

# Endometriosis and Long-term Management Strategy

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Effective 2021 July 9



## Outline 1- What questions you may ask?

- Why “**manage** endometriosis” and **not** “**treat** endometriosis”?
- What kind of patient type we can **start treatment** with Visanne
  - ✓ **Post-surgery**
  - ✓ **Clinical diagnosis**
  - ✓ **Adenomyosis** (endometriosis of uterus)
- What **side effect** we may meet in initial treatment with Visanne
  - ✓ **spotting**
- Is it true that medical treatment will **reduce surgical cases**?



## Outline 2- What questions you may ask?

- **How long** we should recommend patient to take Visanne?
  - ✓ post-surgery
  - ✓ clinical diagnosis
  - ✓ endometriosis of uterus
- Any **safety issue** we should care when we use Visanne over than 2 years?
- Can I prescribe Visanne to **teenager of endometriosis**?
- What is the difference in the ingredient between **branded medicine and generic medicine**?

**Why “manage endometriosis”  
and not “treat endometriosis”?**



# Endometriosis is **chronic inflammation** disease

## Introduction

### Clinical need

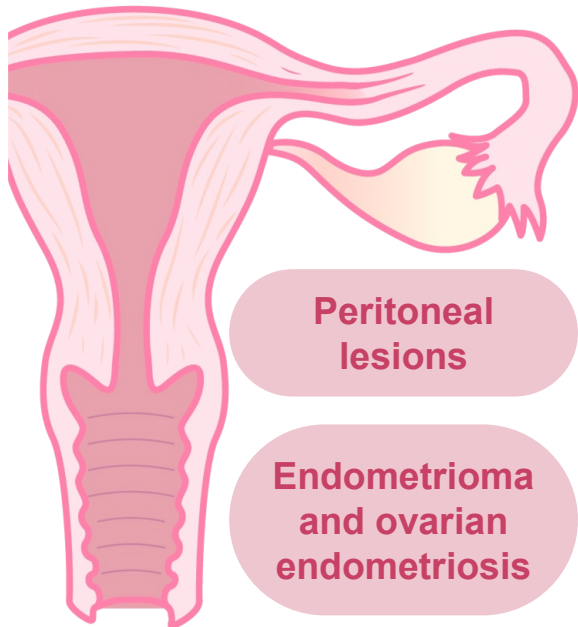
Endometriosis is a chronic inflammatory disease defined as the presence of endometrium-like tissue outside the uterus (Kennedy, *et al.*, 2005). Establishment and growth of such endometriotic tissue is estrogen-dependent (Kitawaki, *et al.*, 2002), thus it is mostly found in women of reproductive age although the clinical consequences of endometriosis and its management can last well into post-menopause.

The exact prevalence of endometriosis is unknown, but estimates range from 2 to 10% within the general female population but up to 50% in infertile women (Eskenazi and Warner, 1997, Meuleman, *et al.*, 2009). Thus, it is estimated that currently at least 190 million women and adolescent girls worldwide are affected by the disease during reproductive age although some women may suffer beyond menopause (Gemmell, *et al.*, 2017, Zondervan, *et al.*, 2020). Whilst not all women with endometriosis are symptomatic, endometriosis-associated pain and infertility are the clinical hallmarks of the disease affecting not only women with endometriosis, but also their partners and families. An impact of endometriosis, and particularly pain symptoms, has been shown on quality of life, but also on a range of activities and life domains including physical functioning, everyday activities and social life, education and work, sex, intimacy and intimate partnerships, and mental health and emotional wellbeing (Culley, *et al.*, 2013). The same review also reported an impact of infertility and concerns about possible infertility on the patient and the relationship with their partner (Culley, *et al.*, 2013).

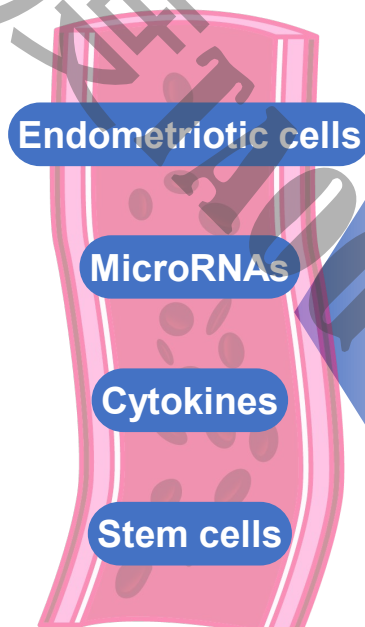


Endometriosis is **not only a gynecological disease**, but it should be regarded as a **systemic inflammatory disease**, where its course will continue to **worsen if left untreated**<sup>1,2</sup>

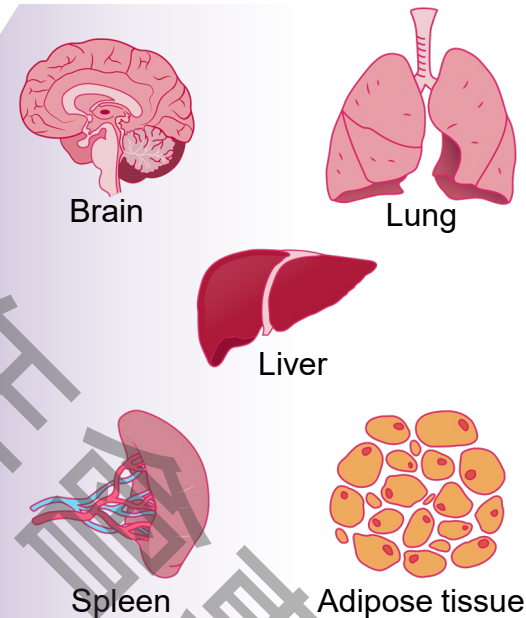
Endometriosis is more than a localized pelvic disease<sup>1</sup>



Circulating factors<sup>1</sup>



Endometriosis has a broad systemic effect<sup>1</sup>



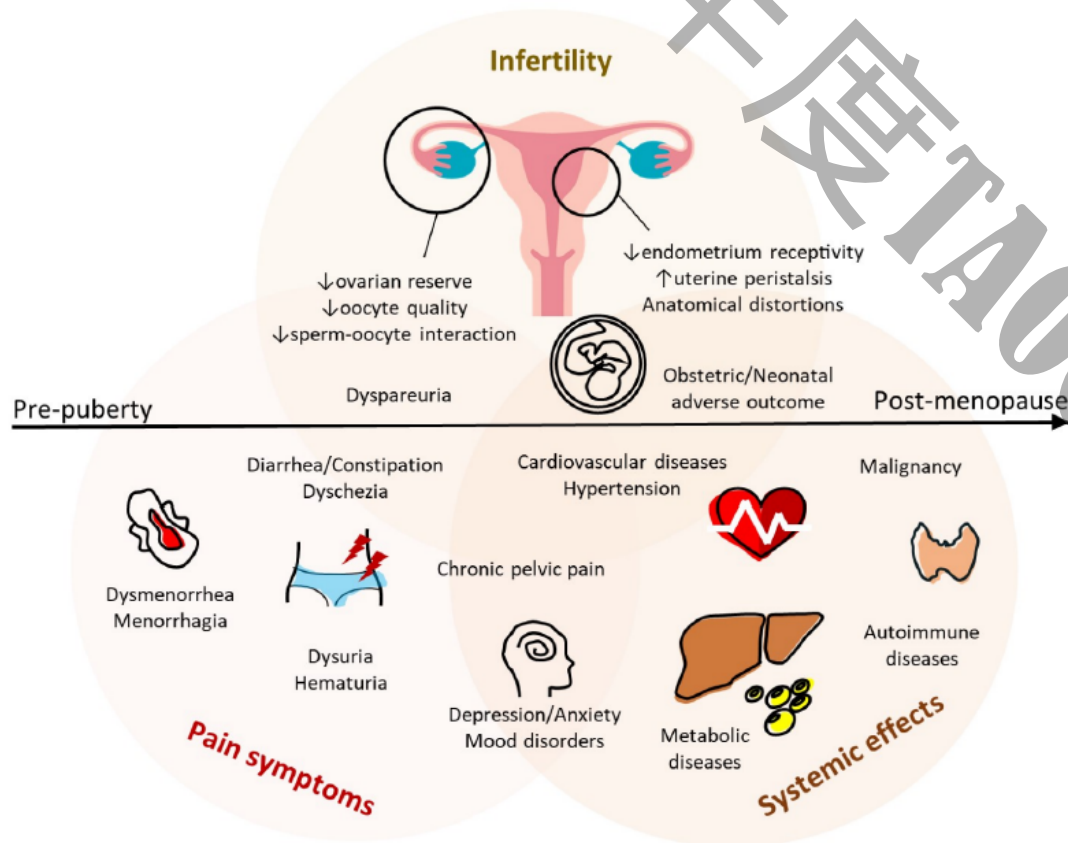
Endometriosis affects metabolism in the **liver and adipose tissue** and leads to **systemic inflammation and alterations in the brain** that cause the increased pain perception and mood and anxiety disorders.<sup>1</sup>

Redefining endometriosis as a systemic inflammatory disease, not a classic gynecological disease.<sup>1</sup>

RNA, ribonucleic acid.

Taylor HS, et al. Lancet. 2021;397:839-52. 2. Chen SF, et al. J Womens Health (Larchmt). 2021;30:1160-4.

# Clinical features of endometriosis and its **lifelong** impact



- **Menstrual disorders** of endometriosis of uterus
- **Endometriosis-associated symptoms**
- **Endometriosis-associated infertility**
- **Endometriosis-associated obstetric complication**
- **Malignancy** potential
- **Long-term systemic disease**



# Endometriosis affect numerous aspects of women's lives

International Journal of General Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

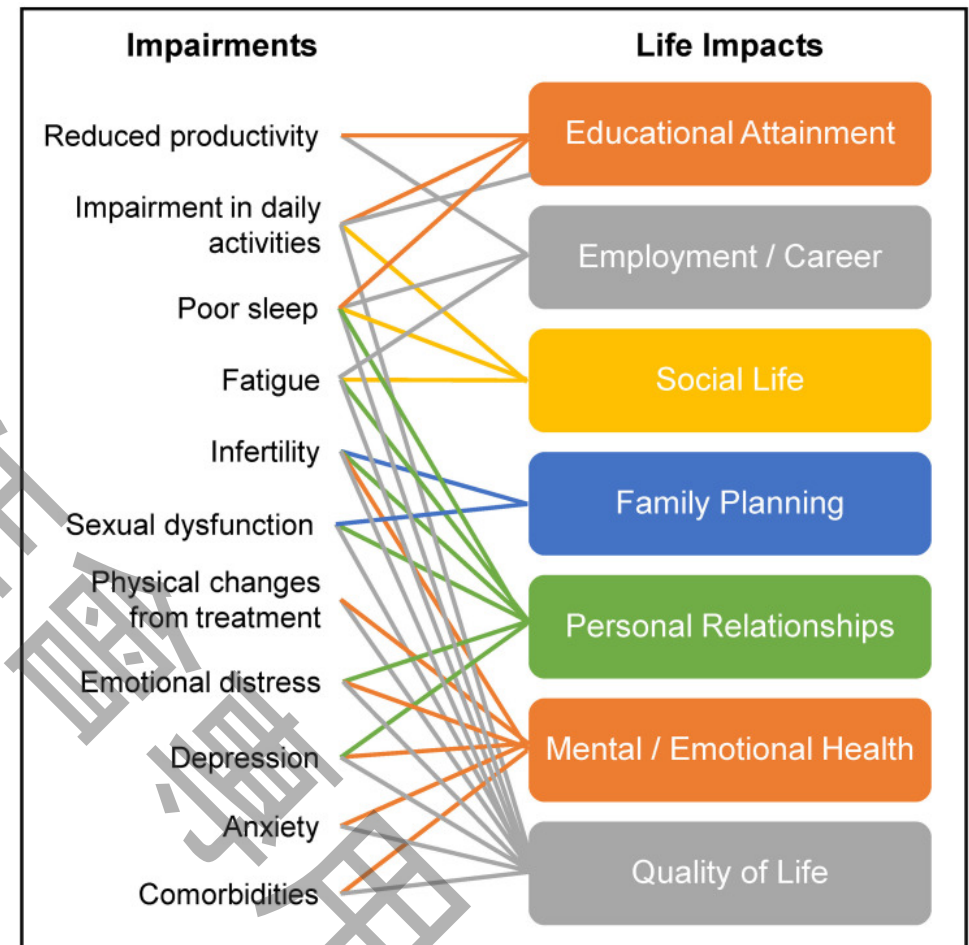
REVIEW

## Impact of Endometriosis on Life-Course Potential: A Narrative Review

This article was published in the following Dove Press journal:  
*International Journal of General Medicine*

