosis of endometriosis: a call to action

Sanjay K. Agarwal, MD; Charles Chapron, MD; Linda C. Giudice, MD, PhD; Marc R. Laufer, MD; Nicholas Leyland, MD; Stacey A. Missmer, ScD; Sukhbir S. Singh, MD; Hugh S. Taylor, MD

Endometriosis has such wide-ranging and pervasive sequelae that it has been described as "nothing short of a public health emergency" requiring immediate action.[1] Population-based data suggest that more than 4 million reproductive-age women have diagnosed endometriosis in the United States.[2] As daunting as this number is, it only tells part of the story, as an estimated 6 of 10 endometriosis

THE PROBLEM: Endometriosis is undiagnosed in a large proportion of affected women, resulting in ongoing and progressive symptoms with associated negative impacts on health and well-being. Current practice standards, which rely primarily on laparoscopy for a definitive diagnosis before beginning therapy, frequently result in prolonged delay between symptom onset, diagnosis, and subsequent treatment.

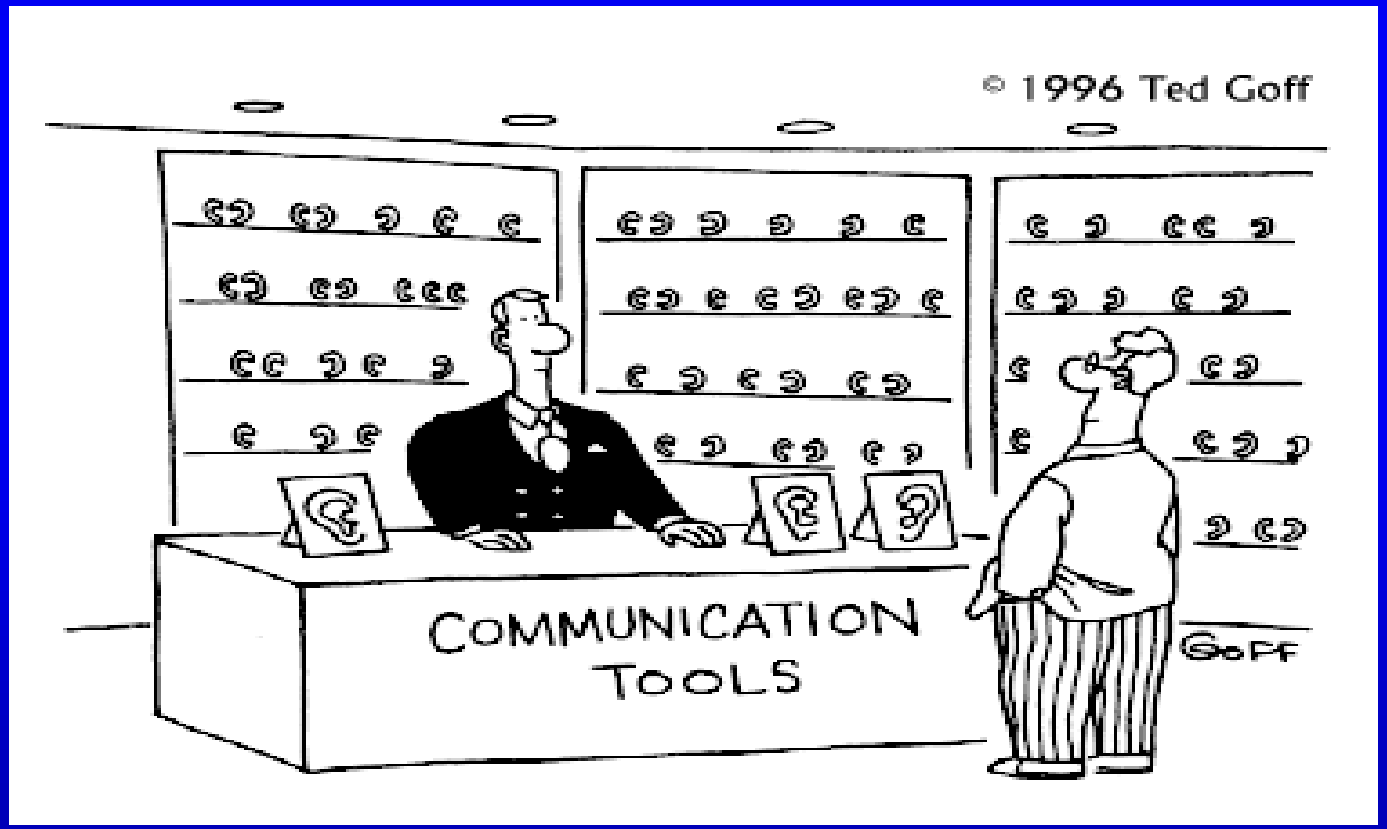
A SOLUTION: Enhanced use of clinical diagnostic techniques may reduce the delay in time to diagnosis and hence bring more rapid relief to affected patients, limit disease progression, and prevent sequelae.

Am J Obstet Gynecol. 2019 Apr;220(4):354.e1-354.e12.

Evaluation of Woman with CPP

"Be quiet and listen to the patient.
She is telling you the diagnosis"

Sir William Osler



THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS
WOMEN'S HEALTH CARE PHYSICIANS

PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

NUMBER 114, JULY 2010 (Replaces Practice Bulletin Number 11, December 1999)

Management of Endometriosis

Endometriosis represents a significant health problem for women of reproductive age. The etiology, the relationship between the extent of disease and the degree of symptoms, the effect on fertility, and the most appropriate treatment of endometriosis remain incomplete. The purpose of this document is to present the evidence, including risks and benefits, for the effectiveness of medical and surgical therapy for adult women who are symptomatic with pelvic pain or infertility or both. Treatment options for adolescents are discussed in other documents (1).

Background

Incidence

Endometriosis is a gynecologic condition that occurs in 6–10% of women of reproductive age (2), with a prevalence of 38% (range, 20–50%) in infertile women (3–6), and in 71–87% of women with chronic pelvic pain (7–9). Contrary to much speculation, there are no data to support the view that the incidence of endometriosis is increasing (10), although improved recognition of endometriotic lesions may have led to an increase in the rate of detection (11). There also appears to be no particular racial predisposition to endometriosis.

A familial association of endometriosis has been suggested, and patients with an affected first-degree relative have nearly a 7–10-fold increased risk of developing endometriosis (12, 13). There is a strong concordance in monozygotic twins (14). The proposed inheritance is characteristic of a polygenic-multifactorial mechanism. A number of genetic polymorphisms have been identified (15).

Etiology

Endometriosis is a chronic gynecologic disorder whose principal manifestations are chronic pain and infertility. The pathogenesis of endometriosis is complex but is still thought to be principally associated with attachment and implantation of endometrial glands and stroma on the peritoneum from retrograde menstruation. Other theories such as hematogenous or lymphatic transport, stem cells from bone marrow, and coelomic metaplasia may explain some clinical circumstances (16).

The complex interaction between aberrant expression of endometrial genes as well as altered hormonal response will predispose patients to the development of endometrial lesions (17–20). Key components in the development of endometriosis are local overproduction of prostaglandins by an increase in cyclooxygenase-2 (COX-2) activity and overproduction of local estrogen by increased aromatase activity. Progesterone resistance dampens the antiestrogenic effect of progesterone and amplifies the local estrogenic effect (19).

