Medical Management of Endometriosis

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Disclosure

- Advisory Board
  - Allergan Inc.
  - Abbvie Inc.

ASRM Practice Committee

- "endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures"

- Practice Committee of the American Society for Reproductive M. Treatment of pelvic pain associated with endometriosis: a committee opinion. Fertil Steril. 2014 Apr;101(4):927-35.

Objectives

- To review the endocrinology of endometriosis
- To review endometriosis medical treatment challenges that could impact treatment success
- To critically appraise the evidence of the current treatment options
- To briefly mention potential future options

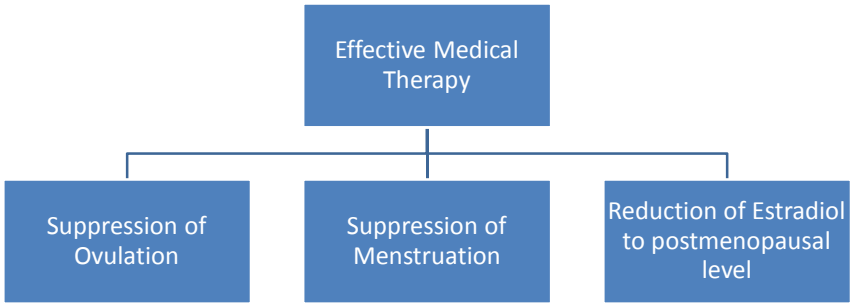
Endocrinology of Endometriosis

Retrograde Menstruation

Key players in endometriosis development:

- Ovulation
- Menstruation
- Estrogen

Sampson JA. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. Am J Obstet Gynecol 14:422, 1927



COCs, Progestins, LNG-IUD, GnRH-a,
Androgens, Aromatase Inhibitors, Anti-estrogens

What are the biological features of endometriosis?

Endometriosis is:

Estrogen Dependent
Progesterone Resistant
Inflammatory
Invasive
Angiogenic

Evidence That Endometriosis is Estrogen Dependent

- Unusual before menarche (has been reported in thelarche)
- Prolongd E2 exposure
  - early menarche
  - nulliparity (more menses)
  - xenoestrogen exposure (Missmer, 2004)
- Animal models
  - trophic effects of E2 in mice implants (Osteen, 2007)
  - another model showed that ERα and ERβ are necessary for the establishment of endometriosis (Burns and Korach 2012)

Endometriosis and Progesterone

- Lesions are P4 resistant
- Progestins are commonly used (counter-intuitive)

Attia et al., 2000
Bedaiwy et al., 2015

2 Enzymes

2 Receptors

2 Enzymes

2 Receptors

Kim, Kurita, Bulun, Endocrine Reviews 2013

Estrogen/Progesterone Interaction in Normal Eutopic Endometrium

- Follicular phase: estrogen acts through the ER to increase transcription and protein levels of the PR, especially the PR-B isoform.
- Luteal phase: P4 acts through PR-B to:
  - down-regulate ER and
  - increase the transcription and secretion of 17β-hydroxysteroid dehydrogenase type 2 which catalyzes the conversion of estradiol to the less active estrone.

Kim, Kurita, Bulun, Endocrine Reviews 2013

Estrogen/Progesterone Interaction in Endometriotic Implants

- ER-α is reduced but ER-β activity is markedly up-regulated leading to complete loss of PR-B and the inability to induce HSD17B2 leading to:

1. Progesterone resistance
2. Augmented estrogen activity.

Kim, Kurita, Bulun, Endocrine Reviews 2013

Disordered Steroidogenesis in Endometriosis

- ER-α reduction
- ER-β activity is markedly upregulated
- Complete loss of PR-B
- PR-A dominance
- Markedly decreased 17β-HSD type 2 activity
- Increased aromatase activity

