

New trend in endometriosis treatment

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(SY32) 2021/09/25 Sat. 1530-1600

大綱

Part 1 Review of endometriosis

Part 2 Experience of Dienogest

110年度TAOG學會專用

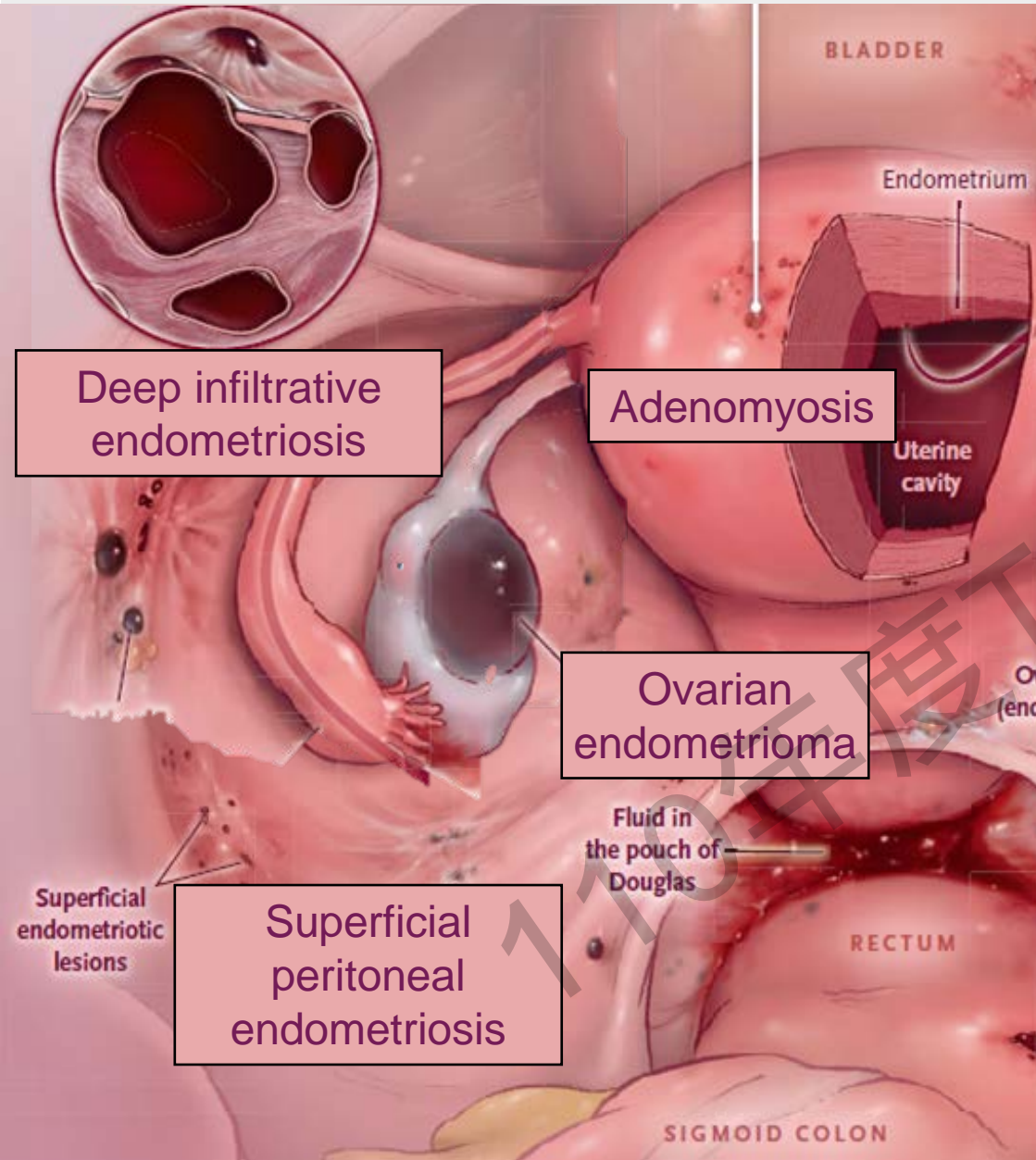
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Part 1 Review of endometriosis

Part 2 Experience of Dienogest

110年度TAOG年會專用

Endometriosis



Definition:

Endometrial tissue outside endometrium

Prevalence:

10% of all reproductive age women

50% **infertile** women

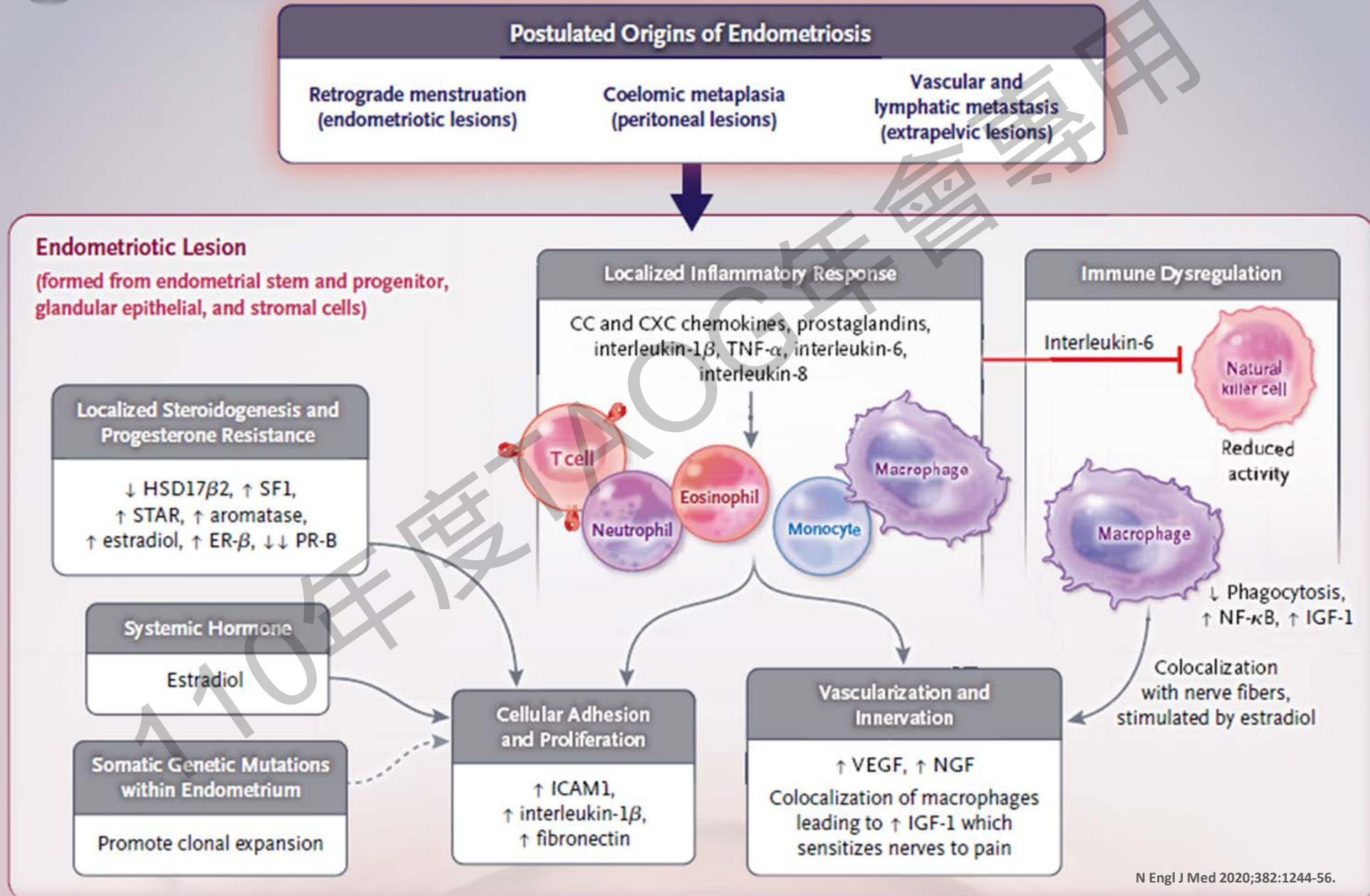
20% pelvic **pain** women

Symptoms:

Pain: Chronic pelvic pain, dysmenorrhea, dyspareunia...

Infertility

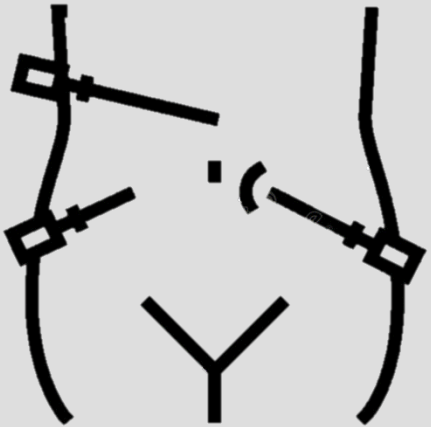
Pathogenesis



Diagnosis of endometriosis

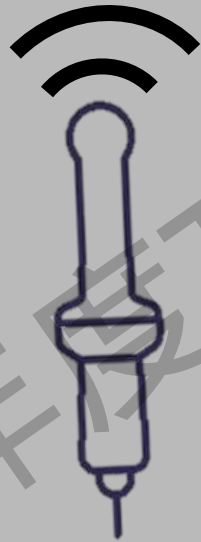
Laparoscopy

Gold standard



Ultrasound

Good at
endometrioma or
DIE



MRI

Good; no cost
effectiveness



History / PE



Delayed diagnosis due to non-specific symptoms, no specific bio markers...

Before

Management

Practice Committee of the ASRM :

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**.

Fertil Steril 2014;101:927–35

Medical treatment not curative but **suppressive**

Recurrent symptoms around 50% of over a period of 5 years, irrespective of the treatment approach.

Management



Medical treatment

- Non-hormone therapy, NSAID
- Hormonal therapy: COC, Progestin, GnRH agonist/ antagonist, others

Surgical treatment

- Medical treatment failure
- Surgical treatment of endometrioma
- Surgical treatment of DIE

Post operative medical treatment

- Post operation medical therapy for prevention recurrence

Management - pros and cons of Mx

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Medical treatment for pelvic pain in endometriosis

Advantages
Avoids risk of damaging pelvic organs during surgery
Avoids risk of postoperative adhesion formation
Treats implants not visualized during surgery
Disadvantages
Side effects of medications
High recurrence rates after discontinuation
No effect on existing adhesions
No effect on endometriomas
Treatments involving suppression of ovulation also prevent pregnancy during the treatment period
No effect on infertility

Medical treatment Non-hormonal therapy

Nonsteroidal anti-inflammatory drugs(NSAID)

NICE : short trial (for example, 3 months) of paracetamol or a NSAID

ESHRE : recommends considering use

ASRM : 1st line

WES : empirical 1st line as well as other analgesia and COC

AEs



Cochrane Database of Systematic Reviews

Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis (Review)

2017

Only 1 trial, endometriosis: Compare Naproxen to placebo
No clear evidence to endometriosis
Effective for primary dysmenorrhea

Medical treatment Non-hormonal therapy

Table 1. Investigated drugs for the treatment of endometriosis.