The resulting endometrial lesions can lead to a chronic inflammatory disorder with increased numbers of activated macrophages and proinflammatory cytokines in the peritoneal fluid that may cause pain and infertility. The most commonly found inflammatory cytokines are tumor necrosis factor alpha and interleukins 1, 6, and 8 (21). These cytokines are associated with pain by several mechanisms, including the induction

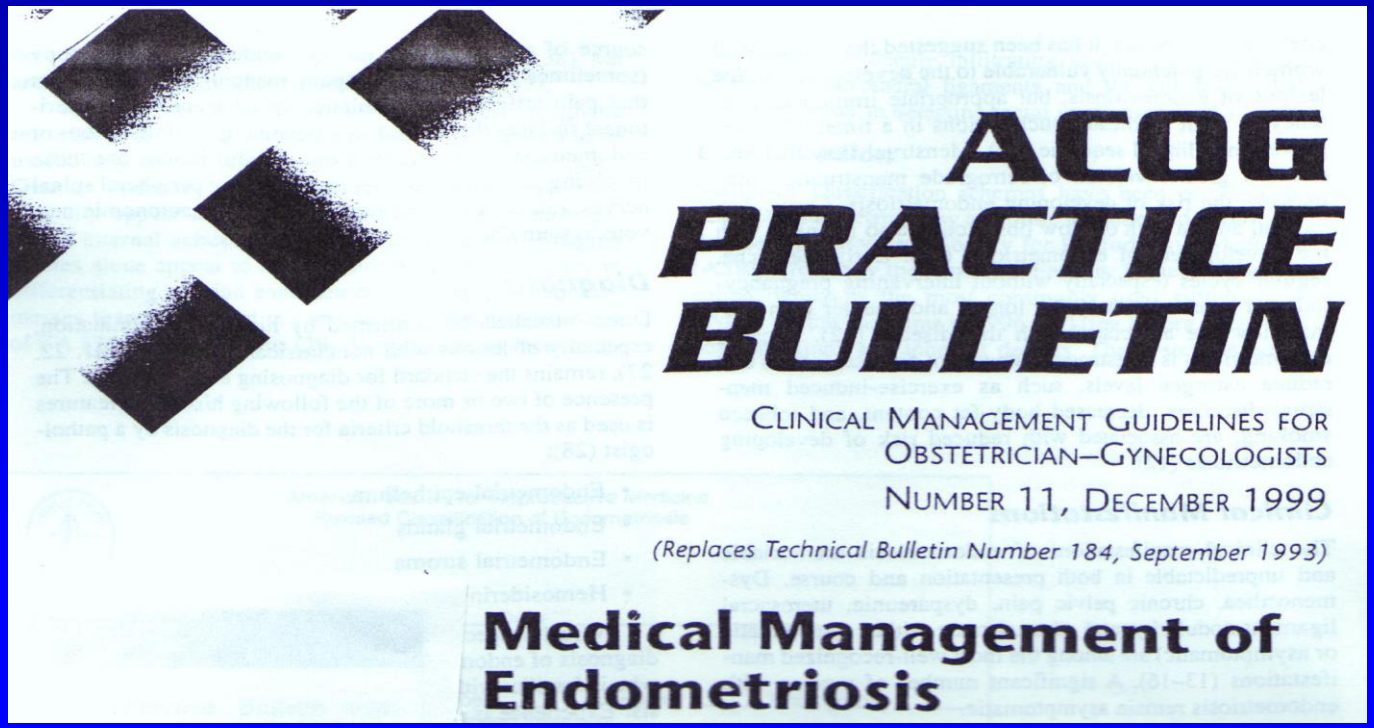
Committee on Practice Bulletins—Gynecology. This Practice Bulletin was developed by the Committee on Practice Bulletins—Gynecology with the assistance of Tommaso Falcone, MD, and John R. Lue, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

Endometriosis has a prevalence of 71-87% in chronic pelvic pain patients

Background

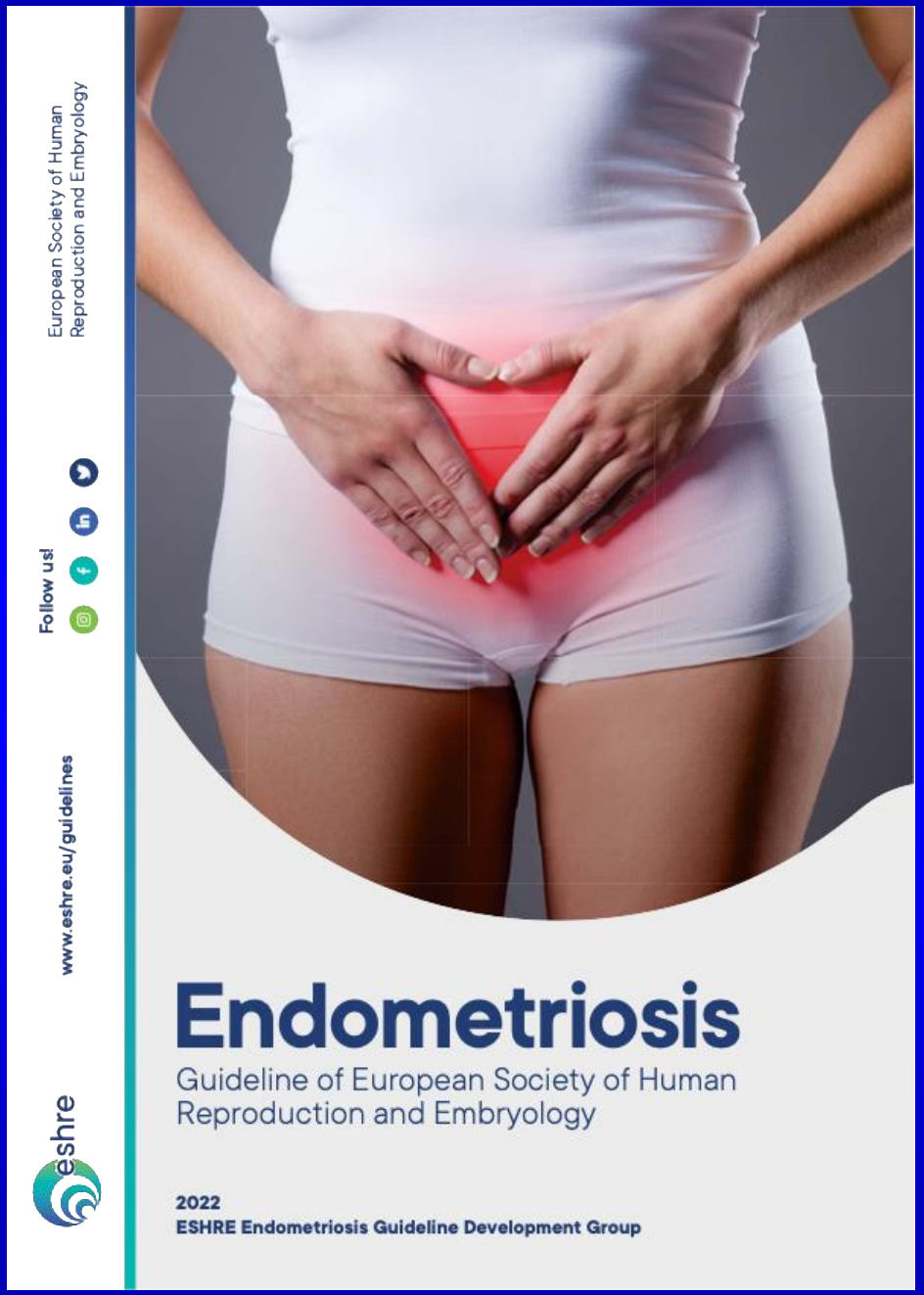
Incidence

Endometriosis is a gynecologic condition that occurs in 6–10% of women of reproductive age (2), with a prevalence of 38% (range, 20–50%) in infertile women (3–6), and in 71–87% of women with chronic pelvic pain (7–9). Contrary to much speculation, there are no data to support the view that the incidence of endometriosis is



"Therapy with a GnRH agonist is an appropriate approach to the management of the woman with chronic pelvic pain, even in the absence of surgical confirmation of endometriosis, provided that a detailed initial evaluation fails to demonstrate some other cause of pelvic pain."