Kim, Kurita, Bulun, Endocrine Reviews 2013

Evidence of Inflammation

- High levels of inflammatory cytokines (IL-8, IL-1, TNF-α) in peritoneal fluid (PF) in women with osis
- PF activated macrophages secrete inflammatory cytokines
- PF activated macrophages cannot phagocytose endometrial cells
- Levels of ENDO I (haptoglobin) increased
- In systemic circulation, higher levels of TNF-α , IL6 and IL-8

Huges et al., 2000
Bedaiwy et al., 2003, 2005, 2006, 2010, 2012, 2015

Invasive/Angiogenic

- Lesions are invasive
  - Matrix metalloproteinase -1, 2, 3, 7, 11
  - Plasminogen activator
  - Cathepsin D
- Lesions are angiogenic
  - VEGF (most studied)

Medical Treatment Challenges

Treatment Initiation Without Histopathological Confirmation

- Laparoscopy with histopathological confirmation is the gold standard of endometriosis diagnosis.
- All international recommendations support treatment initiation with NSAIDs and hormonal treatment without a definitive diagnosis after appropriate counseling
  - ASRM
  - ESHRE
  - ACOG
  - SOGC
- Surgically confirming the diagnosis is preferred:
  - Before initiating medication with significant side effects, such as GnRH agonists or
  - When long-term therapy is recommended

Delay in the Diagnosis

- 10 years in Germany and Austria
- 8 years in the UK and Spain
- 7 years in Norway
- 7–10 years in Italy
- 4–5 years in Ireland and Belgium

Ballard et al., 2006 Nnoaham et al., 2011 Hudelist et al., 2012

Lack of Peripheral Biomarkers

Diagnosis

Treatment success

May KE, HRU 2010

Contraceptive Nature/No Fertility Benefit

- In a systematic review of 25 trials, there is no evidence of benefit in the use of ovulation suppression in infertile women with endometriosis who wish to conceive .
  - Hughes st al., Cochrane Database Syst Rev 2007;18(3):CD000155
- Consequently, in women desirous of pregnancy who have pain caused by endometriosis, NSAIDs appear to be the only medical option.

Ovarian Endometrioma

- Medical therapy does not resolve endometriomas
- In a systematic review and pooled analysis of 237 patients, there was a significant postoperative fall of AMH with weighted mean difference −1.13 ng/ml following OMA surgery.

Raffi F, et al. J Clin Endocrinol Metab 2012

To protect ovarian reserve, there is an increasing trend towards conservative/medical management of ovarian endometrioms

Deep Infiltrating Endometriosis

- DIE is descriptive term of endometriosis involving USL, RVS, bowel, ureters, or bladder.
- Medical therapy with hormonal suppression has been shown to be effective
- Surgery is indicated for women who fail medical management or develop obstructive symptoms

The challenge: No high quality studies to evaluate different medical options

Extrapelvic Endometriosis

- Consider surgical removal of symptomatic extragenital endometriosis, when possible, to relieve symptoms
  - Liang et al., 1996;Marinis et al., 2006; Nisolle et al., 2007;Nissotakis et al., 2010; Nezhat et al.,2011; Song et al., 2011
- When surgical treatment is difficult or impossible, consider medical treatment of extragenital endometriosis to relieve symptoms
  - Bergqvist, 1992; Joseph and Sahn, 1996; Jubanyik and Comite, 1997

The challenge: No high quality studies to evaluate different medical options

Central Sensitization

- An increase in the excitability of the CNS so that normal inputs now evoke exaggerated responses Woolf, 1983
- Multiple studies show that CPP is associated with central changes
  Brawn et al, Hum Reprod Update 2014, Kaya et al. Pain Physician 2013

The challenge: Not diagnosed
Poorly treated

Co-morbidities Challenges

- Abdominal Pain
- Pelvic Floor Pain
- Pelvic Girdle Pain
- Irritable Bowel Syndrome
- Painful Bladder Syndrome

Medical Treatment Options:

Revisiting the evidence

Medical Management of Endometriosis in Patients with Chronic Pelvic Pain

Mohamed A. Bedaiwy, MD, PhD[1] Catherine Allaire, MD[1] Paul Yong, MD, PhD[1] Sukinah Alfaraj, MD[1]