	Class	Drugs	Most advanced study
Hormonal treatment	GnRH antagonist	Cetrorelix ⁽¹⁾ , elagolix ⁽²⁾	III ^(1,2)
	Aromatase inhibitors	Anastrozole ⁽¹⁾ , letrozole ⁽²⁾	III ^(1,2)
	SERM	Bezedoxifene ⁽¹⁾ , raloxifene ⁽²⁾	II ^(1,2)
	SPRM	Mifepristone ⁽¹⁾ , anoprisnil ⁽²⁾	II ^(1,2)
Anti-angiogenic drugs	Anti-VEGF	Bevacizumab ⁽¹⁾	Animal model ⁽¹⁾
	TKIs	Sunitib ⁽¹⁾ , Sorafenib ⁽²⁾ , Pazopanib ⁽³⁾	Animal model ^(1,2,3)
	mTOR	Rapamycin ⁽¹⁾ , Temsirolimus ⁽²⁾ , Everolimus ⁽³⁾	Animal model ^(1,2,3)
	Dopamine agonists	Cabergoline ⁽¹⁾ , quinagolide ⁽²⁾	II ^(1,2)
	Others	TNP-470 ⁽¹⁾	Animal model ⁽¹⁾
Anti-inflammatory	COX-2 inhibitors	Parecoxib ⁽¹⁾ , celecoxib ⁽²⁾	Animal model ^(1,2)
	Anti TNF- α	Etanercept ⁽¹⁾ , infliximab ⁽²⁾ , TNFRSF1A ⁽³⁾ and c5N ⁽⁴⁾	Animal model ^(1,3,4) , phase II ⁽²⁾
	MAPK inhibitors	SB203580 ⁽¹⁾ , FR167,653 ⁽²⁾	Animal model ^(1,2)
Immunomodulators	NfKb inhibitors	I κ B protease inhibitor (TPCK) ⁽¹⁾ , BAY 11-7085 ⁽²⁾ , urinary preparation of human chorionic gonadotropin A (hCG-A) ⁽³⁾ , pyrrolidinedithiocarbamate (PDTC) ⁽⁴⁾ , costunolide ⁽⁵⁾ , curcumin ⁽⁶⁾ ,	Animal model ^(1,2,3,4,5,6) , I-II ⁽⁷⁾
		DLBS1442 ⁽¹⁾ , imiquimod ⁽²⁾ , bentamapimod ⁽³⁾ , V-endo ⁽⁴⁾	Animal model ^(1,2,3) , I-II ⁽⁴⁾
Antioxidants drugs	Statins	Endostatin ⁽¹⁾ , simvastatin ⁽²⁾ , atorvastatin ⁽³⁾ , rosuvastatin ⁽⁴⁾	Animal model ^(1,2,3,4)
	Antidiabetic drugs	Metformin ⁽¹⁾ , ciglitazone ⁽²⁾ , pioglitazone ⁽³⁾ , rosiglitazone ⁽⁴⁾	Animal model ^(1,2,3,4)
	Vitamins	Elocalcitol (Vit D) ⁽¹⁾ , retinoic acid (Vit A)	Animal model ^(1,2)
	Other antioxidants	Omega-3 fatty acids ⁽¹⁾ , N-acetylcysteine ⁽²⁾ , α -lipoic acid ⁽³⁾	Animal model ^(1,3) , II ⁽²⁾
	Epigenetic drugs	Histone deacetylase inhibitors	Trichostatin A ⁽¹⁾ , valproic acid ⁽²⁾

GnRH: gonadotropin releasing hormone; SERM: selective estrogen receptor modulator; SPRM: selective progesterone receptor modulator; NfKb: nuclear factor κ B; MAPK: Mitogen-activated protein kinase

Estrogen :
negative feed-back
X ovulation

Progestin :
X ovary steroidogenesis
endometrium implants
decidualization
atrophy
apoptosis

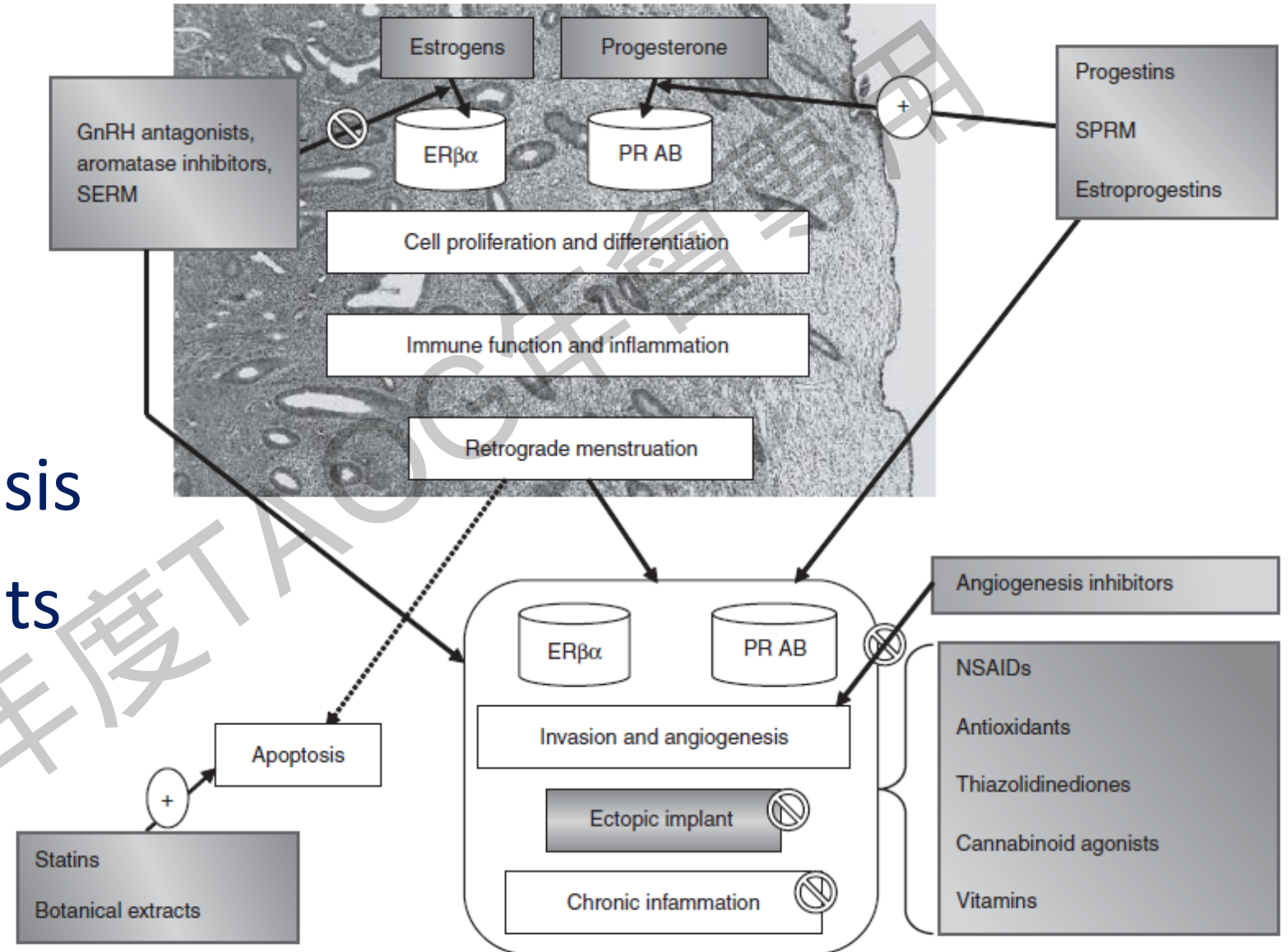
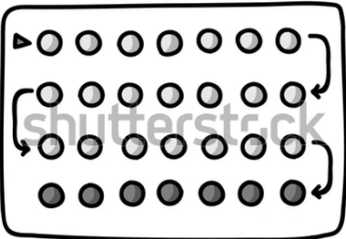


Figure 1. Pathogenesis of endometriosis and mechanisms of action of new treatments.

Medical treatment

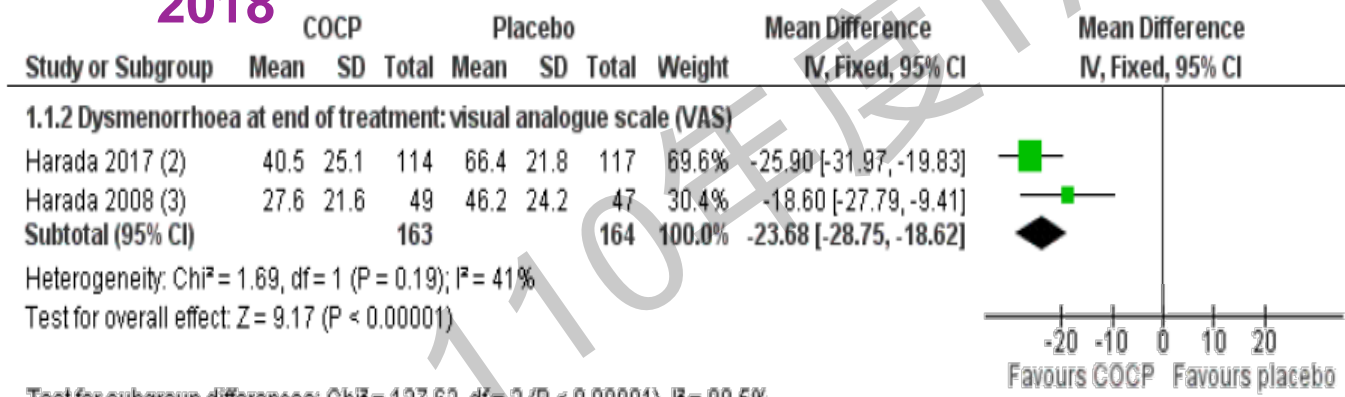
Hormonal therapy - COC



1st line hormone therapy; No one COC better than another
 Begin with low dose 20~30mcg ethinyl estradiol, continuous use > cyclic use



Two trials, 354 women, COC v.s placebo, **improvement** in self-reported dysmenorrhea



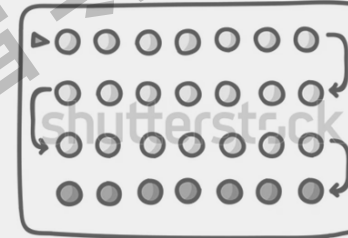
Medical treatment Hormonal therapy - COC

Human Reproduction, Vol.26, No.8 pp. 2028–2035, 2011

Advanced Access publication on June 4, 2011 doi:10.1093/humrep/der156

human
reproduction

ORIGINAL ARTICLE *Gynaecology*



Past COC user for primary dysmenorrhea
=> ↑ endometriosis and ↑ DIE

5mcg EE ~ 0.625 mg CEE ~ 1mg micronized estradiol
20-30 mcg EE => 4-6 X physiology estrogen
Supraphysiology estrogen



IEWS AND REVIEWS | VOLUME 107, ISSUE 3, P533-536, MARCH 01, 2017

Progestin-only pills may be better first-line treatment than COC for endometriosis

Robert F. Casper, M.D.  

Published: February 02, 2017 • DOI: <https://doi.org/10.1016/j.fertnstert.2017.01.003>



Medical treatment

Hormonal therapy - Progestins

Norethisterone acetate (NETA)

Dienogest

Levonorgestrel (LNG-IUS)

Medroxyprogesterone acetate

Proved to be effective,
NETA ~ Dienogest but costs ↑

Management

Other hormonal therapy

2nd line Hormonal therapy

- GnRH agonist +/- add back
- LNG-IUS
- Gestrinone
- Danazole
- Aromatase inhibitor
- Selective progesterone receptor modulator
- Selective estrogen receptor modulator
- GnRH antagonist

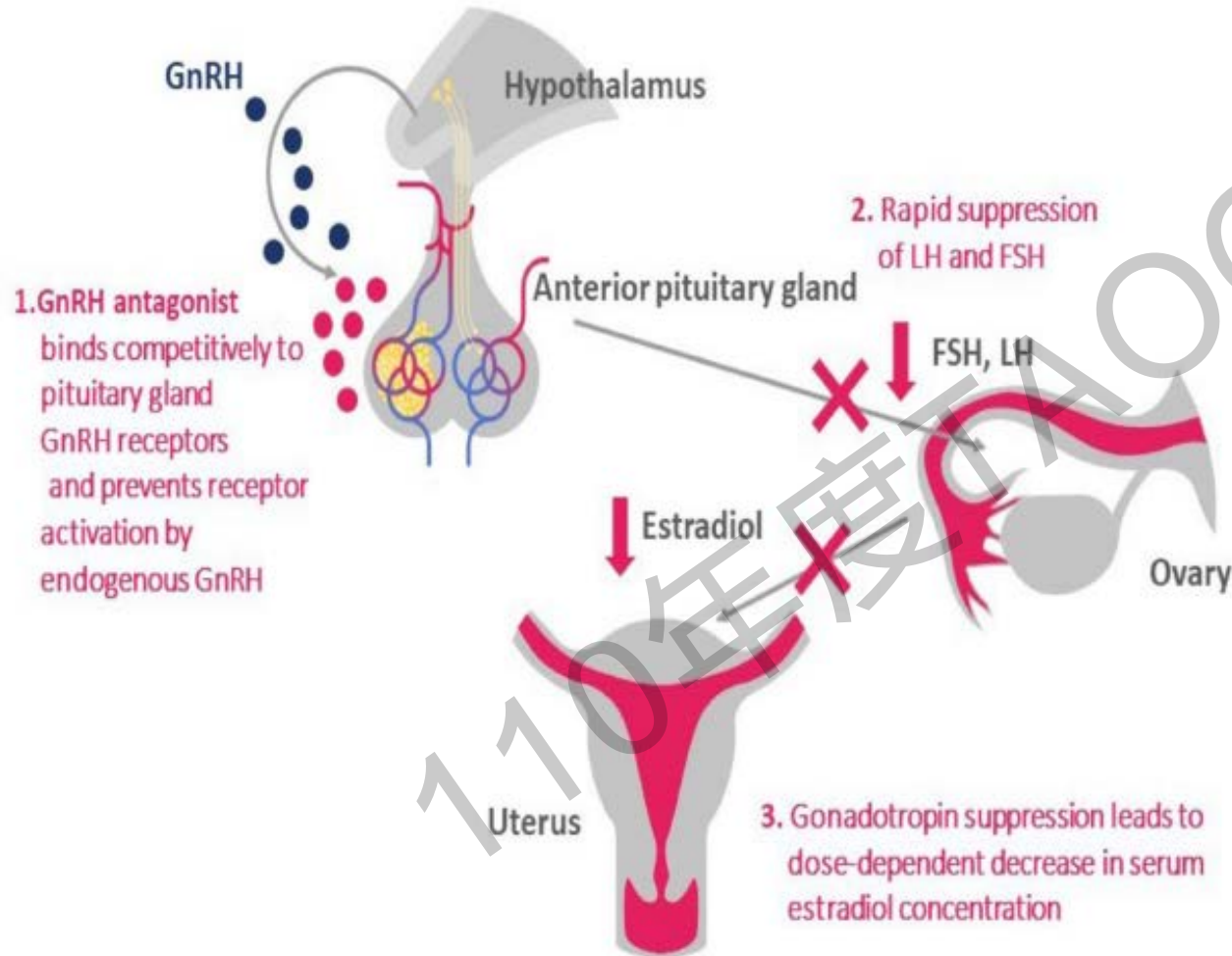
Table 1. Current drug class of the treatment of endometriosis.