2022 ESHRE endometriosis guidelines



Medical therapies

- NSAIDs
- Contraceptives
  - OCPs
  - Progestin releasing IUD
  - Depo-Provera
- Danazol – low dose
- GnRH-agonists +/- add back
- GnRH- antagonists (elagolix, relugolix)

- Aromatase inhibitors, ~~opioids~~

Oral Contraceptives in the Treatment of Endometriosis

- Commonly used as first line management of symptoms in a continuous manner, without periods – "if periods hurt, don't have them"
- Usually tried after analgesics including NSAIDs

- No one pill shown to better than others
  - – so if one does not work x3m try something else.

Common Side Effects of OCs

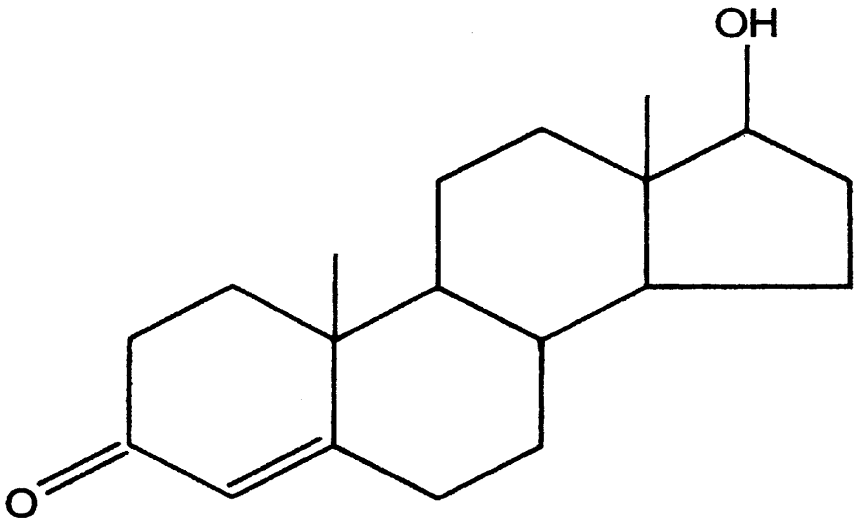
- **Common side effects include:**
  - **Breakthrough bleeding**
  - **Mood swings**
  - **Weight gain**
  - **Breast tenderness**
  - **Bloating**
  - **Nausea**

- **Side effects can limit use**

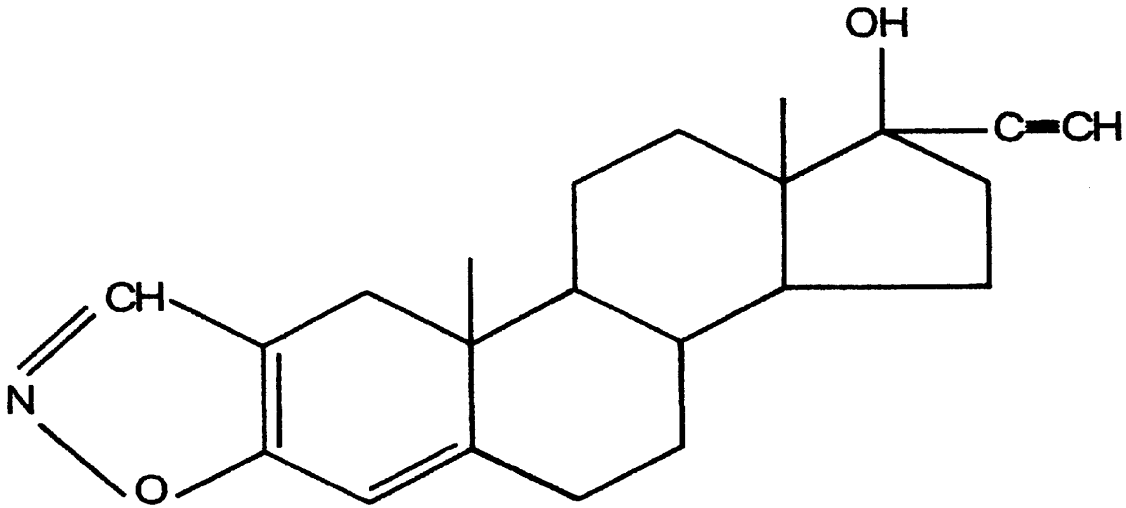
Canavan TP, Radosh L. Postgrad *Med* 2000;107:213–216, 222–224.

Danazol

1st FDA approved medicine to treat endometriosis.



Testosterone



Danazol

Danazol is an isoxazole derivative of the synthetic steroid 17[alpha]-ethinyl testosterone

Androgenic effects with Danazol

- Typical studied dose is 600-800mg/d
- Only FDA approved option that does not impact BMD

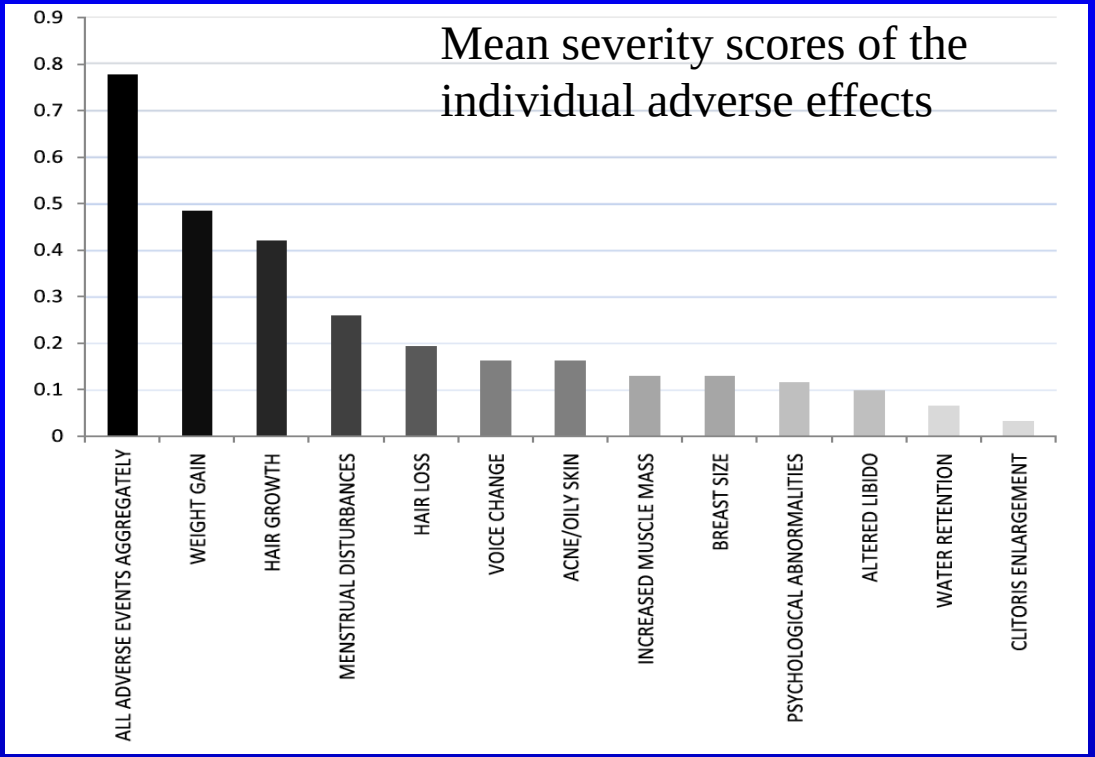
Lowers LH, FSH and Estradiol

Creates an environment that is:

- Anovulatory
- Hyperandrogenic
- Hypoestrogenic

Endometrial effects similar to P4

BJOG 1984, Vol 91, 160-166



Side effects limit use so use 200mg

Zotter et al. Orphanet Journal of Rare Diseases 2014, 9:205

GnRH-agonists
Lupron, Synarel, Zoladex

leuprolide nafarelin goserelin

- **Initially Stimulate FSH / LH Release.**
- **Down-regulate GnRH receptors– leading to "Pseudomenopause" due to suppression of hypothalamic-pituitary-ovarian axis.**