Combined estrogen-progestin oral contraceptive pills (OCPs)

- ACOG
- ASRM
- ESHRE
- CFAS

Pelvic Pain Results With Cyclic OCPs

Citation	Tx	Relief (%)	Sample
Kistner, 1956	Enovid	79	110
Riva, 1961	Enovid	90	83
Riva, 1962	Enovid	69	132
Kourides, 1969	EE/Norgestrel	84	19
Vercellini, 1993	EE/Desogstrl	88	24
Harada, 2008	EE/NET	$P<.0001$	51

Only one placebo-controlled RCT

- The effectiveness of OCPs for pelvic pain and dysmenorrhea in patients with endometriosis
- 100 patients
- 50% reduction of dysmenorrhea
- No change in the non menstrual pain and dyspareunia

Harada T, fertil and steril 2008

Frequent switching between OCPs is a surrogate of ineffectiveness

- Two thirds of women had used multiple OCPs for relief of endometriosis pain
- 44% had been prescribed between 3 and 10 different OCPs for endometriosis
- Ocps relatively ineffective

Why might an OCP be relatively ineffective in diminishing the activity of endometriosis implants when it is so effective in thinning the eutopic endometrium?

Why OCPs may not be effective?

- Low dose pills contain 20-30 mcg of EE
  - 4-6 times the physiologic dose of E2
  - leading to estrogen dominance in the presence of progesterone resistance,
- The presence of supraphysiologic concentrations of estrogen with the OCP, during what should be the low-estrogen menstrual phase
  - may rescue endometrial cell clusters deposited in the pelvis during retrograde menses.
    - Vercillini HRU 2011

Why OCPs may not be effective

- A recent meta-analysis showed an increase in endometriosis risk in past users of OCPs
  - Vercillini HRU 2011
- In a cross sectional study of 566 patients without visible endometriosis at surgery as controls, and 410 patients with histologically proven endometriosis:
  - Past OCP users are more likely to have:
    - endometriosis (adjusted OR = 2.79, 95% (CI) 1.74-5.12, P = 0.002)
    - likely to develop DIE (adjusted OR = 16.2, 95% CI 7.8-35.3)
      - Chapron HU R 2011

Other considerations

- COCs are contraindicated in:
  - Women older than 35 years who smoke
  - Women at increased risk of myocardial infarction, stroke, or venous thromboembolism
- Limited room for increased dosing
- Prolonged use of OCPs leads to thin endometrium no responsive to E2 with reproductive implications
  - Takudar obstet and Gynecol 2012

Progestins Are Used Despite Progesterone Resistance (counter-intuitive)

- P4 alone, in mg doses, generally inhibit ovulation and induce amenorrhea, which should prevent dysmenorrhea.
- Decrease in gonadotropin secretion induced centrally by potent progestins ----hypoestrogenic state that suppress endometriosis and prevent progression of the disease.
- Because they
  - have anti-angiogenic effects
  - are immunomodulatory
  - are anti-inflammatory
  - oppose E2 action
  - decrease expression of matrix metalloproteinases, thereby decreasing the invasiveness of endometriosis implants

Evidence

- In contrast to the OCP for endometriosis, there are several placebo-controlled trials showing the efficacy of progestins alone in alleviating:
  - Menstrual pain (dysmenorrhea)
  - Non menstrual chronic pelvic pain

Oral Progestin Tx

Author	Rx, mg	N	Time (mo)	Relief (%)
Luciano, 1988	MPA, 50	21	4	88
Schlaff,1990	Mgstrl, 40	9	4	86
Vercellini, 2002	CyprAc, 2.5	45	12	33
Delale	NET Ac, 5-70	52	> 6	94
Vercellini, 2009	NET Ac, 2.5	45	12	80
Herada, 2009	Dienogest 2	128	6	*P*<.05

