
بسم الله الرحمن الرحيم

Medical Treatment of Endometriosis

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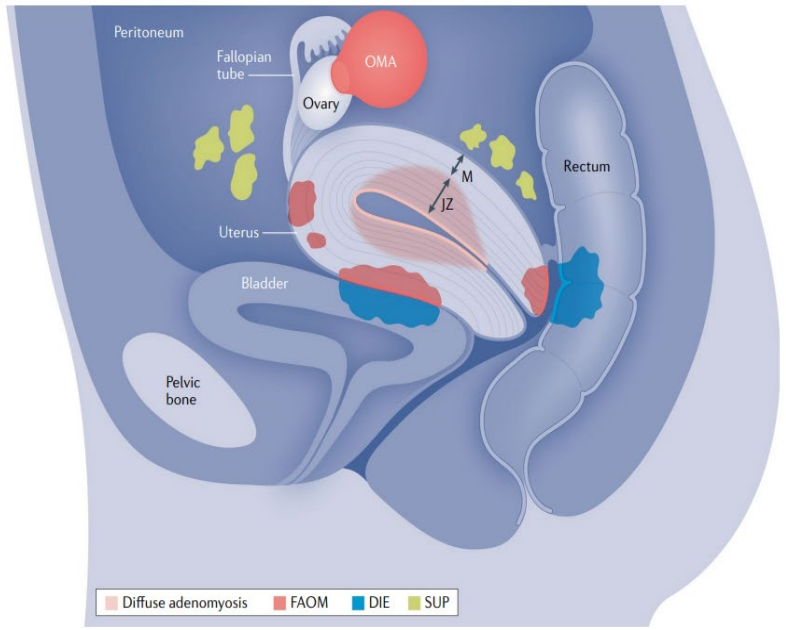
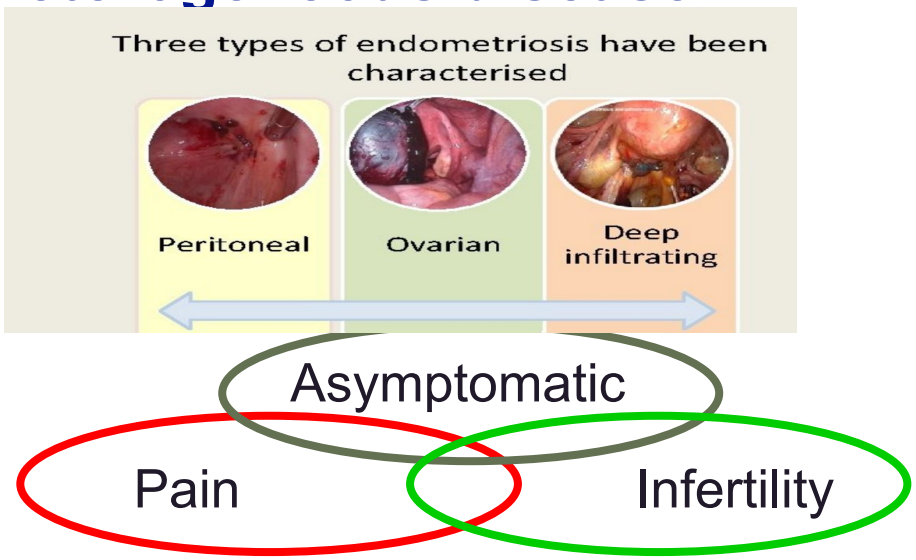
SEUD membership

Endometriosis

Heterogeneous disease





10% of women of reproductive age
20-50% of infertile women
30-80% of women with chronic pelvic pain

Rethinking mechanisms, diagnosis and management of endometriosis

Charles Chapron **NATuRE NOVEMBER 2019 |**

Endometriosis

- infammatory entity
- the presence of endometrial-like tissue outside the uterine cavity
- women of reproductive age(10%)
- chronic pelvic pain, dysmenorrhea, infertility, dyspareunia, dysuria, dyschezia and fatigue estrogen-dependent condition
- delayed diagnosis
- major health issue with socioeconomical impact