GnRH agonist Therapy

Common Side Effects – predictable from menopause

- **Reversible bone mineral density loss**
- **Vasomotor symptoms**
- **Vaginal dryness**
- **Mood alteration**
- **Diminished libido**

FDA approval limited to 6m

Side effects limit use

Maintaining efficacy while decreased side effects
Add-Back Therapy

- 30mcg OCPs
- MPA 100mg/d[1]
- CEE 0.3 or 0.625mg/d + MPA 5mg/d[2]
- 17β-E_2 2mg/d + Net 1mg/d[3]
- 17β-E_2 25μg patch + MPA 5mg/d[4]
- Tibolone 2.5mg/d[5,6]
- Estradiol +/- Testosterone[7]

[1]Makarainen L, Ronneberg L, Kauppila A. *Fertil Steril* 1996;65:29-34
[2]Moghissi KS, Schlaff WD, Olive DL, Skinner MA, Yin H.. *Fertil Steril* 1998;69:1056-62
[3]Kiiholma P, Korhonen M, Tuimala R, Korhonen M, Hagman E. *Fertil Steril* 1995;64:903-8
[4]Edmonds D, Howell R. *Br J Obstet Gynecol* 1994;101:24-6
[5]Taskin O, Yakinoghe AH, Kucuk S, Uryan I, Buhur A, Burak F. *Fertil Steril* 1997;67:40-5
[6]Lindsay PC, Shaw RW, Bennink HJ, Kicovic P. *Fertil Steril* 1996;65(2):342-8.
[7]Agarwal SK, Daniels A, et al. BioMed Res Int, 2015, Article ID 934164, Pages 1-9

Leuprolide Acetate Depot and Hormonal Add-Back in the Management of Endometriosis-Associated Pelvic Pain: A One-Year Prospective Clinical Trial

- Multi-center, prospective, randomized, double-blind trial, n=201
- All patients given leuprolide acetate depot 3.75 mg IM every 4 weeks
- Patients assigned to one of four treatment groups:
  - Group A received placebos for progestin and estrogen
  - **Group B received norethindrone acetate 5 mg** + placebo for estrogen
  - Group C received norethindrone acetate 5 mg + CEE 0.625 mg daily
  - Group D received norethindrone acetate 5 mg + CEE 1.25 mg daily

Led to FDA approval of leuprolide to increase from 6m to 1 year if used with add-back

Hornstein M, et al. Obstet Gynecol. 1998.

The prevailing situation

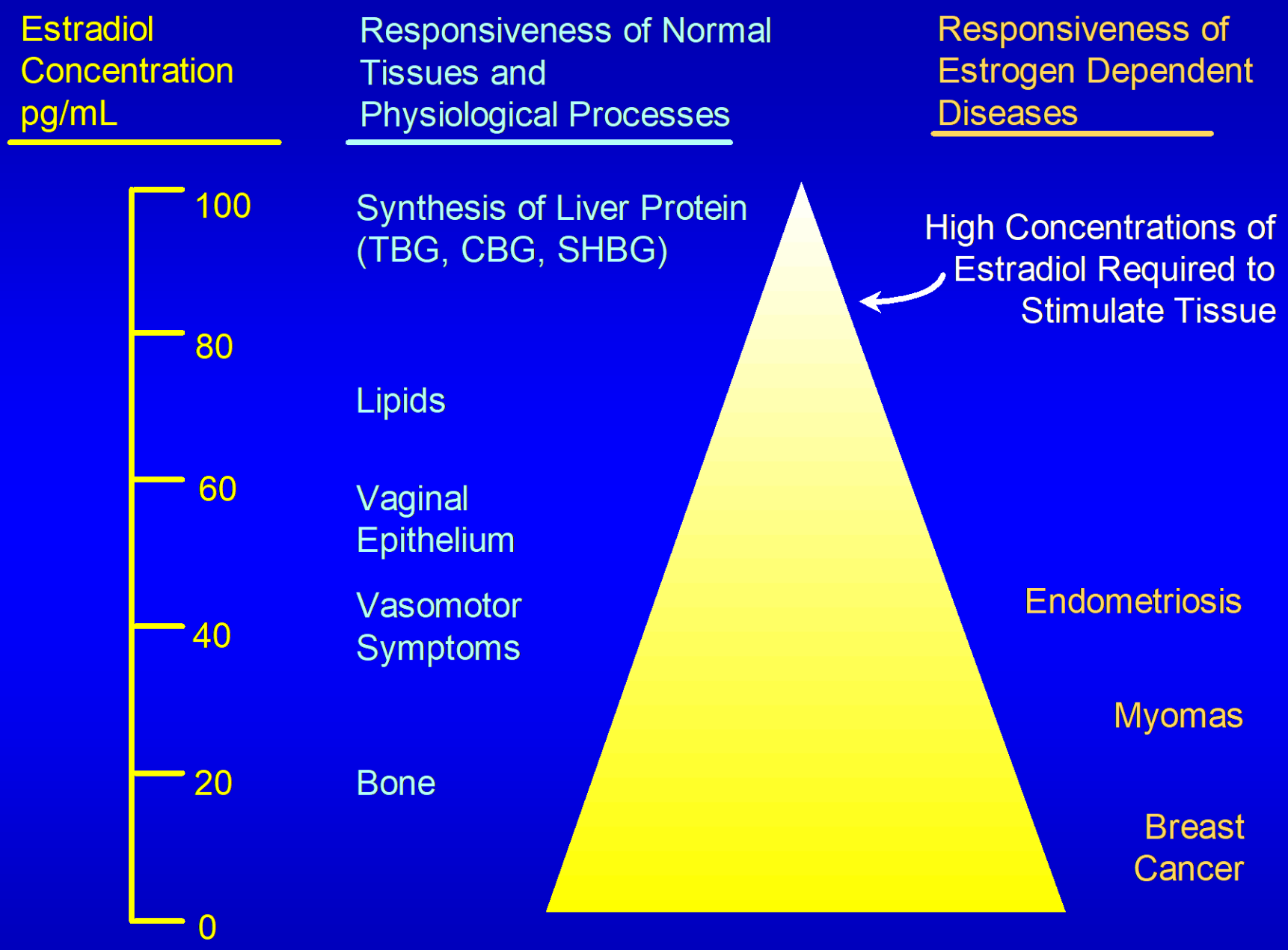
Strategies to overcome GnRHa induced side effects

~~1) Add-Back~~

~~Rationale: Over suppression of HPO axis. Replacement of sex steroids can maintain efficacy whilst reducing side effects~~

