The Future Directions in Management of Endometriosis

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TRIO
ADVANCING REPRODUCTIVE CARE

Disclosures

- SABs: Abbvie, Bayer, Ferring, EMD Serono, Merck, Pfizer
- Consultant: Boehringer Ingelheim, Fertility Nutraceuticals, Fertilify
- Stock: OvaScience, Circadian-ZircLight
- Royalties: Teva, Up-To-Date
- Medical Director: Insception-LifeBank cord blood bank
- Scientific Director: TRIO Fertility

Endometriosis

- Estrogen-dependent ectopic endometrial tissue
- Chronic inflammatory process
- Overproduction of cytokines, prostaglandins, and other inflammatory mediators
- Neoangiogenesis
- End result can be chronic pelvic pain, adhesion and scarring, as well as infertility

Problems with Endometriosis Research

- Heterogeneous nature of the disease
- Need for new therapies to be individualized
- RCTs vs Prospective Cohort Follow-up studies

- Lack of adequate rodent models
- Results from rodent models not always applicable to human endometriosis

Individualized Therapy

- Endometriosis is likely a heterogeneous disease
- Future research needs to focus on treatments for individuals
- Is a randomized controlled trial really the gold standard in this case?

Randomized Controlled Trials

- Inclusion and exclusion criteria used to define the subject population including those with the disease and no confounding problems

Example of Key inclusion/exclusion criteria

Inclusion Criteria:

- Premenopausal women between 18-49 years old
- Surgical diagnosis of endometriosis in the previous 10 years
- Moderate or severe endometriosis-associated pain

Exclusion Criteria:

- At screening, Z score of less than -1.5 for bone mineral density at the lumbar spine, femoral neck, or total hip
- Clinically significant gynecologic conditions
- Chronic pain conditions unrelated to endometriosis

Taylor HS et al. N Engl J Med 2017;377:28-40.

Randomized Controlled Trials

- Subjects randomized to two different treatments and outcome compared
- Results reflect average response of each group to the various treatment
- **Therefore, the RCT design focuses on treatments, not on individuals**

Prospective cohort follow-up study

- A better design for individualized therapy
- Subjects with a disease selected and assumed to be heterogeneous
- Given one treatment and followed prospectively
- Responders and non-responders identified
- Look for predictors of response
- Focus is now really on the individual

