



Koningin Mathilde
Moeder- en kindcentrum



LOK

Endometriose

Christine De Bruyn MD. PhD.

UZ Antwerp | Gynaecology & Obstetrics | Senior Staff Member

University of Antwerp | Antwerp Surgical Training, Anatomy and
research centre | Gynaecology, Obstetrics and Fertility



Epidemiologie

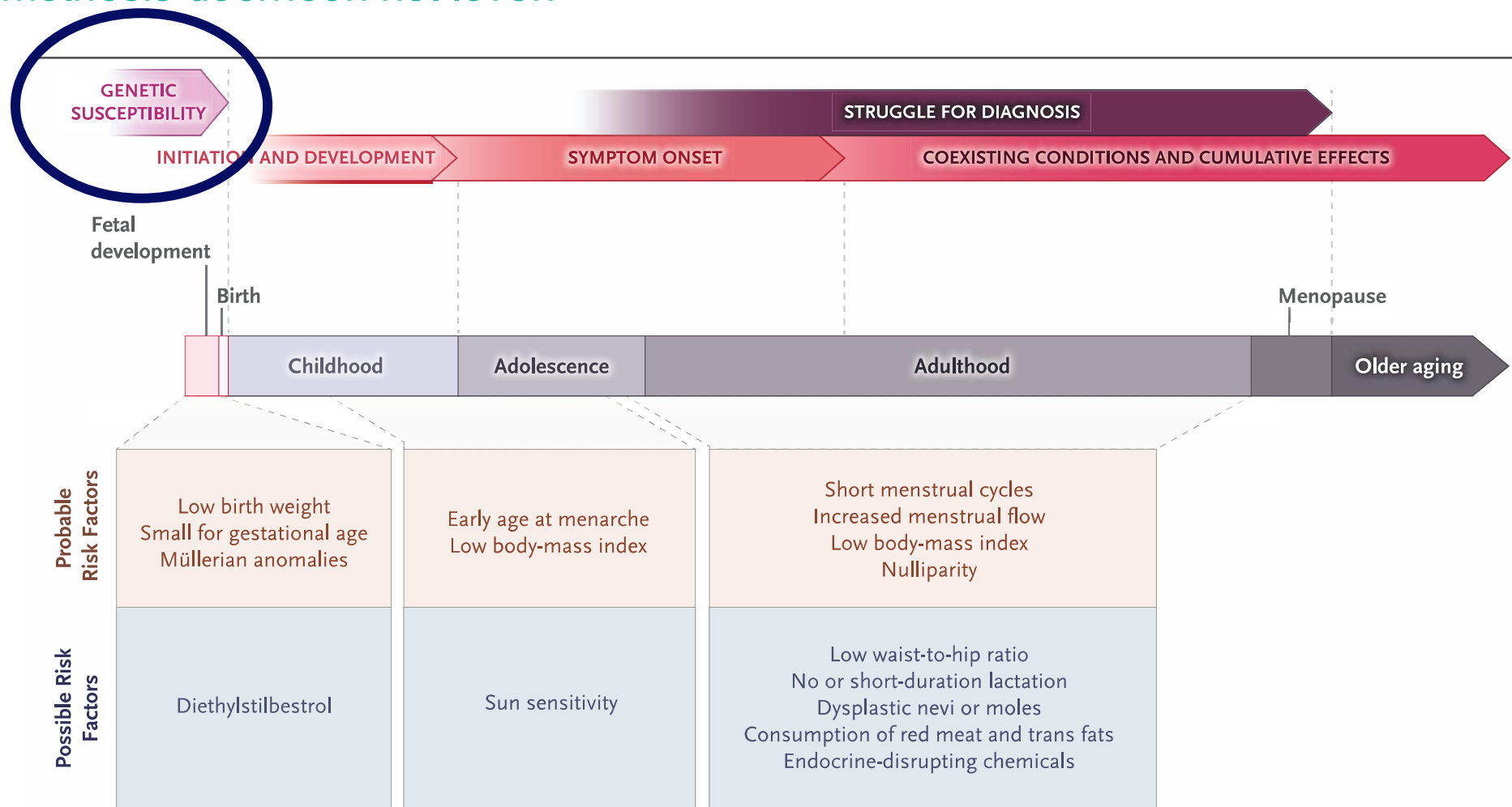
10% van de vrouwen

Enkele prevalentie cijfers

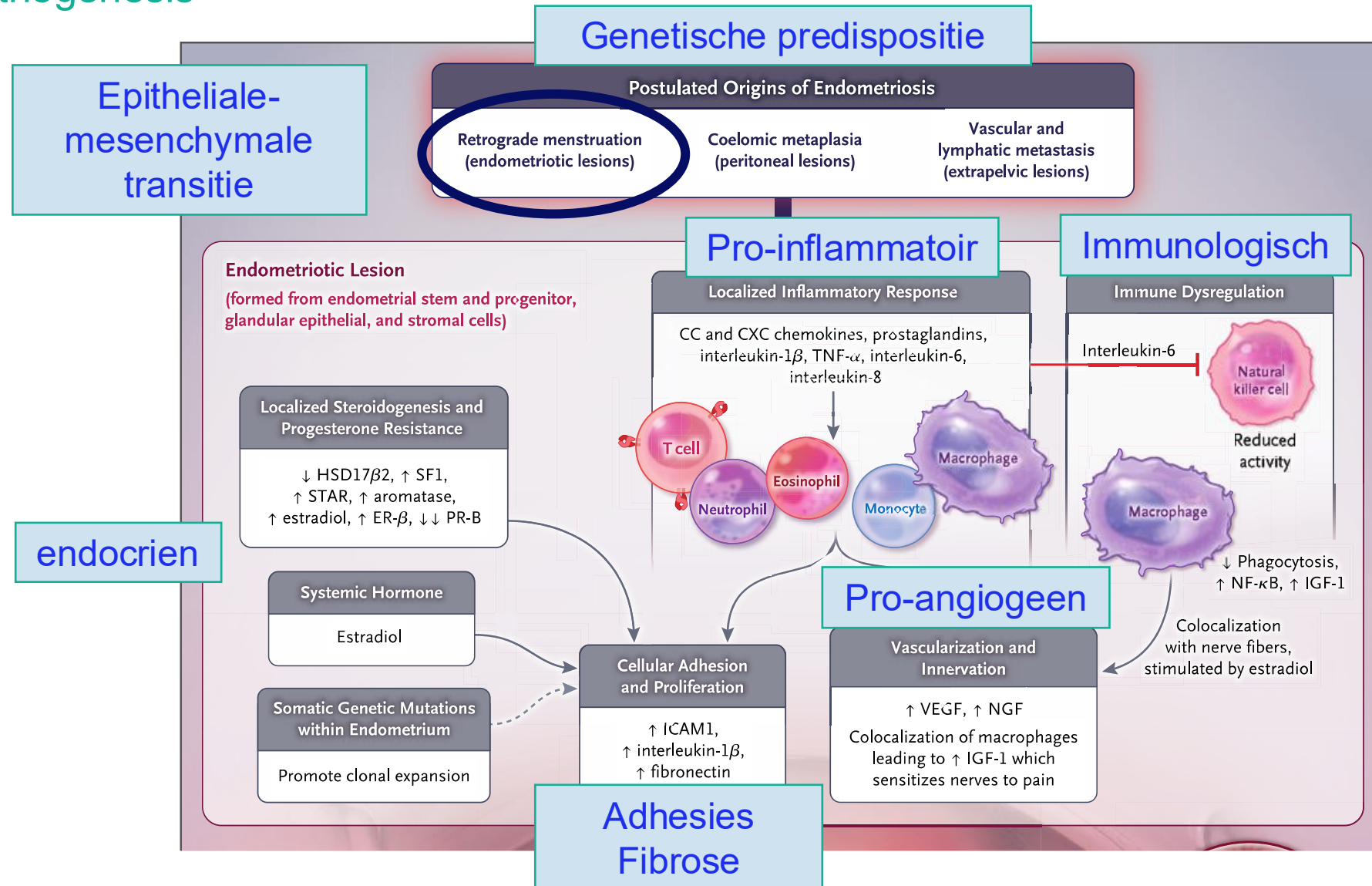
- Asymptomisch populatie: 2-11%
- Infertiliteit: 5-50%
- Hospitalisatie voor pelviene pijn: 5-21%
- Symptomatische adolescenten:
 - 49% bij chronische pelviene pijn
 - tot 75% niet reagerend op medicamenteuze behandeling