Dienogest

Author (Date)	n	Intervention	Duration of treatment	Effect on Pain reduction
Strowitzki T (2010)	144	DNG 2mg/d	12wk	> Placebo
Patraglia F (2012)	152	DNG 2mg/d	36-52wk	Safe effective to use for 52wk
Cosson M (2002)	120	1. DNG 2mg/d 2. Triptorelin 3.75mg IM/mo	16 wk	G1=G2
Harada T (2009)	271	1. DNG 2mg/d 2. Buseelin acetate 900mg IN/d	24 wk	G1=G2
Strowitzki T (2017)	229	1. DNG 2mg/d 2. Leuprolide acetate 3.75 mg IM/mo	24wk	G1=G2

Practical Implications

- Oral progestins alone
  - can be used at any age
  - do not increase the risk of thrombosis
  - capable of inhibiting ovulation and inducing amenorrhea
  - very few side effects.

What do you do when POPs fail?

Bedaiwy et al., 2013

Danazol Therapy

Author	N	Time (mo)	Dose (mg)	↓AFS Score%	↓Pain (%)
Dmowski	10	6	800	65	88
Shaw	103	6	600	52	68
Kennedy	24	6	600	20	87
Rock	107	6	400-800	33	75
Henzl	80	6	800	43	78

GnRH Agonist Therapy

Author	Agonist	N	Duration	↓ Score	↓ Pain
Diugi	LeuAc	52	6	-	89
Surrey	LeuAc	10	6	55	72
Henzl	Naf	77	6	43	73
Steingld	Histrln	16	6	78	63
Rock	Gosrln	208	6	56	75
Shaw	Gosrln	204	6	60	74
Dmwski	Busrln	22	6	67	69
Wright	LeuAc	9	3	20	-

Progestins as Add-Back

- MPA: reduces vasomotor instability, not effective at suppressing disease or symptoms (20 - 30mg/d x 6 mo)[1]
- MPA: effective at 100mg[2]
- NET: effective at up to 2.4mg/d x 6 mo, but ↓BMD[3]
- NETA: effective at 5mg/d x 12 months[4]

1. Cedars *Obstet Gynecol* 1990, 75; 641-645
2. Surrey *Fertil Steril* 1990, 53; 620-626
3. Bergovist *Gynecol Endocrinol* 1997, 11;187-194
4. Hornstein *Obstet Gynecol* 1998, 91;15-24

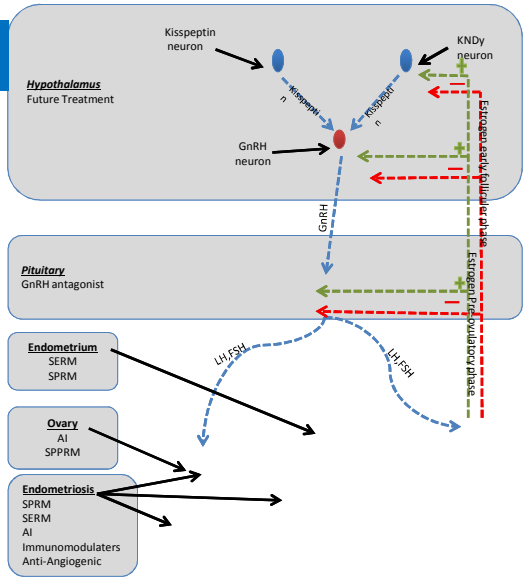
Norethindrone Acetate as Add-Back: Mechanisms of Action

- NETA undergoes hepatic metabolism to EE
- 2-pronged effect:
  - EE provides bone effect and reduces vasomotor instability
  - It has direct effect on endometrium
- Result: Synergy with GnRHa

Medical Therapies Under Investigation

- Oral GnRH antagonists
- Aromatase Inhibitors
- P4 receptor modulators
- TNF-α blockers
- Angiogenesis inhibitors
- Metalloproteinase inhibition
- Estrogen receptor inhibition
- PPAR-γ agonists
- Chinese herbs (nociceptor neurons)
- Nutrition: omega-3, green tea