Endometriosis

- chronic inflammatory disease
- requires lifelong management
- Three main therapeutic options exist for endometriosis management:
- **medical treatment**
- **surgery**
- **ART**
- Several arguments can be made for the use of medical treatment in endometriosis for lifelong management

PATHOGENESIS

- Sampson's theory :retrograde menstruation
- Coelomic metaplasia : transformation of peritoneal tissue
- Mullerianosis: residual cells from embryonic Mullerian duct migration retain the ability to differentiate into endometrial tissue

More recently, theories have implicated stem cells/progenitor cells from the bone marrow as the culprit

Genetic

- Genetically, endometriosis is considered a complex trait that exhibits familial aggregation, with an up to six fold increased risk for first-degree relatives of patients with endometriosis
- heritability is 50%
- the identification of the genetic factors driving the disease is still incomplete

- Two chromosomal areas of significant linkage were observed on 10q26 and 7p13–15 (containing genes such as CYP2C19, INHBA, SFRP4 and HOXA10)

Role of environmental factors

- The role of environmental factors in endometriosis, such as endocrine disrupting chemicals, remains highly controversial
- Currently, no direct evidence exists showing that endocrine disrupting chemicals are involved in endometriosis

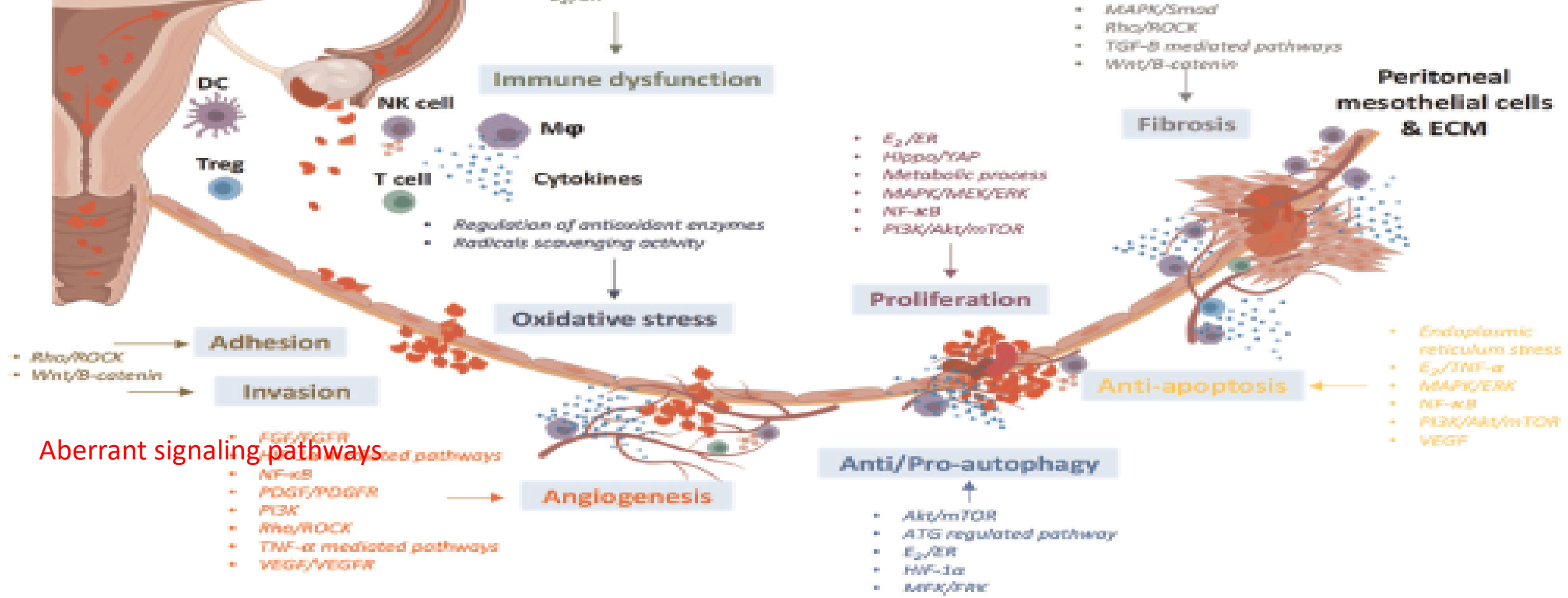


FIGURE 1 Pathophysiology of endometriosis. The schematic diagram was created using BioRender.com. Akt, protein kinase B; ATG, autophagy-related genes; DC, dendritic cells; E_2, estrogen; ECM, extracellular matrix; ER, estrogen eceptor; ERK extracellular signal-regulated kinase; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptors; HIF, hypoxia-inducible factors; MΦ, macrophages; MAPK, mitogen-activated protein kinase; MEK, ERK kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; NK, natural killer; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PI3K, phosphoinositide 3-kinases; Rho, Ras homolog family; ROCK, Rho-associated coiled-coil kinase; VEGF, vascular endothelial growth factor; TGF, transforming growth factor; TNF, tumor necrosis factor; Treg, regulatory T cells; Wnt, wingless-type mouse mammary tumor virus integration site family; YAP, Yes-associated protein

Endometriosis-related pain

Several mechanisms :

refluxed endometrial cells located outside the uterus

stimulate the infiltration of immune cells (such as, macrophages and mast cells) into lesions, which secrete inflammatory mediators (such as, proinflammatory cytokines, chemokines and nerve growth factor), finally resulting in an inflammatory peritoneal microenvironment. In addition, a strong topographical relationship exists between endometriotic foci and nerves

TABLE 1

Criteria for the ideal medication for endometriosis.

Curative rather than suppressive
Treats pain and fertility at the same time
Acceptable side effect profile
Long-term use should be safe and affordable
Noncontraceptive nature
No interference with spontaneous ovulations and normal implantation
Enhances spontaneous conception
No teratogenic potential and safe to use periconceptionally
Inhibits the growth of already existing lesions
Aborts the development of new lesions
Efficacious for all endometriosis phenotypes including superficial disease, endometriomas, deep infiltrating endometriosis, and extrapelvic endometriosis and adenomyosis

Bedaiwy. Future of endometriosis medical therapy. Fertil Steril 2017.