Drug class	Advantages	Disadvantages
NSAIDs	<ul style="list-style-type: none"> • First-line therapy • Efficacious in improving moderate women pain symptoms • Not expensive 	<ul style="list-style-type: none"> • They only act on symptoms • Does not block of ovulation
Estroprogestins	<ul style="list-style-type: none"> • First-line therapy • Not expensive • Low rates of AEs • Multiple route of administration available 	<ul style="list-style-type: none"> • Between one-fourth and one-third of patients treated do not respond to them
Progestins	<ul style="list-style-type: none"> • First-line therapy • Not expensive • Lower thrombotic risk • Low rates of AEs • Multiple route of administration available 	<ul style="list-style-type: none"> • Only two progestin approved for contraception purpose (DSG, ENG-subdermal implant and LNG-IUS) • Between one-fourth and one-third of patients treated do not respond to them
Gn-RH-as	<ul style="list-style-type: none"> • Secondary-line therapy (efficacious in treating patients who did not respond to COCs or progestins) 	<ul style="list-style-type: none"> • Not oral administration (subcutaneous) • Expensive • High rate of AEs (estrogen-related)
Danazol	<ul style="list-style-type: none"> • Not expensive 	<ul style="list-style-type: none"> • Low popularity due to the androgenic AEs
Aromatase inhibitors	<ul style="list-style-type: none"> • Efficacy in women refractories to other traditional hormonal treatments (should be used only in scientific setting) 	<ul style="list-style-type: none"> • Expensive • High rate of AEs (myalgia, osteoporosis etc.)

GnRH-as = gonadotropin-releasing hormone agonists; GnRH-ant = gonadotropin-releasing hormone antagonists; AE = adverse effect; DSG = desogestrel; ENG = etonorgestrel; levonorgestrel releasing intrauterine device

Management

New oral hormonal therapy - GnRH antagonist



Clinical Benefits of GnRH Antagonists

- 1 Oral delivery
- 2 Rapid reversibility
- 3 Immediate gonadotropin suppression – no flare effect
- 4 Dose-dependent partial or full estrogen suppression

Table 1. Efficacy and side effect of different doses of GnRH antagonist at 24 weeks.

Assessments	Elagolix				Linzagolix			Relugolix	
	150 mg Elaris-I	200 mg Elaris-I	150 mg Elaris-II	200 mg Elaris-II	75 mg	100 mg	200 mg	40 mg CT Spirit-1	40 mg CT Spirit-2
Pelvic Pain (OPP)	-	-	-	-	70.8	66.7	77.3	-	-
Dysmenorrhea (% responders)	42.1	75.3	46.2	76.9	58.3	82.1	84.1	75.5	75.2
NMPP (% responders)	45.7	62.1	51.6	62.2	72.9	64.1	72.7	58.5	66
BMD loss lumbar spine (%)	-0.32	-2.41	-0.72	-2.49	-0.80	-1.37	-2.60	-0.70	-0.78
Hot flushes %	23.7	42.3	22.6	47.6	19.0	28.8	45.6	10.4	13.6

Elagolix 150 mg once daily; elagolix 200 mg twice daily; linzagolix 75 mg, 100 mg and 200 mg once daily; and relugolix 40 mg plus add-back therapy once daily. OPP: overall pelvic pain; NMPP: non-menstrual pelvic pain.

Table 2. Efficacy and side effects of different doses of GnRH antagonist at 52 weeks

Assessments	Elagolix				Linzagolix			Relugolix	
	150 mg Elaris-III	200 mg Elaris-III	150 mg Elaris-IV	200 mg Elaris-IV	75 mg	100 mg	200 mg	40 mg CT Spirit-1	40 mg CT Spirit-2
Pelvic Pain (OPP)	-	-	-	-	69.2	53.8	82.4	-	-
Dysmenorrhea (% responders)	52.1	78.1	50.8	75.9	69.2	69.2	64.7	-	-
NMPP (% responders)	67.8	69.1	66.4	67.2	69.2	53.8	76.5	-	-
BMD loss lumbar spine (%)	-0.63	-3.60	-1.10	-3.91	-1.14	-1.40	-2.19	-	-
Hot flushes %	44	72	36	77	22	27	60	-	-

Elagolix 150 mg once daily, elagolix 200 mg twice daily, linzagolix 75 mg, 100 mg and 200 mg once daily). Patients randomized to linzagolix 200 mg were switched to linzagolix 100 mg at week 24.

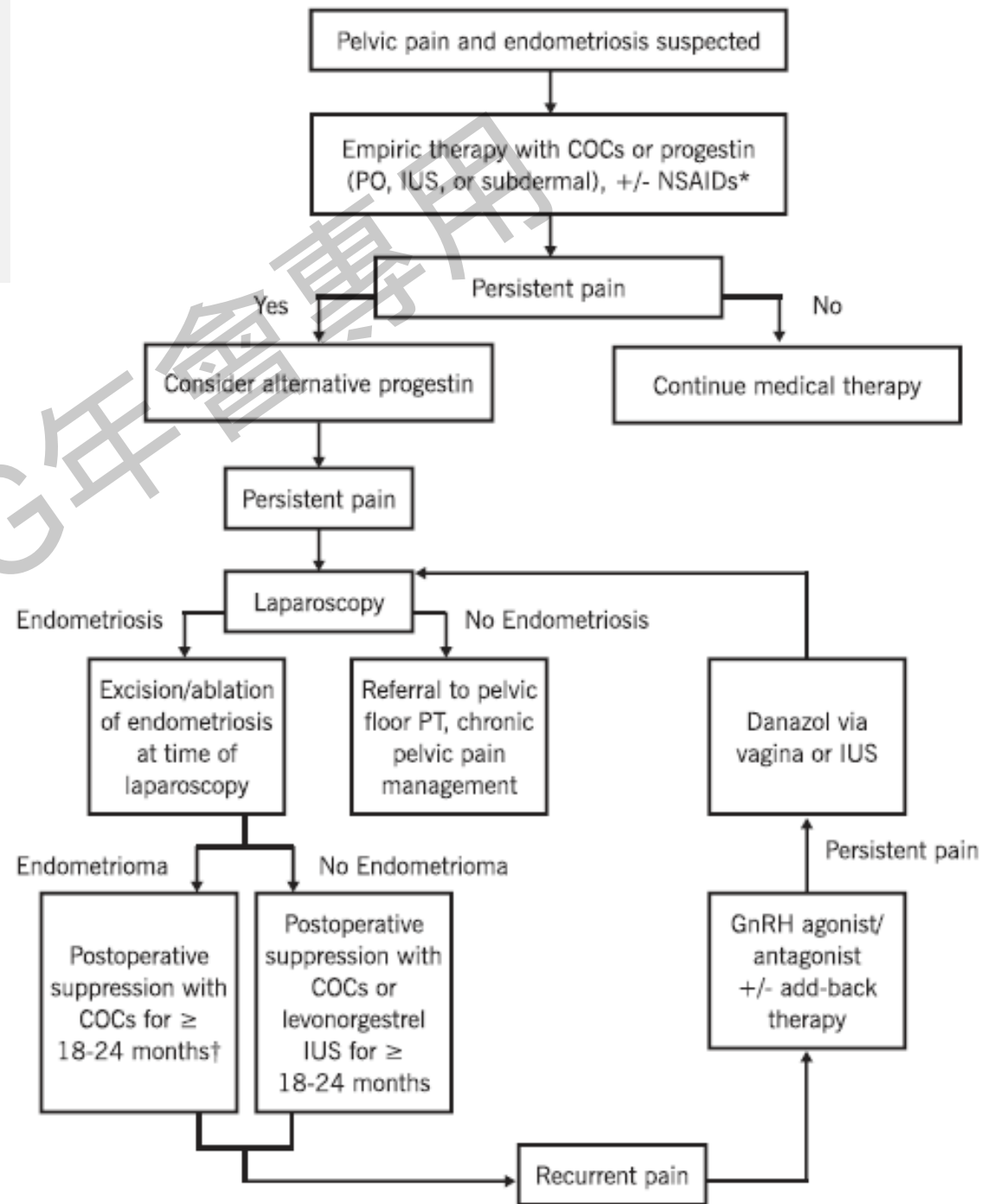
Management

Surgical management

Medical treatment failure
Hollow organ obstructed DIE
Ovarian endometrioma
Infertility

NICE National Institute for Health and Care Excellence

With post surgery medication



Management

Post surgical treatment- Prevention of recurrence



2020

20 studies enrolled for post surgical treatment to placebo or no medical therapy

Pre- and postsurgical medical therapy for endometriosis surgery (Review)

Summary of findings 2. Postsurgical medical therapy compared with placebo or no medical therapy

WES: COC prevention of endometrioma recurrence after surgery

ESHRE : > 18~24 month recommended

Outcomes	placebo	Postsurgical medical therapy	Relative effect (95% CI)
√ Pain recurrence < 12month	255/1000	178/1000	0.70 (0.52-0.94)
√ Disease recurrence < 12 months	171 /1000	51/1000	0.30 (0.17-0.54)
√ Pregnancy rate	344/1000	409/1000	1.19 (1.02-1.38)

Adopted from Pre- and postsurgical medical therapy for endometriosis surgery. Cochrane Database of Systematic

Conclusion

Often delayed diagnosis

**Lifelong disease,
medical treatment and
avoiding repeated
surgical procedures**

10% recurrent rate a year

Medical treatment

- Non-hormone therapy, NSAID
- Hormonal therapy: COC, Progestin, GnRH agonist/ antagonist, others

Surgical treatment

- Medical treatment failure
- Surgical treatment of endometrioma
- Surgical treatment of DIE

Post operative medical treatment

- Post operation medical therapy for prevention recurrence

大綱

Part 1 Review of endometriosis

Part 2 Experience of Dienogest

110年度TAOG學會專用

1 收案狀況

110年度TAOG年會專用

收案狀況

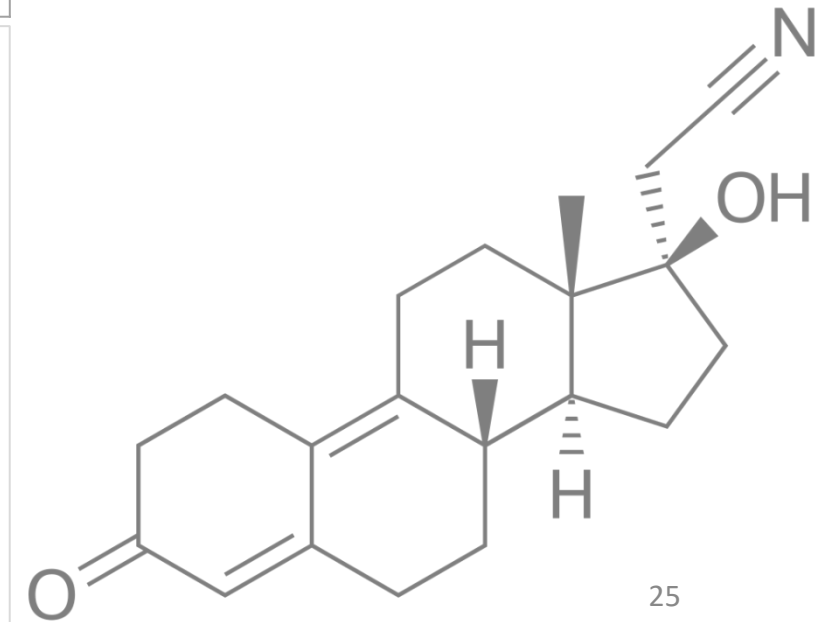
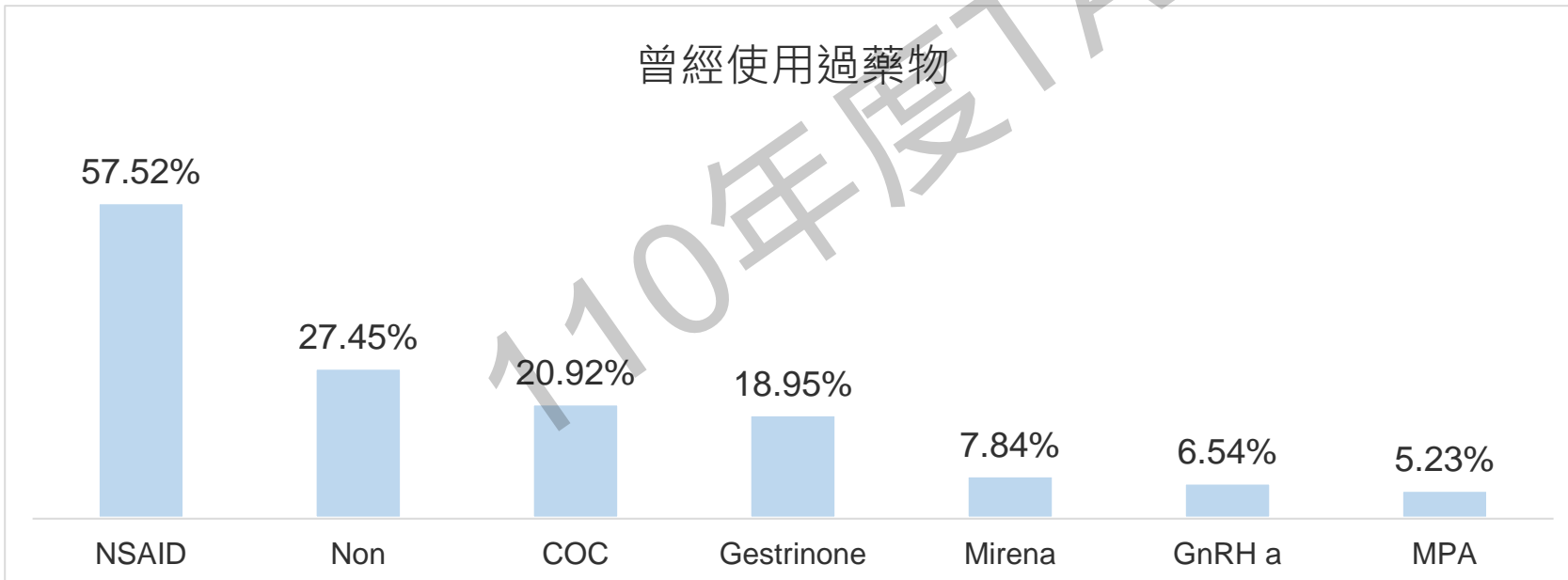
Time period: Prospective, 2018/01/01-2020/12/31