Guidelines for medical therapy

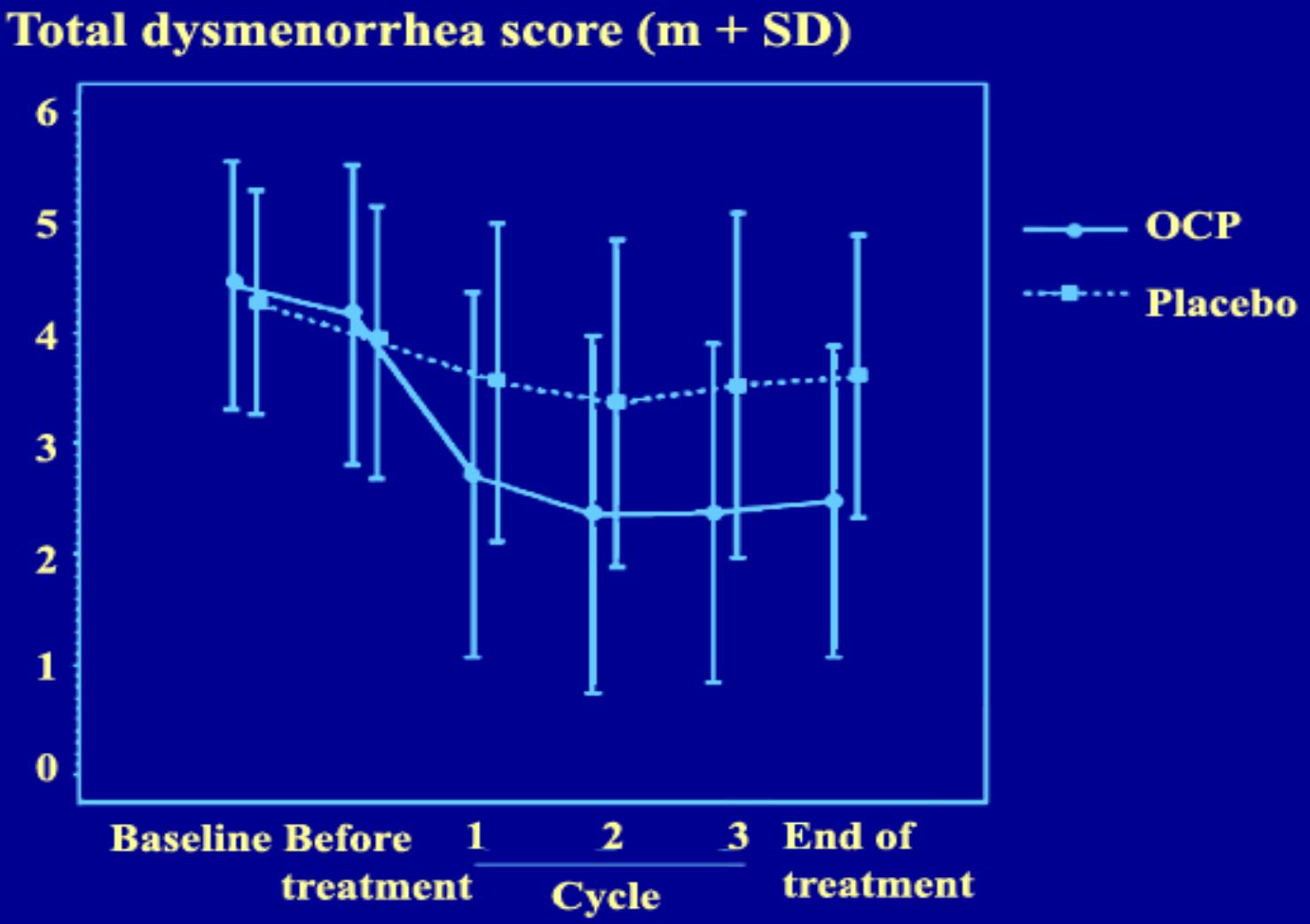
- All gynecologic societies recommend combined E and P oral contraceptives as first line therapy
- Are they the best first line treatment in view of individualized therapy?

RCT of Oral Contraceptives

- 100 women with endometriosis and pain randomized to low dose OCP or placebo for 4 cycles
- Conclusion: Significant relief of dysmenorrhea with OCP vs placebo
- No difference in non-menstrual pelvic pain

Harada T et al. Fertil Steril 2008

Oral Contraceptives



Harada T et al. Fertil Steril 2008

Endometriosis has Progesterone Resistance

- ER normal in endometriotic lesions
- PR-A markedly decreased and PR-B absent
- Progestin unable to antagonize ER
- Unable in increase enzyme that metabolizes estradiol to estrone
- Result is progesterone resistance and estrogen sensitivity

Bulun SE et al. Mol Cell Endocrinol 2006

OCPs contain supra-physiologic estrogen doses

- Low dose OCPs contain 20 to 30 µg of ethinyl estradiol (EE) and a progestin
- 5 µg of EE equivalent to 1 mg of micronized estradiol (E2) or 0.625 mg of conjugated equine estrogen (CEE)
- EE 20 to 30 µg is therefore 4 to 6 times the physiologic dose of estrogen
- OCPs do not induce a hypoestrogenic state

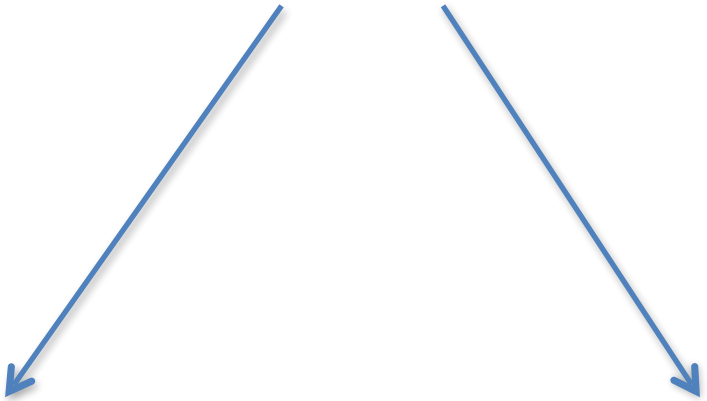
Prospective cohort follow-up trial

- 58 women with laparoscopically documented endometriosis and chronic pelvic pain
- All treated with the same OCP for 3 months