### Influence of Endometriosis on Life Domains:

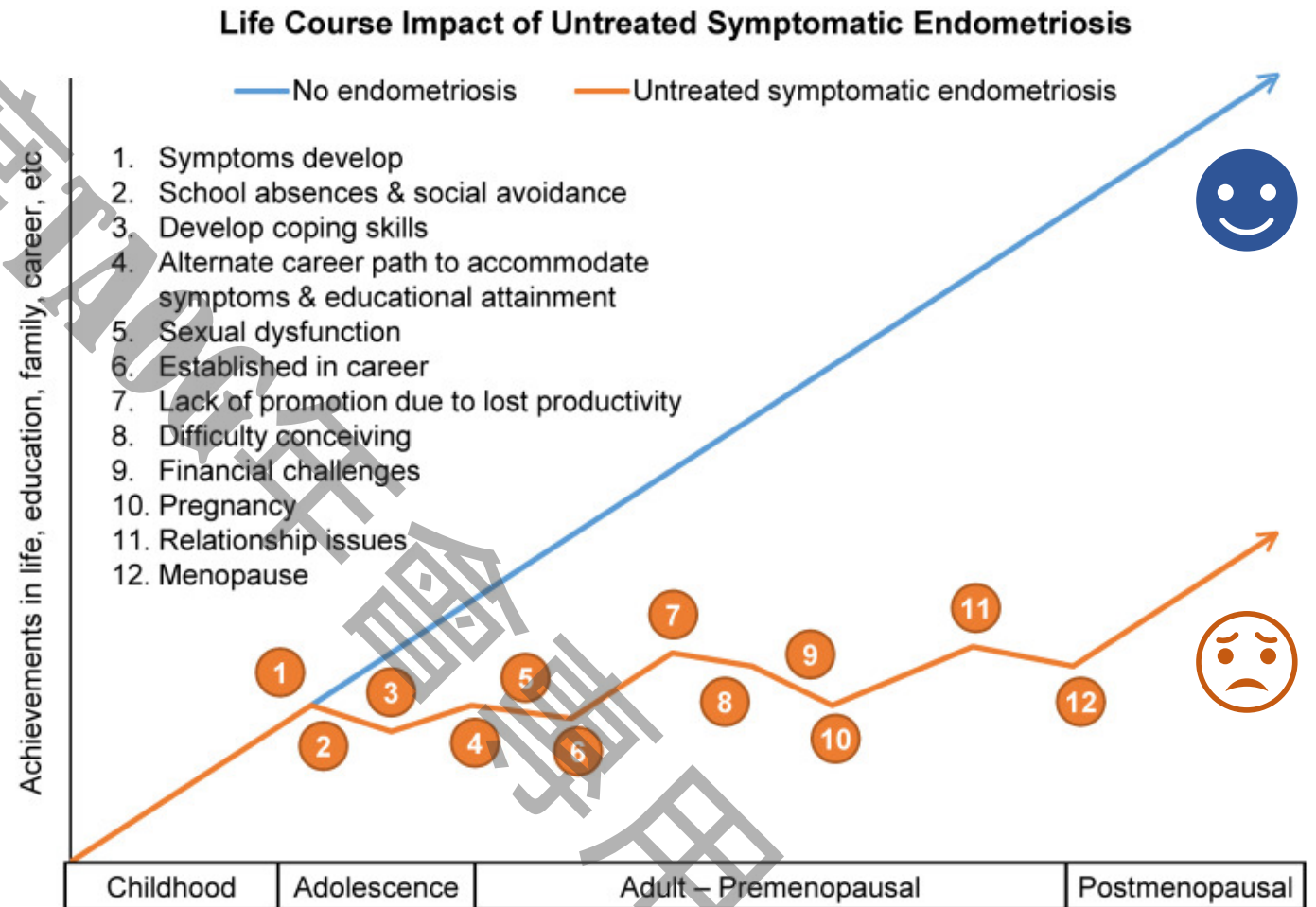
- Educational Attainment
- Employment and Career
- Social Life
- Fertility
- Personal Relationships
- Quality of Life
- ...



# Endometriosis may begin to **alter life-course trajectory in adolescence** & continue to have effects **throughout life until menopause**

Theoretical effects of endometriosis on life-course trajectory. Life exposures and their influences on a patient's attainments in life, **education, family, career**, etc.

A comparison of **untreated or persistently** symptomatic endometriosis **vs no** endometriosis :



# What kind of patient type we can start treatment with Visanne?



113年  
Bayer  
113年  
113年  
113年

# Post-surgery patient





# The **ESHRE 2022 guidelines** pay more attention to "**recurrence**" and emphasize that medication should be continued for **at least 18-24 months after surgery**

## Medical therapies for prevention of recurrence

After surgical management of ovarian endometrioma in women **not immediately seeking conception**, clinicians are recommended to **offer long-term hormone treatment** for the secondary **prevention** of endometrioma and endometriosis-associated related symptom **recurrence**. (**Strong recommendation**)

- **Progestogens (e.g. dienogest)**
- COCs
- GnRH agonists

## At least 18-24 months of treatment

Clinicians should consider prescribing the postoperative use of LNG-IUS or a combined hormonal contraceptive for **at least 18–24 months** for the secondary prevention of endometriosis-associated dysmenorrhea. (**Strong recommendation**)

## COCs + progestins as first-line therapy

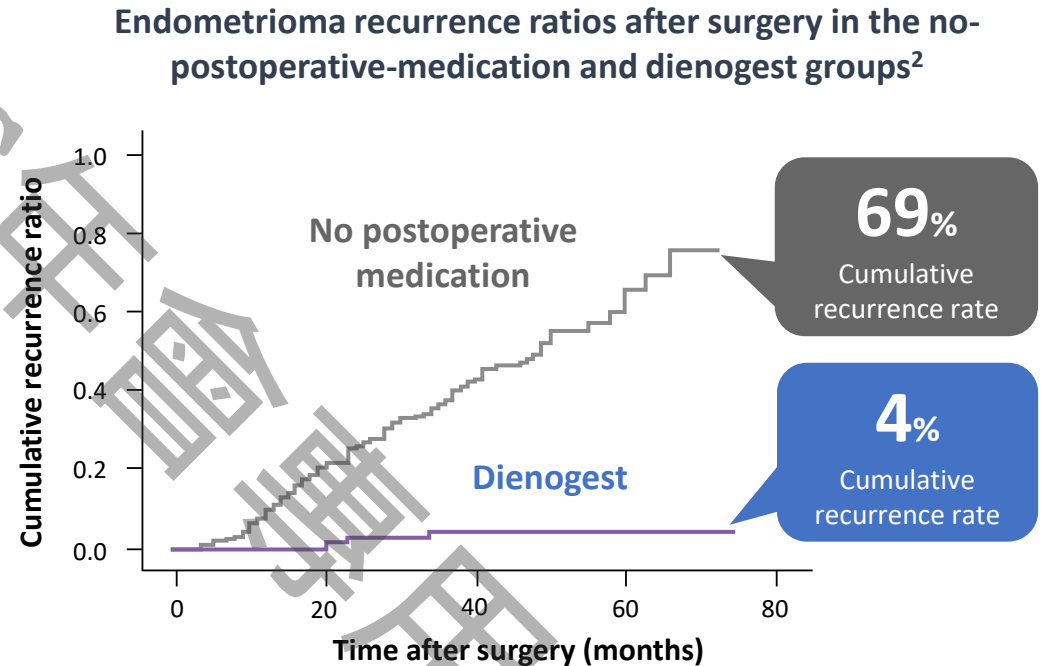
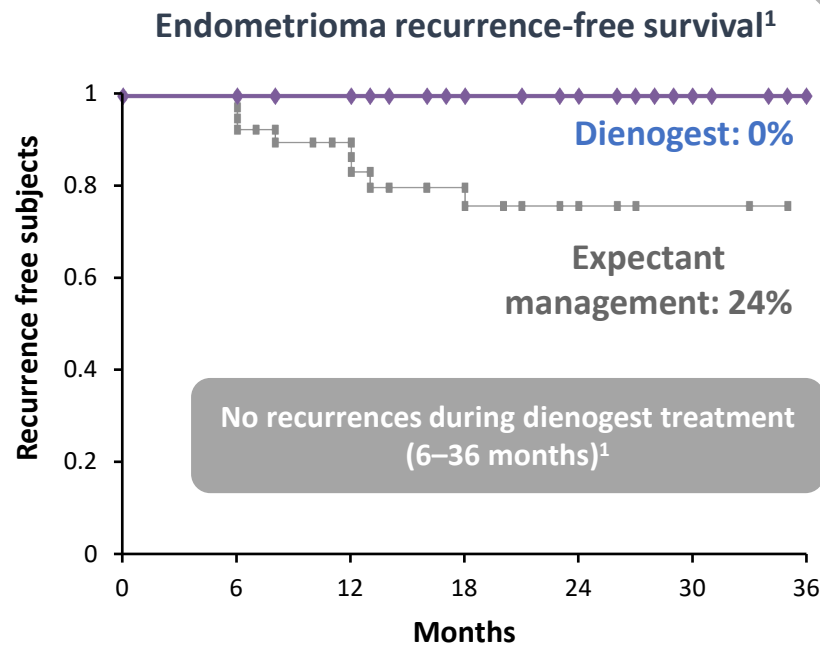
COCs, preferably in a continuous regimen, and **progestins** can be considered feasible options as **first-line treatments**.