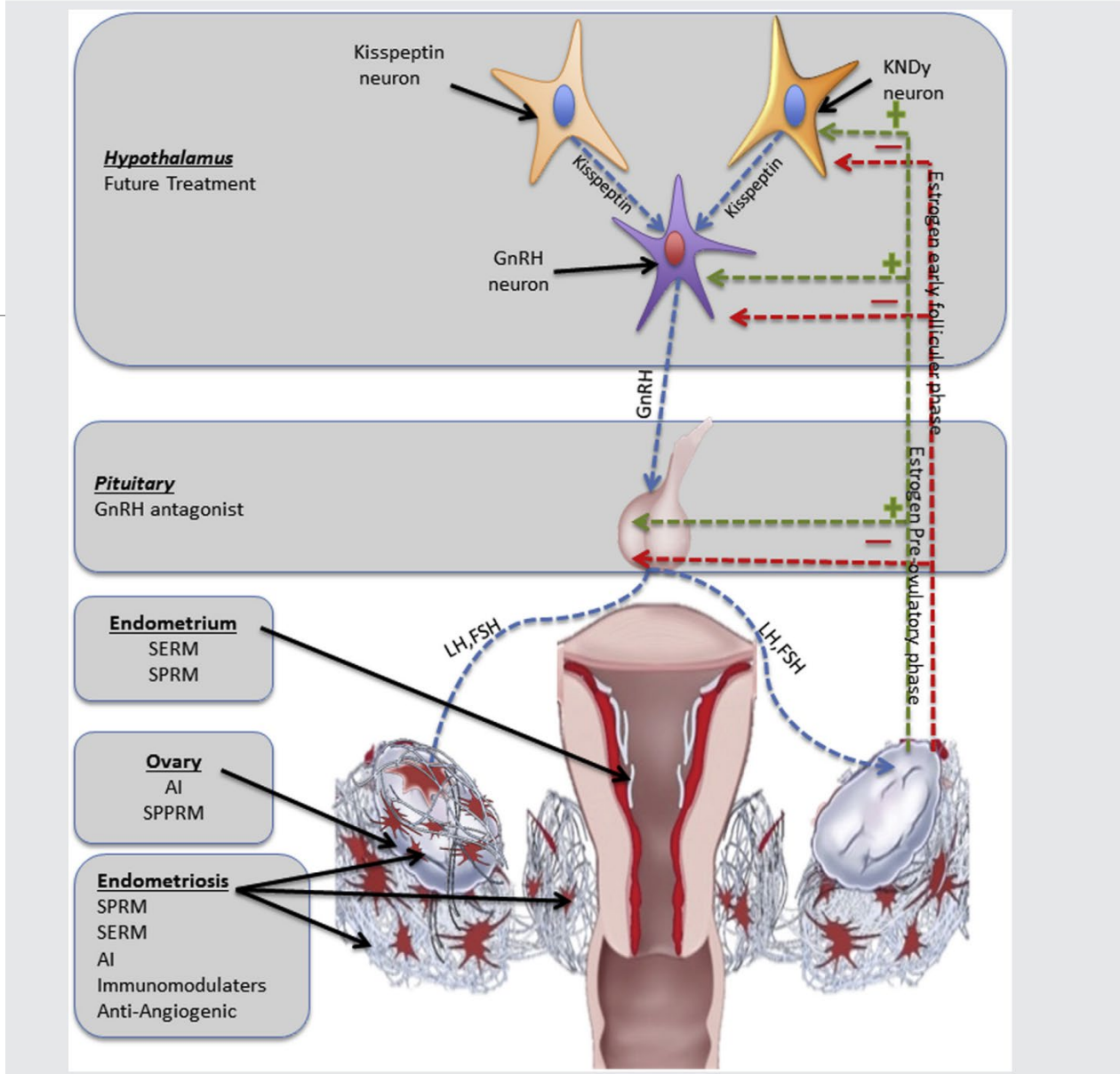

Kisspeptin neuron
KNDy neuron
Hypothalamus
Future Treatment
Kisspeptin
Kisspeptin
GnRH neuron
Estrogen early follicular phase
GnRH
Pituitary
GnRH antagonist
Estrogen Pre-ovulatory phase
Endometrium
SERM
SPRM
LH,FSH
LH,FSH
Ovary
AI
SPPRM
Endometriosis
SPRM
SERM
AI
Immunomodulaters
Anti-Angiogenic

Table 3. Hormonal therapies

	Hormone	Delivery method	Contraceptive	Administration	Side effects	Contraindications
Combined oral contraceptive pill	No evidence of superiority of any one preparation	Oral, vaginal ring or transdermal patch	Yes	Cyclical or continuous Continuous further reduces dysmenorrhoea	Nausea, headaches, weight gain, breakthrough bleeding, mood disturbance, VTE	History of VTE, IHD, migraine with aura, ≥35 years smoker ≥15/day, breast cancer, severe liver disease
Progestogens					Breast tenderness, irregular bleeding, amenorrhoea, acne, mood disturbance	Breast cancer, severe liver disease, unexplained vaginal bleeding
	Levonorgestrel 52 mg (Mirena)	Intrauterine device	Yes	Replace 5 yearly	PID, expulsion, perforation, post-insertion cramping, ovarian cyst formation	PID, active STI, cervical or endometrial cancer
	Medroxyprogesterone 150 mg (Depo-Provera)	Intramuscular injection	Yes	Injection 3 monthly	Injection site pain, delayed return to fertility, reduced BMD[A]	Refer above
	Etonogestrel 68 mg (Implanon)	Subdermal implant	Yes	Replace 3 yearly	Implant site pain, infection, migration	
	Medroxyprogesterone	Oral	No	10 mg 3 times daily	Refer above	
	Dienogest	Oral	No	2 mg once daily		
	Norethisterone	Oral	Yes	5–10 mg once daily		
	Drospirenone[B]	Oral	Yes	4 mg once daily		
Gonadotropin-releasing agonists (under specialist supervision)				Maximum 6 months		
	Goserelin	Subcutaneous	No	3.6 mg injection 4 weekly	Hot flushes, vaginal dryness, sexual dysfunction, amenorrhoea, reduced BMD	Breastfeeding, pregnancy, unexplained vaginal bleeding, osteoporosis
	Nafarelin	Intranasal	No	200 µg twice daily		