Future Treatments

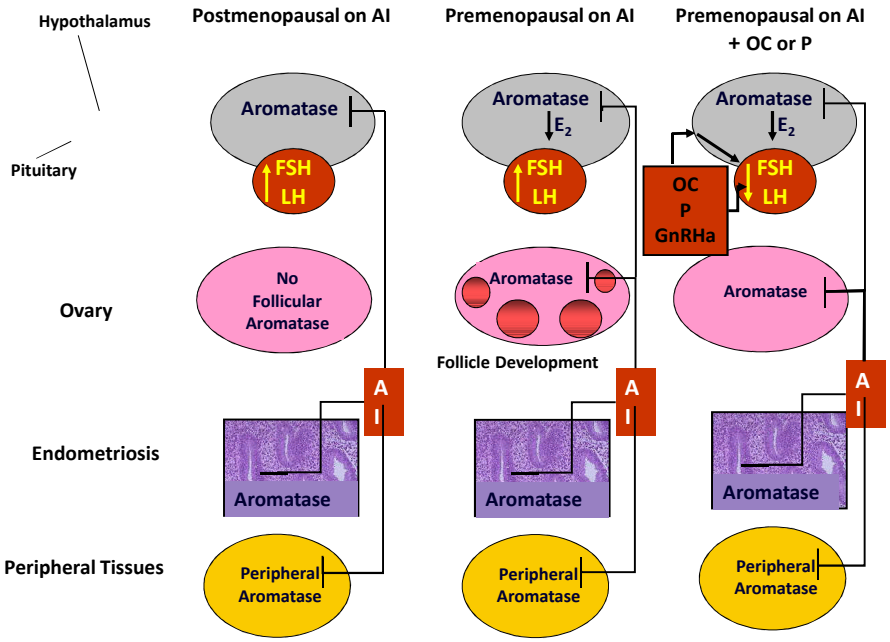


Bedaiwy et al., Fertil & Steril 2017

- 150 mg/day or 200 mg BID of elagolix were effective in improving dysmenorrhea and nonmenstrual pelvic pain during a 6-month period in women with endometriosis-associated pain.
- The two doses of elagolix were associated with hypoestrogenic adverse effects

The Promise/Challenge

- Orally administered
- Effective for menstrual and non menstrual pain
- Partial estrogen suppression
- Does not suppress ovulation
- BMD
- Lipid profile
- Efficacy beyond 6 month
- Teratogenicity



Takayama et al, Fertil Steril, 1998; Ailawadi et al, Fertil Steril, 2004; Soysal et al, Human Reproduction, 2004; Amsterdam et al, Fertil Steril, 2005; Abushahin et al, Ferti Steril, 2011

Letrozole + Norethisterone Acetate

- Study design: open-label, nonrandomized 6 month trial
- N = 82
- N = 41, Letrazole 2.5mg/NETAc 2.5mg/Calcium/Vit D, 1000mg/800IU daily
- N = 41, NETAc 2.5mg daily

» Ferrero, *Hum Reprod* 2009, 24; 3022-3041

Letrazole + NETAc: Results

- Significant decrease in pain by 3 months in both groups (*P*<.001)
- At 3 and 6 months, pain (*P*<.001) and dyspareunia (*P*=.002) less in letrazole group
- Adverse events more frequent with letrazole (P=.02): vasomotor sx, mood, myalgias, BTB

Ferrero *Hum Reprod* 2009

Summary

- The beneficial effect of OCPs observed in the past may have been entirely due to relief of primary dysmenorrhea with little effect on the underlying endometriosis.
- Once endometriosis is suspected or proven as the cause of CCP, an OCP may not be the best treatment option and could potentially lead to progression of the disease according to recent data
- Progestins have demonstrated benefits in reducing pain and suppressing the anatomic extent of endometriotic lesions.
- Dienogest and NETA appear to be equally effective in alleviating pain and decreasing lesion size in endometriosis.
  - Although NETA is less expensive, dienogest is slightly better tolerated because of fewer side effects