# Visanne significantly reduced post-surgery lesion recurrence at 5 years vs no treatment

A retrospective study of **81 patients** was performed in **Japan**. Patients had a 6-month minimum follow-up after **laparoscopic surgery** for ovarian endometriomas performed. Patients who chose to receive **2 mg dienogest QD (n = 41)** and those who were **managed expectantly (n = 40)** postoperatively were included.<sup>1</sup>

A retrospective cohort study enrolled **568 women** with MRI-based diagnosis of ovarian endometrioma. Recurrence rates and side effects **over 5 years** were investigated in **417 without postoperative medication** and **151 who received dienogest postoperatively at 2 mg**.<sup>2</sup>

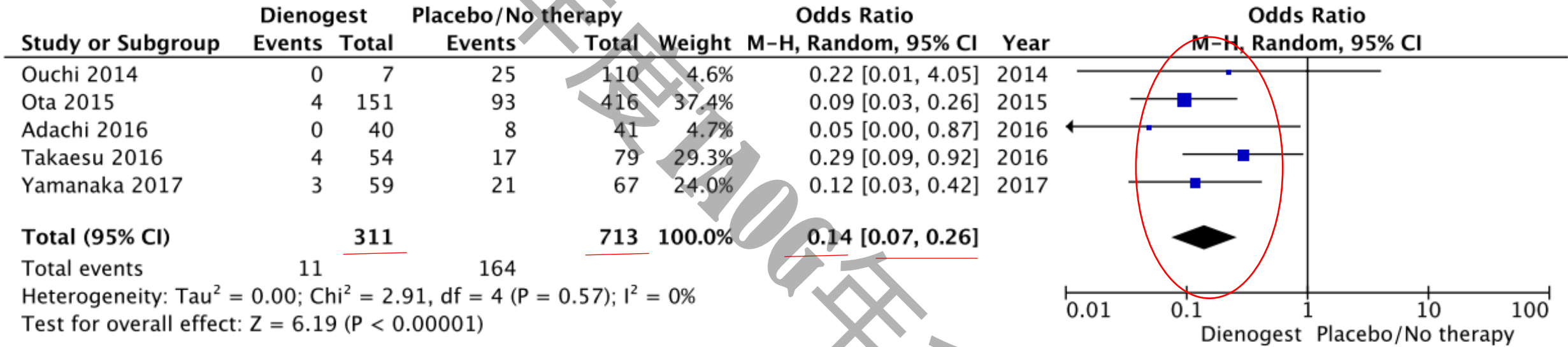


MRI, magnetic resonance imaging.

• 1. Adachi K, et al. Gynecol Endocrinol. 2016;32:646-9. 2. Ota Y, et al. J Endometr Pelvic Pain Disord. 2015;7:63-7.



# Better efficacy in Visanne for **recurrence prevention** vs placebo/no treatment



**Fig. 2** Forest plot: endometriosis recurrence with post-operative dienogest compared to placebo/no therapy

Reproductive Sciences (2023) 30:3135–3143



# Visanne is the better optimal hormonal regimen as **maintenance therapy** to **prevent recurrence post endometriosis resection surgery**

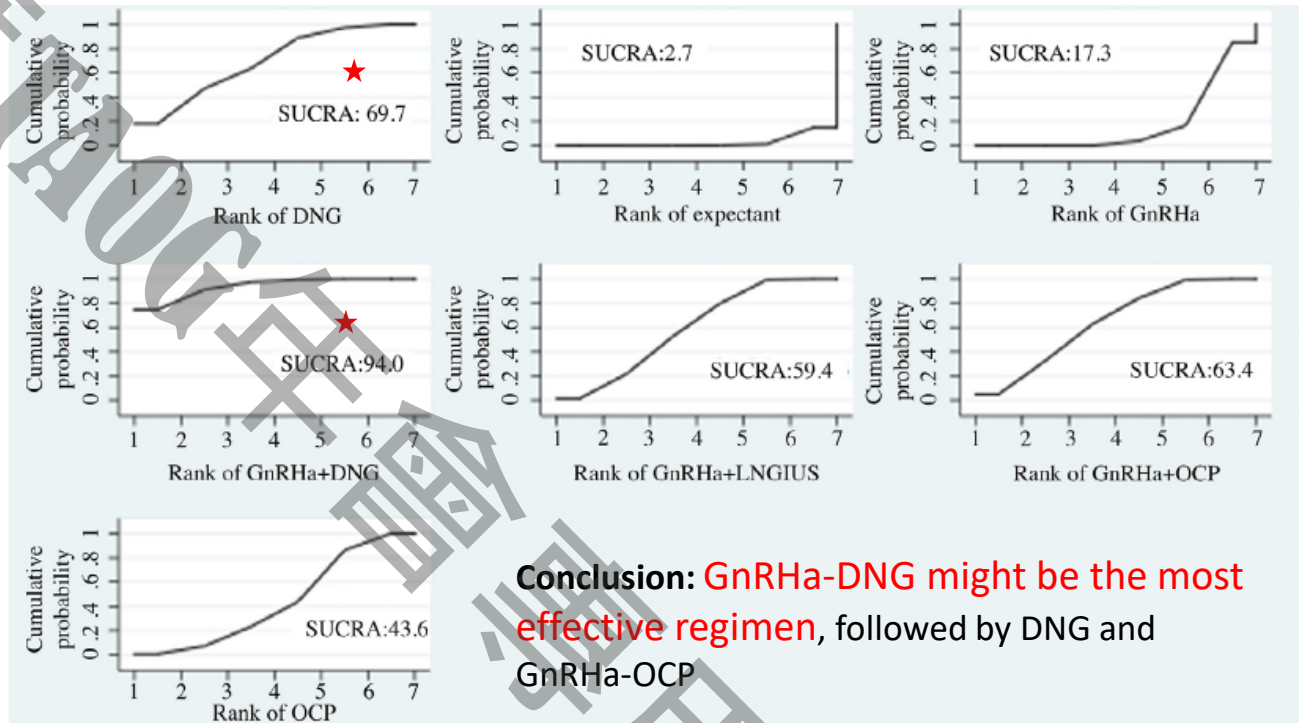
## Review Article

### Maintenance Therapy for Preventing Endometrioma Recurrence after Endometriosis Resection Surgery – A Systematic Review and Network Meta-analysis

Chui-Ching Chiu, MD, Teh-Fu Hsu, MD, Ling-Yu Jiang, MD, I-San Chan, MD, Ying-Chu Shih, MD, Yen-Hou Chang, MD, Peng-Hui Wang, MD, PhD, and Yi-Jen Chen, MD, PhD

From the Department of Obstetrics and Gynecology (Drs. Chiu, Jiang, Chan, Shih, Chang, Wang, and Chen), Department of Emergency Medicine (Dr. Hsu), Taipei Veterans General Hospital, School of Medicine, Institute of Clinical Medicine, National Yang Ming Chiao Tung University (all authors), and Institute of Clinical Medicine (Drs. Chiu, Jiang, Chan, Shih, Wang, and Chen), National Yang Ming University, Taipei, Taiwan.

Results of network rank test. SUCRA is a numeric presentation of the ranking with each treatment. The closer the SUCRA value to 100%, the greater the likelihood that the treatment is in the top rank. DNG = dienogest; GnRHa = gonadotropin releasing hormone agonists; LNGIUS = levonorgestrel-releasing intrauterine system; OCP = oral contraceptive pills; SUCRA = surface under the cumulative ranking curve.



**Conclusion: GnRHa-DNG might be the most effective regimen, followed by DNG and GnRHa-OCP**

- **Study design:** Network meta-analysis of 11 trials (included 2 randomized controlled studies and 9 cohort studies). A total of 2394 patients were treated with 6 interventions and expectant management.
- **Objective:** to rank the long-term efficacy (follow-up >2 years after surgery) of the different hormonal regimens in the prevention of endometrioma recurrence.



# Clinical diagnosis patient



# Case 1 – Patient profile



Age: 24



Obstetrics history: G0 P0  
(unmarried)

Profile: desire for a maintenance treatment to avoid another surgery  
Treatment expectation:  
1. Prevent recurrence  
2. To avoid another surgery



## Chief complaint

- Dysmenorrhea with diarrhea



## Present illness

- Elevated CA-125 (44)
- Presence of ovarian endometrioma

# Case 1 - Diagnostic work-up



## Physical examination

- Abdominal examination
  - tenderness (-)
  - rebound tenderness (-)



## Diagnostic work-up

- Imaging study
  - Pelvis US: left ovarian hypoechoic cyst 8.7



## Diagnosis

- Ovarian endometrioma



# Case 1 – Treatment plan

## Past history

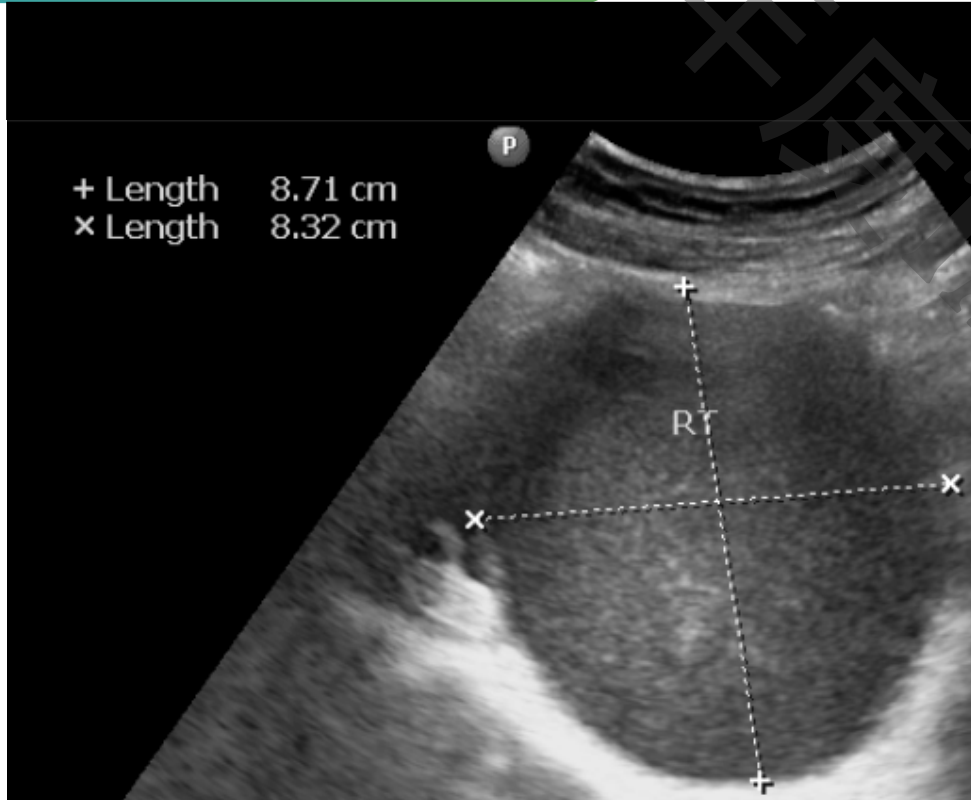
- Surgical (-)
- Medication (-)

## Treatment plan

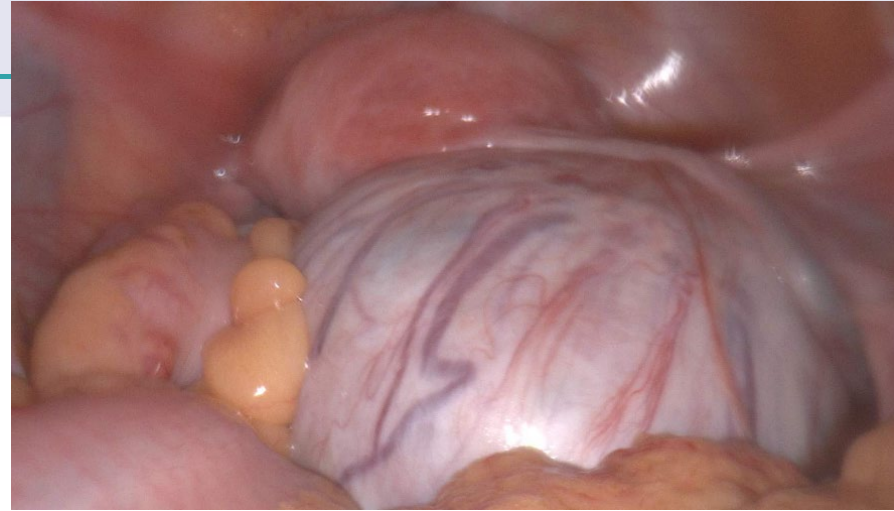
- LSC operation
- Post operative Medical treatment
- Visanne 2mg

# Case 1 – Treatment : LSC ovarian cystectomy

## Treatment course



**Baseline  
8.7 cm**



The case study herein has been written by healthcare professionals in this therapeutic area based on actual patients they have managed. Clinical outcome may differ for others.