Single institute: NCKUH, Tainan

Case number: 153 patient

	Endometrioma	Adenomyosis	Both	Others	Total
Case number	62(40.5%)	51 (33%)	36(23.5%)	4(2.6%)	153
Mean age	38.0	45.2	39.8	37	40.4
術後使用	45(72.5%)	7 (13.7%)	10 (27.8%)	2(50%)	64(41.8%)

Others
Cervix endometriosis
DUB
Pelvic endometriosis
Peritoneum endometriosis



2. 治療效果

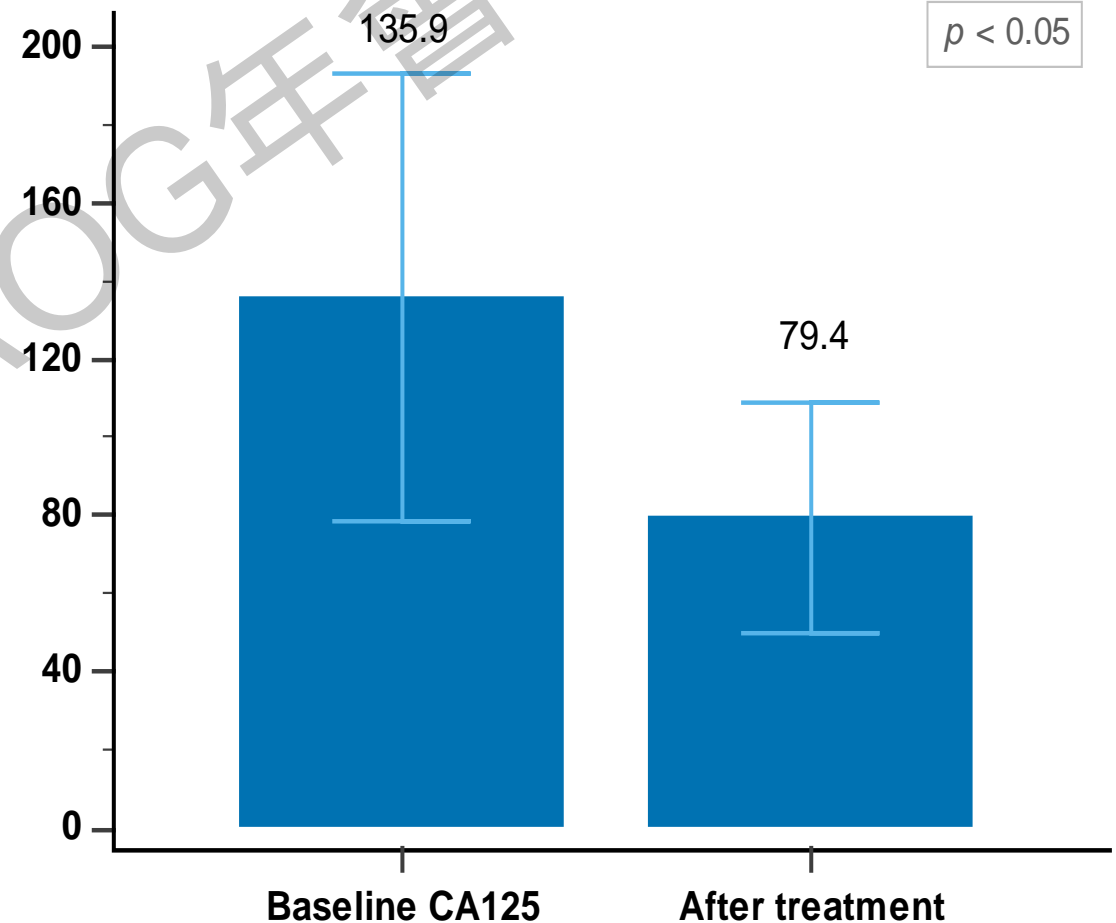
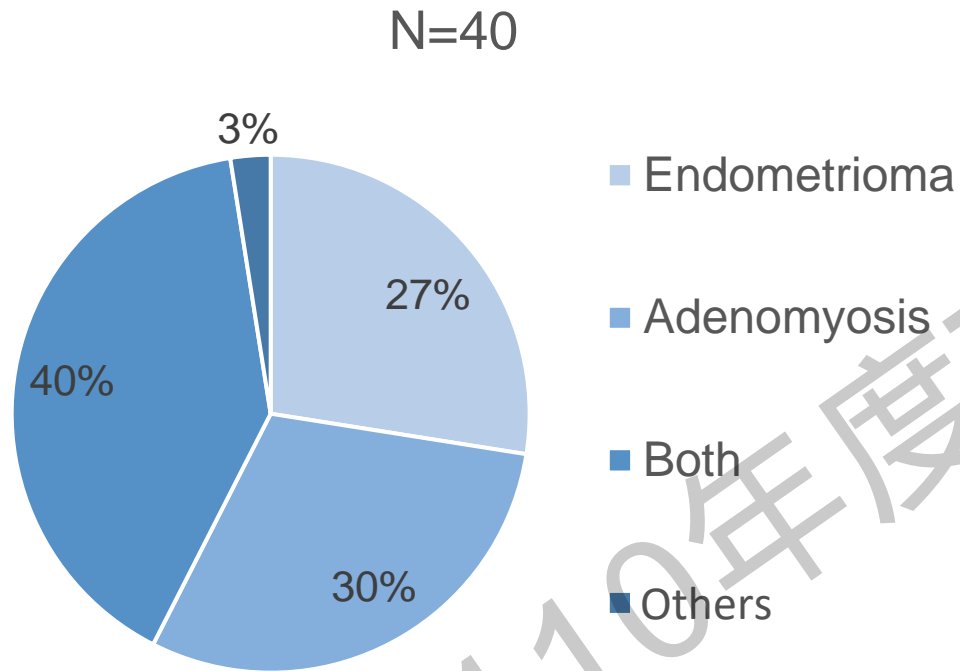
110年度TAOG年會專用

治療效果

追蹤40位endometriosis病人

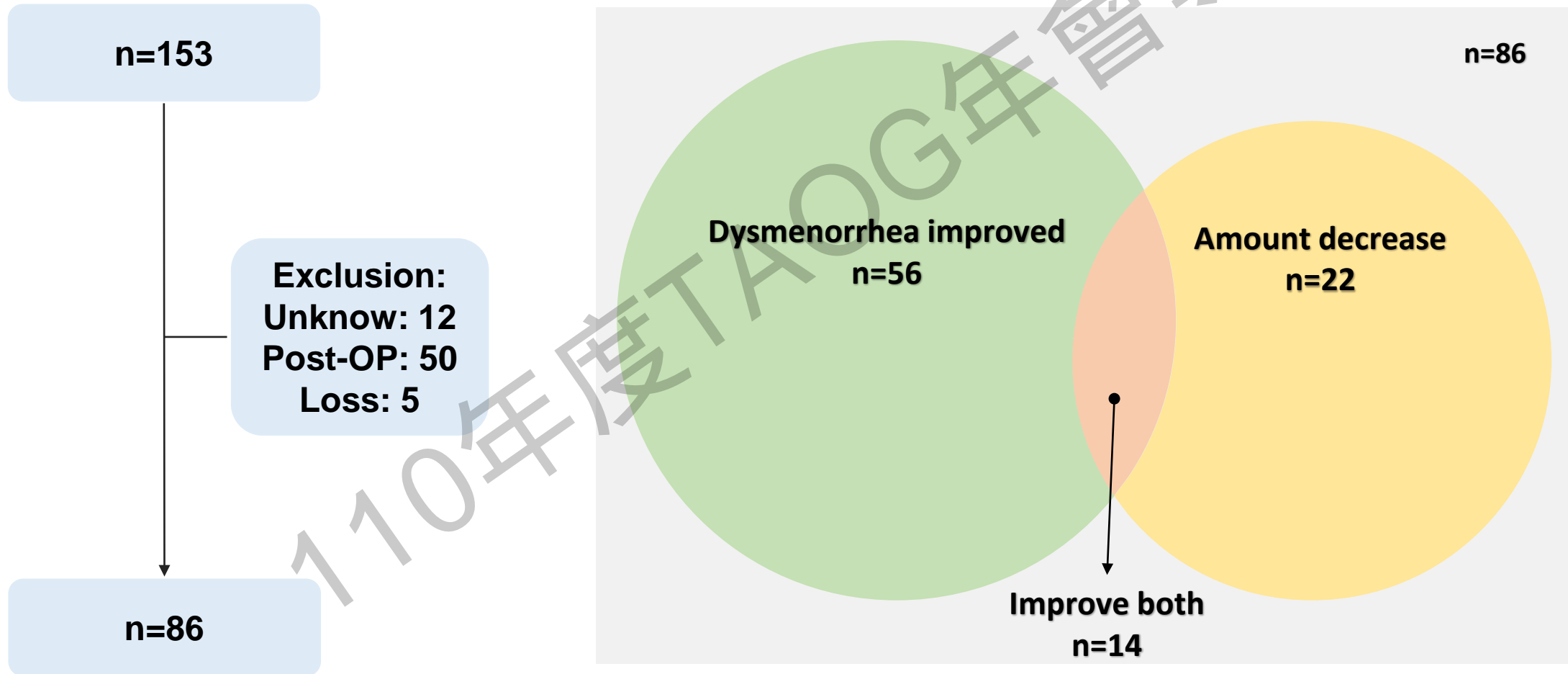
平均使用 Dienogest時間: 6.9 months (2-19 months)