Hormonal treatments for endometriosis

- suppressing hormonal fluctuations (gonadotropin and ovarian hormones)
- inhibition of ovulation and menstruation
- downstream decrease in inflammation

  - combined oral contraceptives (COCs)
  - progestins
  - gonadotropin-releasing hormone analogues (GnRHa)

Treatment of Pain in Endometriosis

Table 1 Treatment of Pain in Endometriosis

Treatment of **Pain** in Endometriosis

Guidelines	Surgery									Pharmacological treatment												Complementary treatment			
	Ablation	Excision	Excision OMA	Ablation OMA	Excision DIE	Hysterectomy	Adhesiolysis	PSN	LUNA	COC	Danazol	Dienogest	MPA	LNG-IUD	Gestrinone	NSAID	AI	GnRH-agonist	GnRH-antagonist	SPRM	SERM	Acupuncture	TENS	Dietary	Chinese medicine
WES 2011	w	w	s	s	w			s [sc]	s	s	s [b]	s	s	w	s	s	w	w	w	w	s	w	w	w	w
NICE 2018	-	-	-	-		-				-		- [a]	- [a]			GPP [c]		-						-	-
CNGOF 2018	B	B	A	B	C	GPP				A		B	B	B		c , b		B [c]							sc
SOGC 2010	A	A	A	A	A			A	A	A	b	A [a]	A [a]	A		GPP [c]		A							
ESHRE 2013	C	C	A	A	B	GPP	B	A	A	B	A [b]	A	A	B	A	GPP	B	A [b]				GPP	GPP	GPP	GPP
S2k 2014		-	-	-	-					-		- [a]	- [a]	-				- [c]							
ACOG 2010			A	A		-		- [b]		-	-	- [a]	- [a]			B		A [c]							
ASRM 2014	-	-	-	-		- [sc]		- [b]		-	- [b]	-	-	-	-		-	-				-			-

first-line therapy
second-line therapy
third-line therapy
additional therapy
not recommended
no recommendation
insufficient evidence of use in endometriosis

A Level of evidence A
B Level of evidence B
C Level of evidence C
GPP Expert opinion
- No information about evidence
s strong recommendation
w weak recommendation

[a] don't differ between subgroups of gestagens
[b] critical because of side-effects
[c] for a limited time of treatment
[m] moderate endometriosis
[s] severe endometriosis
[sc] only for special cases

Treatment of endometriosis: a review with comparison of 8 guidelines
Kalaitzopoulos et al. BMC Women's Health (2021)