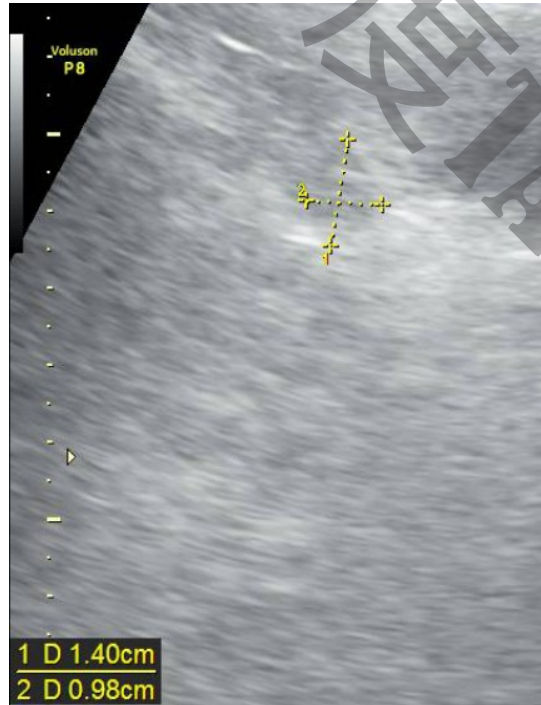
# Case 1 – Treatment outcomes

## Treatment course

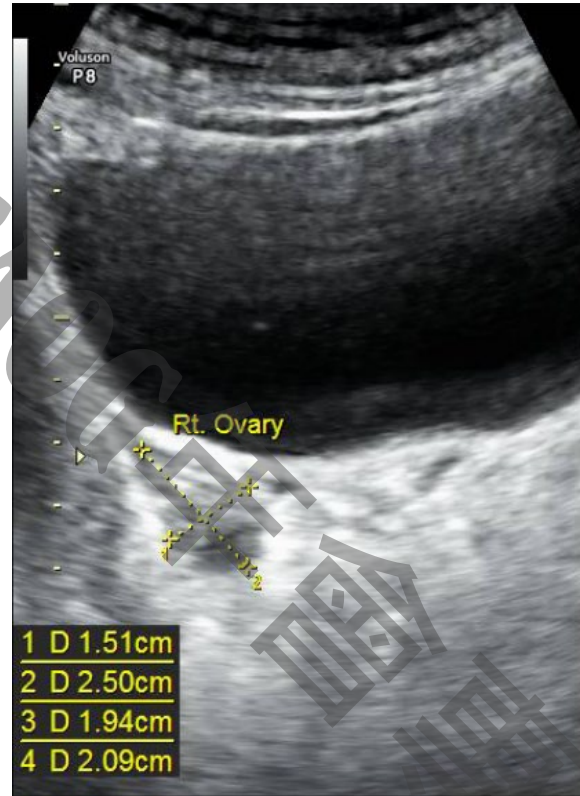
- No recurrence (ultrasound imaging)



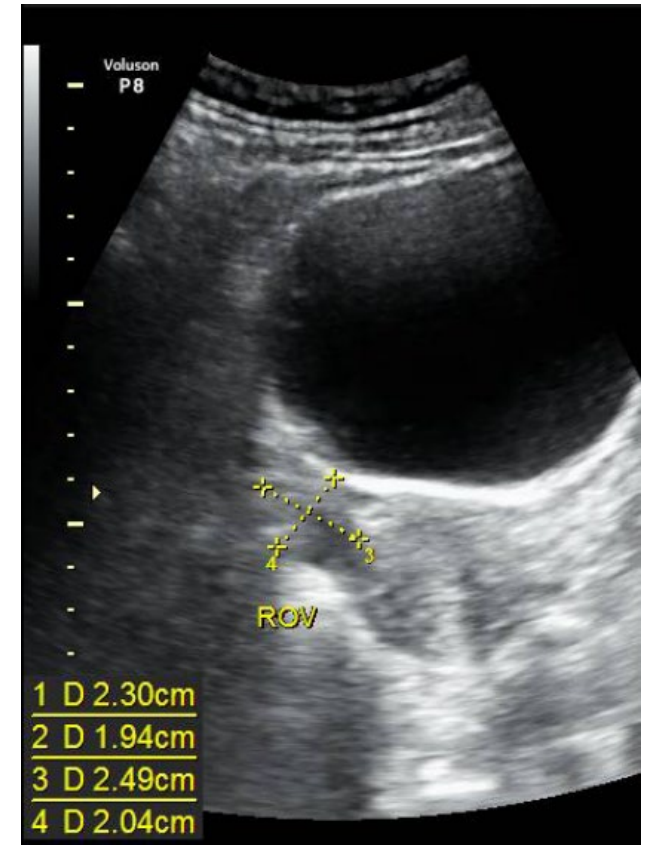
**Baseline**  
**8.7 cm**



**24 months**



**36 months**



**48 months**

The case study herein has been written by healthcare professionals in this therapeutic area based on actual patients they have managed. Clinical outcome may differ for others.

## Case 2 – Patient profile



Age: 39( 105-03-19)



Obstetrics history: G1 P0 A1  
(unmarried)

**Profile: desire for a maintenance treatment to avoid another surgery**

**Treatment expectation:**

1. Prevent recurrence
2. To avoid another surgery



### Chief complaint

- Sudden onset of severe lower abdominal pain
- Emergency department



### Present illness

- Dysmenorrhea every month

## Case 2 - Diagnostic work-up



### Physical examination

- Abdominal examination
  - tenderness (+)
  - rebound tenderness (+)



### Diagnostic work-up

- Imaging study
  - Pelvis US: left ovarian hypoechoic cyst 6.6



### Diagnosis

- Ovarian endometrioma





## Case 2 – Treatment plan

### Past history

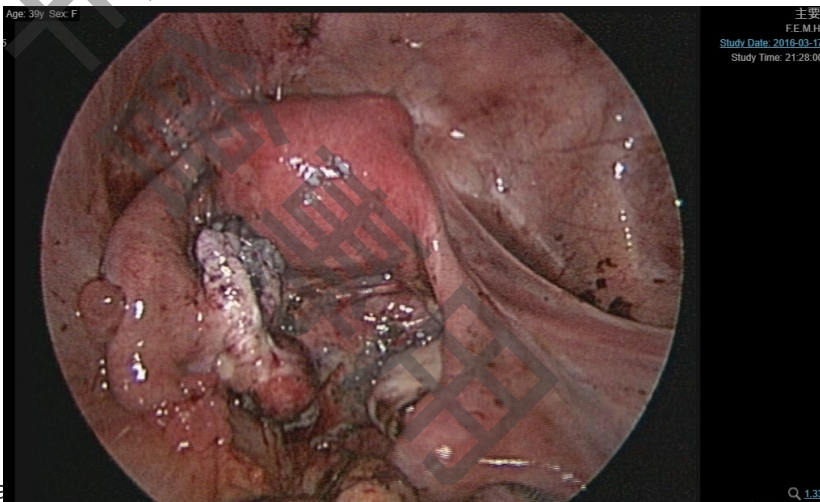
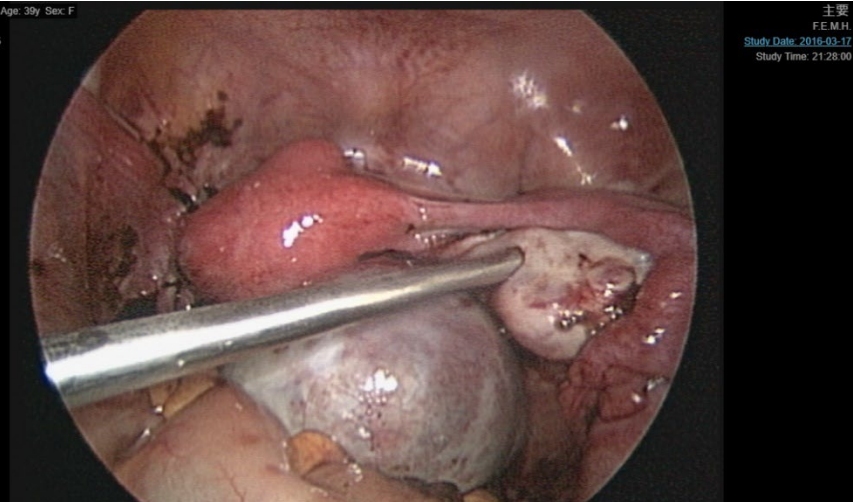
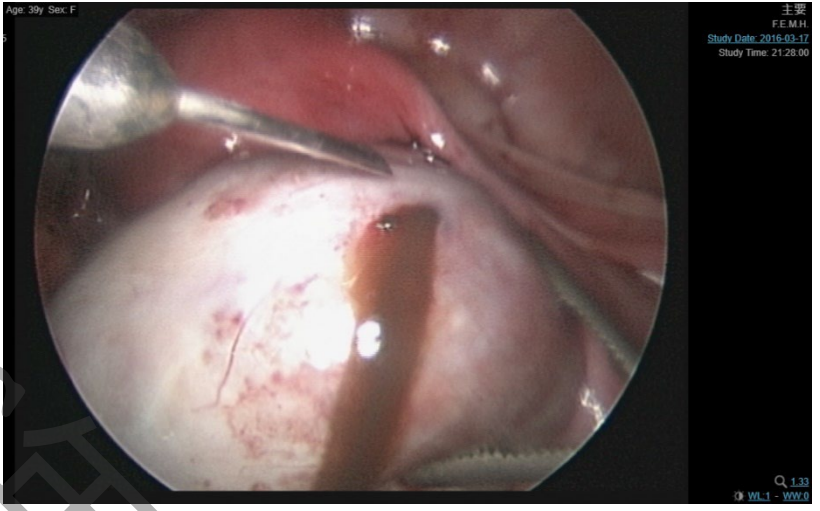
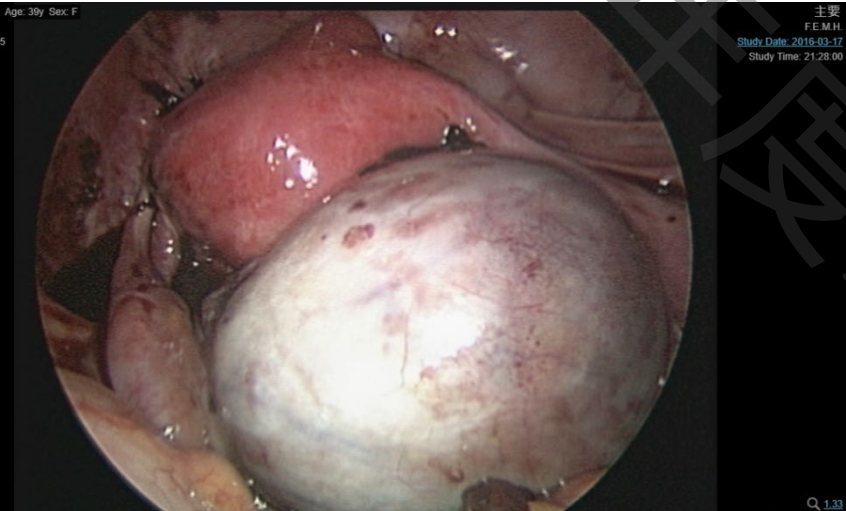
- Surgical (-)
- Medication (-)