評估CA125變化



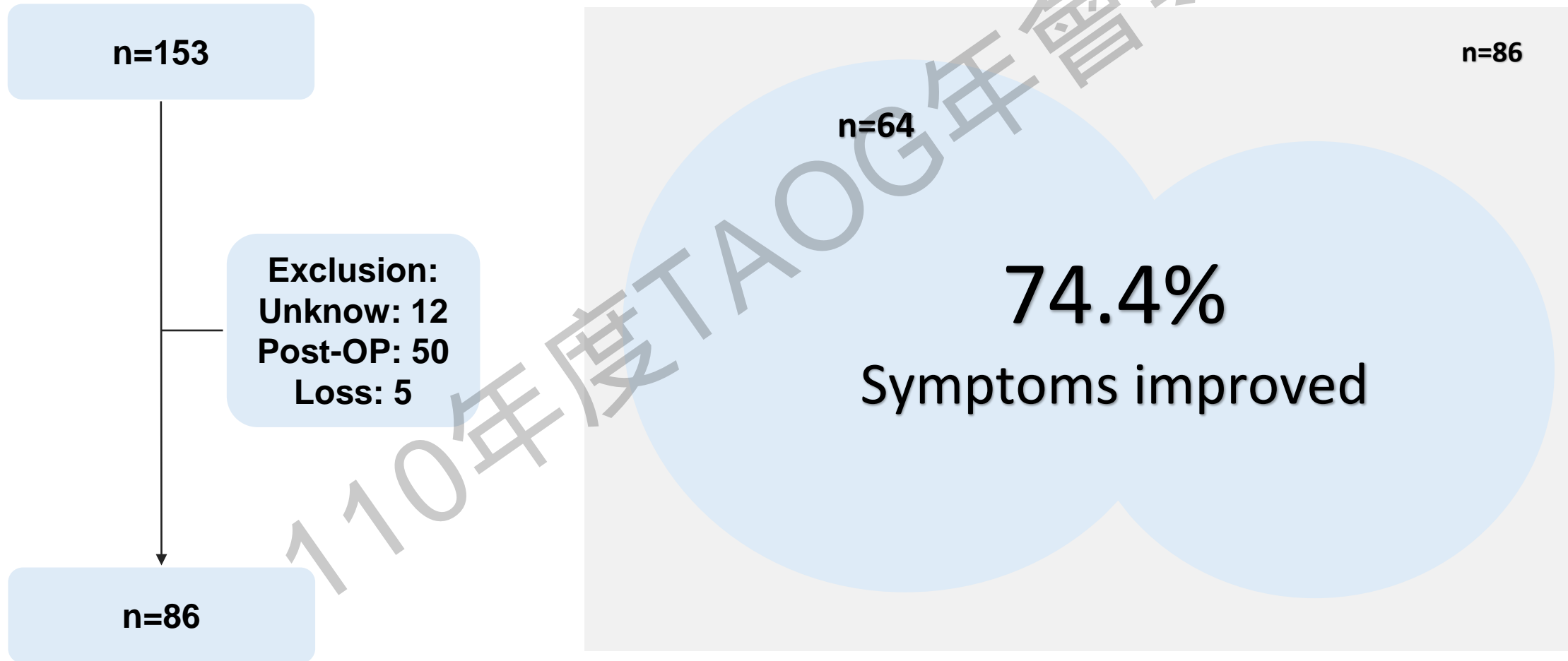
治療效果

評估病人主觀回報症狀改善狀況



治療效果

評估病人主觀回報症狀改善狀況

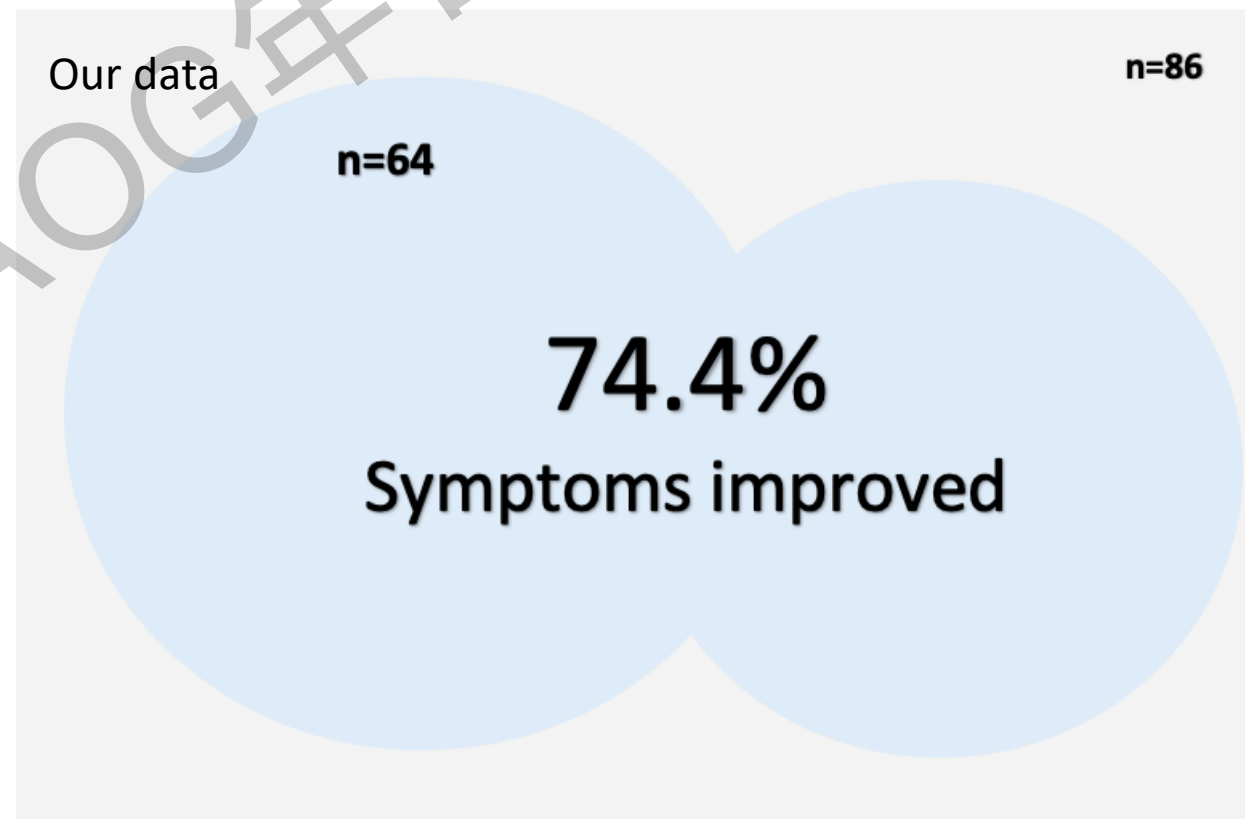
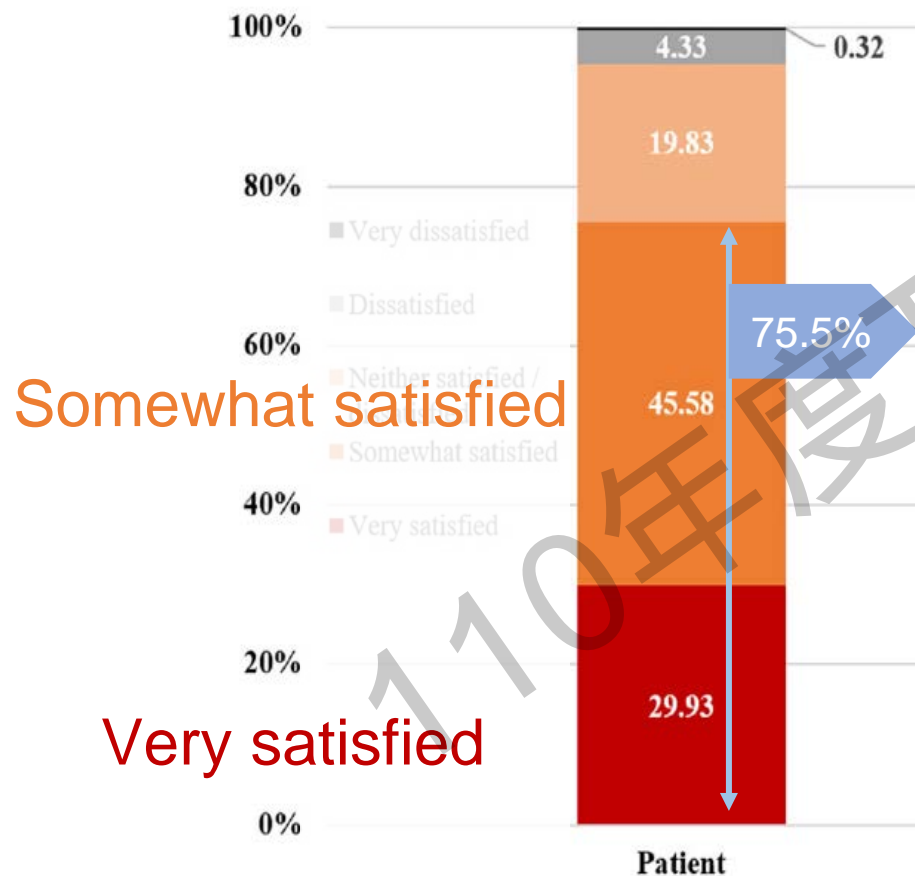




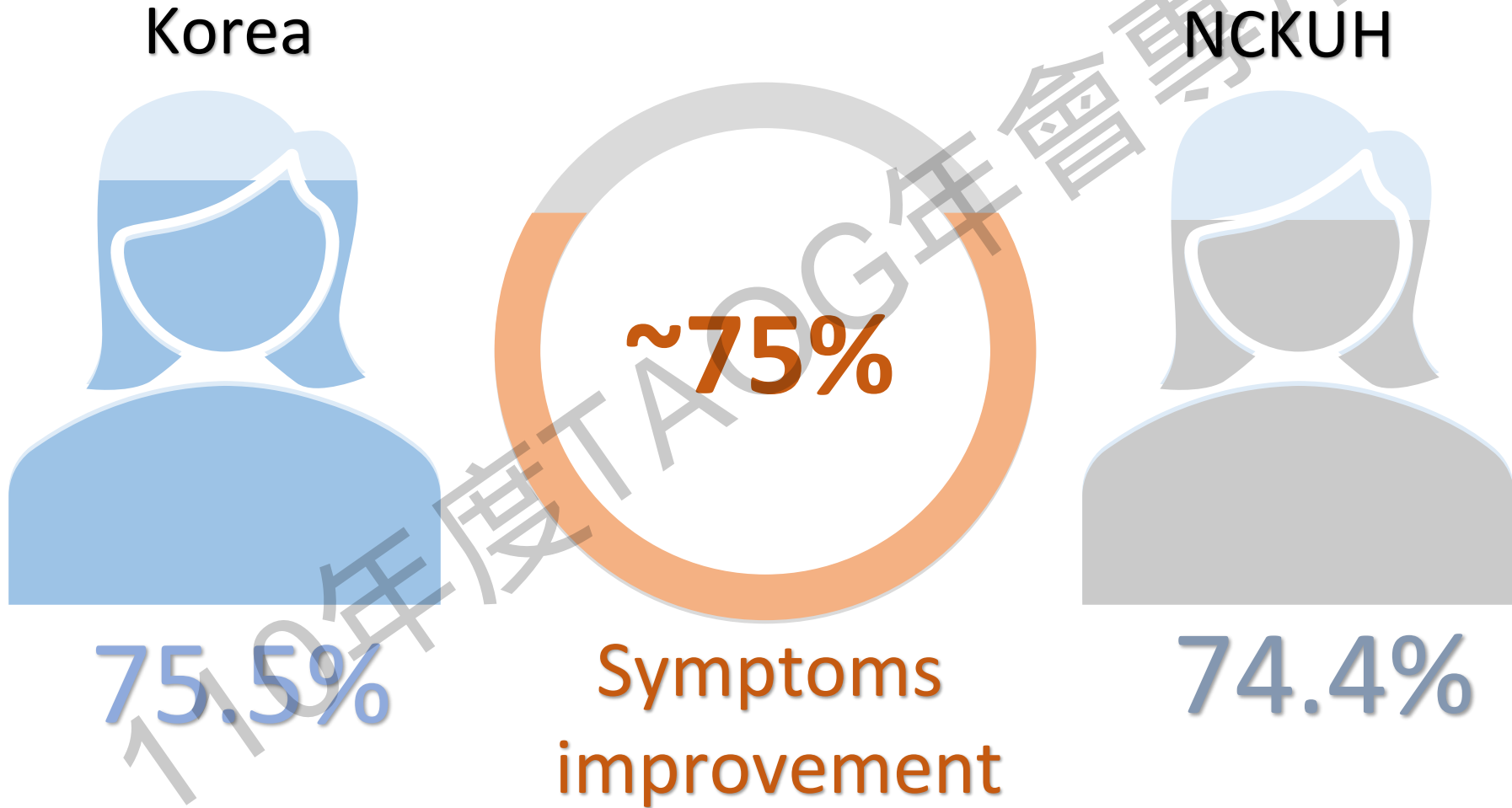
治療效果

Comparative to Korea large prospective cohort Safety and Effectiveness of Dienogest (Visanne®) for Treatment of Endometriosis: A Large Prospective Cohort Study

Fig.4 Patient's subjective assessment of therapeutic effect and tolerability (%) (left) investigator's assessment of overall symptom development (%)



Almost 75% of patients have symptoms improved



3. 副作用/不良反應

110年慶典MOG年會專用

Adverse event

Table 2 Incidence of adverse events (AEs)/adverse drug reactions (ADRs)