*Endometrium-like tissue
outside the uterus*

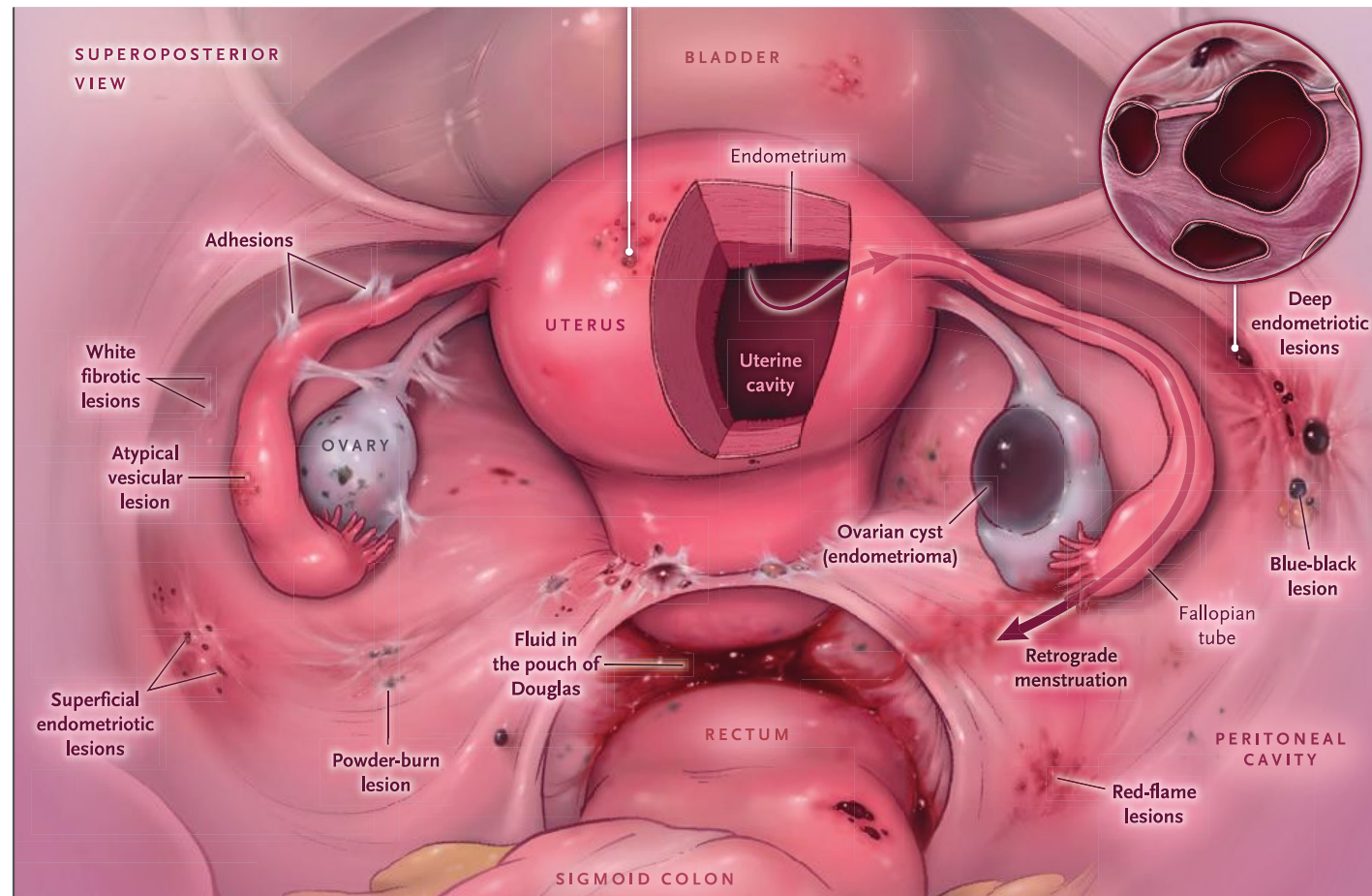
Endometriosis doorheen het leven



Pathogenesis



Lokaties



Extrapelvien:

- Thoracaal
- Neus
- Hersenen
- Litteken (sectio!)

Klinisch beeld

Symptoms

Asymptomatic
Dysmenorrhea
Acyclic pelvic pain
Dyspareunia
Dyschezia
Dysuria
Infertility
Somatosensory amplification
Fatigue

Coexisting Conditions and Subsequent Disorders

Gynecologic
 Uterine fibroids, adenomyosis
Pain
 Fibromyalgia, migraine
Central sensitization
Gastroenterologic
 Irritable bowel syndrome, ulcerative colitis
Genitourinary
 Interstitial cystitis
Mental health
 Depression, anxiety
Immunologic
 Rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis,
 allergies, asthma
Cancer
 Ovarian cancer, melanoma, thyroid cancer
Cardiovascular disease

Geen correlatie tussen intensiteit van pijn en uitgebreidheid/lokalisatie van endometriose letsels

Endometriose en IBS

Overlap: chronische buikpijn, krampen, bloating, angst, jonge vrouwen

- gedeelde genetische factoren
- beide chronische ontstekings reactie + viscerale overgevoeligheid
- microbiom van de darm → darm-hersen-as

Vrouwen met endometriose verhoogd risico op IBS (HR 1,58 (95%CI 1,38-1,82))

	Endometriose	IBS
Comorbiditeiten	gerelateerd aan genito-urinair systeem (vb. myomen, abnormaal uterine bloedverlies, infertiliteit, adenomyosis)	gerelateerd aan spijsvertering (vb. lactose intolerantie, gastritis, functionele dyspepsie)
Symptomen	cyclisch	Meer ernstige gastro-intestinale symptomen Vb diarree, constipatie
Medicatie	hormonen	Meer medicatie van darmdysfunctie
Initiële trigger	Menarche	Infectie Antibiotica behandeling

Klinisch onderzoek

Speculum onderzoek

Palpatie

Bekkenbodem

Vergeet niet de klassieke gynaecologische zaken te beoordelen of uit te sluiten
vb cervixcytologie, infectie

Pijn

Perifeer – inflammatoir

- Chemokines en cytokines in peritoneaal vocht

30% van endometriose patiënten ontwikkelen chronische pelviene pijn welke niet behandelbaar is.

Centraal – centrale sensitisatie

- structurele en volume verandering van de hersenen
- modificaties van autonoom zenuwstelsel
- veranderingen in gedrag
- veranderingen als reactie op schadelijke stimuli

Adhesiolyse noch LUNA verbetering van pijnklachten op 12 maanden.