### Treatment plan

- LSC operation
- Post operative Medical treatment
- GNRH agonist 6 months

# Case 2 – Treatment : LSC ovarian cystectomy

## Treatment course



The case is for informational purposes only. Clinical outcome may differ for others.

ic area based on actual

## Case 2 – Treatment : LSC ovarian cystectomy

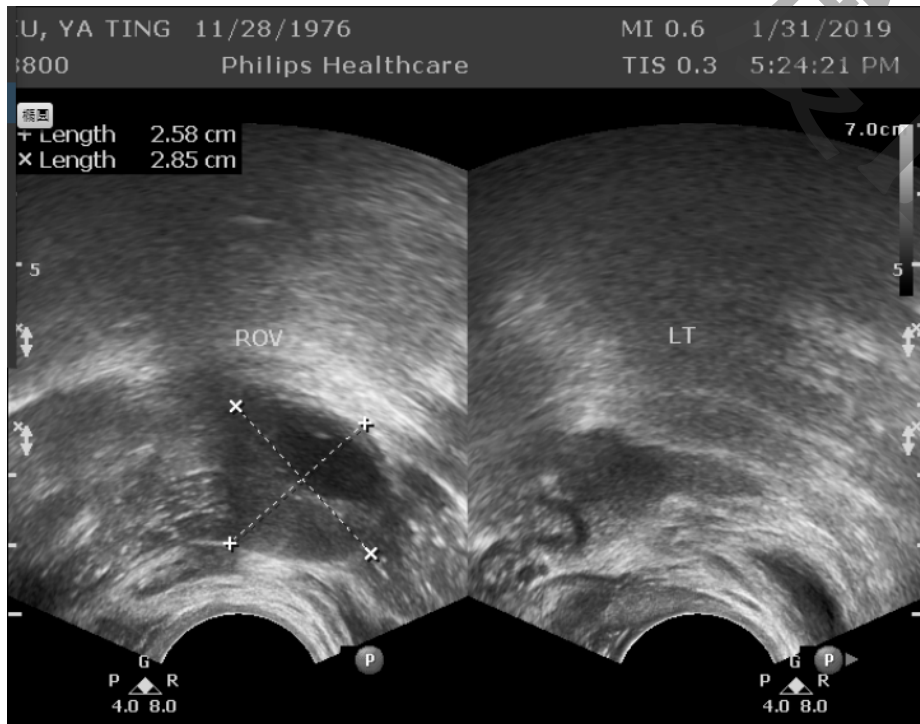
### Treatment course

- 105-03 ~ 105-09:  
GNRH agonist months : Diphereline \* 2 dose
- Loss follow up
- 107-09 :Recurrent ovarian chocolate cyst by LMD
- 107-09~107-11 : visanne 1# QD \*28 days \* 3 months
- 107-11 ~ 113-02 : 連續處方簽 \* 3 months \* (5年5個月)

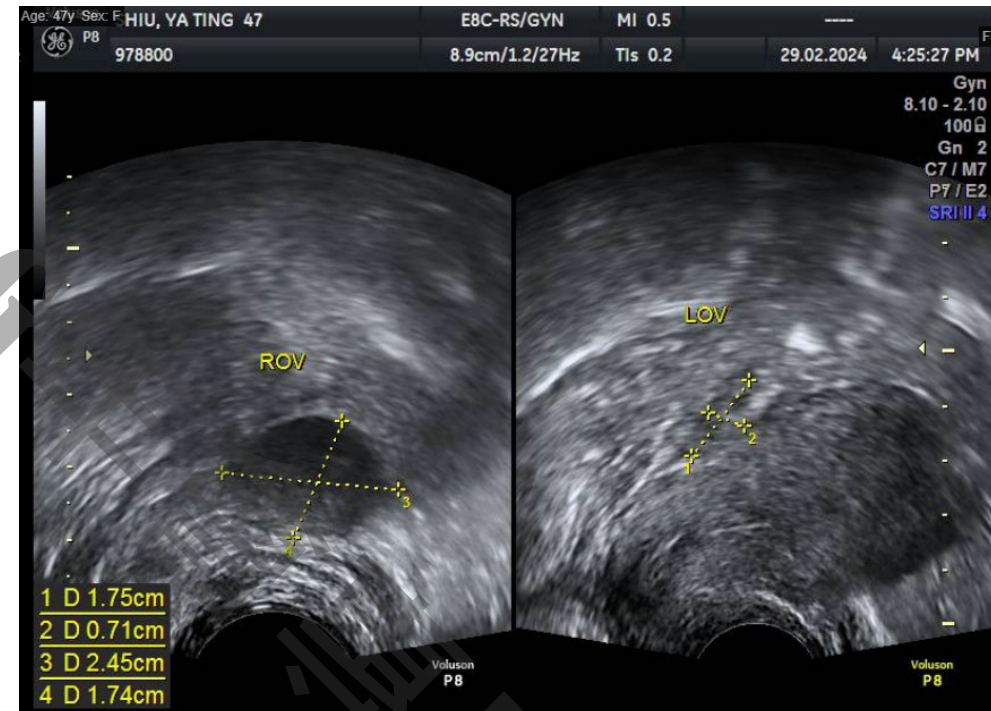
# Case 2 – Treatment outcomes

## Treatment course

- No recurrence (ultrasound imaging)



4 months



65 months

The case study herein has been written by healthcare professionals in this therapeutic area based on actual patients they have managed. Clinical outcome may differ for others.

# Visanne藥品給付規範

(1)有關台灣婦產科醫學會建議增訂治療子宮內膜異位症之含 dienogest 成分藥品(如 Visanne)之藥品給付規定案。

說明：詳附錄會議資料報告事項第 4 案之(1)報告內容。

決定：同意健保署之初核結果，暫不訂定含 dienogest 成分藥品之給付規定。

報告案第 4 案之(1)：已收載成分藥品給付規定異動案 (不同意修訂)

案由	案件經過	給付規定章節碼及成分類別	原給付規定	異動後給付規定	說明
有關「台灣婦產科醫學會」建議增訂治療子宮內膜異位症之含 dienogest 成分藥品(如 Visanne)之藥品給付規定案。	<p>1. 依台灣婦產科醫學會建議事項辦理。</p> <p>2. 本藥品經主管機關核准之適應症為：治療子宮內膜異位症伴隨之骨盆疼痛。</p> <p>3. 本藥品於 106 年 9 月 1 日納入健保給付，健保支付價為每粒 48.8 元。由於健保給付範圍與適應症相同，有關是否訂定藥品給付規定一節，相關會議討論結果如下：</p> <p>(1) 106 年 6 月藥物共同擬訂會議：本案藥品為治療子宮內膜異位症之藥品，可增加生育年齡婦女受孕機會，倘非臨床治療需要應不至濫用，不須另訂藥品給付規定，惟治療前應以病理學診斷確認為子宮內膜異位症，請健保署將此列入審查注意事項。</p> <p>(2) 本案經請台灣婦產科醫學會、台灣醫院協會及中華民國醫師公會全國聯合會協助提供子宮內膜異位症治療前應以病理學診斷確認為之審查建議，其中，台灣婦產科醫學會建議增訂審查注意事項條文，台灣醫院協會意見為不同意修訂，中華民國醫師公會全國聯合會則未回復意見。案經 106 年 10 月 13 日全民健康保險醫療費用審查注意事項 106 年度研修案西醫分科專家諮詢會議第 2 次會議討論，決議不另增列審查注意事項。</p> <p>4. 台灣婦產科醫學會於 106 年 12 月來函建議增訂本藥品給付規定為「需經手術(如腹腔鏡)或病理報告，確診為子宮內膜異位症，合併骨盆疼痛」，並建議限婦產科專科醫師使用。</p>	無	無	無異動	<p>1. 子宮內膜異位症之診斷方式包含：病史詢問、<u>骨盆檢查、影像學檢查及腹腔鏡術</u>，<u>臨床上通常不會為了診斷子宮內膜異位症而進行腹腔鏡術</u>，是否需要手術則依病情需要，手術方式也須依據病患是否有懷孕的需求。目前陰道超音波是診斷子宮內膜異位症的首選，歐美先進國家對子宮內膜異位症治療，只要痛經及超音波之影像佐證，即可建議藥物治療。</p> <p>2. 現行健保給付用於治療子宮內膜異位症的藥品，除高價藥品 Gn-RH analogue 有給付條件限制外，其他治療藥品(例如：含 gestrinone 及 danazol 成分藥品)皆無限制其需經手術(如腹腔鏡)或病理報告確診為子宮內膜異位症方能使用；又本案藥品自納入健保給付至今甫滿一年，並未觀察到用藥浮濫情形。</p> <p>3. 綜上所述，本案暫不另訂藥品給付規定。</p>

## 說明

1. 子宮內膜異位症之診斷方式包含：病史詢問、骨盆檢查、影像學檢查及腹腔鏡術，臨床上通常不會為了診斷子宮內膜異位症而進行腹腔鏡術，是否需要手術則依病情需要，手術方式也須依據病患是否有懷孕的需求。目前陰道超音波是診斷子宮內膜異位症的首選，歐美先進國家對子宮內膜異位症治療，只要痛經及超音波之影像佐證，即可建議藥物治療。
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3. 綜上所述，本案暫不另訂藥品給付規定。

全民健康保險藥物給付項目及支付標準共同擬訂會議第35次(107年12月)會議紀錄, [衛生福利部中央健康保險署](#)

**Laparoscopy is no longer** the diagnostic gold standard,  
**but clinical symptoms** should be the focus

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### ESHRE 2022 Guidelines

“Laparoscopy is no longer the diagnostic gold standard, and it is **now only recommended** in patients with **negative imaging results** and/or **where empirical treatment was unsuccessful or inappropriate.**”

## DIAGNOSIS OF ENDOMETRIOSIS

### SIGNS AND SYMPTOMS

*Consider Endometriosis when the woman reports one or more of these symptoms*

Dysmenorrhoea  
Deep dyspareunia  
Dysuria  
Dyschezia 排便疼痛  
Painful Rectal bleeding  
Haematuria

Shoulder tip pain  
Catamenial pneumothorax 月經性氣胸  
Cyclical cough/haemoptysis /chest pain  
Cyclical scar swelling and pain  
Fatigue  
Infertility

A symptom diary  
or app can be  
helpful in  
the history taking  
process



# APAC Consensus: Protocol for **early** diagnosis

## Questions for women of reproductive age



Pelvic-abdominal **pain** and/or infertility?



Gynaecological symptoms (**dysmenorrhoea, non-cyclical pelvic pain, deep dyspareunia or fatigue**)?



Non-gynaecological cyclical symptoms (**dyschezia, dysuria, haematuria, rectal bleeding or shoulder pain**)?



Adolescents with intractable pain unresponsive to NSAIDs?