	Adverse event (AE)		Adverse drug reaction (ADR)	
	No. of subjects with AE N (%)	No. of AEs	No. of subjects with ADR N (%)	No. of ADRs
Reproductive system and breast disorders	198 (6.36),	207	185 (5.94),	194
Abnormal uterine bleeding ^a	130 (4.18%)	131	129 (4.14%)	130
Breast discomfort ^b	39 (1.25),	39	35 (1.12),	35
Dysmenorrhea	7 (0.22),	8	6 (0.19),	7
Others	29 (0.93),	29	22 (0.71),	22
Investigations	84 (2.70),	84	82 (2.63),	82
Weight increased	81 (2.6%)	81	80 (2.57%)	80
Others	3 (0.10),	3	2 (0.06),	2
Gastrointestinal disorders	60 (1.93),	66	49 (1.57),	54
Nausea	20 (0.64),	20	18 (0.58),	18
Dyspepsia	12 (0.39),	12	11 (0.35),	11
Abdominal pain	10 (0.32),	10	9 (0.29),	9
Others	23 (0.74),	24	15 (0.48),	16
Skin and subcutaneous tissue disorders	57 (1.83),	62	50 (1.61),	54
Acne	24 (0.77),	24	23 (0.74),	23
Alopecia	10 (0.32),	10	9 (0.29),	9
Urticaria	7 (0.22),	9	6 (0.19),	7
Others	19 (0.61),	19	15 (0.48),	15
Nervous system disorders	56 (1.80),	59	51 (1.64),	53
Headache	41 (1.32%)	42	38 (1.22)	39
Dizziness	7 (0.22),	7	6 (0.19),	6
Migraine	4 (0.13),	4	3 (0.10),	3
Others	6 (0.19),	6	5 (0.16),	5
Psychiatric disorders	50 (1.61),	54	44 (1.41),	48
Depressed mood/depression ^c	24 (0.77),	24	22 (0.71),	22
Insomnia	17 (0.55),	17	16 (0.51),	16
Sleep disorder	3 (0.10),	3	1 (0.03),	1
Others	10 (0.32),	10	9 (0.29),	9
Other SOC	109 (3.50),	118	65 (2.09),	69
Total	470 (15.10),	650	413 (13.27),	554

Korean 3356 cohort Study



Safety analysis set (N = 3113)

1 Abnormal uterine bleeding

2 Weight increased

3 Headache

110年度TACG

^a "Abnormal uterine bleeding" includes metrorrhagia, polymenorrhea, menorrhagia, hypomenorrhea, menstruation irregular, oligomenorrhea, menometrorrhagia, and polymenorrhagia

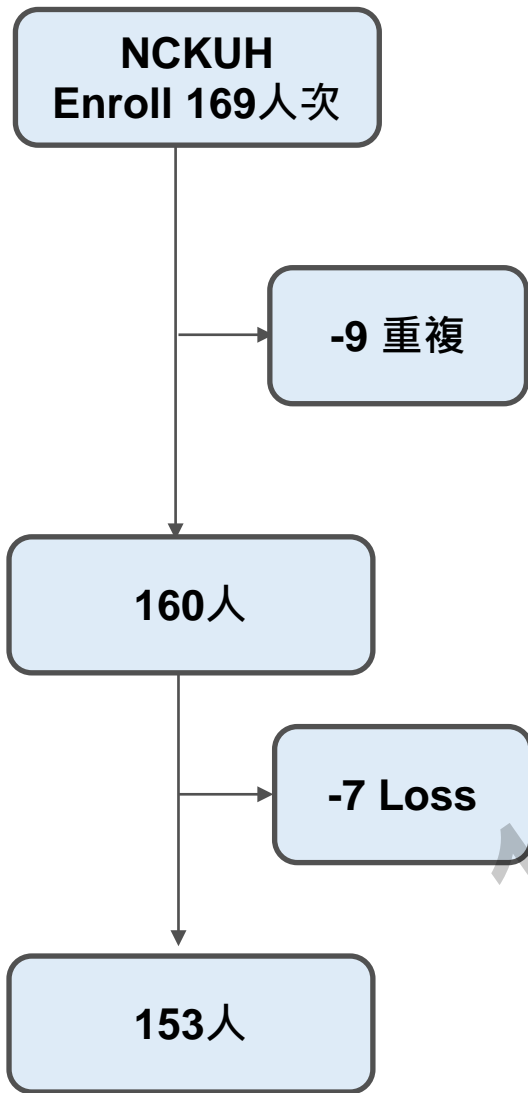
^b "Breast discomfort" includes breast tenderness and breast pain

^c Depressed mood and depression

Adverse event

	Adverse event(AE)	
	No. AE N	No.of AEs (%)
Reproduction system and breast disorders	86	56%
Abnormal uterine bleeding	72	47%
Breast discomfort	7	5%
Others	4	3%
Investigations	11	7%
Weight increased	11	7%
Gastrointestinal disorders	23	15%
Nausea	1	1%
Dyspepsia	3	2%
Abdominal pain	15	10%
Others-Constipation	4	3%
Skin and subcutaneous tissue disorders	7	5%
Acne	2	1%
Alopecia	4	3%
Urticaria(蕁麻疹)	1	1%
Nervous system disorders	23	15%
Headache	19	12%
Dizziness	4	3%
Psychiatric disorders	15	10%
Depressed mood/depression	3	2%
Insomnia	10	7%
Others	2	1%
Other SOC	7	5%

Abnormal uterine bleeding = persistent spotting (66) + massive bleeding (6)



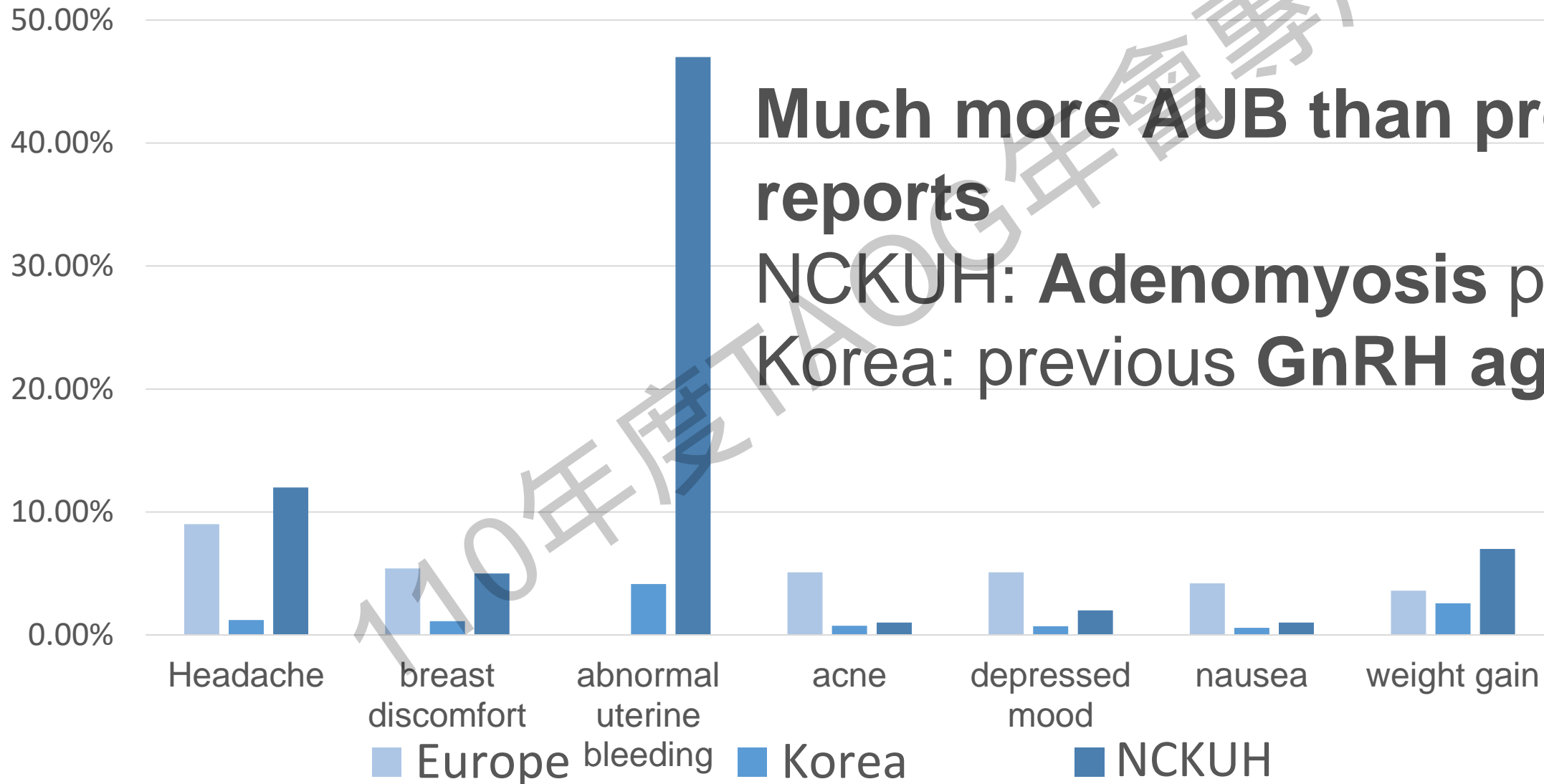


Adverse event

Comparing NCKUH ,Europe and Korea

Reprod Sci. 2020 Mar;27(3):905-915.

Int J Womens Health. 2015;7:393-401



Much more AUB than previous reports

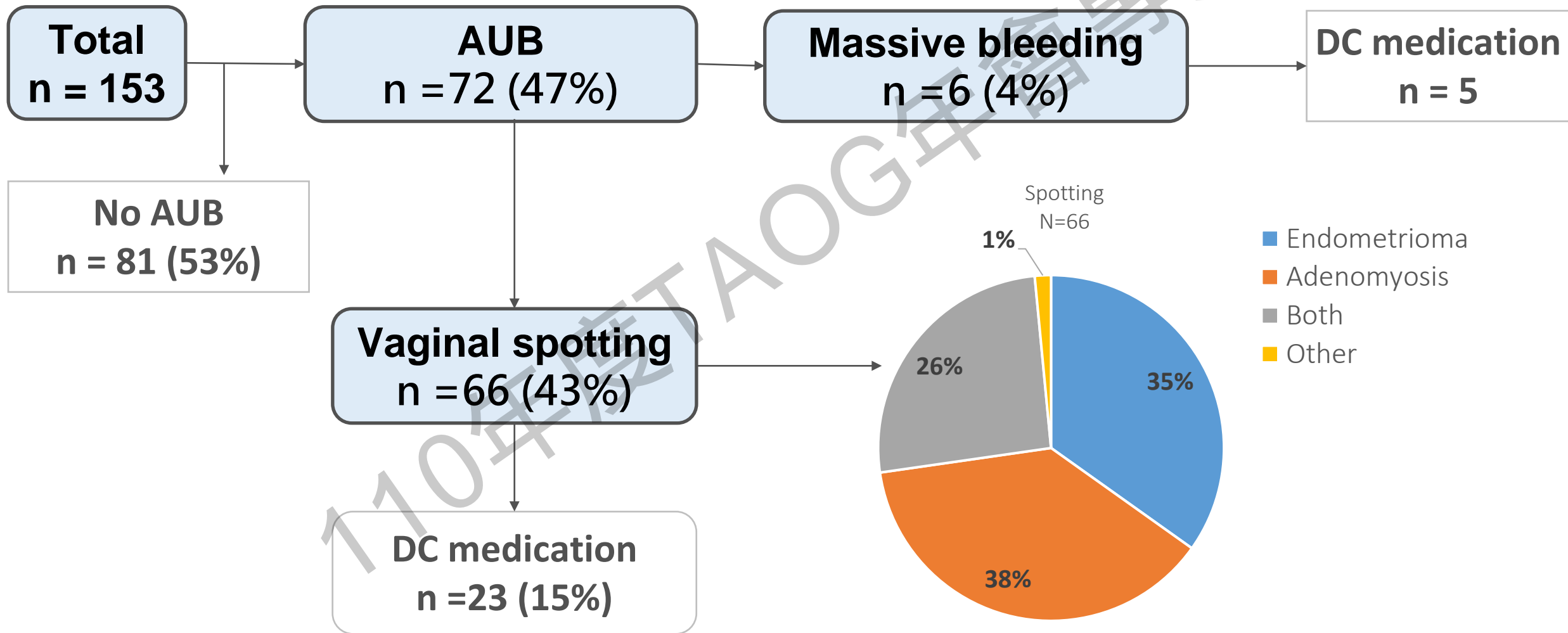
NCKUH: Adenomyosis patient

Korea: previous GnRH agonist

4. Abnormal uterine bleeding

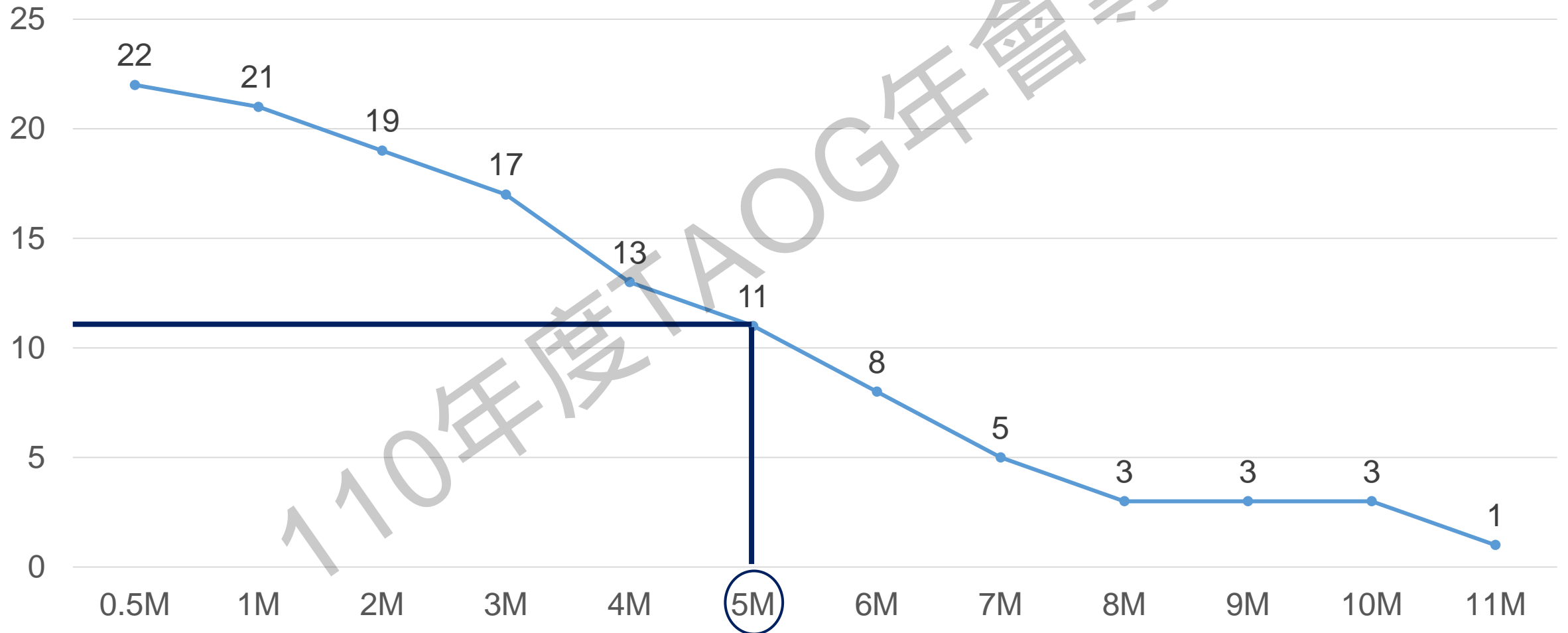
Massive bleeding and persistent spotting