Summary

- GnRH-a are second line options and should be used with hormonal add-back.
- There is growing evidence about the utility of Letrozole and and orally active GnRH antagonists in endometriosis associated CPP

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- Dr. Lori Brotto
- Dr. David Huntsman
- Dr. Sarka Lisonkova
- Dr. Tony Ng
- Dr, Andrew Horne

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- Physicians: Catherine Allaire, Christina Williams, Paul Yong, Mohamed Bedaiwy
- Fellow: Dr. Pira Korsieporn
- Nurses: Catherine Maurer, Victoria Martin
- Physiotherapist: Susannah Britnell
- Counsellor: Holly Yager

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- CIHR
- UBC Dept/Divisions
- UBC FoM
- VGH & OvCaRe
- WHRI

Thank You

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Author (Date)	n	Intervention	Duration of treatment	Effect on Pain reduction
Cobellis L (2004)	28	Rofecoxib,25mg/d	6mo	> Placebo
Strowitzki T (2010)	144	DNG 2mg/d	12wk	> Placebo
Patraglia F (2012)	152	DNG 2mg/d	36-52wk	Safe effective to use for 52wk
Loverro G (2008)	60	Triptorelin depot 3.75 mg IM	3mo	= Placebo
Ling FW (1999)	100	Depot leuprolide (3.75mg Im/mo)	3 mo	> Placebo

Author (Date)	n	Intervention	Duration of treatment	Effect on Pain reduction
Cobellis L (2011)	61	1. N-Palmitoylethanol-aminetranspolydtin (400 mg+ 40mg twice a day 2. Placebo 3. Celecoxib 200mg twice for 7days.	3 mo	Group3>Group1>Placebo
Kamencic and Thiel (2008)	49	1. Naproxen, hydromorphone 2. Pentoxifyline	3 mo	Group1>Group2
Saracchioli R (2010)	274	1.No treatment 2.Cyclic combined OC 3.Continuous compind OC: ethinyl E2, 0.020 mg+gestodene, 0.075mg daily.	24 mo	Group 3>Group2>Group1

Author (Date)	n	Intervention	Duration of treatment	Effect on Pain reduction
Bayoglu Tekin Y (2011)	240	1. LNG-IUS; Mirena 2. GnRH-a	24m	G1=G2
Vercellini P (1996)	80	1. Depot medroxyprogestrone acetate 150mg/ 3mo IM 2. Ethinyl estridol 0.02mg, desogestrel 0.15 mg) combind with oral danazol 50mg a day for 21	12 mo	G1= G2
Refidor PA (2001)	48	1. LAD 3.75 mg subcu/ month 2. LYN 5mg twice/day	6mo	G1=G2
Walch K (2009)	41	1. Implanon 2. DMPA	12mo	G1>G2
Bergqvist and orell (2001)	48	1. Nafarelin 200μg IN twice/day 2. Medroxyprogestrone acetate 15mg+ placebo nasal sparay.	12mo	G1=G2
Razzi S (2007)	40	1. Desogestrel (75 μg/day) 2. Ethinyl estradiol 20μg plus desogestrel 150μg	6 mo	G1=G2

Author (Date)	n	Intervention	Duration of treatment	Effect on Pain reduction
Vercellini P (2002)	90	1. Oral cryoproterone acetate, 12.5 mg/d 2. Continuous oral contraception estradiol, 0.02 mg+ desogestrel, 0.15 mg)	6 mo	G1=G2
Schlaff WD (2006)	274	1. DMPA-SC (104 mg) 2. Leuprolide acetate 11.25 mg/3 mo	6 mo	G1=G2
Cosson M (2002)	120	1. DNG 2mg/d 2. Triptorelin 3.75mg IM/mo	16 wk	G1=G2
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Granese R (2015)	278	1. Estradiol valerate 20mg for 22d+ DNG 2mg for 5d, 3mg for 17d 2. Leuprorelin acetate 3.75 mg/ mo	9mo for G1 6mo for G2	G1=G2