Non hormonal **imunomodelators**

			effective in treating endometriosis-associated CCP without compromising fertility.
Nonhormonal Imunomodulaters[e]			
Etanercept	Barrier et al., 2004 (51)	Baboons	Statistically significant decreases endometriotic lesion surface area.
IFN-2b	Badawy et al., 2001 (52)	Human cell culture	Caused statistically significant suppression of endometrioma.
	Ingelmo et al., 2013 (53)	Rats	Caused greater reduction in implant size compared with placebo.
Loxoribine	Keenan et al., 1999 (54)	Rats	Reduced NK cells and endometriotic lesions.
Lipoxin	Xu et al., 2012 (55)	Mice	Inhibited endometriotic lesion development, suppressed MMP-9, and decreased VEGF.
	Kumar et al., 2014 (56)	Mice	A4 compound decreased PGE2 production, aromatase expression, and estrogen signaling.
Rapamycin	Ren et al., 2016 (57)	Mice	Reduced VEGF serum level and MVD, led to decreased endometriotic lesions in SCID mice.
	Laschke et al., 2006 (58)	Hamsters	Decreased VEGF and MVD, led to inhibition of endometriotic cell proliferation.
Infliximab	Koninckx et al., 2008 (59)	Humans	No effect in endometriosis-related pain.
Pentoxifylline	Kamencic and Thiel, 2008 (60)	Humans	Patients with better VAS score after 2 and 3 mo from surgery compared with controls.
	Vlahos et al., 2010 (61)	Rats	Caused reduction in VEGF-C, decreased volume and no. of endometriotic implants.

Bedaiwy. Future of endometriosis medical therapy. Fertil Steril 2017

Non hormonal

antiangiogenesis

			no. of endometriotic implants.
Antiantiangiogenics[f]			
Caplostatin	Backer et al., 2006 (62)	Mice	Suppression of VEGF.
Endostatin	Jiang et al., 2007 (63)	Mice	VEGF in peritoneal fluid after treatment statistically significantly lower than in control group.
	Zhang et al., 2012 (64)	Rats	Gene therapy resulted in lower VEGF, MMP-2, and MVD compared to control.
	Ma and He, 2014 (65)	Mice	Significant decrease in endometriosis volume and MVD.
Angiostatin	Dabrosin et al., 2002 (66)	Mice	Gene transfer therapy caused eradication of endometriosis in all treated mice, decreased estradiol and progesterone production.
Lovastatin	Esfandiari et al., 2007 (67)	In vitro human tissue	Inhibited angiogenesis and cell proliferation.
Atorvastatin	Oktem et al., 2007 (68)	Rats	Decreased VEGF level and area of implants.
	Sharma et al., 2010 (69)	Human cell culture	Inhibited gene expression of COX-2, VEGF, RAGE, and EN-RAGE in endometrial and endometriotic cell culture.
Simvastatin	Bruner-Tran et al., 2009 (70)	Mice	Decreased endometrial implants and MMP-3.
	Almassinokiani et al., 2013 (71)	Humans	Comparable to GnRH-a in the management of endometriosis-related pelvic pain.
Lodamin	Becker et al., 2011 (72)	Mice	Caused reduction of endothelial progenitor cells, resulting in suppression of endometriotic tissue growth.
Romidepsin	Imesch et al., 2011 (73)	Human cell culture	Decreased VEGF secretion.
Icon	Krikun et al., 2010 (74)	Mice	Destroyed endometriotic implants through vascular disruption without toxicity, effect on fertility, or teratogenicity.
Cabergoline Bromocriptine	Novella-Maestre et al., 2009 (75)	Mice/human cell culture	Cabergoline, decreased VEGF and VEGFR-2 protein expression.
Quinagolide	Delgado-Rosas et al., 2011 (76)	Mice	Cabergoline and quinagolide, equal effect in reducing endometriotic lesions as antiangiogenic agents.
	Ercan et al., 2015 (77)	Rats	Cabergoline and bromocriptine, comparable to GnRH agonist in reducing endometriotic lesion.
	Hamid et al., 2014 (78)	Humans	Cabergoline, better result in reducing endometrioma size compared with triptorelin acetate.
Fenofibrate	Onalan et al., 2009 (79)	Rats	Reduction of endometriotic lesion and VEGF.
	Herington et al., 2011 (80)	Mice	Decrease in endometriosis-related postsurgical adhesion in immunocompromised mice.
Rosiglitazone	Lebovic et al., 2007 (81)	Baboons	Statistically significant reduction of endometriotic lesion compared with placebo.
	Chang et al., 2013 (82)	Human cell culture	Inhibited aromatase and COX-2 expression, led to decreased PGE2 production.
Ciglitazone	Lebovic et al., 2004 (83)	Rats	Statistically significantly decreased explant size and weight compared with control.
	Lebovic et al., 2013 (84)	Human cell culture	Decreases PGE2 and aromatase expression.
Bentamapimod	Hussein et al., 2016 (85)	Baboons	Alone or combined with medroxyprogesterone acetate led to lower surface area and volume of lesions.