AUB



AUB

Vaginal spotting events ↓ 50% after 5 months



5. 停藥分析

110年度TAOG年會專用

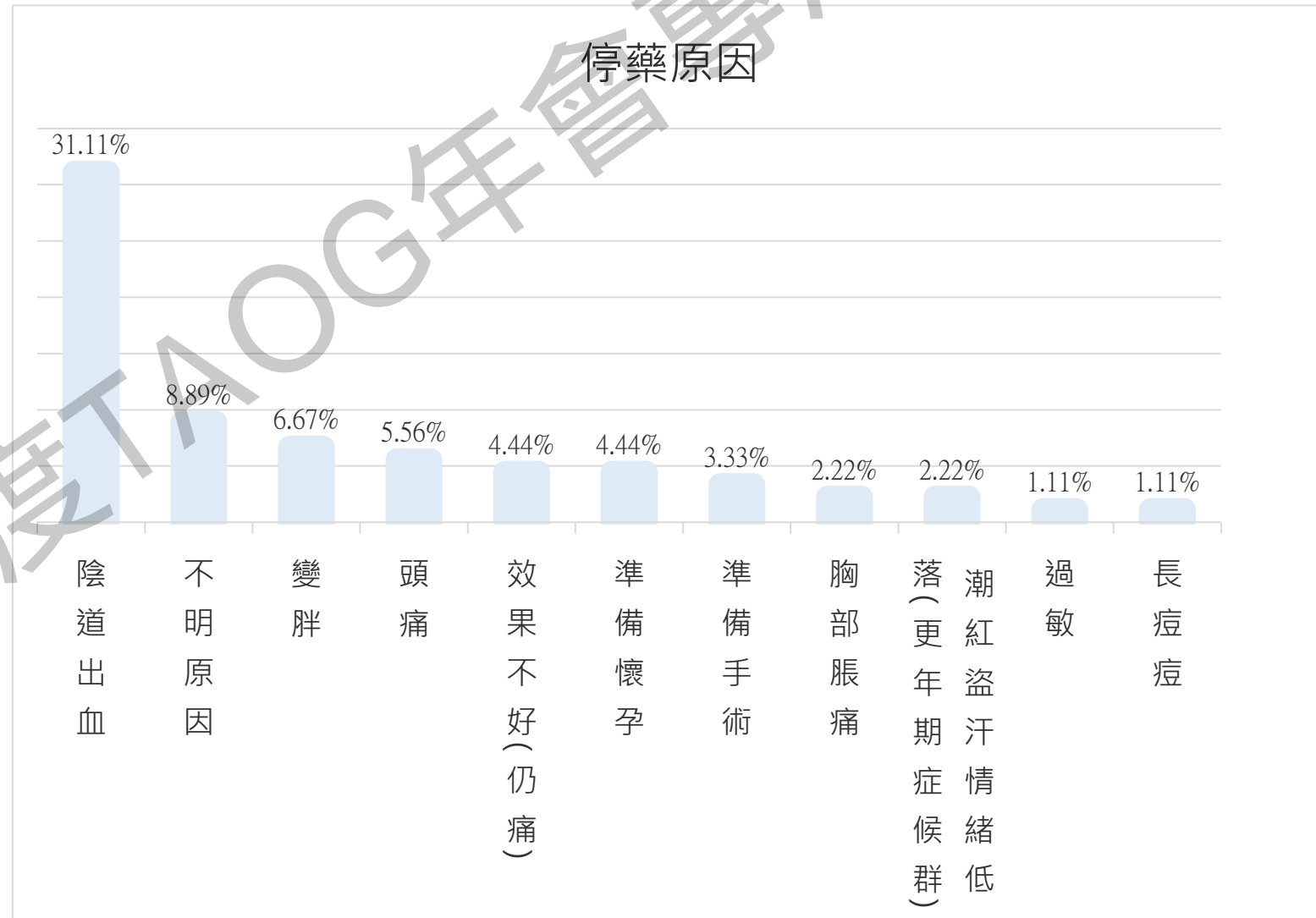
停藥分析

停藥人次114次

Loss follow up 24 人次

分析90 人次

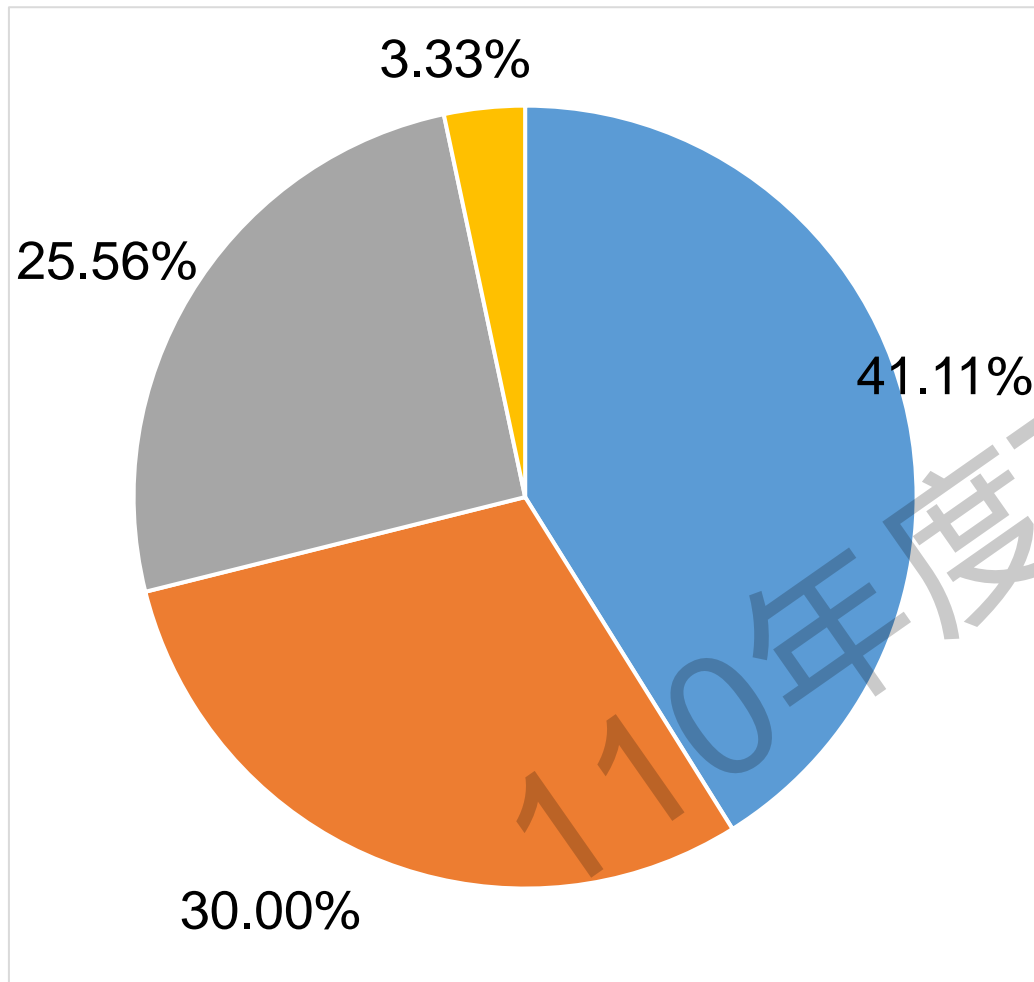
分類	n (人次)	平均停藥時間(月)
全部停藥	90	6.7[5.79 - 7.61]
非計劃性停藥	61	5[3.97-6.03]
非計劃性停藥原因	n (人次)	平均停藥時間(月)
陰道出血	28	4.3
不明原因	8	3.9
變胖	6	6.3
頭痛	5	7.2
效果不好(仍痛)	4	3.3
準備懷孕	4	9.3
準備手術	3	9.7
胸部脹痛	2	1.5
更年期症候群	2	6
過敏	1	1
長痘痘	1	5