Diagnostiek

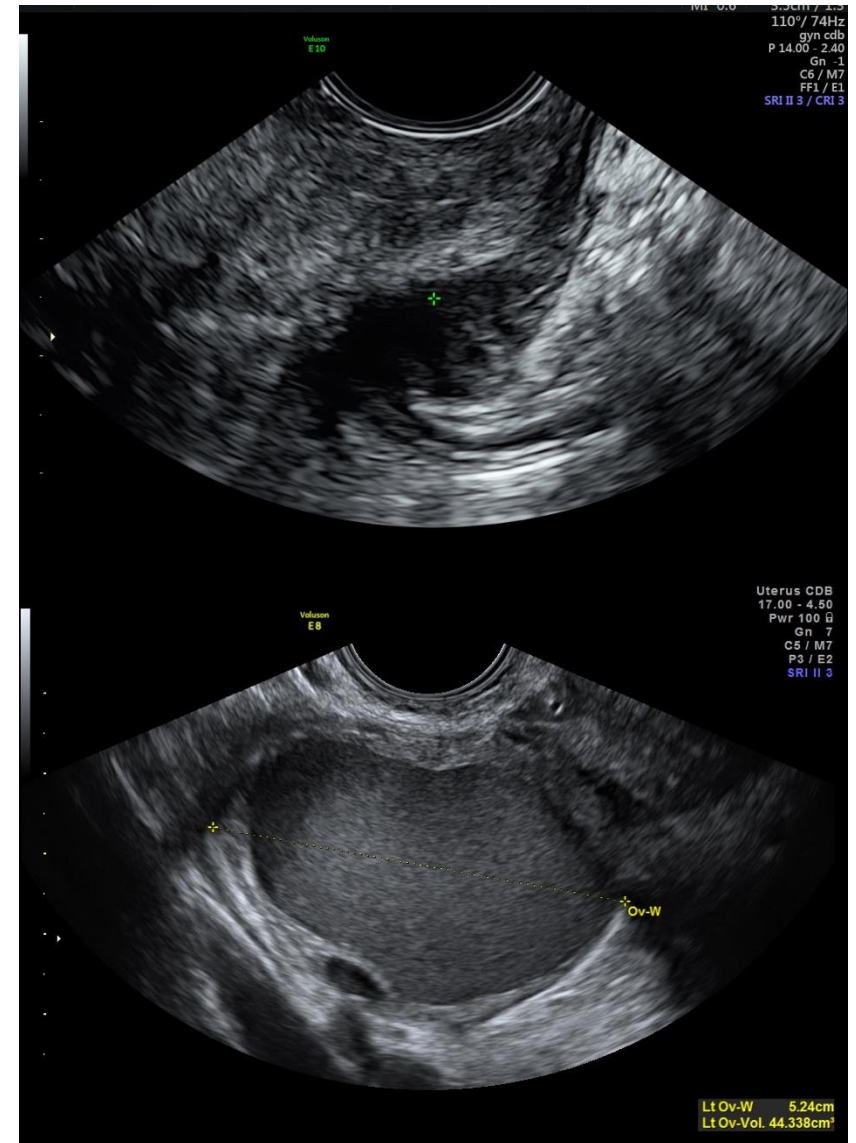
Ultrasound – expert

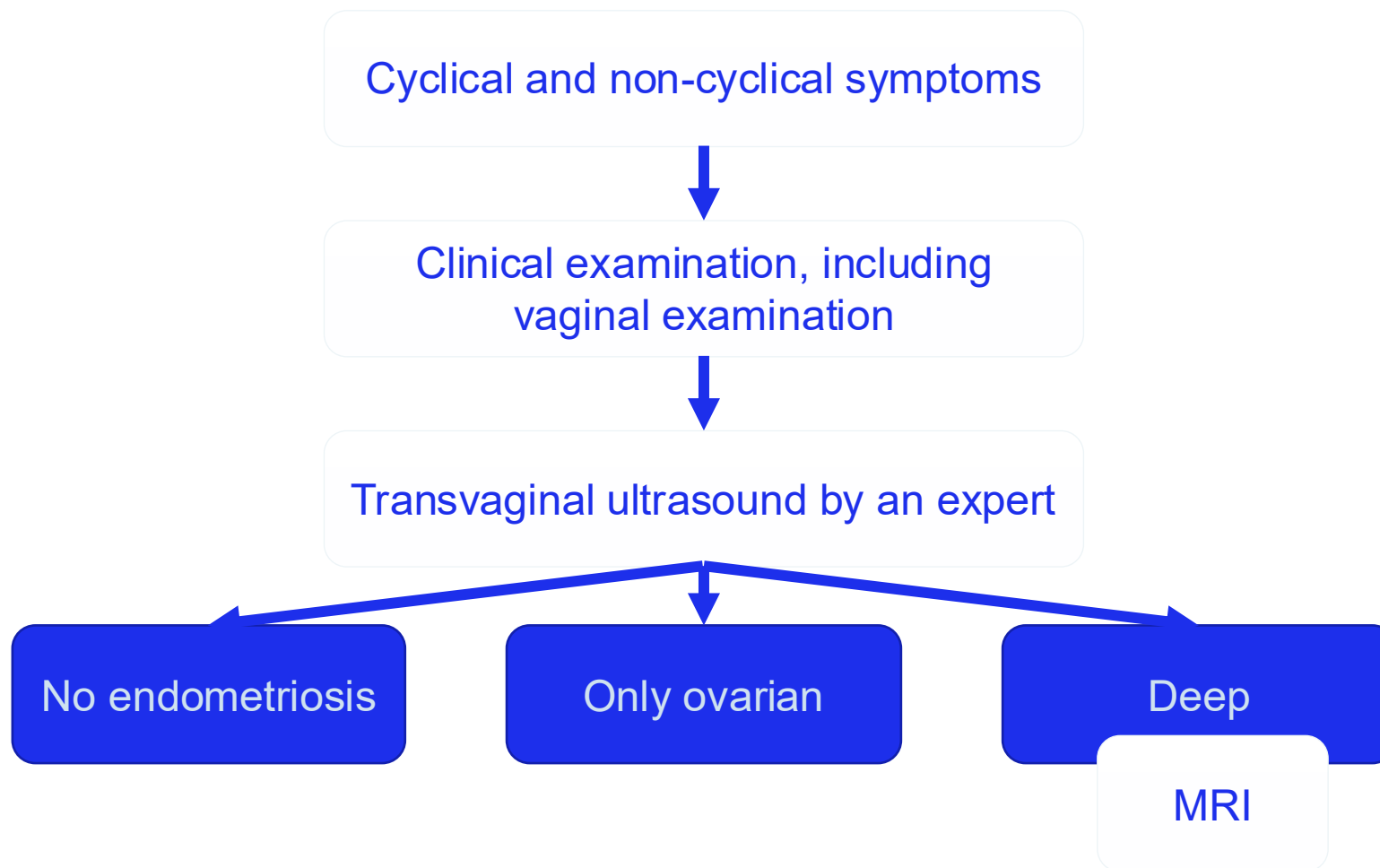
MRI Pelvic or specific regio

(Diagnostic laparoscopy)*

*in negative imaging results and/or empirical treatment not
unsuccessful/inappropriate

Laparoscopy \neq diagnostic golden standard





Ultrasound versus MRI



	TVUS		MRI	
	Sensitivity	Specificity	Sensitivity	Specificity
Superficial endometriosis	65%	95%	79%	72%
Ovarian endometriosis	93%	96%	95%	91%
Deep endometriosis	79%	94%	94%	77%
Rectosigmoid	90%	96%	90%	96%



Diagnostic laparoscopy if medical treatment is failing

CA 125

Table 2. Sensitivity analyses

	Studies	Endometriosis diagnosed/ controls	Sensitivity (95% CI)	Specificity (95% CI)	LR ⁺ (95% CI)	LR ⁻ (95% CI)	DOR (95% CI)
Cut-off level ≥ 30							
Total	14	1584/1336	52.4 (37.9–66.4)	92.7 (89.4–95.1)	7.2 (4.2–12.3)	0.5 (0.4–0.7)	14.0 (6.3–31.4)
Sensitivity analysis*	13	1353/807	51.8 (36.0–67.3)	93.0 (89.0–95.6)	7.4 (4.0–13.5)	0.5 (0.4–0.7)	14.2 (5.8–34.7)
Cut-off level < 30							
Total	6	331/221	58.1 (39.7–74.5)	79.4 (60.1–90.8)	2.8 (1.6–4.8)	0.5 (0.4–0.7)	5.3 (3–9.5)
Sensitivity analysis**	5	214/140	54.6 (33.6–74.2)	83.2 (67.8–92.1)	3.3 (2.0–5.4)	0.5 (0.4–0.8)	6 (3.1–11.3)

*Without Cho et al.⁹

**Without Vodolazkaia et al.¹¹

- Low sensitivity
- More increased in Stage III/IV (rARSM grading)
- Negative result does not rule out endometriose
- Elevated in other clinical situations: PID, pregnancy, ovarian cancer, ...



ENDOMETRIOSIS EDUCATION

A negative ultrasound does **NOT** rule out endometriosis

A normal scan may simply mean:

- Disease is superficial
- Disease is below current imaging resolution
- The scan was not dedicated to endometriosis
- The operator was not trained to look for it

Findings:
No sonographic evidence of endometriosis.

Negative imaging does not equal no disease.

Based on work by Mathew Leonardi, MD, PhD

ENDOMETRIOSIS EDUCATION 7/9

Never use a negative scan to dismiss symptoms

“A negative ultrasound should never invalidate patients or normalize symptoms.”

LISTEN BELIEVE VALIDATE

If the history fits, patients deserve to be **heard, investigated, and treated** — not told everything is ‘normal’.

Based on work by Mathew Leonardi, MD, PhD

ENDOMETRIOSIS EDUCATION

The take-home

- Ultrasound can **RULE ENDOMETRIOSIS IN.**
- Ultrasound cannot **RULE ENDOMETRIOSIS OUT.**
- Ask for a dedicated endometriosis ultrasound performed by someone trained to look for it.

IN ✓

OUT ✗

BETTER IMAGING. BETTER ANSWERS. BETTER CARE.

Based on work by Mathew Leonardi and colleagues
Selected works: Leonardi et al. 2020, 2022, 2024

Endometriomata

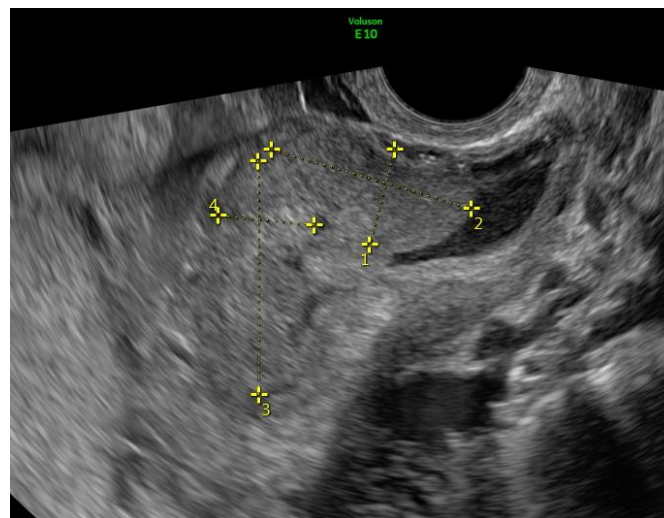
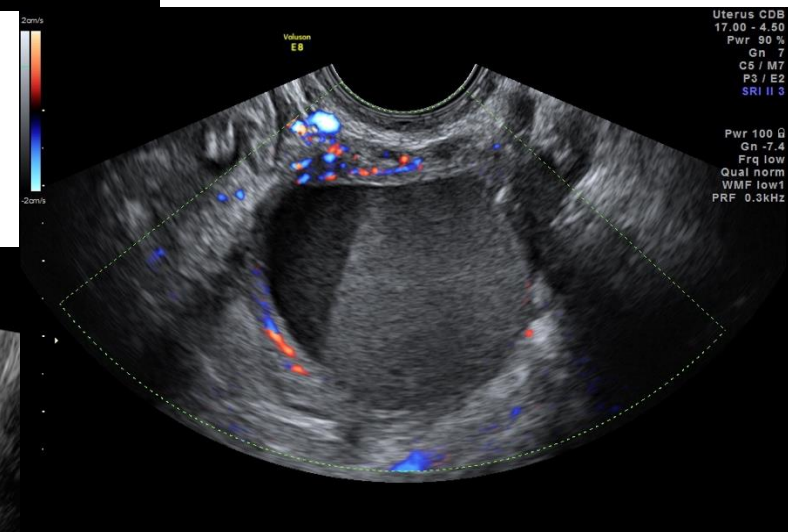
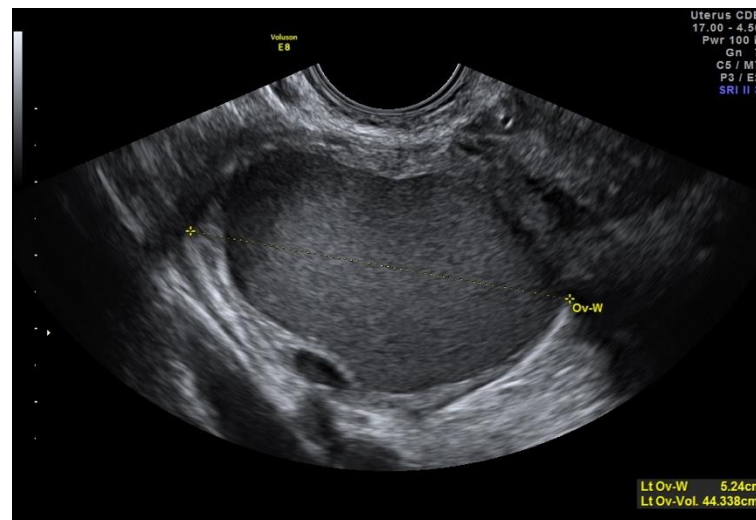
Typical

Atypical endometriomata

- unilocular-solid mass
- ground glass echogenicity
- 1 papillary projection
- colour score 1 or 2
- no flow in papillary projection