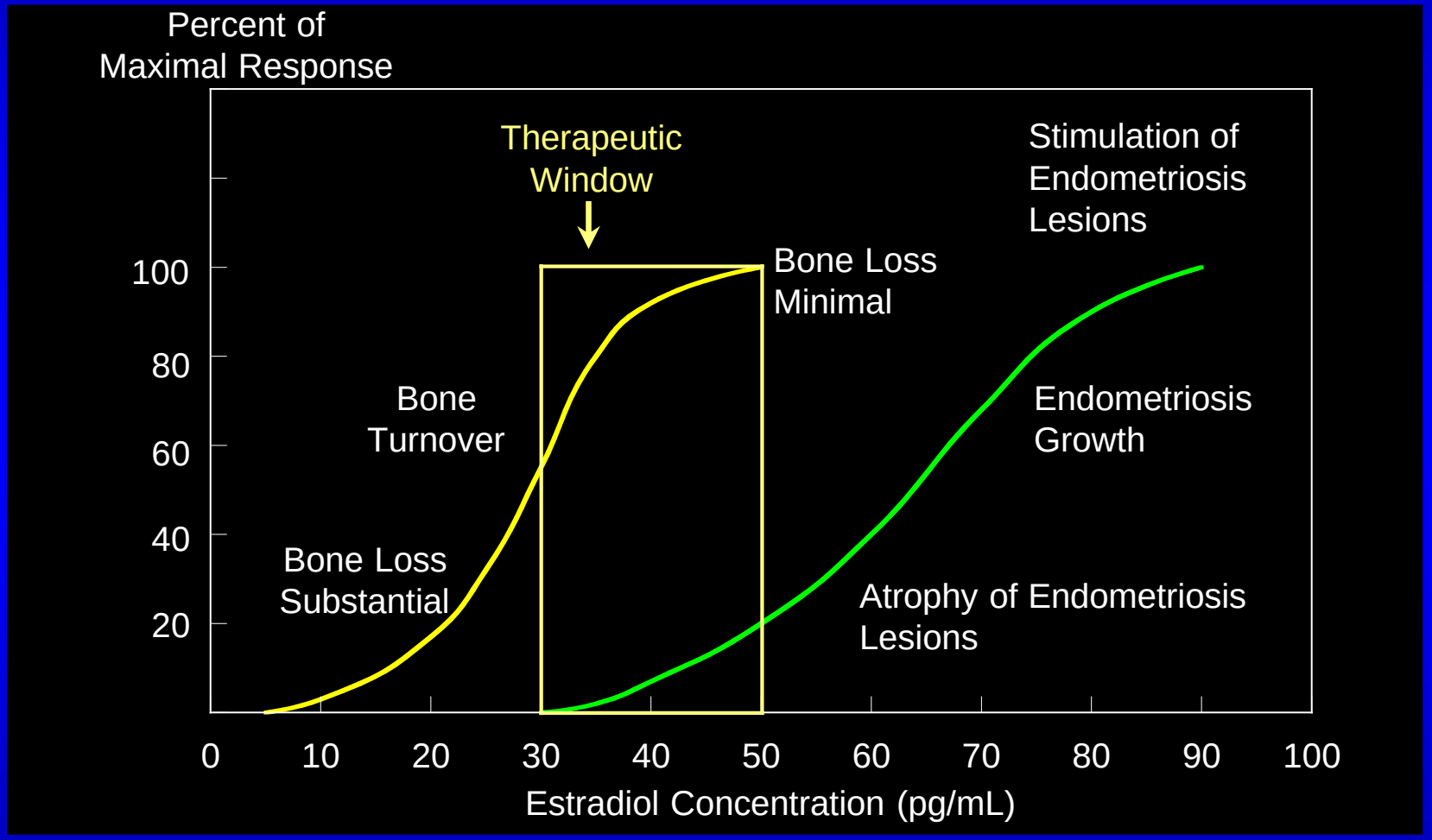
2) Low dose GnRHa

Rationale: Variably suppress the HPO axis to prevent excess hypoestrogenemia



Barbieri RL, Am J Obstet Gynecol 1992;166:740

Estradiol Therapeutic Window



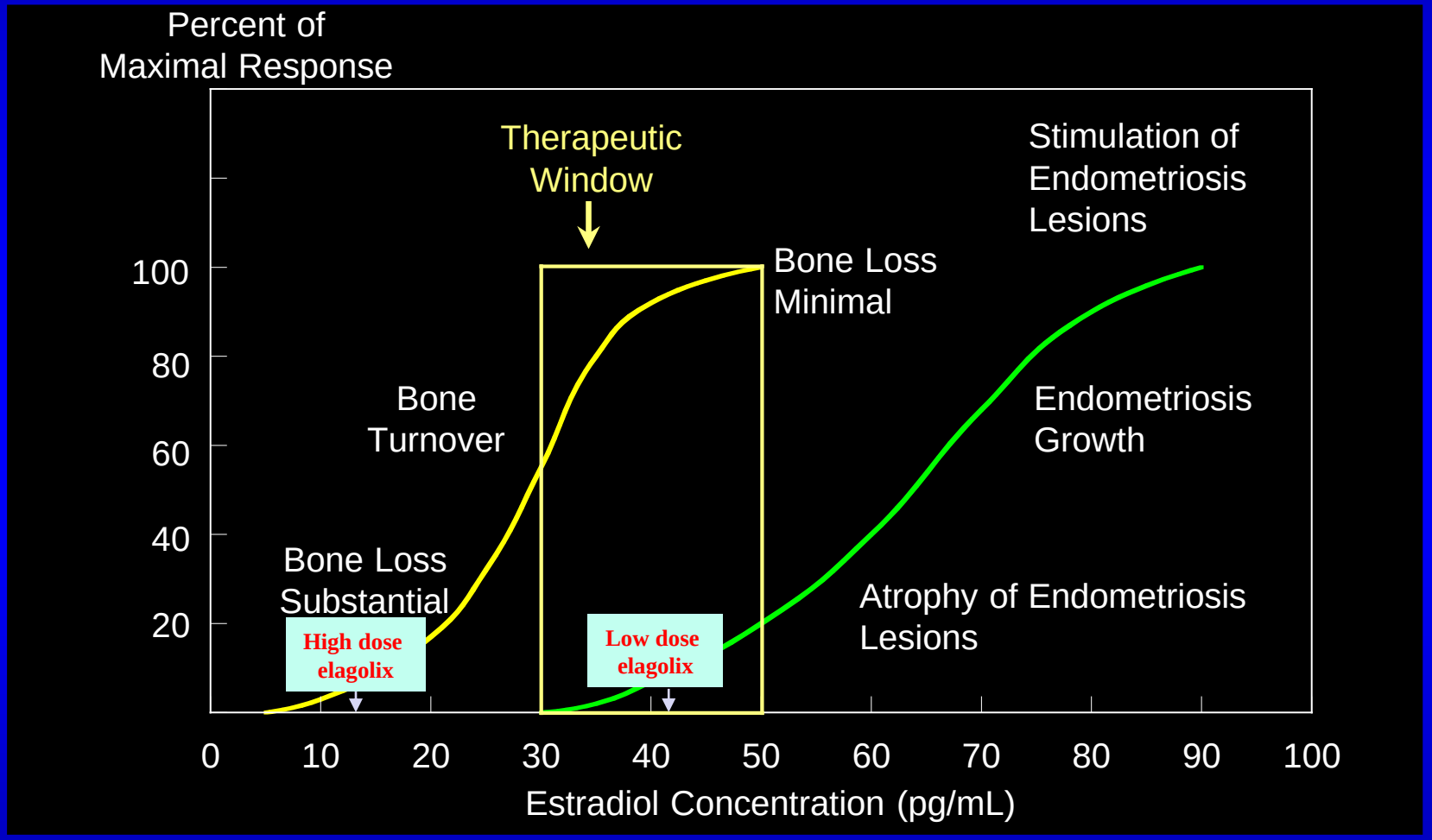
Barbieri RL, Am J Obstet Gynecol 1992;166:740

July 2018: FDA approval of Elagolix

- First new formulation approved for endometriosis since 1990s
- The first oral GnRH antagonist
- 2 doses (150 mg daily or 200mg twice daily)
- Dose dependent suppression of estrogen

Relugolix also now FDA approved
Linzagolix in trials

Estradiol Therapeutic Window



Barbieri RL, Am J Obstet Gynecol 1992;166:740

Overcoming some of the shortfalls in current endometriosis care

Current endometriosis care

- *A disconnect between healthcare utilization and outcomes*

HEALTHCARE UTILIZATION

- Multiple consultations in search of a diagnosis and relief of symptoms
- 46% have receive at least three medical treatments
- 42% have undergone at least three surgeries
- 20% have repeat laparoscopy within 2y and 40-50% within 5y
- Frequent ER visits
- $$$ spent at least comparable to other chronic conditions such as on IBD, asthma, migraine