If the answer is:

**Yes**

## Pelvic examination, including vaginal palpation, speculum and rectovaginal examination



Painful induration, tenderness of the uterus

DE suspected



Visible vaginal lesions, **nodules in the posterior vaginal fornix and retroverted uterus**

DE suspected



Adnexal mass  
Endometrioma suspected



Normal/no pathological findings

Endometriosis suspected

Clinical diagnosis



Imaging/TVS

If TVS is not appropriate, use TAS or TRS

**Endometriosis**

(including endometrioma and DE)

DE, deep endometriosis; NSAIDs, non-steroidal anti-inflammatory drugs; TAS, transabdominal sonography; TRS, transrectal sonography; TVS, transvaginal sonography

# Endometriosis of uterus (Adenomyosis)





## Case 3– Patient profile



Age: 40



Obstetrics history: G1 P1  
(married)

### (40+Aged):

Profile: desire for a maintenance treatment to avoid another surgery until menopause

Treatment expectation:

1. Prevent recurrence
2. To avoid another surgery



### Chief complaint

- Recurrent Dysmenorrhea
- LSC op for chocolate cyst 6 years ago
- No hormonal treatment post-surgical



### Present illness

- Elevated CA-125 (121.9)
- Presence of Endometriosis of uterus

Adenomyosis=Endometriosis of uterus

## Case 3 - Diagnostic work-up



### Physical examination

- Abdominal examination
  - tenderness (-)
  - rebound tenderness (-)



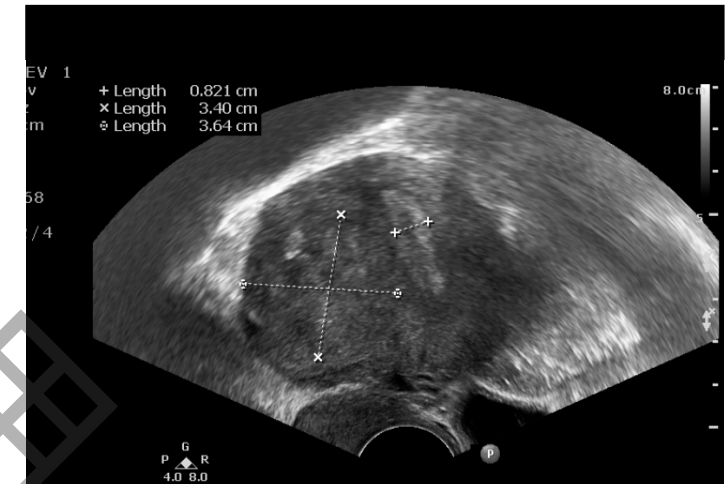
### Diagnostic work-up

- Imaging study
  - Pelvis US: Adenomyoma of uterus 3.4cm



### Diagnosis

- adenomyoma



Adenomyosis=Endometriosis of uterus

## Case 3 – Treatment plan

### Past history

- Surgical (+) LSC op for chocolate cyst 6 years ago
- Medication (-) No hormonal treatment post-surgical

### Treatment plan

- Medical treatment for Adenomyosis
- Visanne 2mg

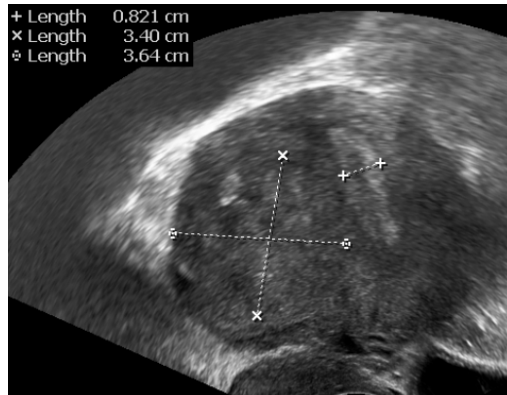
Adenomyosis=Endometriosis of uterus

This case study has been written by a healthcare professional in this therapeutic area using data based on an actual patients who the healthcare professional has managed

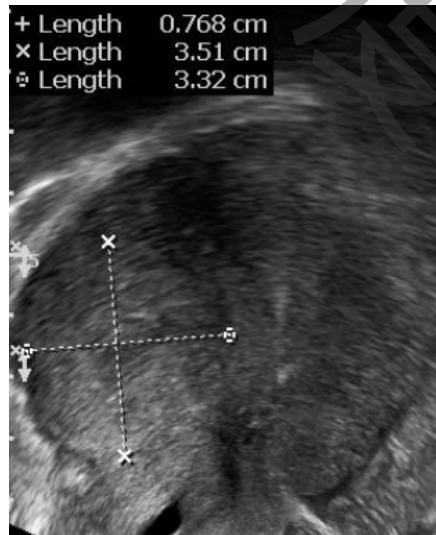
# Case 3– Treatment outcomes

## Treatment course

- Lesion reduction (ultrasound imaging)



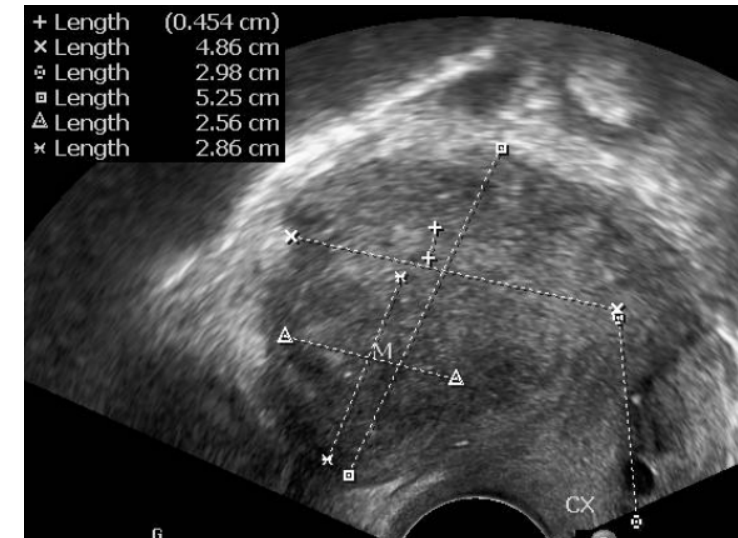
**Baseline**  
**3.4 cm**



**3 months**  
**3.5cm**



**6 months**  
**3.0 cm**



**12 months**  
**2.8 cm**

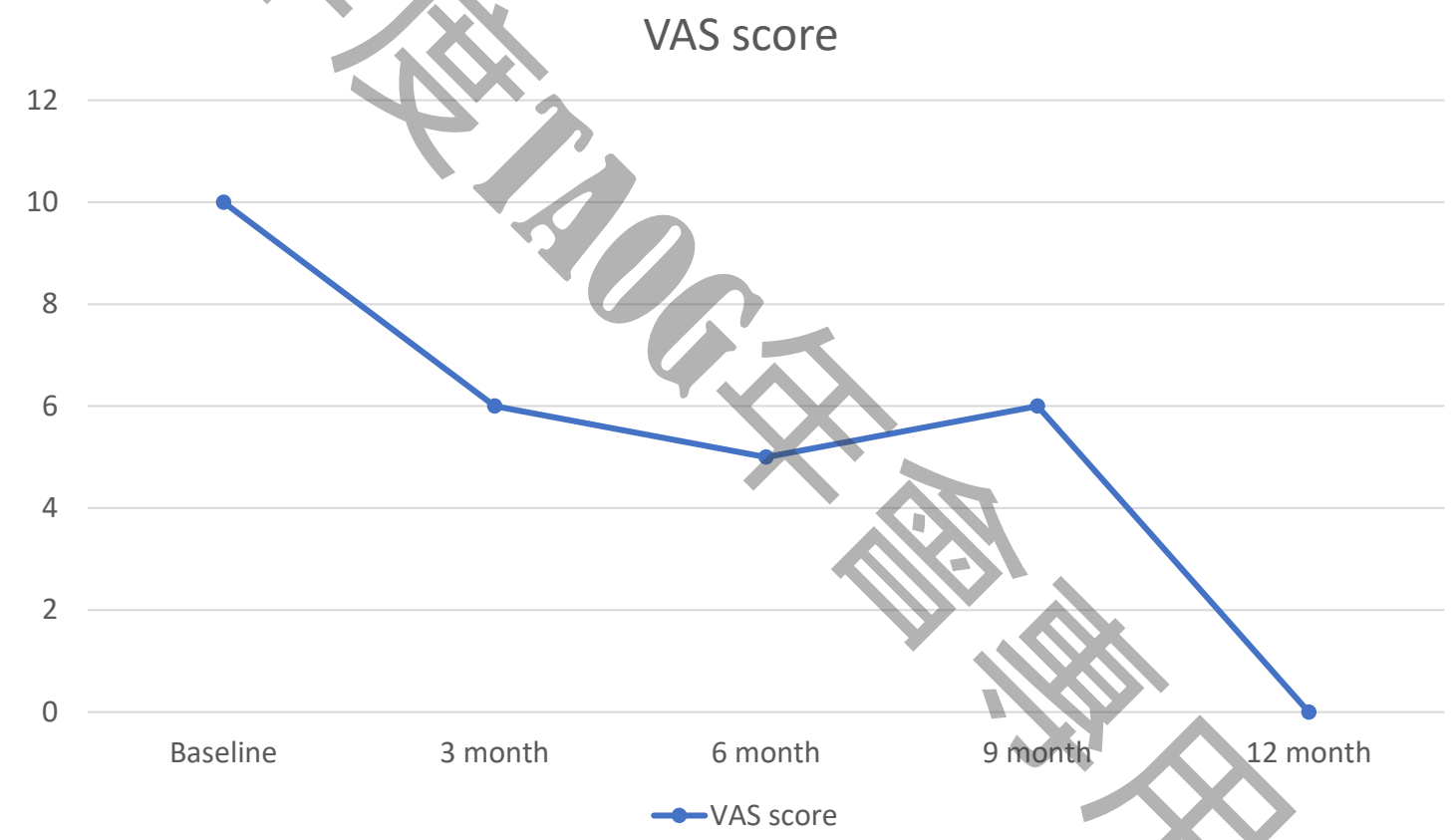
Adenomyosis=Endometriosis of uterus

The case study herein has been written by healthcare professionals in this therapeutic area based on actual patients they have managed. Clinical outcome may differ for others.