Decidualisation in pregnancy

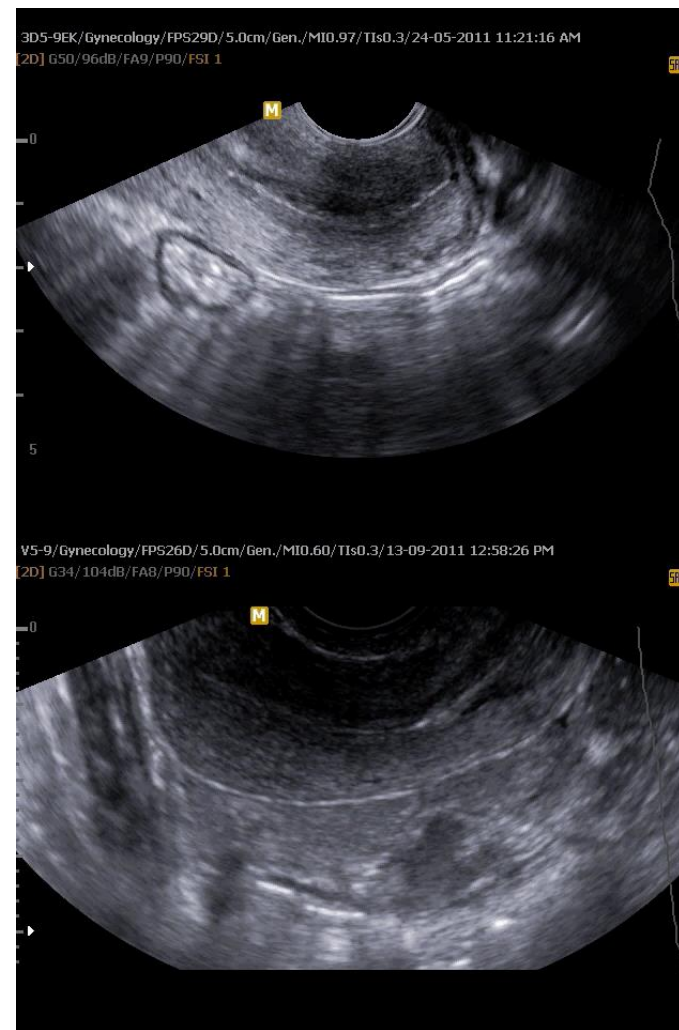
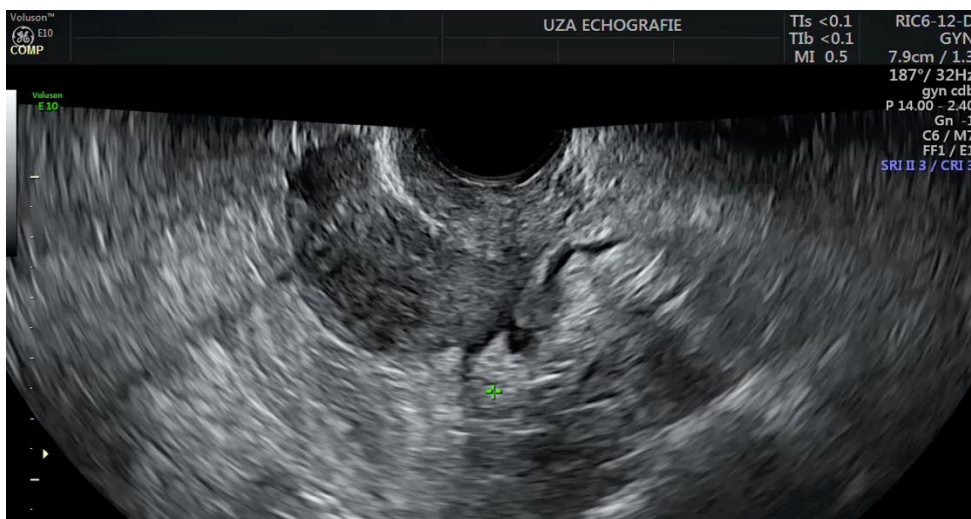
Malignisation



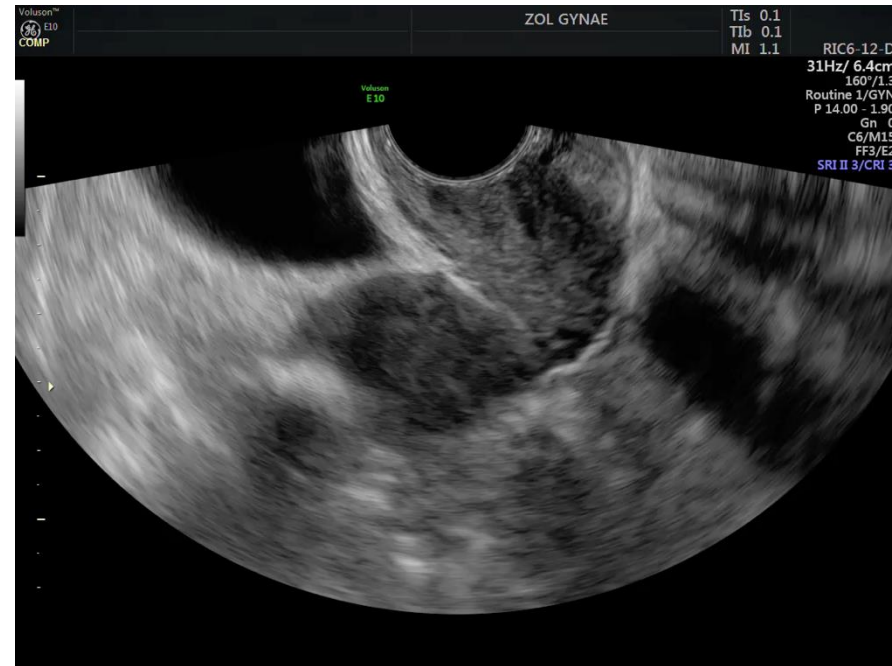
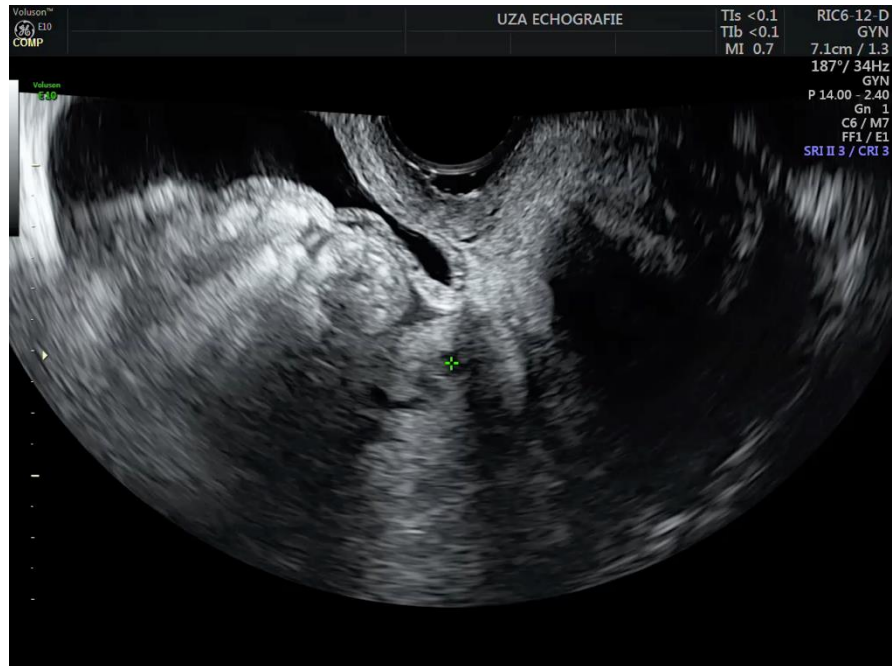
Sliding sign posterior compartment

Freely movement of the anterior rectal wall against posterior aspect of the cervix AND upper uterus AND fundus

- Presented: sliding sign posterior is positive, pouch of douglas is not obliterated