Author (Date)	n	Intervention	Duration of treatment	Effect on Pain reduction
Carr B (2014)	252	1. Elagolix (150mg/d) 2. Elagolix 75mg twice/d 3. Subcutaneous depot medroxyprogesterone acetate (DMPA-SC) 104 mg/0.65 ml /day)	24 wk	G1=G2
Ferrero S (2011)	35	1. Letrazole (2.5mg/d) +norethsterone acetate (2.5mg/d) 2. Letrozole (2.5mg /d) +Triptorlin 11.25mg/3m	6 mo	G1=G2
Alborzi S (2011)	144	1. Letrozole PO 2.5 mg/d 2. Triptorelin 3.75 mg IM/ 4 wk 3. No treatment	2 mo	G1=G2

What an Ideal Medical Treatment of Endometriosis Be Like?

- Curative rather than suppressive.
- Treat pain and fertility at the same time
- Acceptable side effect profile.
- Long-term use should be safe and affordable.
- Non-contraceptive nature
- No interference with spontaneous ovulations and normal implantation

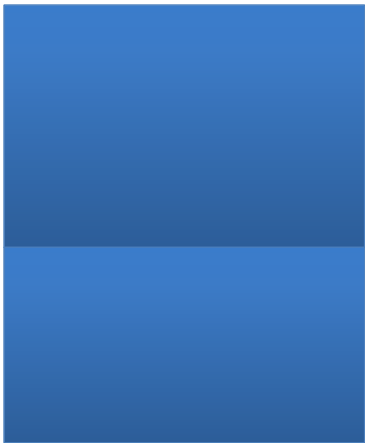
What an Ideal Medical Treatment of Endometriosis Be Like?

- Enhance spontaneous conception.
- No teratogenic potential and safe to use periconceptionally.
- Inhibit the growth of already existing lesions
- Abort the development of new lesions
- Efficacious for all phenotypes including superficial disease, edometriomas, DIE and extrapelvic endometriosis and adenomyosis

Unmet Needs: Endometriosis

- In patients with chronic pelvic pain, endometriosis, a useful diagnostic test geared towards response to a specific treatment is needed.
- The key challenge is to treat endometriosis and -associated pelvic pain not responding to currently available modalities. At least half of the patients with this diagnosis are not satisfied with the available treatments.
- Endometrios-associated infertility is poorly understood, and there are no specific medical treatments.

Biomarker Development



Eur J Hum Genet. 2012 Nov;20(11):1105-11.
doi: 10.1038/ejhg.2012.96. Epub 2012 Jun 20.

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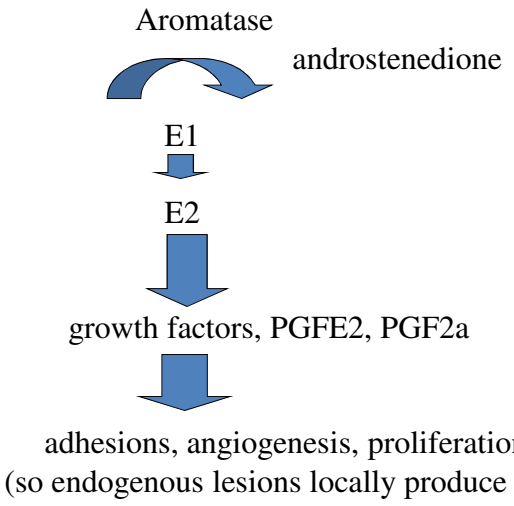
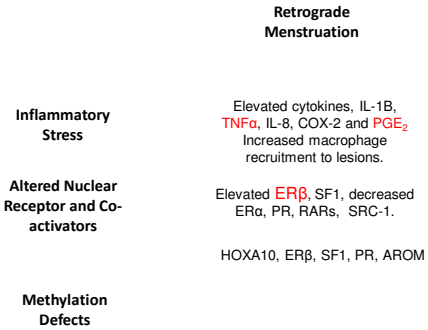
- ER-α reduction
- ER-β activity is markedly upregulated
- Complete loss of PR-B
- PR-A dominance
- Markedly decreased 17β-HSD type 2 activity
- Increased aromatase activity