HEALTHCARE OUTCOMES

- Delay in diagnosis of 6-12 years
- 49% still on opioids 12m after laparoscopic surgery
- No medical treatment that reduces pain and allows for fertility
- 70% women live with unresolved pain despite high levels of healthcare utilization
- CDC: Leading indication for hysterectomy in women <35y

De Graaff A, D'hooghe TM, Dunselman GAJ, et al. Hum Reprod. 2013;28(10):2677–2685. doi:10.1093/humrep/det284
Fourquet J, Gao X, Zavala D, et al. Fertil Steril. 2010;93 (7):2424–2428. doi:10.1016/j.fertnstert.2009.09.017
Sinaii N, Cleary SD, Younes N, Ballweg ML, Stratton P. Fertil Steril. 2007;87(6):1277–1286. doi:10.1016/j.fertnstert.2006.11.051
Soliman A, Du EX, Yang H, Wu EQ, Haley JC. J Womens Health. 2017;26(6):644–654. doi:10.1089/jwh.2016.6043

Endometriosis: delay in diagnosis

By geography:[1–4]

United States:
11.73 years[1]

United Kingdom:
7.96 years[1]
9.0 years[2]

Brazil:
7.0 years[3]

The Netherlands:
7.4 years[4]

1. Hadfield R et al. *Hum Reprod*. 1996 Apr;11(4):878–80;
2. Pugsley Z, Ballard K. *Br J Gen Pract*. 2007 Jun 1;57(539):470–6;
3. Arruda MS, et al. *Hum Reprod*. 2003 Apr;18(4):756–9;
4. Staal AHJ et al. *Gynecol Obstet Invest*. 2016;81(4):321–4.

You know it's a problem when the Government apologizes!

The Guardian

Greg Hunt apologises to women with endometriosis and announces action plan

Australian health minister hears stories from women with disease before setting up national plan to improve treatment

Gabrielle Jackson

Wed 6 Dec 2017
03.27 EST

Health minister Greg Hunt has announced a national action plan and some research funding for endometriosis. Photograph: Mick Tsikas/AAP

The Turnbull government announced on Wednesday that it will create the first national action plan for endometriosis to improve the treatment, understanding and awareness of a disease that affects more than 600,000 Australian women.

UC San Diego

Center for Endometriosis Research and Treatment (CERT)

www.cert.ucsd.edu

- A multidisciplinary program since 2010 based on the beliefs that:
  - It's not just the pain but also the consequences of the pain that matters
  - Optimal *long-term care* requires a comprehensive, patient focused model
  - The model requires like-minded colleagues with complementary skills
  - Facilitation and stimulation research and education is critical

International Journal of Women's Health

Dovepress

open access to scientific and medical research

Open Access Full Text Article

COMMENTARY

Rethinking endometriosis care: applying the chronic care model via a multidisciplinary program for the care of women with endometriosis

This article was published in the following Dove Press journal:
International Journal of Women's Health

Sanjay K Agarwal[1]
Warren G Foster[1,2]
Erik J Groessl[3,4]

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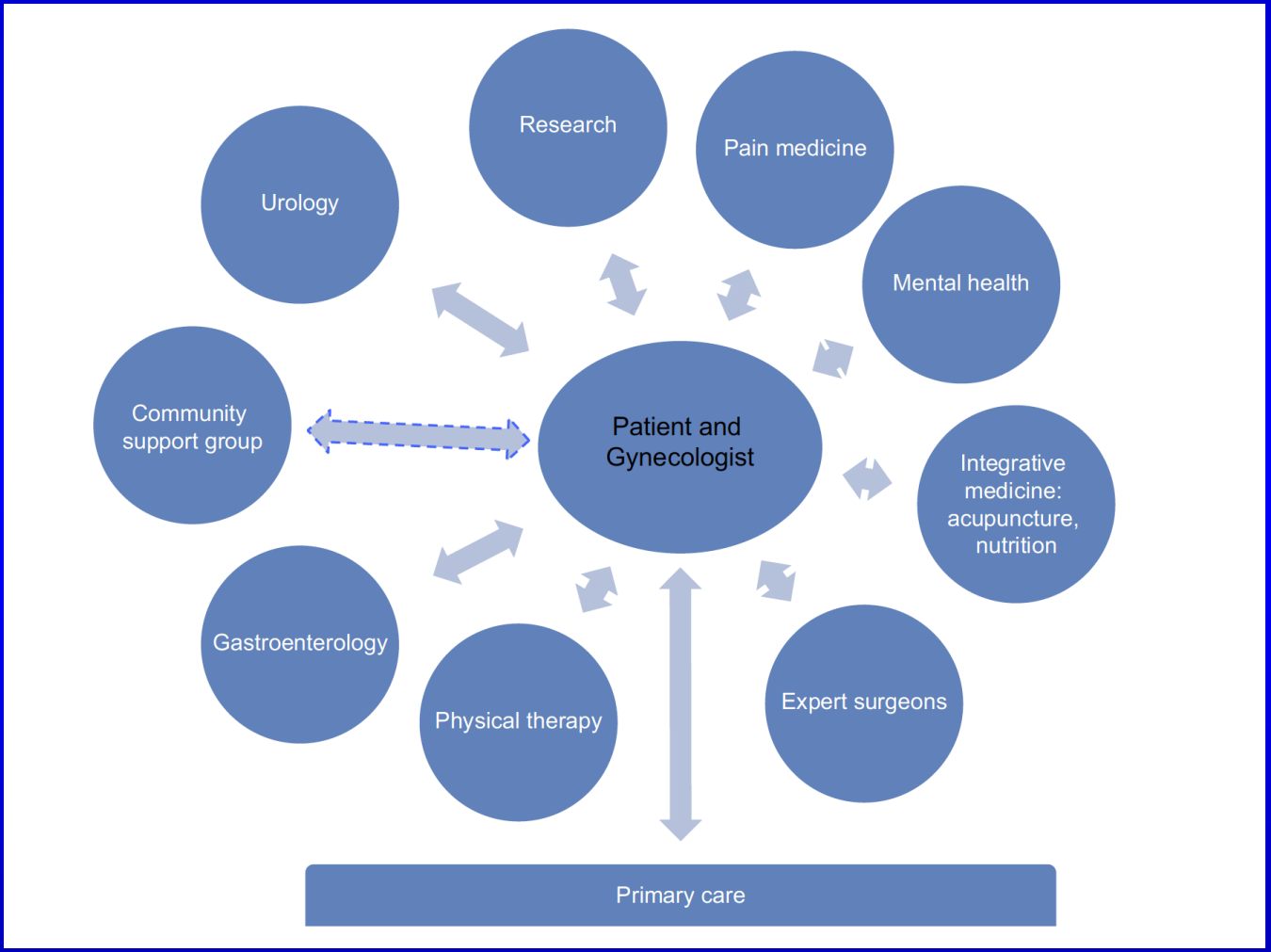
Abstract: Endometriosis is a chronic, painful disease without a cure. Due largely to chronic pain, endometriosis can lead to significant physical, mental, relationship, and financial burdens. Within the conventional single provider model of care—in which the patient is primarily taken care of by her physician and complementary strategies based on psychology, nutrition, pain medicine, pelvic physical therapy, and so on may not be readily available in a coordinated manner—most women with endometriosis live with unresolved pain and the consequences of that pain. We therefore propose that there is an urgent need to search for alternative models of care. In the current paper, we discuss our experiences with an model of care in which we adopt a long-term, patient-focused, and multidisciplinary chronic care model for women with endometriosis. Our objective is to improve long-term clinical outcomes for women with endometriosis. For geographical areas and healthcare systems in which it is feasible, we propose consideration of this multidisciplinary model of care as an alternative to the single provider model and offer guidance for those considering establish-

Int J Womens Health. 2019 Jul 23:11:405-410.