Sliding sign anterior compartment



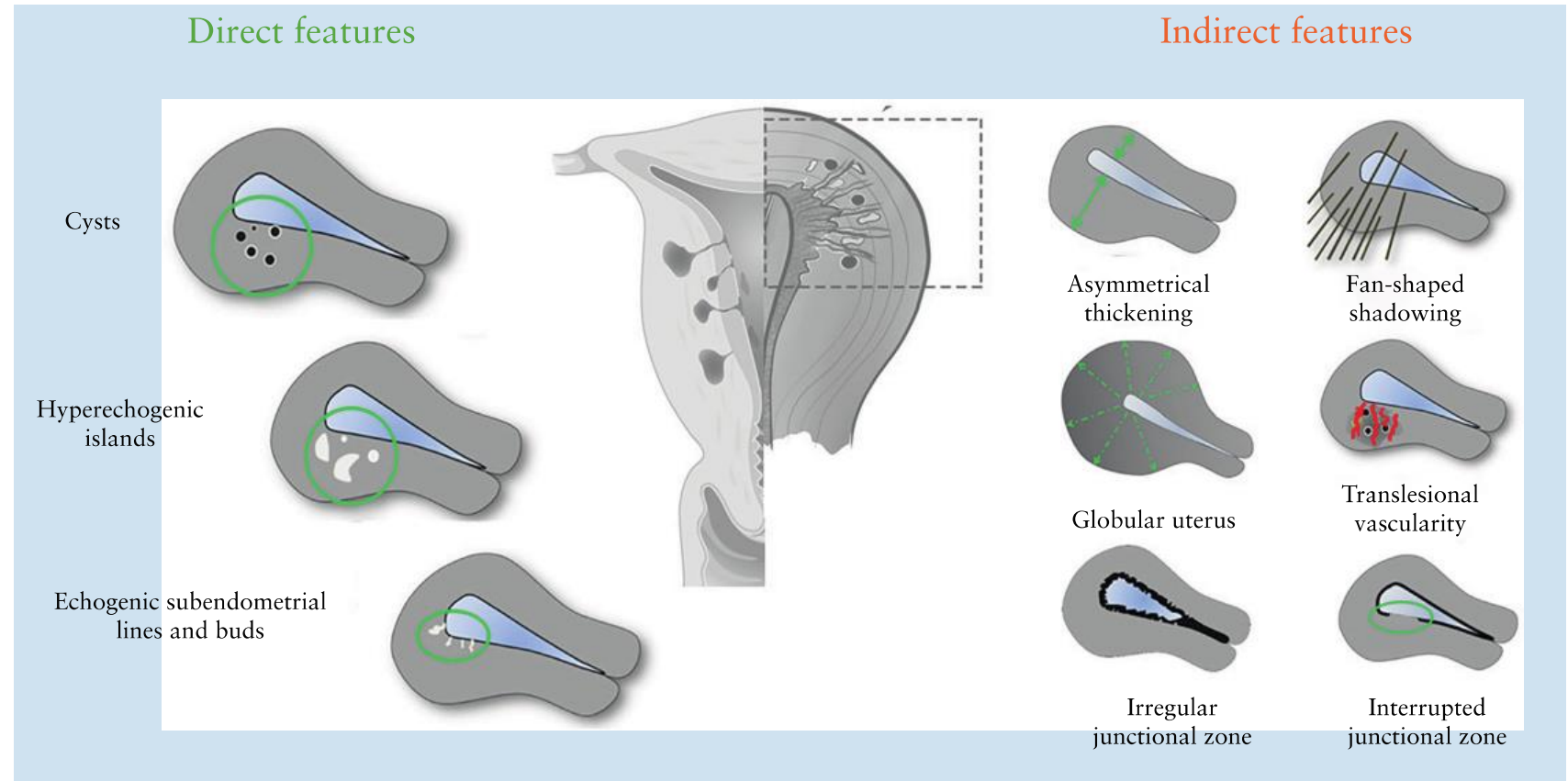
Adenomyosis

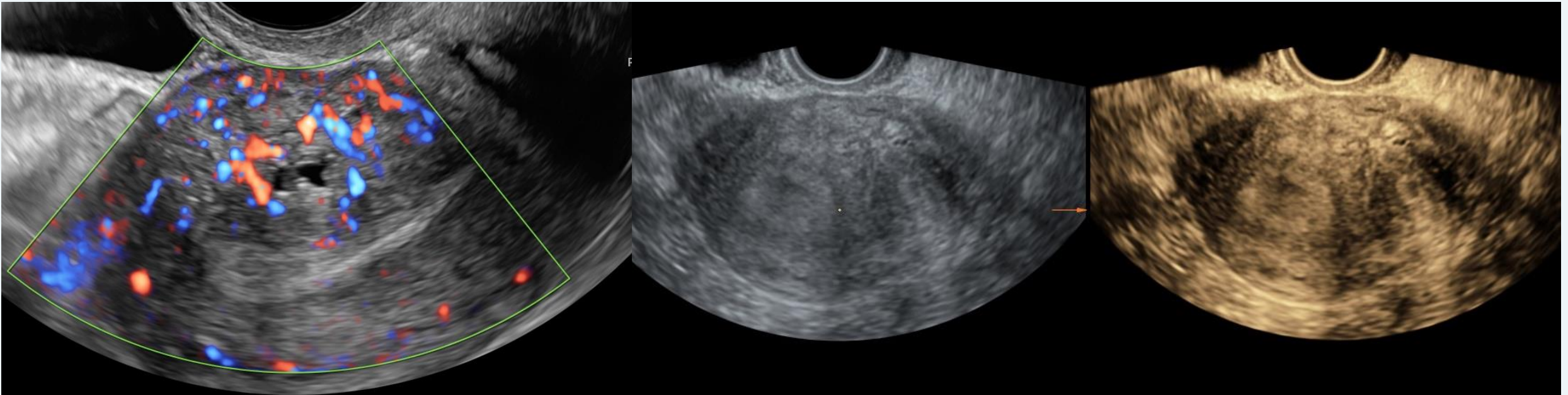
20% of women with
endometriosis

Abnormal uterine bleeding

- Menorrhagia
- Intermenstrual bleeding

Dysmenorrhoea





Multidisciplinary:
Gynaecologist, fertility specialist, Rectal surgeon, urologist

Hormones

Surgery

Progestogens

Combined Oral
anticonceptives (COC)

LNG-IUS

(GnRH analogen)

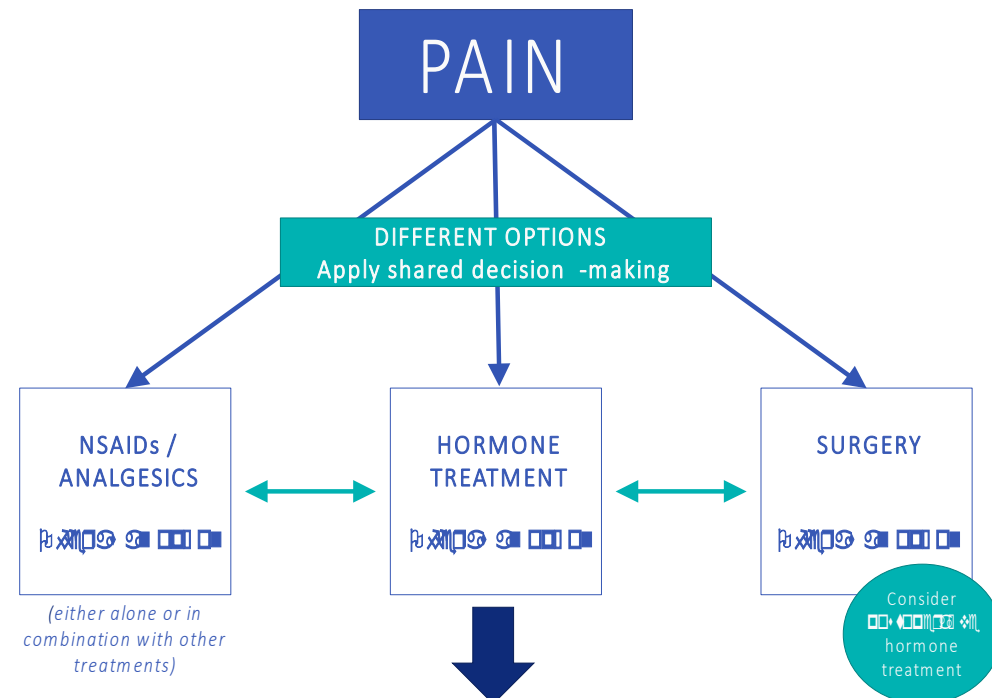
GnRH antagonisten

Preoperative preparation

- Echo/MRI
- hormones
- Ureters/rectum

Complete resection

Followed by hormones



Take individual preferences, ...

<p>...</p>	
<p>...</p>	<ul style="list-style-type: none"> Oral, vaginal ring, or transdermal ...
<p>Progestogens</p>	<ul style="list-style-type: none">
<p>GnRH agonists</p>	<ul style="list-style-type: none"> As second-line treatment, based on side-effects Consider combined hormone addback therapy to prevent bone loss and hypoestrogenic symptoms
<p>GnRH antagonists</p>	<ul style="list-style-type: none"> As second-line treatment Evidence for ... and the need for add-back therapy
<p>Aromatase inhibitors</p>	<ul style="list-style-type: none"> As second/third line treatment For pain, refractory to other medical or surgical treatment ...

NON-PHARMACOLOGICAL TREATMENTS FOR PAIN?
 Discuss non-medical strategies to address quality of life and well-being.

Kinesithérapie
 Psycholoog
 Osteopathie
 Pijnteam

Endometriosis recurrence

Prevention

- Surgery
 - Ovarian cystectomy, instead of drainage and electrocoagulation
 - CAVE! Risk of reduced ovarian reserve
 - Medical therapy:
 - Pain recurrence: RR 0.7 (95%CI: 0.47-1.03)
 - Disease recurrence: RR 0.4 (95%CI: 0.27-0.58)
- no evidence to support particular treatments over others
- expert-opinion
1. Combined oral contraceptives (continuous) or Progestins
 2. LNG-IUS

Shared decision making

Impact of endometriosis on pregnancy

Possible complications during pregnancy from pre-existing endometriosis lesions

→ RARE/case reports – underreported

- Endometrioma: infection, enlarged, rupture, (torsion)
- Intestinal: perforation (decidualisation, scar tissue)
- Urinary: hematuria
- Uterus: rupture
- Spontaneous hemoperitoneum in Pregnancy (SHiP)

Impact of endometriosis on pregnancy

Miscarriage: OR 1.3 (95%CI: 1.25-1.35)

Ectopic pregnancy: OR 2.16 – 2.66

Gestational diabetes: conflicting results

Preterm birth/PPROM: OR 1.7 (95%CI: 1.4-2.06) and OR 2.33 (95%CI: 1.39-3.9), respectively. In both natural conception and ART

Placenta praevia: OR 3.09 (95%CI: 2.04-4.68) → Abnormal frequency and amplitude of uterine contractions

Hypertension/pre-eclampsia: probably increased risk: OR 1.18 (95%CI: 1.03-1.36)

Stillbirth: OR 1.25 (95% CI: 1.08-1.45)

Caesarean section: OR 1.98 (95%CI: 1.64-2.38)

Placental abruption: OR 1.87 (95%CI: 1.65-2.13)

IUGR: OR 1.28 (95%CI: 1.11-1.49)

Endometriosis and menopause

Can be still active/symptomatic after menopause: 4%

- Due to hormone therapy, extra-ovarian estrogen (e.g. fat tissue)

Treatment options

1. Surgery
2. Medications: Aromatase inhibitors (e.g. letrozol)

Hormonal substitution in menopause: not estrogen-only regimens → higher risk of malignant transformation

Risk of ovarian cancer: +1.2%

- Clear cell ovarian cancer: SRR 3.44
- Endometrioid ovarian cancer: SRR 2.33

Hormonale behandeling



De pil en de stemming

Depressieve klachten of stemmingswisselingen bij 1-10% van pilgebruikster
MAAR ook bij 1-10% in de controle groep

Swich naar low-dose POP of hormoonspiraal weinig verschil

Voorkeur voor condoom, koperspiraal gebruik

Wat met dat libido?