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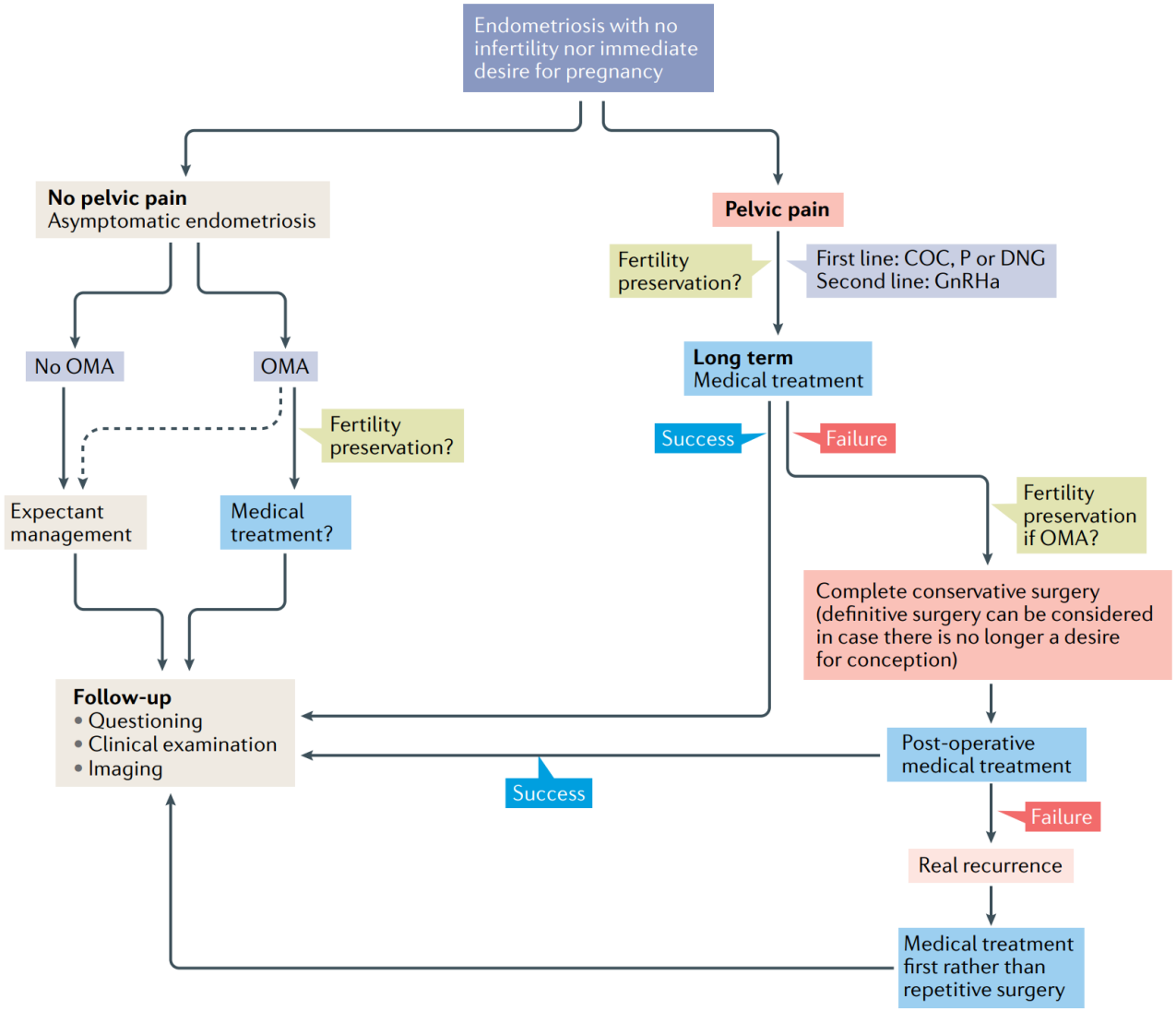
Surgical procedures? central sensitization