The UC San Diego Health
Center for Endometriosis Research and Treatment
for multidisciplinary, individualized endometriosis care

www.cert.ucsd.edu

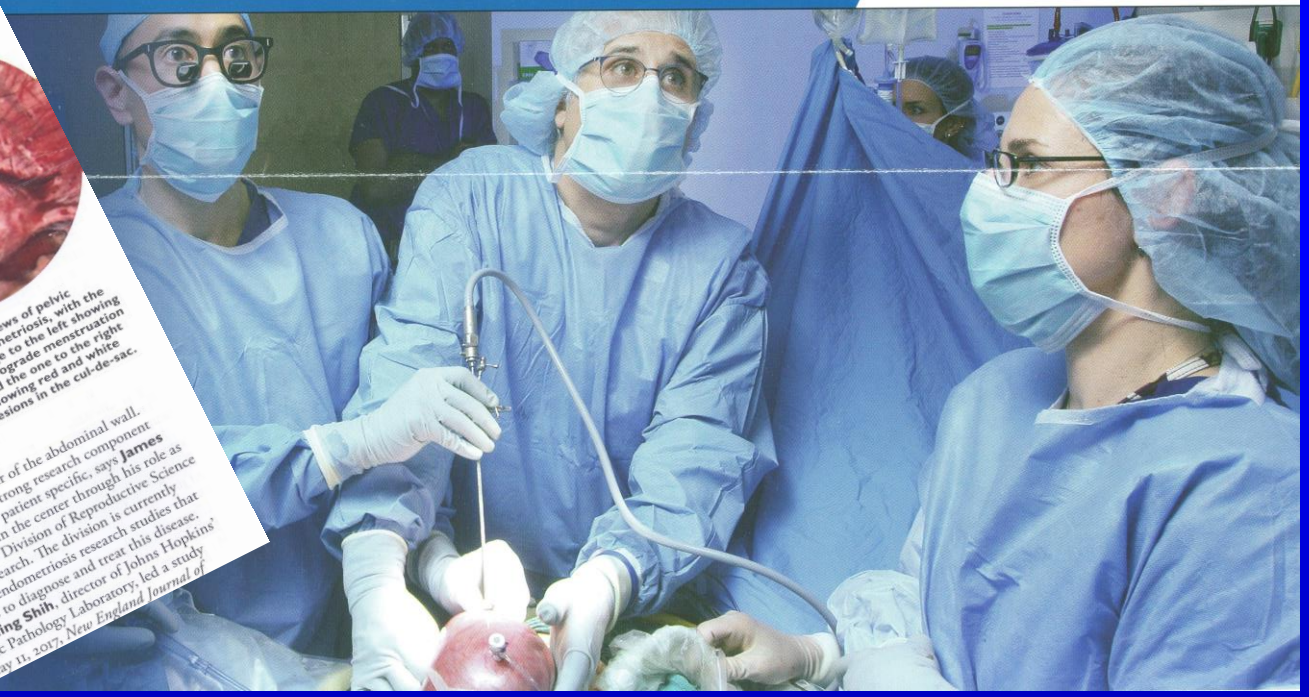


Agarwal SK, Foster WG, Groessl EJ. Rethinking endometriosis care: applying the chronic care model via a multidisciplinary program for the care of women with endometriosis. Int J Women's Health 2019.

JOHNS HOPKINS
Gynecology & Obstetrics
NEWS FROM THE JOHNS HOPKINS DEPARTMENT OF GYNECOLOGY AND OBSTETRICS

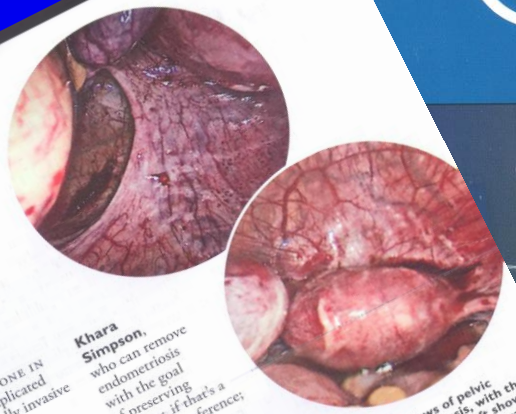
WINTER 2018

JOHNS HOPKINS MEDICINE



COORDINATED CARE

New Center to Take Multidisciplinary Approach to Endometriosis



Two views of pelvic endometriosis, with the image to the left showing retrograde menstruation and the one to the right showing red and white lesions in the cul-de-sac.

ENDOMETRIOSIS, WHICH AFFECTS ABOUT ONE IN 10 women of reproductive age, can be complicated and complex, says Johns Hopkins minimally invasive gynecologic surgeon **Karen Wang**.

That's why Wang and other specialists at Johns Hopkins are creating a virtual multidisciplinary center specifically for treating endometriosis and its associated symptoms.

"Our ideal would be to build collaborations with different specialties to attack this condition from a variety of viewpoints that are individualized to the specific patient," she says.

Patients with endometriosis may experience pain, fertility problems or both, but their symptoms don't necessarily correlate with the severity of the disease. Some women will have minor growth of endometrial tissue outside the uterus, while others will have substantial involvement with the uterus, ovaries, bladder, ureters, intestines, lungs, abdominal wall and other adjacent organs.

Because presentation and symptoms vary, treatment can involve a variety of specialists, and isn't always optimal for patients, Wang explains. It can be difficult to coordinate communication between the various providers, who may even provide conflicting recommendations.

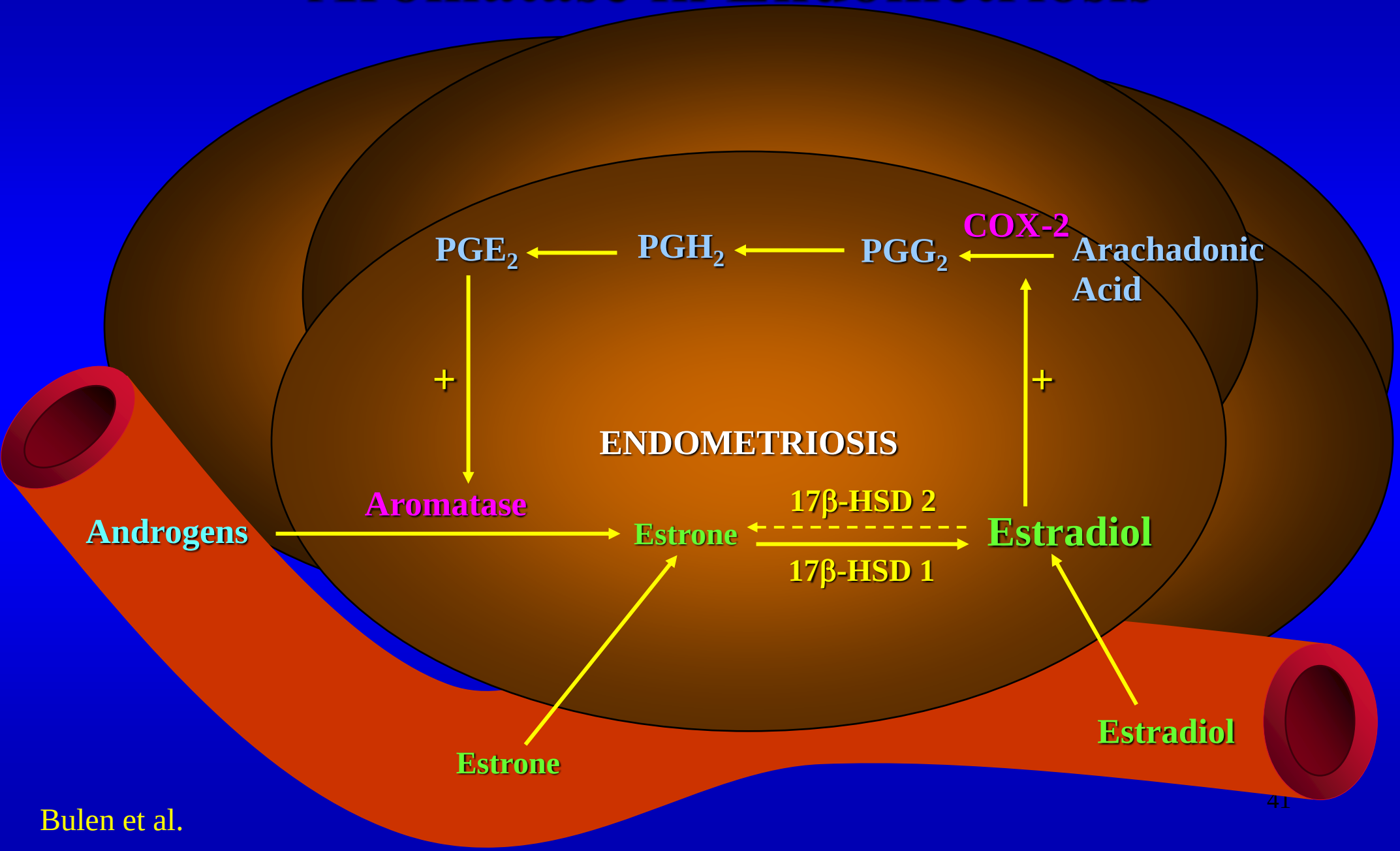
The multidisciplinary center, Wang says, will provide a better patient experience and more consistent care at Johns Hopkins, which is a tertiary referral center equipped to handle the most severe cases of this disease.