Jenkins TR et al. J Minim Invasive Gynecol 2008

58 patients with endometriosis
documented by laparoscopy and pathology

OCP



22 patients (38%)
partial or complete improvement

36 patients (62%)
no improvement

Jenkins TR et al. J Minim Invasive Gynecol 2008

Response to oral contraceptives by site of endometriosis

Location	Responders No. (%)	Non-responders No.(%)
Any location	22/58 (38)	36/58 (62)
Anterior rectum	18/38 (47)	20/38 (53)
Pelvic cul-de-sac	15/38 (39)	23/38 (61)
Left pelvic sidewall	14/33 (42)	19/33 (58)
Right pelvic sidewall	14/33 (42)	19/33 (58)
Anterior peritoneum	6/9 (66)	3/9 (33)

Jenkins TR et al. J Minim Invasive Gynecol 2008

Oral Contraceptive Study

- Attempted to find predictors of response based on anatomic location of endometriosis implants
- Not successful
- More interesting study may be to look at expression of PR in the pathologic sections of endometriosis biopsied during laparoscopy

Jenkins TR et al. J Minim Invasive Gynecol 2008

Multiple different OCPs used for endometriosis

TABLE 1

Number of different oral contraceptive pills (OCPs) used for relief of symptoms in 441 women with diagnosed endometriosis globally and broken down by country.

No. of OCPs tried	Global (n = 441)	United States (n = 110)	Canada (n = 53)	Italy (n = 60)	France (n = 25)	Germany (n = 32)	United Kingdom (n = 48)	Brazil (n = 76)	South Korea (n = 7)
1	28	28	34	40	52	32	25	20	46
2	28	23	22	35	36	15	36	33	29
3–5	28	29	28	16	8	41	31	27	24
6–10	15	15	16	8	4	13	6	20	0
>10	2	3	0	0	0	0	2	0	0

Note: Values are percentages unless otherwise indicated.
Source: Bernuit et al. 2011 (10). With permission from Bayer Global; data on file.

Casper. *Progestin-only pills for endometriosis. Fertil Steril 2017.*

Bernuit et al, J Endometriosis Pelvic Pain Dis 2011;3:59

Multiple different OCPs used for endometriosis

Number of OCPs tried	Global (n=440)	Italy (n=60)
1	28%	40%
2	28%	35%
3-5	28%	16%
6-10	15%	8%
>10	2%	0%

Bernuit et al, J Endometriosis Pelvic Pain Dis 2011;3:59

Search for Potential New Treatments

Emerging Therapies

- Small molecule oral GnRH antagonists
- Selective progesterone receptor modulators
- Aromatase inhibitors

- Newer treatments are experimental, either in vitro or in rodent models

Rodent Models

- Advantages
  - inexpensive
  - easy to care for
  - genetic manipulation using knockout/ transgenic mice is possible

Rodent Models

- Very different from humans in phylogenetics, reproductive anatomy and physiology
- Lack of menstrual cycle
- Lack of peritoneal fluid
- Lack of spontaneous endometriosis

D'Hooghe et al, Reprod Sci 2009

Rodent Models

- Induction of endometriosis by autologous uterine tissue transplantation and high dose estrogen is questionable
- Unphysiological ‘‘endometriotic lesions’’ with different phenotype compared to endometriosis in women
- May have normal progesterone receptors

D’Hooghe et al, Reprod Sci 2009

Rodent Models

- Human endometrial fragments transplanted into immunosuppressed mice appears to be an attractive model
- But lack of immune cells leads to questions about relevance to human endometriosis