# Case 3– Treatment outcomes

## Treatment course

- VAS score

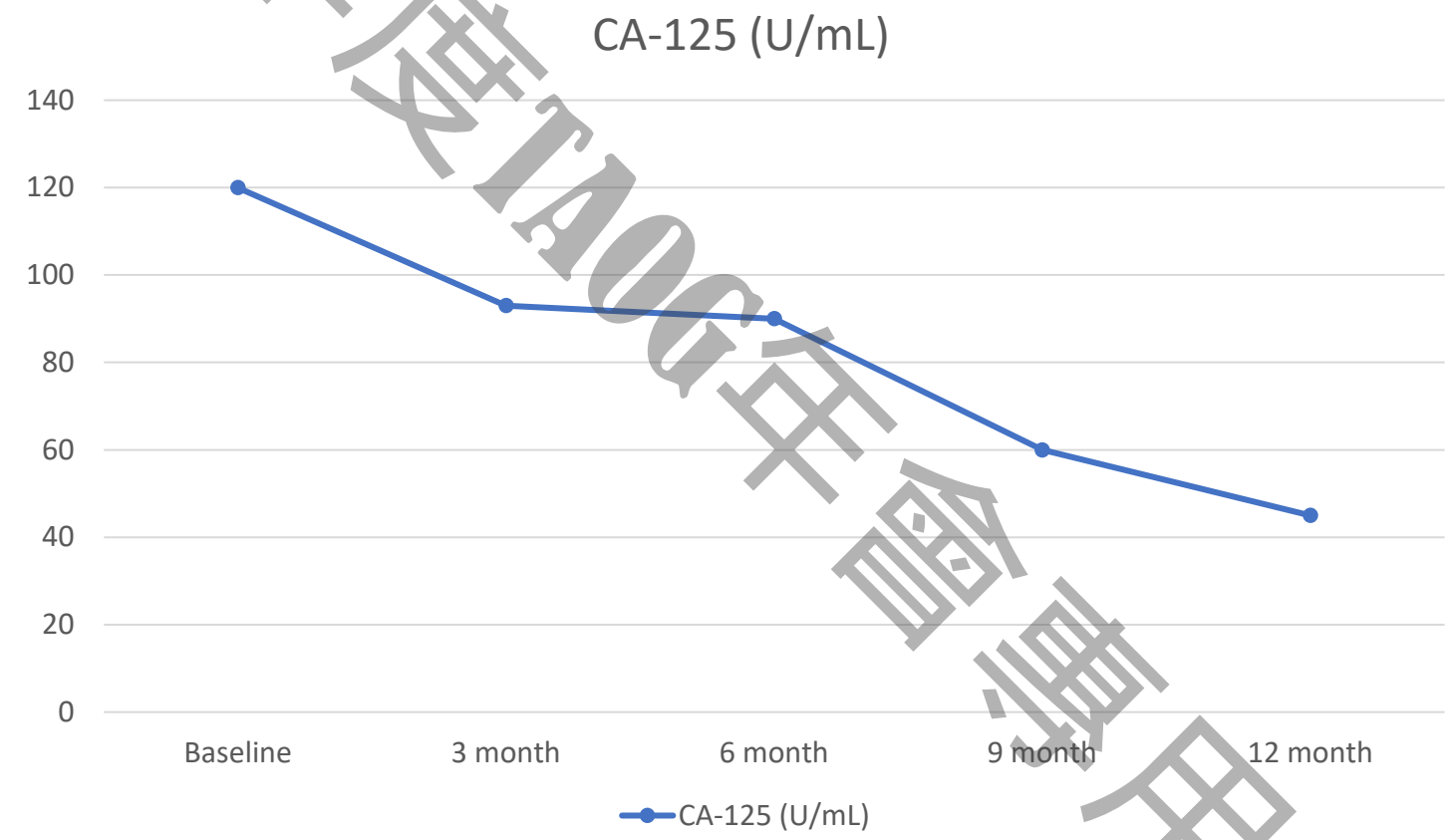


Adenomyosis=Endometriosis of uterus

# Case 3– Treatment outcomes

## Treatment course

- CA-125

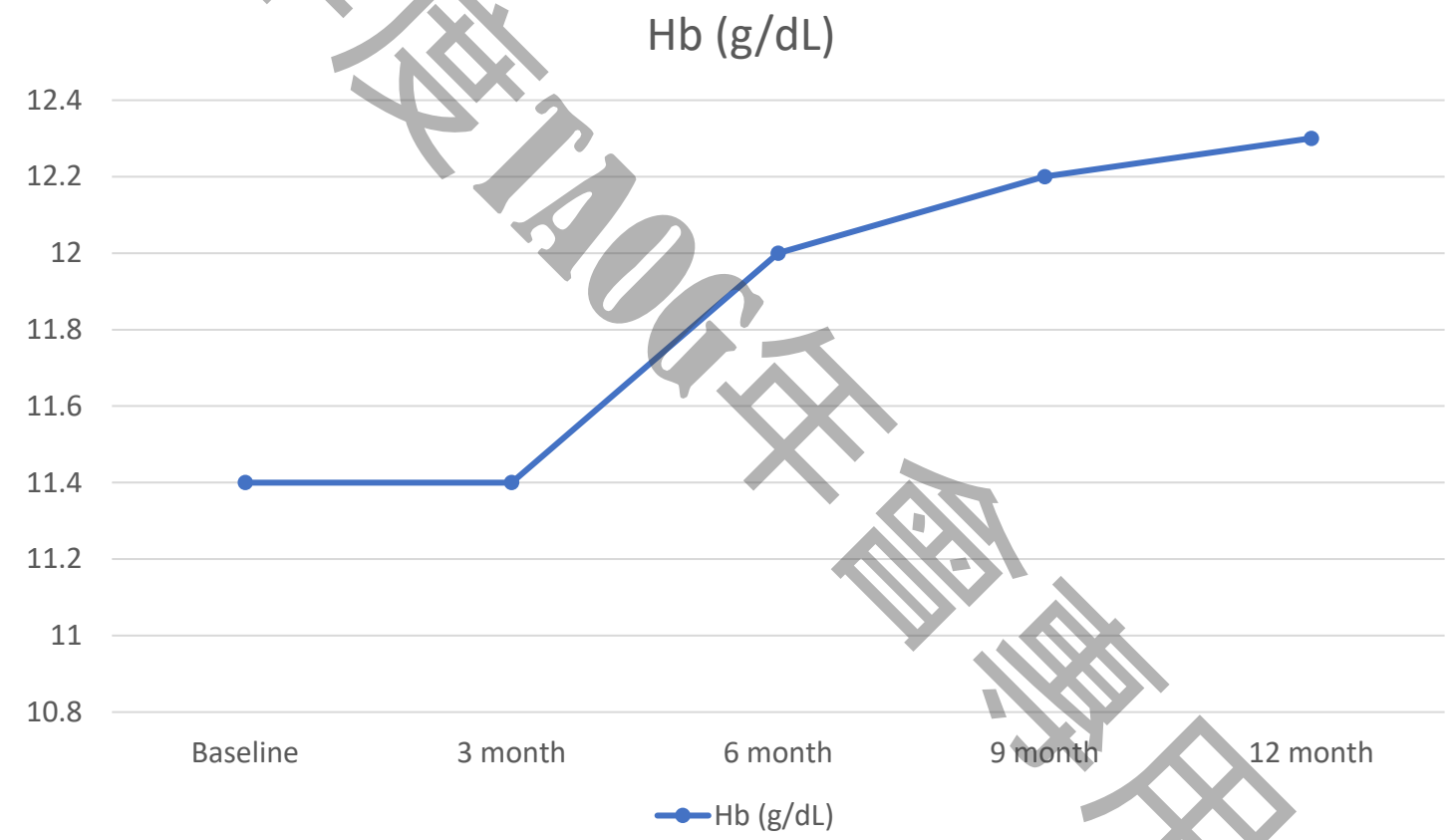


Adenomyosis=Endometriosis of uterus

# Case 2– Treatment outcomes

## Treatment course

- Hb level



Adenomyosis=Endometriosis of uterus

## Case 4– Patient profile



Age: 40(108-05-30)



Obstetrics history: G2 P2  
(married)

### (40+Aged):

Profile: desire for a maintenance treatment to avoid another surgery until menopause

Treatment expectation:

1. Prevent recurrence
2. To avoid another surgery



### Chief complaint

- Dysmenorrhea, aggravated for 1 year, poor response with NSAID



### Present illness

- Presence of adenomyosis

Adenomyosis=Endometriosis of uterus



## Case 4 - Diagnostic work-up



### Physical examination

- Abdominal examination
  - tenderness (-)
  - rebound tenderness (-)



### Diagnostic work-up

- Imaging study
  - Pelvis US:
    - adenomyoma
    - Uterine myoma



### Diagnosis

- Adenomyosis
- Uterine myoma

Adenomyosis=Endometriosis of uterus

## Case 4 – Treatment plan

### Past history

- Surgical (-)
- Medication (-)

### Treatment plan

- Medical treatment for Endometrioma of uterus
- Visanne 2mg

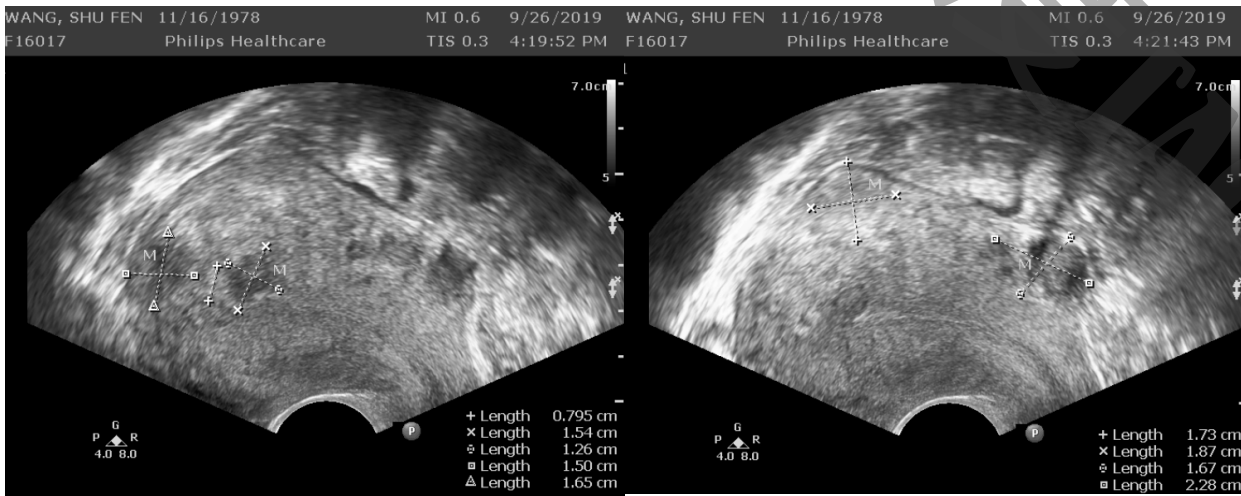
Adenomyosis=Endometriosis of uterus

This case study has been written by a healthcare professional in this therapeutic area using data based on an actual patients who the healthcare professional has managed

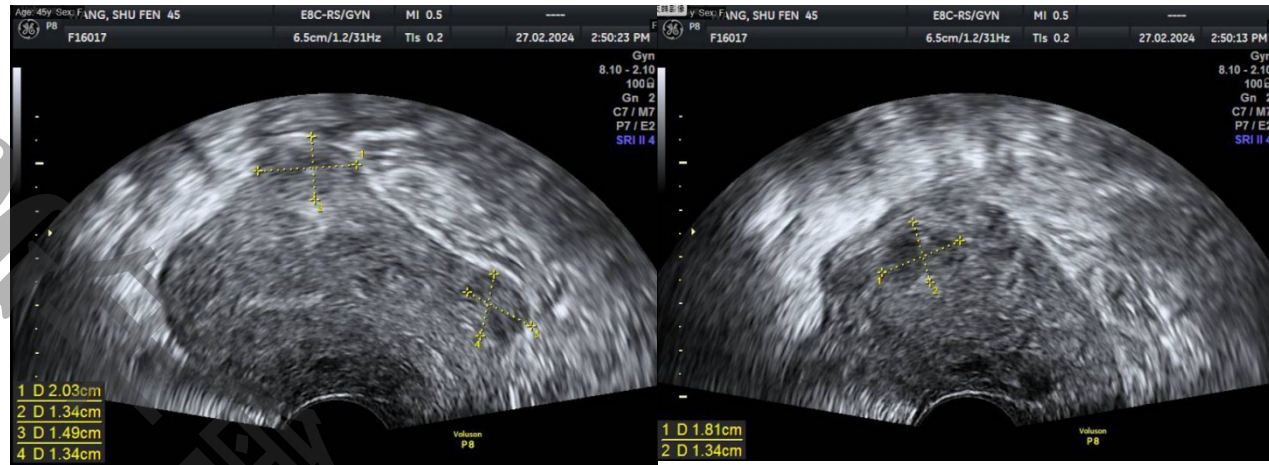
# Case 4– Treatment outcomes

## Treatment course

- (ultrasound imaging)