Verschillende factoren die invloed hebben op libido

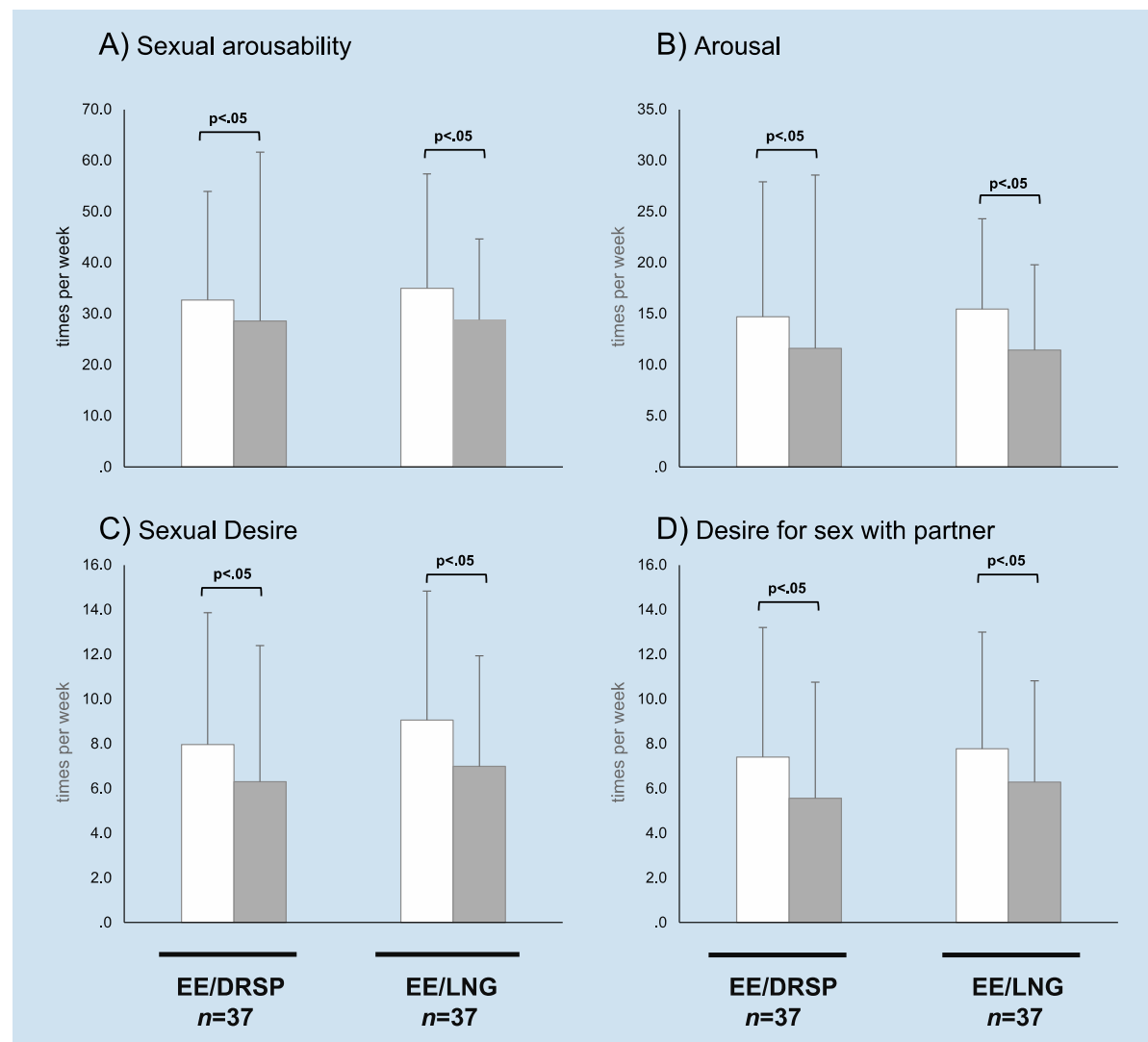
→ COC is er een van de vele

Switch tussen methoden? “Natuurlijke E2”?

Andere methode geen studie gegevens
ev. LARC (koper IUD)

Seksuoloog/informeren/ ...

Androgeen suppletie? → effect op libido beperkt



Contraceptie

Zwangerschapskansen

Pil amenorree \approx normaal

tgV progestageen en te lage dosis oestrogeen
voorbijgaand

Persisterende amenorree na pil stop = 0,8% = incidentie van amenorree in niet
pilgebruiksters

Herstarten van cyclus kan wel enkele maanden duren soms.

tgV transiënte stijging van AMH na pilstop tgV hernemen
follikelrekrutering

vertraging in conceptietijd uitgedrukt in
menstruatrice cycli na het stoppen van de
methode vergeleken met barrièremethoden:

-prikpil: 5-8

-pleister: 4

-combinatiepil 3

-hormoon / koperspiraal: 2

(BMJ.2020;371:m3966)

Contraceptie

Combinatiepil

Doorbraakbloedingen

tgV relatief te laag oestrogeen

NIET 2 pilen/dag

Eventueel switch naar hoger dosis EE (van 20 μ gr naar 30 μ gr)

Eventueel acuut 2mg oestradiolvaleraat toevoegen

Eventueel van 21+7 schema naar 24+4 schema gaan

Denk aan andere pathologie: chlamydia, ectropion, fibroom, carcinoom

Contraceptie

Progesteron only methoden

20% amenoree, 40% onregelmatige bloeding, 40% cyclisch bloedverlies (min. 3 mnd nemen)

Bijwerkingen: acne, bloating, stemming, libidoverlies (min. 3 mnd nemen)

⚠️ Prikpil ⚠️

- Gewichtstoename van 2-3 kg
- Herstel van fertiliteit: 6-12 maanden
- Spotting!

E2 1 mg 10-21d
COC ged 1-3 mnd
Doxycyline 100mg
2dd ged 5d

Bloedingsprofiel

Klinische factoren die bloedingsprofiel beïnvloeden

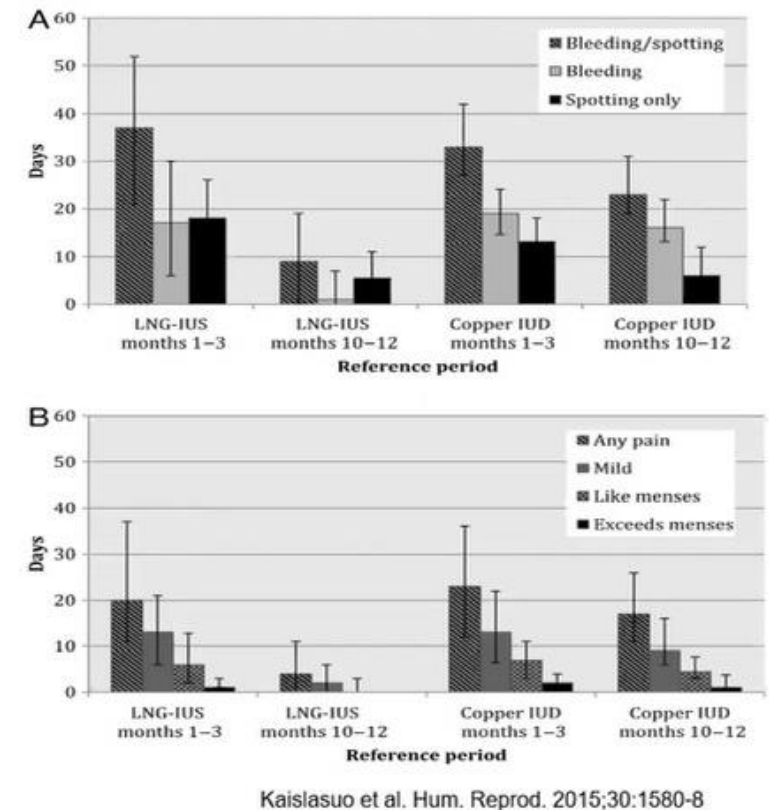
- Grootte van uterus
- Aanwezigheid van goedaardige uterine pathologie vb. myomen, adenomyosis, poliep
- Verhoogde bloedingsneiging
- BMI

EE 30µgr geeft sneller bloedingscontrole dan EE 20µgr

E2/E4 meer tussentijds bloedverlies bij opstart dan EE

POP meer tussentijdsbloedverlies dan EE+Prog

Koperspiraal meer bloeding en tussentijds bloedverlies



Thrombose risico

Enkele algemene regels ...

Hoe hoger de dosis EE, hoe hoger risico op arteriële en veneuze thrombose
(50 μ g versus 20 μ g – factor 2)

Risico op trombose neemt toe met aanwezigheid van andere risicofactoren
Roken (7x), obesitas (2x), leeftijd (5x), hypertensie (10x), trombofilie* (11x)

Levonorgestrel (2^{de} generatie) < 3^{de} generatie, drospiridon, cyproteron acetaat (x1,5-2)

Meer bij orale dan bij pleister of vaginale ring – first pass effect op lever?????