- Numerous inadequate and unnecessary surgical procedures are performed for endometriosis;
- surgical exeresis of endometriotic lesions has no effect on retrograde menstruation
- high rates of symptom and lesion recurrence are observed after surgical treatment
- surgery is not effective for treating pain owing to central sensitization

Therefore, medical treatment should be considered for the management of pain and inflammation associated with endometriosis for patients who do not want to become pregnant

Rethinking mechanisms, diagnosis and management of endometriosis

Charles Chapron NOVEMBER 2019

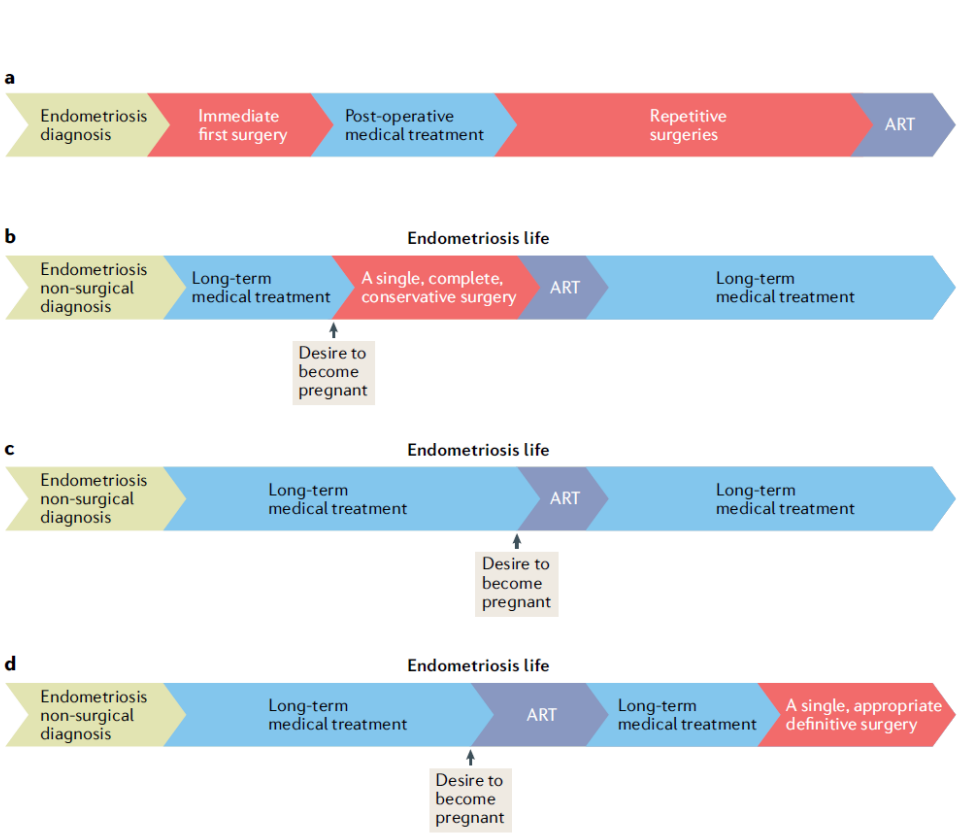


Endometriosis management algorithm for patients without an immediate desire for pregnancy

Endometriosis Life

Rethinking mechanisms, diagnosis and management of endometriosis

Charles Chapron[1,2,3]*, Louis Marcellin[1,2,3], Bruno Borghese[1,2,3] and Pietro Santulli[1,2,3]




THANKS FOR YOUR ATTENTION