Agents effective in vitro or in rodents

- **Anti-angiogenesis**
  - Bevacizumab
  - Tyrosine kinase inhibitors (Pazopanib, sorafenib, sunitinib)
  - mTOR inhibitors (rapamycin, temsirolimus, everolimus)
  - TNP-470
  - DA-agonists (cabergoline, **quinagolide**)
- **Statins**
  - **Simvastatin, lovostatin, atorvastatin**
- **Others**
  - Metformin
  - PPAR-γ agonists (tosiglitazone, ciglitazone or pioglitazone
  - **Raloxifene**, bazedoxine
  - omega-3 fatty acids
- **Vitamins**
  - Vitamin A, etocalitol
  - α-lipoic acid
- **Anti-inflammatory**
  - Cox-2 inhibitors (celecoxib, parecoxib)
  - TNF-α inhibitors (etanercept, **infliximab**)
  - p38 MAPK inhibitors
- **Immunomodulators**
  - inhibitors of NF-kB (TPCK, thalidomide, BAY 11-7085, hCG-α, PDTC and costunolide)
  - Curcumin
  - Imiquimod, bentamapimod
- **Epigenetic modulators**
  - trichostatin A
  - Valproic acid

Grech et al, Expert Opin Invest Drugs, in press

Results from Rodent Models vs Clinical Trials

- Raloxifene suppressed endometriosis in a rodent model in 2 RCTs
- Clinical trial of raloxifene vs placebo in 93 women with endometriosis
- Stopped early because of increased pain in the raloxifene group
- Raloxifene group required second surgery sooner

Stratton et al, Obstet Gynecol 2008

Results from Rodent Models vs Clinical Trials

- Infliximab, a monoclonal antibody directed against TNF-α, successfully decreased size of experimental endometriosis lesions in mice
- RCT in 21 women with severe pain and rectovaginal endometriosis of at least 1 cm
- Infliximab did not affect size of endometriotic implants and did not improve pain

Koninckx et al, Hum Reprod 2008

Results from Rodent Models vs Clinical Trials

- Lovostatin shown to inhibit endometrial cell proliferation and angiogenesis in a human *in vitro* model of endometriosis (Esfandiari et al, Fertil Steril 2007)
- Three different statins had beneficial effects in rodent models to reduce size and vascularity of experimental endometriosis lesions
- Two positive studies in baboon model
- Clinical study by us stopped due to lack of efficacy (unpublished)

Results from Rodent Models vs Clinical Trials

- Dopamine agonist, quinagolide, reduced lesions size and angiogenesis through decrease VEGF expression in 3 rodent models
- Proof of concept clinical trial showed reduced endometriosis lesion size on second-look laparoscopy (Gomez et al, Fertil Steril 2011)
- No further publications

New Concept

- Endometriosis may be related to cell senescence
- Study from Brazil showed reduced expression of laminin B1 in ectopic endometrium
- Suggested that senescent cells could be playing a role in the inflammation and progression of endometriotic lesions

Malvezzi et al, Archives Gynecol Obstet, 2018

Cell Senescence

- Refers to irreversible growth arrest of cells subjected to potentially mutagenic insults
- Triggers include critically short telomeres, oxidative damage, oncogene activation, hypoxia and others

Tchkonia et al., 2013

Senescent Cells

- Senescent cell number in aging or diseased tissues is low (~ 15%)
- But senescent cells secrete pro-inflammatory cytokines, chemokines, angiogenic factors and extracellular matrix proteases
- Constitute the senescence-associated secretory phenotype (SASP)
- Result is damage to surrounding cells leading to tissue or organ dysfunction typical of aging

Senescent Cells

- Normally, SASP would induce apoptosis
- Anti-apoptotic, pro-survival mechanisms appear to be up-regulated
- Senescent cells can withstand stresses such as serum deprivation better than non-senescent cells