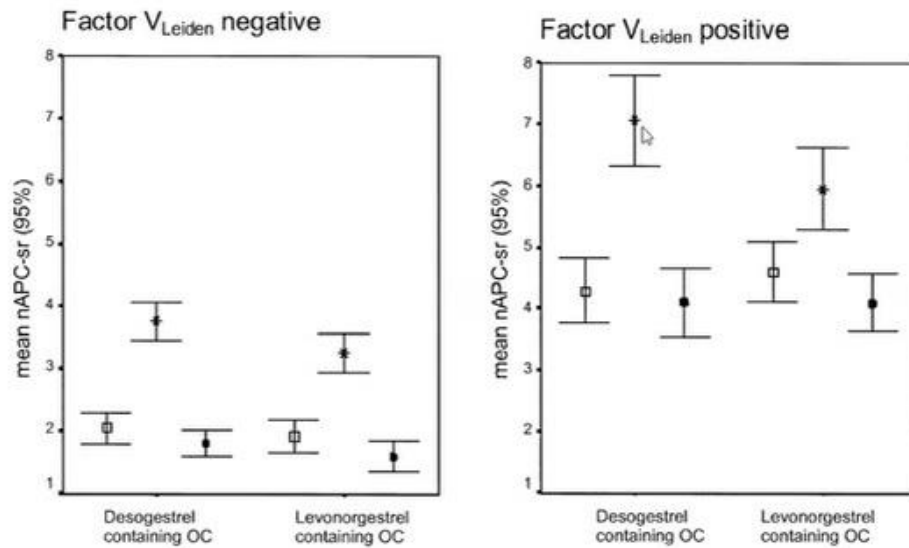
Voornamelijk tijdens 1^{ste} jaar, neemt niet verder toe bij langdurige gebruik

Starten/stoppen van pil is risico op trombose ← Endometriose patiënten!

Nieuwe generatie van oestrogenen (E2/E4)?

* Trombofilie:
Factor V Leiden,
prot S, Prot C,
antithrombine III
def, prothrombine
mutatie

Low dose POP
Levonorgestrel IUD



Kemmeren *et al.* Blood 2004;103:927-33

Table Serum concentrations (medium value [range]) of SHBG and plasma levels of hemostatic markers during COC use

	Baseline	LNG/EE	DG/EE	LNG/EE vs DG/EE
SHBG (nmol/L)	46.3 (21.9-96.4)	72.4 (31.4-115) <i>P</i> < .0001	175 (92.8-318) <i>P</i> < .0001	<i>P</i> < .0001
Fibrinogen (g/L)	3.63 (2.33-5.52)	3.77 (2.54-6.86) NS	4.15 (3.21-6.50) <i>P</i> < .001	<i>P</i> < .05
Antithrombin activity (%)	100 (79-118)	97 (71-106)	94 (68-114)	NS
APC ratio	3.40 (1.80-4.10)	3.20 (1.90-4.10) <i>P</i> < .05	3.00 (1.70-3.80) <i>P</i> < .0005	<i>P</i> < .005
Protein S, free (%)	73.0 (52.4-91.6)	80.2 (59.8-108.3) <i>P</i> < .01	66.2 (43.7-79.2) <i>P</i> < .001	<i>P</i> < .001
Fragment 1+2 (nmol/L)	0.60 (0.27-1.58)	0.74 (0.51-1.72) <i>P</i> < .001	0.83 (0.50-1.35) <i>P</i> < .001	NS
tPA antigen (IU/mL)	6.33 (2.80-13.6)	3.50 (1.95-8.47) <i>P</i> < .001	3.83 (1.97-7.06) <i>P</i> < .001	NS
PAI-1 activity* (IU/mL)	5.71 (0.92-66.8)	0.85 (0.32-18.1) <i>P</i> < .0001	0.81 (0.05-13.3) <i>P</i> < .0001	NS
PAP (μg/L)	269 (146-765)	556 (237-1187) <i>P</i> < .005	488 (266-1204) <i>P</i> < .0001	NS
TAFI activity (μg/mL)	8.04 (1.98-12.7)	9.11 (2.98-16.3) NS	9.70 (3.49-14.3) <i>P</i> < .005	NS

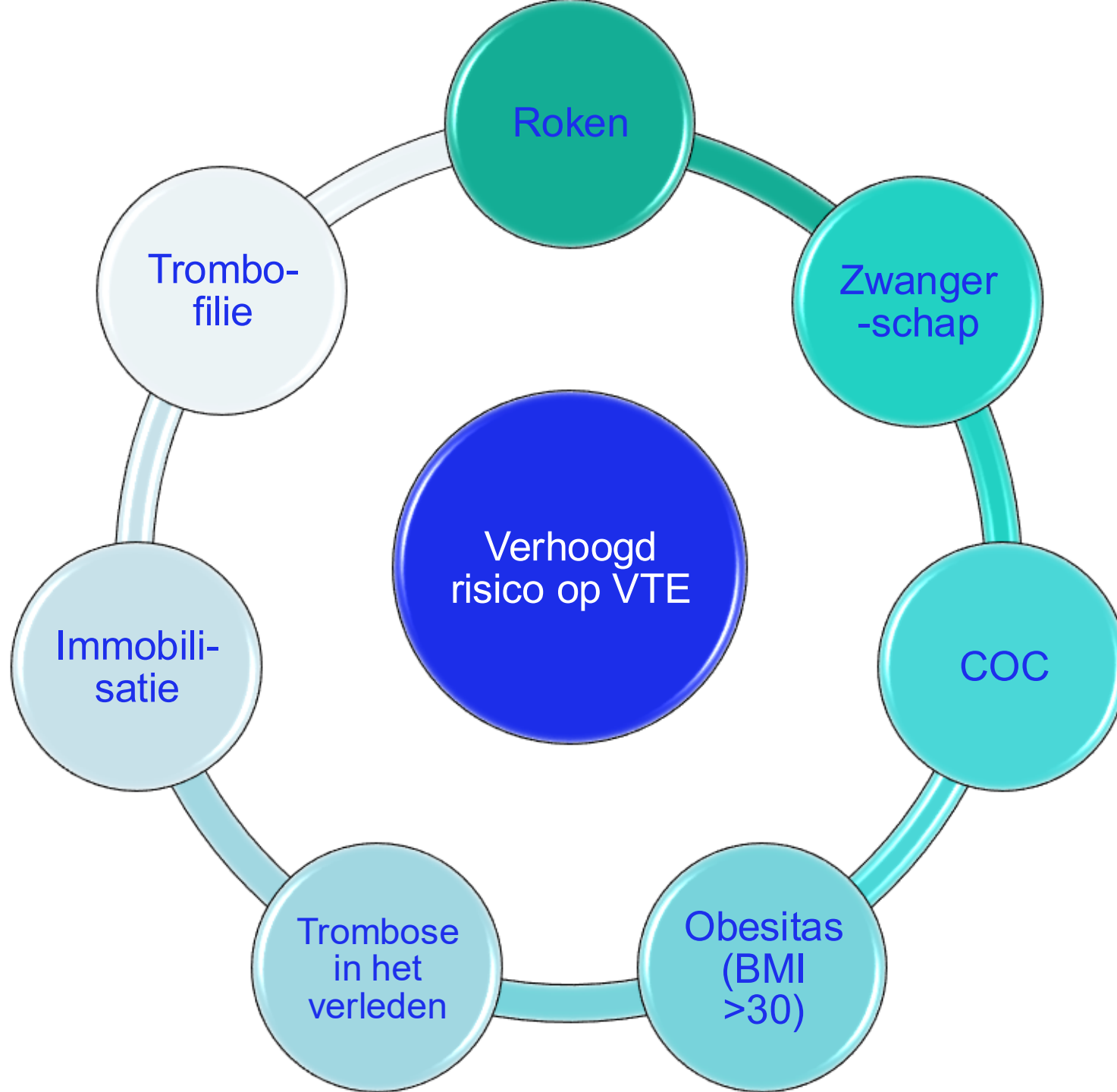
SHBG, Sex hormone-binding globulin; COC, combined oral contraceptives; DG, desogestrel; EE, ethinylestradiol; LNG, levonorgestrel; APC, activated protein C, tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor 1; PAP, plasmin antiplasmin complex; TAFI, thrombin activatable fibrinolysis inhibitor.

* Statistical differences calculated on log-transformed values. *P* values denote differences between treatment and baseline and between the 2 treatments.

Trombose risico

In perspectief ...