Kim, Kurita, Bulun, Endocrine Reviews 2013

Local E2 Production in Endometriosis



Molecular Aberrations in Endometriosis



Therapeutic implications

- Attar and Bulun 2009
- Burns and Korach 2012
- Strubble, Reid, Bedaiwy, JMIG 2016
- Bedaiwy et al., 2002, 2003, 2006, 2010, 2016

Grey matter changes in endometriosis

Endometriosis and CPP:

- Decreased grey matter in thalamus, cingulate gyrus, putamen compared to controls

CPP no Endometriosis:

- Decreased grey matter

Endometriosis and no CPP:

- No decrease in GM
  As-Sanie et al., Pain 2012

Continuous OCPs

- N = 50 monitored prospectively
- No control
- Rx: EE 0.02mg / Desogestrel 0.15mg
- Mode: continuously for 2 years
- Conclusion: Pain relief in 96%

» Vercellini, *Fertil Steril*, 2003; 80(3), 560-563

Depot MPA v GnRHa

- Prospective, double blind, multi-center
- N=136 (depot MPA 104mg)
- N=138 (depot GnRHa 11.25mg, q 3 mo x 2 with 12 mo follow-up)
- Drop-outs (%): MPA, 35 ; GnRHa, 26

– Schlaff, *Fertil Steril* 2006, 85;314-325

Depot MPA v GnRHa: Results

- Pain, dysmenorrhea, dyspareunia: equal improvement
- Greater improvement in duration: agonist
- MPA: less vasomotor instability, more BTB
- Bone density loss:
  - Spine : MPA (1.1%) , GnRHa (3.95%)
  - Hip : MPA (0.3%) , GnRHa (1.65%)

Schlaff, 2006

Levonorgestrel IUS (Mirena)

- Prospective, randomized trial (N = 82)
- N = 39 (LNG-IUS)
- N = 43 (GnRHa)
- Results
  - Equivalent pain reduction both groups
  - No differences in QOL improvement between groups
  - More bleeding events in IUS group

Petta, *Hum Reprod* 2005, 20; 1993-1998

Mechanisms of Current Medical Options

- Inhibit inflammation: (NSAIDs)
- Minimize menstrual volume/frequency: (OCPs, progestogens/ L-IUS, anti-progestogens - RU486, gestrinone)
- Oppose E2 action: (OCPs, progestogens/L-IUS, anti-progestogens)
- Aromatase inhibitors (inhibits E2 synthesis)
- Create a hypoestrogenic state: (GnRHa)
- Create a hyperandrogenic state: (Danazol)

Long-Term GnRHa and Progestin Add-Back for Endometriosis: One Year Clinical Trial

- RCT, prospective, double-blind, n = 201
- FOUR treatment groups:
  - GnRHa + daily placebo tabs
  - GnRHa + daily NetAc (5mg)
  - GnRHa + daily NetAc (5mg) + CEE (0.625mg)
  - GnRHa + daily NetAc (5mg) + CEE (1.25mg)

- Horstein, Surrey, Weisberg, Casino *Obstet Gynecol* 1998,91:16-24

Long Term GnRHa: Results

- Pelvic Pain: Improved in all groups (with higher estrogen doses, less pain improvement and more dropout)
- Vasomotor: virtually eliminated in all 3 add-back groups
- BMD: no significant bone loss in all 3 add-back groups

Long-Term Follow-up For Prolonged GnRHa

- Endpoints: Patients in the 1-year study were followed for 12 months after completion for symptom recurrence and return to normal BMD
- Pain: suppressed pain up to 12 months post-therapy
- GnRHa alone: needs 18 months for BMD to return to normal
  - » Surrey *Obstet Gynecol* 2002, 99;709-719