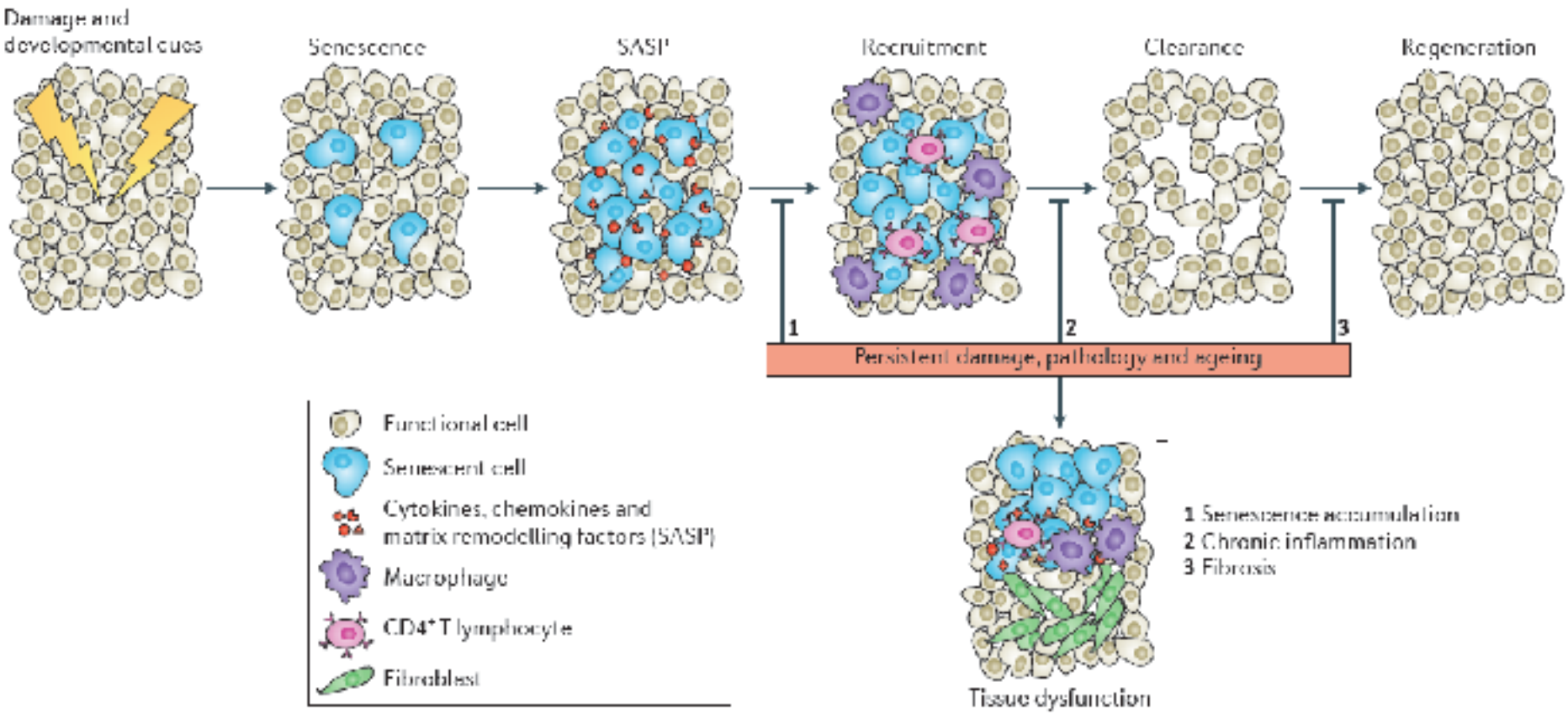
Similarities

- ENDOMETRIOSIS
  - Chronic inflammatory process
  - Overproduction of cytokines, prostaglandins, and other inflammatory mediators
  - Neoangiogenesis
  - Increased MMP
  - Resistance to apoptosis
- SENESCENT CELLS
  - Chronic inflammatory process
  - pro-inflammatory cytokines and chemokines
  - Secrete angiogenic factors
  - Increased extracellular matrix proteases
  - Apoptosis resistance

Senescent Cells

- In vivo, senescent cells appear to be removed by the immune system rather than by apoptosis or necrosis

Cell Senescence



Muñoz-Espín and Serrano, Nature Reviews, 2014

Cell Senescence

- Interfering with anti-apoptotic activity leads to selective elimination of senescent cells
- Clearing senescent cells has been done by activating drug-inducible ‘suicide’ genes
- Also by some biologic chemotherapeutics and other small molecule drugs

Conclusion

- Future research in endometriosis should focus more on individualized treatments (personalized medicine)
- In vitro and rodent models may not be accurate in detecting clinically relevant treatments
- New concepts of endometriosis etiology and disease progression are needed to direct future research