	VTE/10.000 vrouwen/jaar
Basisrisico (niet zwanger, geen pil gebruik)	1-5
Pil gebruik	10-15
EE + Levonorgestrel	5-7
EE + drospirenone of gestodene	9-12
EE + dienogest	8-11
E2 valeraat + dienogest	3-4
Zwangerschap	5-20
Postpartum (6-12 weken)	40-65



**Counseling over tekenen en
symptomen van VTE/ ateriële
thrombose zonder angst te
creeëren**

Dysmenorree

Sport
Warmte
NSAID's: inhibitie van PG actie
COC: inhibitie van productie van Progesterone

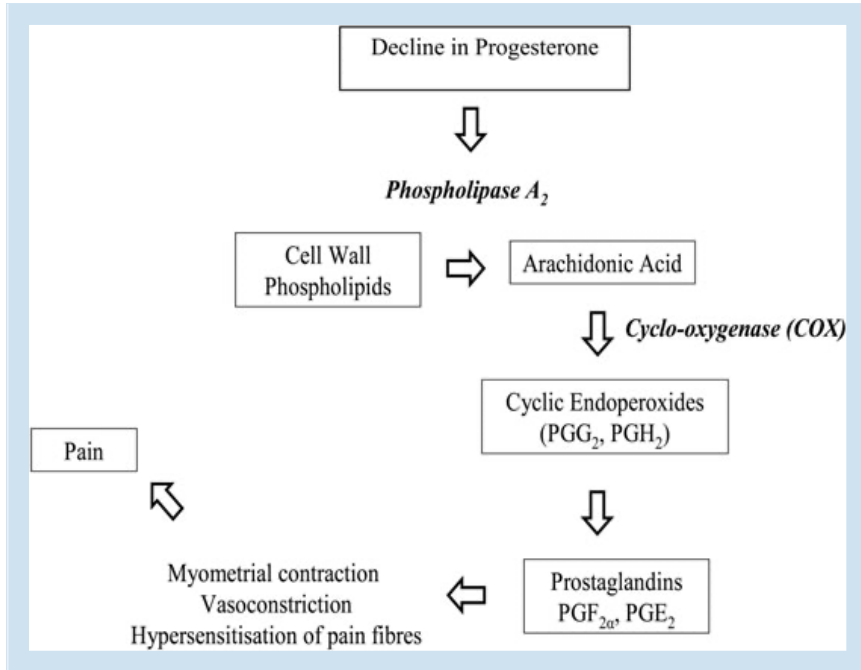
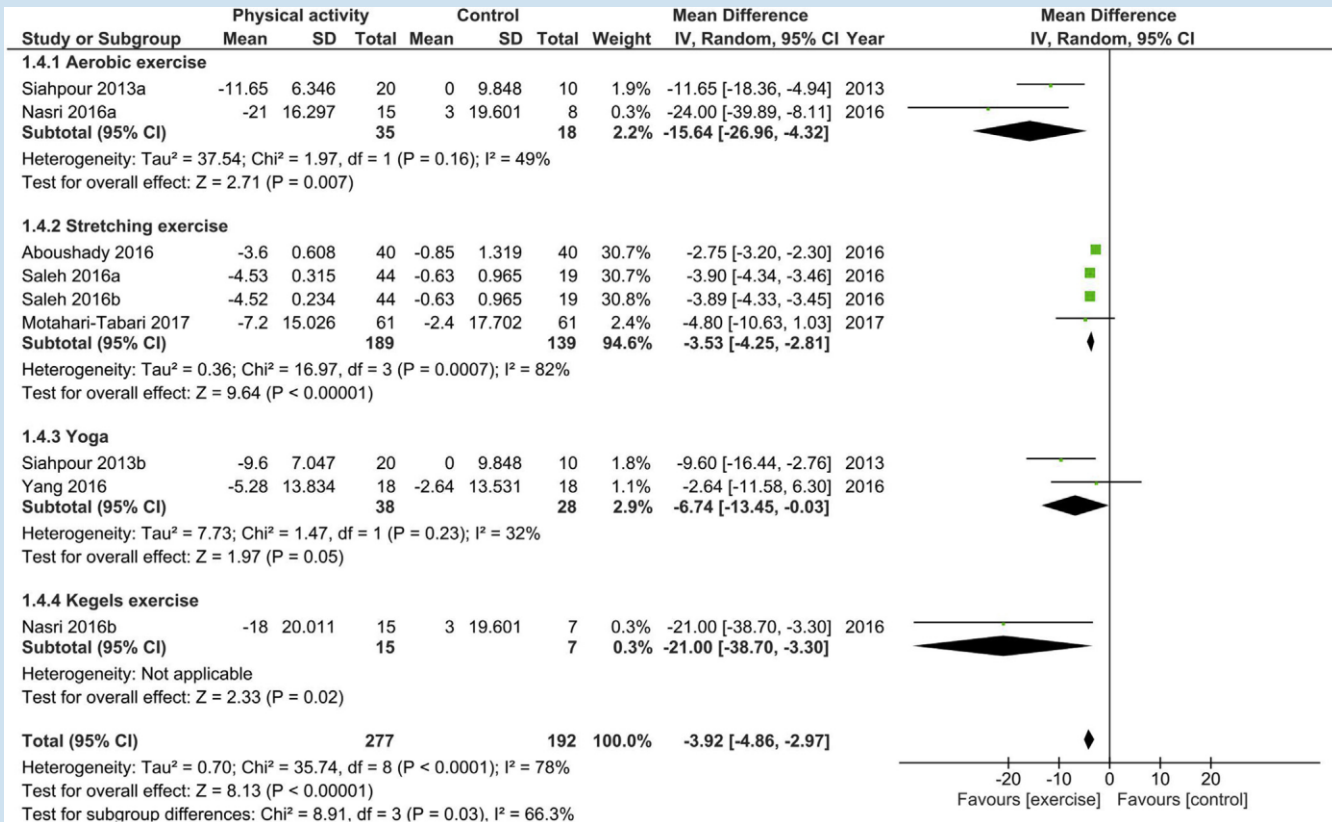


FIGURE 2
Pain duration meta-analysis



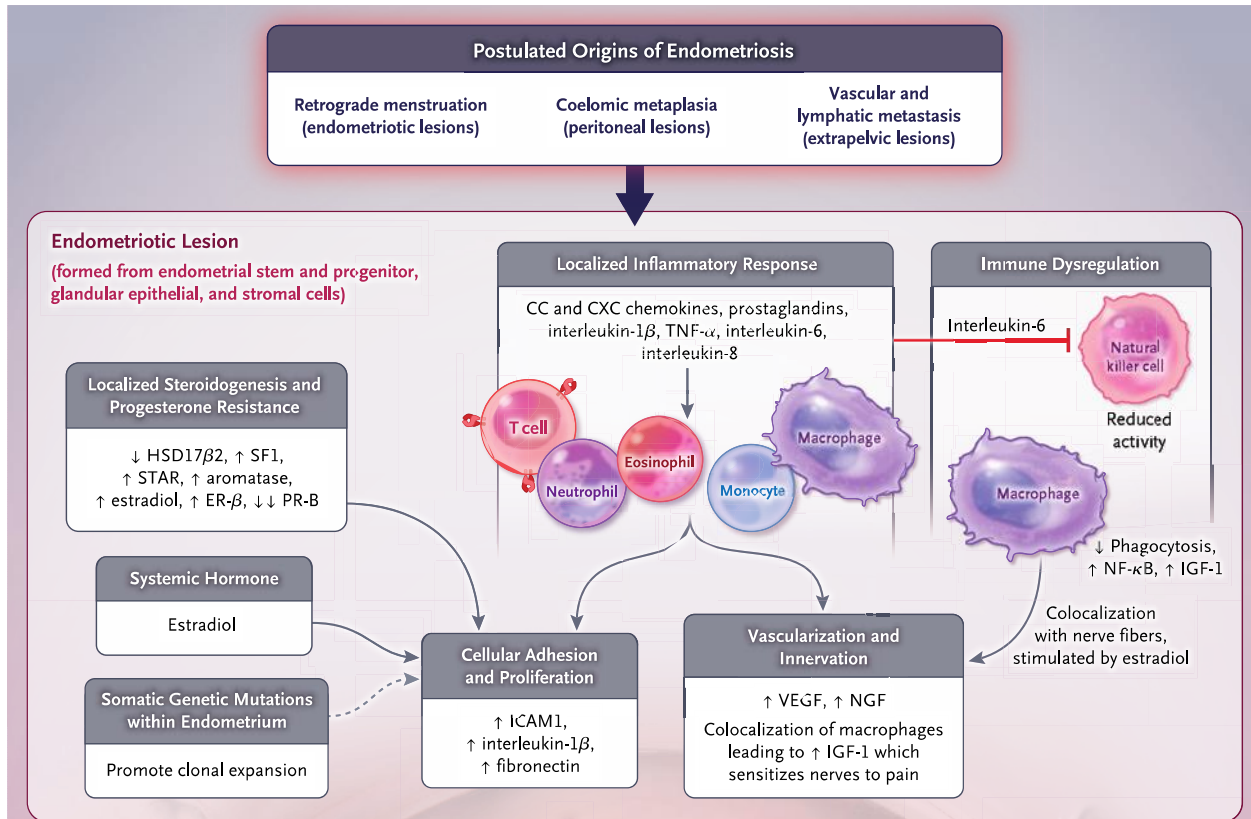
Iacovides e.a. 2015 Hum Reprod Update
Matthewman e.a. 2018 Am. J. Obstet Gynecol

Random effects meta-analysis of pain duration in hours.

CI, confidence interval.

Matthewman. Physical activity for primary dysmenorrhea. Am J Obstet Gynecol 2018.

Endometriose



Zondervan e.a. NEJM 2020

Type of Hormonal Medication	Application	Possible Side Effects [#]
Short Acting Progestins	Daily oral pill	Changes in bleeding pattern, skin changes, bloating, nausea, changes in appetite, mood disturbances, breast tenderness, headaches
Delayed release progestins	Subcutaneous implant, Intramuscular injection, Intrauterine contraceptive device	Changes in bleeding pattern, skin changes, bloating, mood disturbances, weight gain, headaches, loss of bone density*
Progestin only oral contraceptive pill	Daily oral pill	Changes in bleeding pattern, skin changes, bloating, changes in appetite, mood disturbances, headaches, breast tenderness
Combined oral contraceptives	Daily oral pill for 28 days with 4-7 day break or continuous daily intake	Changes in bleeding pattern**, skin changes, bloating, mood disturbances, migraines, thromboembolic events, stroke
Gonadotropin releasing hormone agonists [#]	Monthly or tri-monthly subcutaneous injection	Menopausal symptoms, bone loss, headaches, mood change
Gonadotropin releasing hormone antagonist [#]	Daily oral pill	Menopausal symptoms, bone loss, headaches, mood change
Aromatase inhibitors [#]	Daily oral pill	Development of ovarian cysts, multiple pregnancy, menopausal symptoms, bone loss

* Depot provera injections or medroxyprogesterone acetate; ** Breakthrough bleeding with continuous use;

*** Long term use combined with hormone replacement therapy (HRT); [#] Not an inclusive list