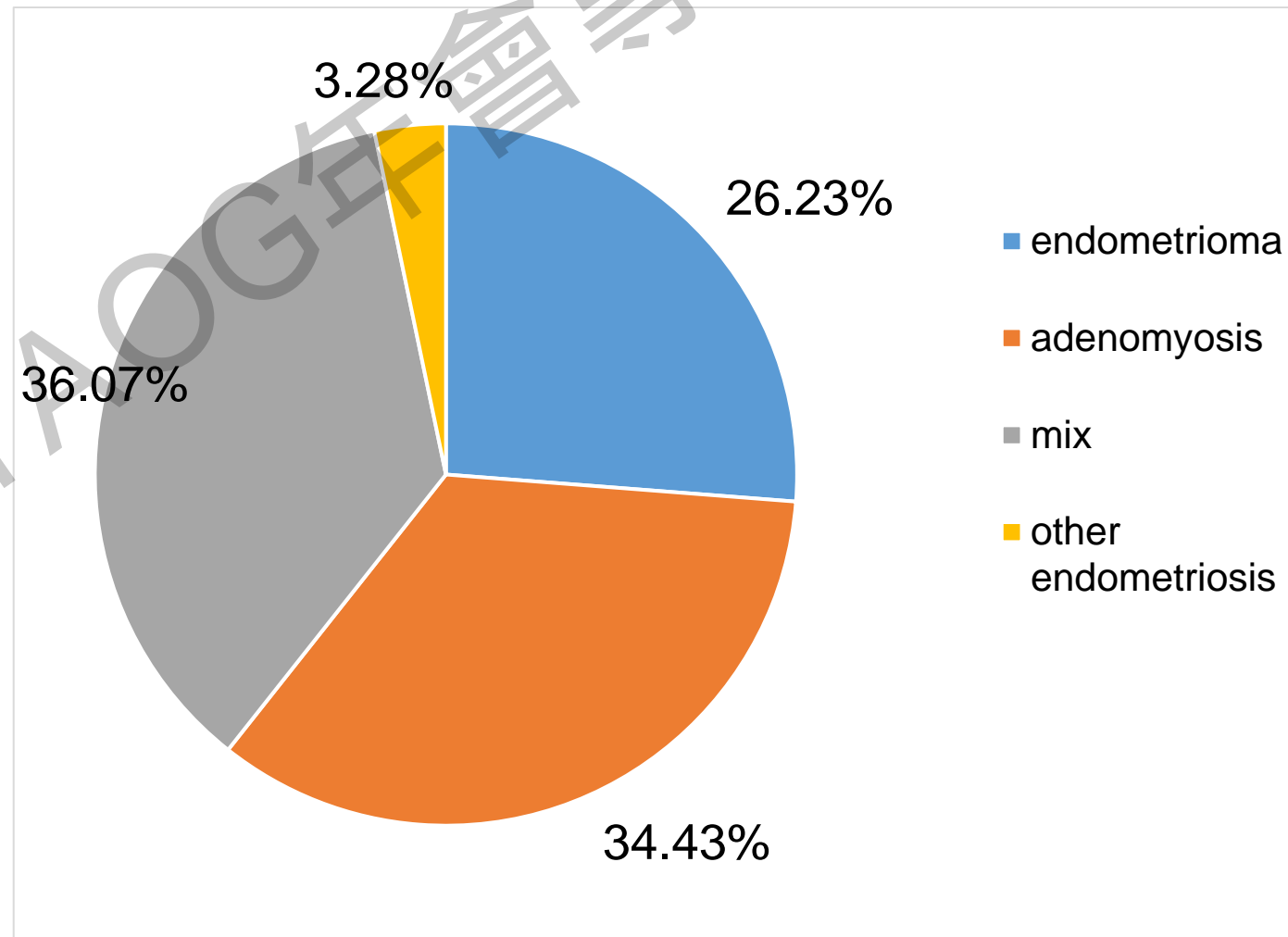
停藥分析

停藥診斷分佈

全部停藥診斷分佈



排除計畫性停藥診斷分佈



- endometrioma
- adenomyosis
- mix
- other endometriosis

6. Recurrence

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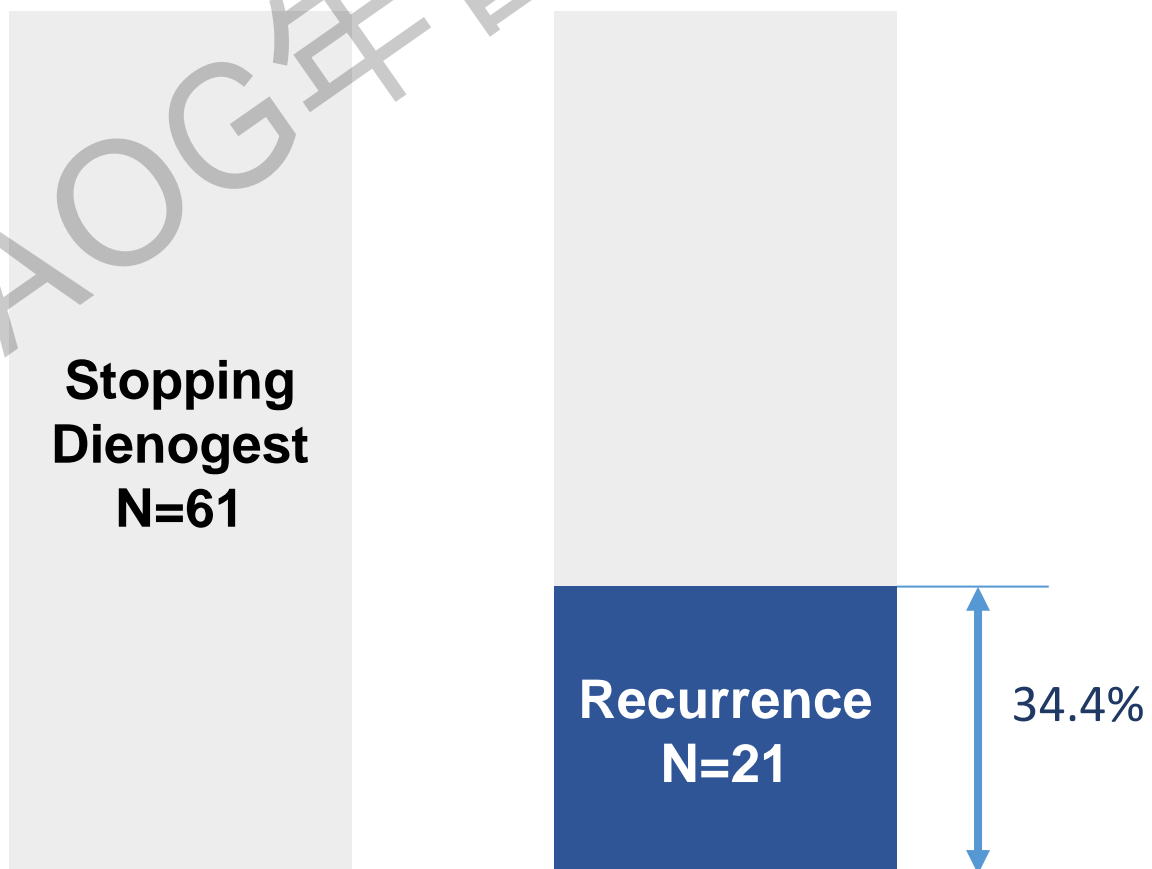
復發分析

Analyze the number of recurrence after stopping use dienogest in 2018-2020

34.4 % recurrent rate in 3 years

Mean recurrent time 5.62 (4.27-6.97) months

分類	n (人次)	平均停藥時間(月)
全部停藥	90	6.7[5.79 - 7.61]
非計劃性停藥	61	5[3.97-6.03]
非計劃性停藥原因	n (人次)	平均停藥時間(月)
陰道出血	28	4.3
不明原因	8	3.9
變胖	6	6.3
頭痛	5	7.2
效果不好(仍痛)	4	3.3
準備懷孕	4	9.3
準備手術	3	9.7
胸部脹痛	2	1.5
更年期症候群	2	6
過敏	1	1
長痘痘	1	5



7.再次使用分析

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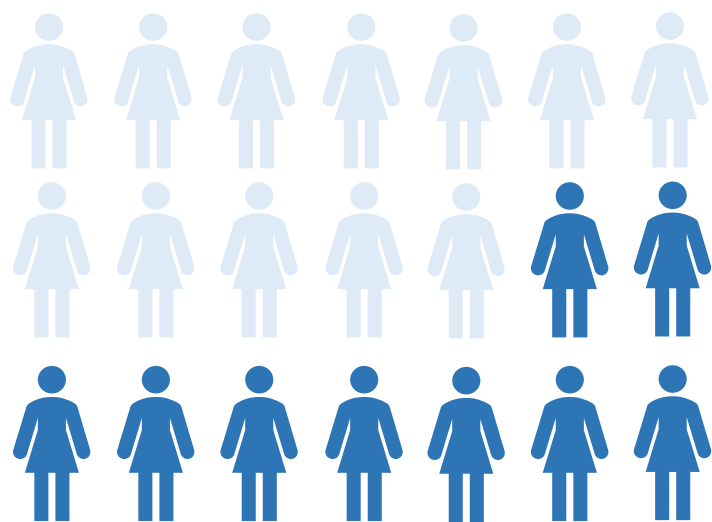
停藥後再度使用

共九人停藥後再度使用藥物

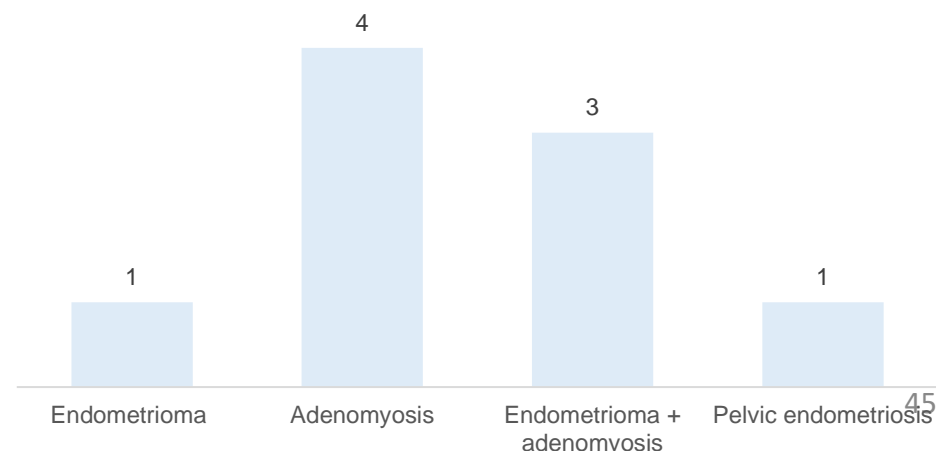
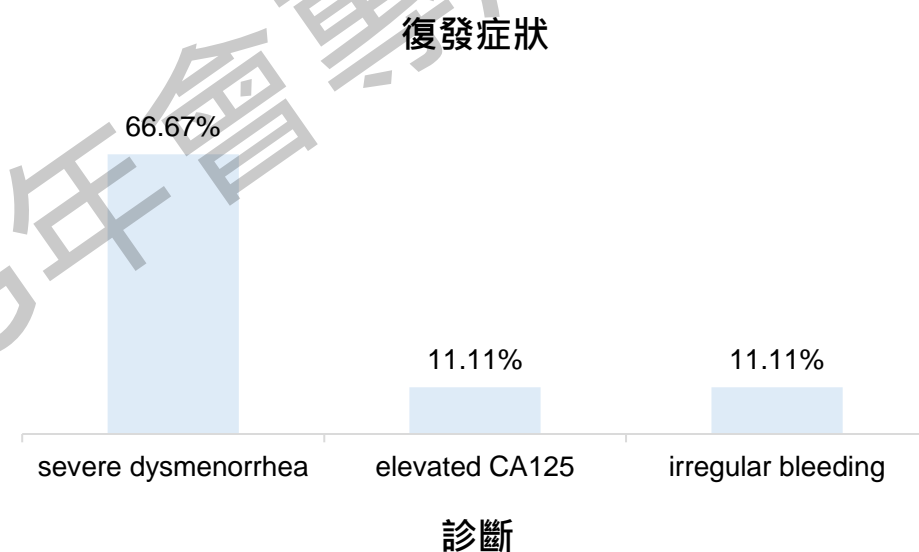
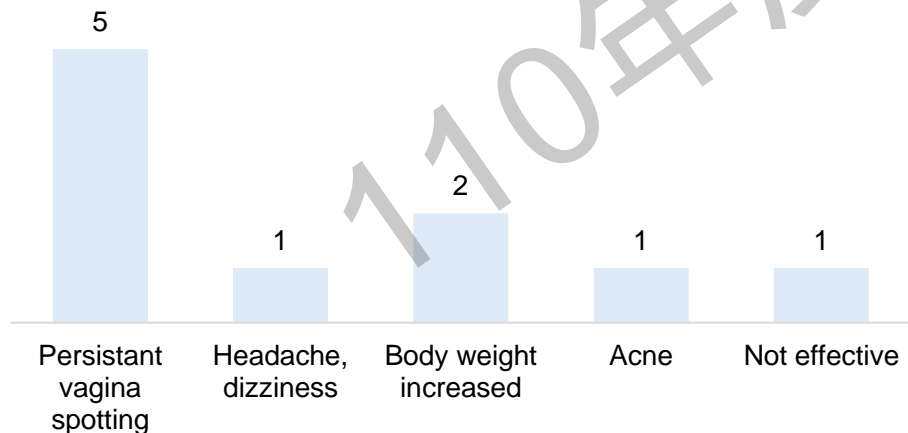
停藥後 5.6 (2-11) 個月症狀復發

平均停藥時間 7.9 (3-11) 個月後再度開始使用

其中一人三度使用



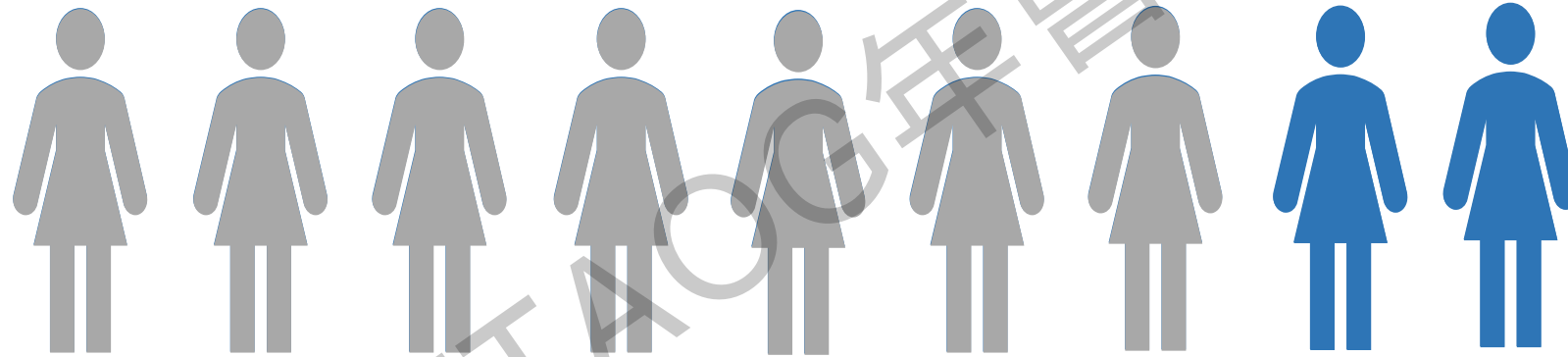
停藥原因



停藥後再度使用

77.8% patient use other medication before resume Dienogest

77.8%(7/9) choose



Patient	A	B	C	D	E	F	G
NSAID	✓	✓	✓	✓	✓	✓	
OCP			✓				
Gestrin						✓	✓
Danazol							✓

Conclusion

47 % patient in NCKUH cohort with either **persistent vaginal spotting** or **massive bleeding** after Dienogest use

Vaginal spotting event will decrease with time, 50% in 5 months

31.1% patient stopped Dienogest use due to persistent vaginal spotting

Symptoms recurred at mean **5.62** months after stoping Dienogest

42.9% patient had **resume** Dienogest after **7.9 months** after symptoms recurred

Thank you for your attention

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