Once a patient is seen in the Endometriosis Center, coordination of care with other pertinent providers will take visits more convenient and minimize travel for [illegible]. Providers will also meet as a group periodically, discuss and reach consensus on each patient's **Khara Simpson**, who can remove endometriosis with the goal of preserving fertility, if that's a patient's preference; reproductive endocrinologists who can improve fertility outcomes and manage hormonal changes; pain specialists; interventional radiologists who can better assess a patient's disease; gynecologic oncology for patients whose disease has spread beyond the gynecologic organs; and plastic surgery for those whose disease is so severe that treatment will involve repair of the abdominal wall.

The center will also have a strong research component that will be incorporated and patient specific, says **James Segars**, who will be active in the center through his role as director of Johns Hopkins' Division of Reproductive Science and Women's Health Research. The division is currently conducting a variety of endometriosis research studies that could lead to new ways to diagnose and treat this disease.

For example, **Ie-Ming Shih**, director of Johns Hopkins' TeLinde Gynecologic Pathology Laboratory, led a study published in the May 11, 2017, *New England Journal of*

Aromatase in Endometriosis



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International Journal of Women's Health

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CLINICAL TRIAL REPORT

Pilot Study of IL-1 Antagonist Anakinra for Treatment of Endometriosis

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Sullender R, et al. Int J Womens Health. 2024 Sep 27:16:1583-1593.

Clinical findings

Table 2 Questionnaire Outcomes and Menstrual Cycle Changes on Treatment versus Placebo

Scale	Anakinra Mean (SD)	Placebo Mean (SD)	p-Value[a]
Modified Dysmenorrhea (B&B)	1.4 (0.9)	1.6 (0.7)	0.40
VAS (Dysmenorrhea)	37.5 (22.3)	42.6 (19.4)	0.26
EHP-30 (Quality of Life)			
Pain	46.3 (14.2)	49.4 (11.5)	0.21
Control and powerlessness	**54.5 (23.5)**	**63.3 (19.8)**	**0.04**
Emotional well-being	39.1 (18.8)	44.7 (17.5)	0.20
Social support	45.1 (30.0)	50.8 (22.5)	0.11
Self-image	**58.1 (28.6)**	**66.7 (23.0)**	**0.03**
Number of bleeding days[b]	5.0 (1.7)	5.3 (1.3)	0.28
Menstrual cycle length[c]	29.3 (7.4)	27.7 (3.3)	0.56

Notes: N = 15 patients with at least 1 follow-up survey in each treatment period. Bolded numbers indicate statistical significance $p<0.05$. For all scales, higher score = worse pain. [a] p-value based on paired t-tests for mean scores averaged across treatment cycles. [b] n = 12 patients with at least 1 period length in each treatment period. [c] n = 7 patients with at least 1 cycle length in each treatment period.

Abbreviation: SD, Standard deviation.

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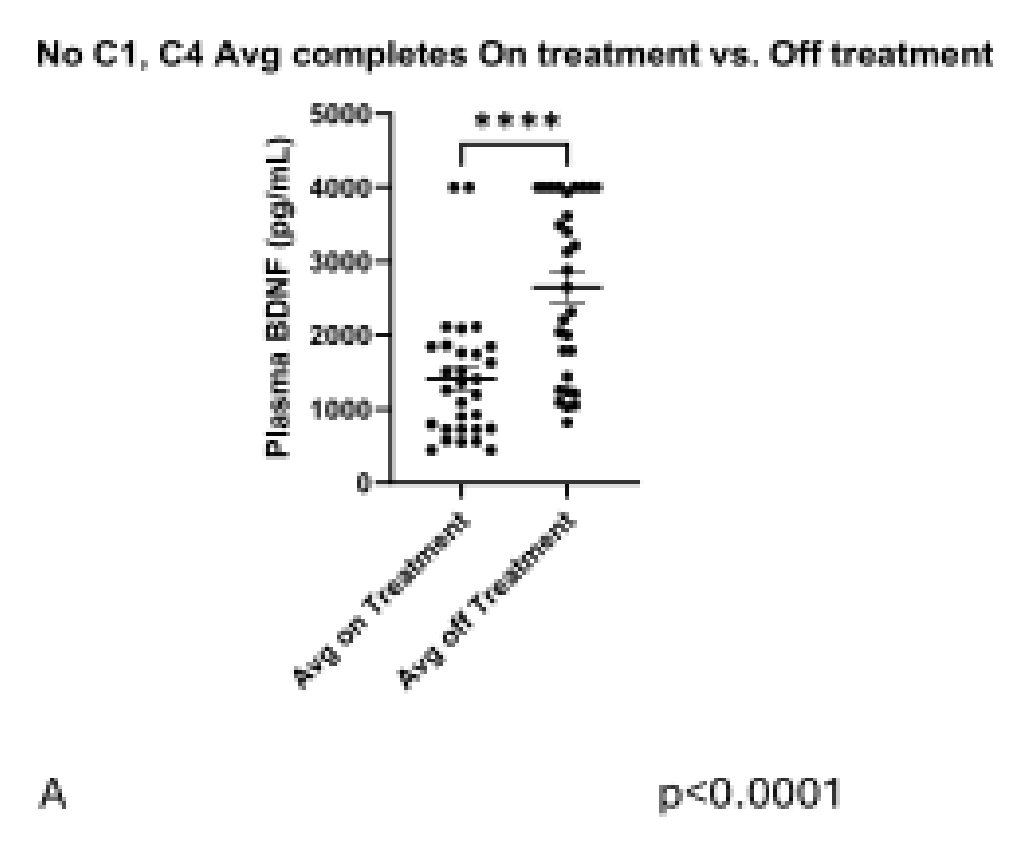
BDNF endometriosis biomarker on and off treatment



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Complementary options?

A whole food plant-based dietary intervention for the management of endometriosis related pain: Impact on clinical, microbiome, and inflammatory parameters.

Foster WG[1,2], Saxe G[3], Khatib L[4], McDonald D[4], Shekhtman T3, Holt T, Golshan S[6], Knight[4,7,8,9,10] R, Wessels JM[2], Agarwal SK[5].

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Please remember….

- Pain is not normal.
  - Consider screening for chronic pelvic pain
- Per ACOG,
  - 80% chronic pelvic pain is due to endometriosis
  - Surgical diagnosis is not required prior to initiating treatment.
- Focus on improving pain and QoL
    - If 3m of contraceptives don't help consider a GnRH antagonist or referral to CERT