**4 months**



**57 months**

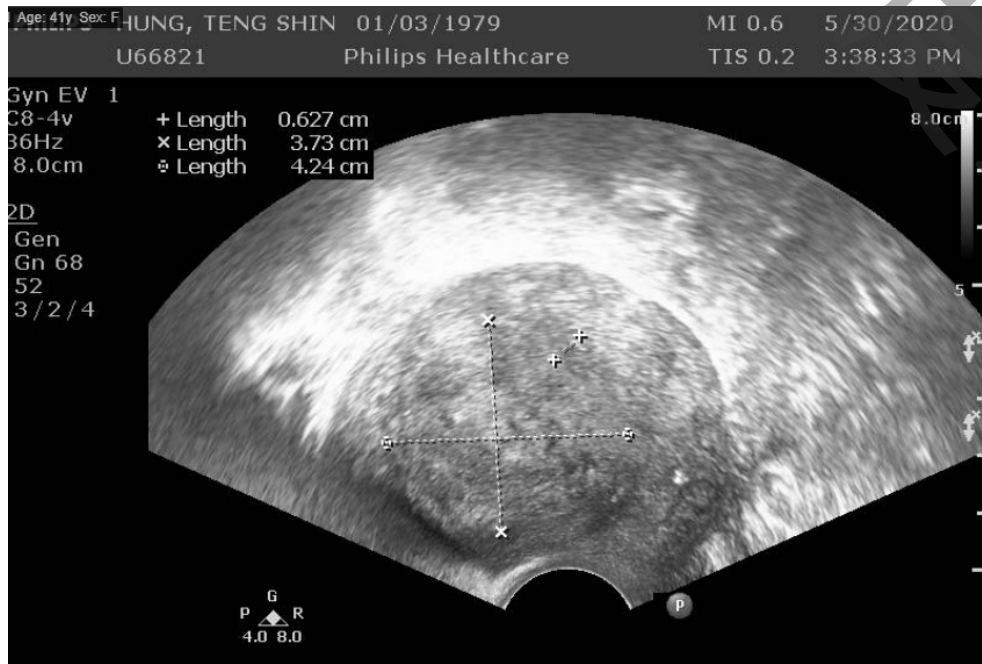
Adenomyosis=Endometriosis of uterus

The case study herein has been written by healthcare professionals in this therapeutic area based on actual patients they have managed. Clinical outcome may differ for others.

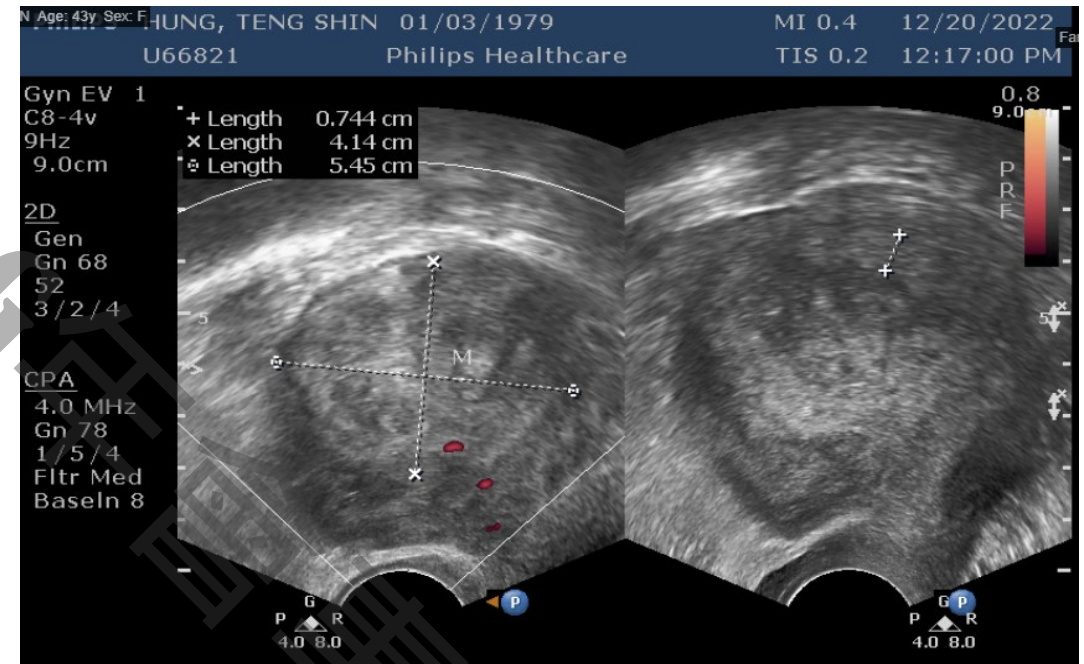
# Case 5– Treatment outcomes

## Treatment course

- (ultrasound imaging)



**6 months**



**36 months**

Adenomyosis=Endometriosis of uterus

The case study herein has been written by healthcare professionals in this therapeutic area based on actual patients they have managed. Clinical outcome may differ for others.

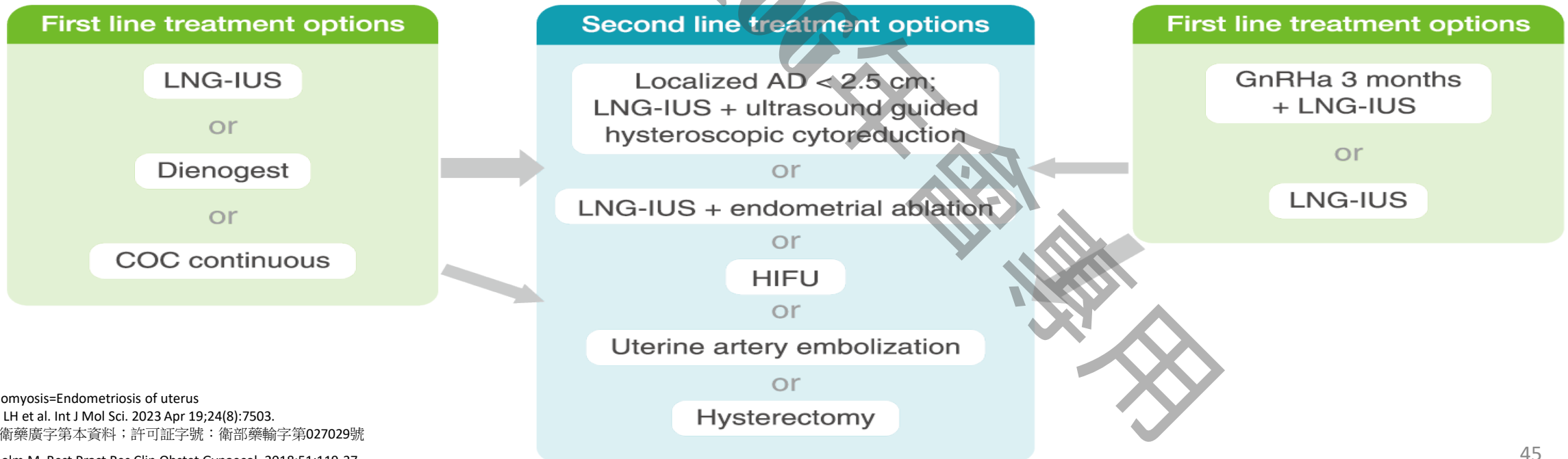
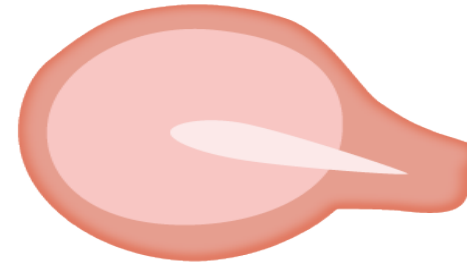
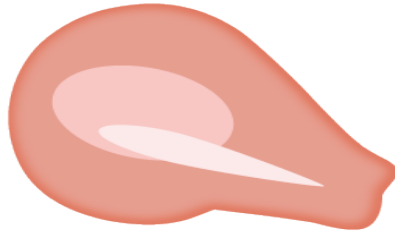


# Visanne can be used as **first-line medication** for patients with **moderate symptoms** of Endometriosis of uterus

經痛 ± 經血過多的子宮腺肌症病人建議治療方式

• Moderate symptoms & uterus < 100-150 mL

• Severe symptoms & uterus > 100-150 mL



Adenomyosis=Endometriosis of uterus  
Chen LH et al. Int J Mol Sci. 2023 Apr 19;24(8):7503.  
北市衛藥廣字第本資料；許可証字號：衛部藥輸字第027029號

Dueholm M. Best Pract Res Clin Obstet Gynaecol. 2018;51:119-37.

AD, adenomyosis; COC, combined oral contraceptive; GnRHa, gonadotropin-releasing hormone analogue; HIFU, high-intensity focused ultrasound; LNG-IUS, levonorgestrel-releasing intrauterine system.

It is the Society of Obstetricians and Gynaecologists of Canada (SOGC) policy to review the content five years after publication, at which time the document may be revised to reflect new evidence or the document may be archived.

No. 437, June 2023

## Guideline No. 437: Diagnosis and Management of Adenomyosis

(En français : Directive clinique no 437 : Diagnostic et prise en charge de l'adénomyose)

The English document is the original version. In the event of any discrepancy between the English and French content, the English version prevails.

This clinical practice guideline was prepared by the authors and overseen by the SOGC Clinical Practice—Gynaecology Committee. It was reviewed by the SOGC Diagnostic Imaging and Reproductive Endocrinology and Infertility committees and approved by the SOGC Guideline Management and Oversight Committee.

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### Hormonal Medications

#### Progestins

Progestins induce endometrial decidualization and atrophy, with anti-proliferative and anti-inflammatory effects. Both local and oral administration have been studied, specifically in adenomyosis. The levonorgestrel-releasing intrauterine system (LNG-IUS) is the best-studied medication for symptomatic adenomyosis. A randomized controlled trial

The best-studied oral progestin for treatment of dysmenorrhea from adenomyosis is dienogest (at a dosage of 2 mg daily). A multicentre RCT of 67 patients with dysmenorrhea

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Original Research

## Compare the Efficacy of Dienogest and the Levonorgestrel Intrauterine System in Women with Adenomyosis

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### ARTICLE INFO

**Key words:**

Adenomyosis

Dienogest

Levonorgestrel intrauterine system

Visual analog scale scores

### ABSTRACT

**Purpose:** The goal of this study was to examine the efficacy and safety of the levonorgestrel intrauterine system (LNG-IUS) versus dienogest (DNG) in female subjects with symptomatic uterine adenomyosis.

**Methods:** This study enrolled 117 women with symptomatic adenomyosis who visited our hospital from May 1, 2019, to June 30, 2022. Participants were randomized to either the LNG-IUS group (n = 48) or the DNG group (n = 79) in an as-controlled clinical trial for 36 months. Visual analog scale (VAS) scores, uterine volume, endometrial thickness, serum carcinoma antigen 125 level, estradiol, follicle-stimulating hormone, luteinizing hormone, and side effects were assessed to compare the efficacy of LNG-IUS and DNG.

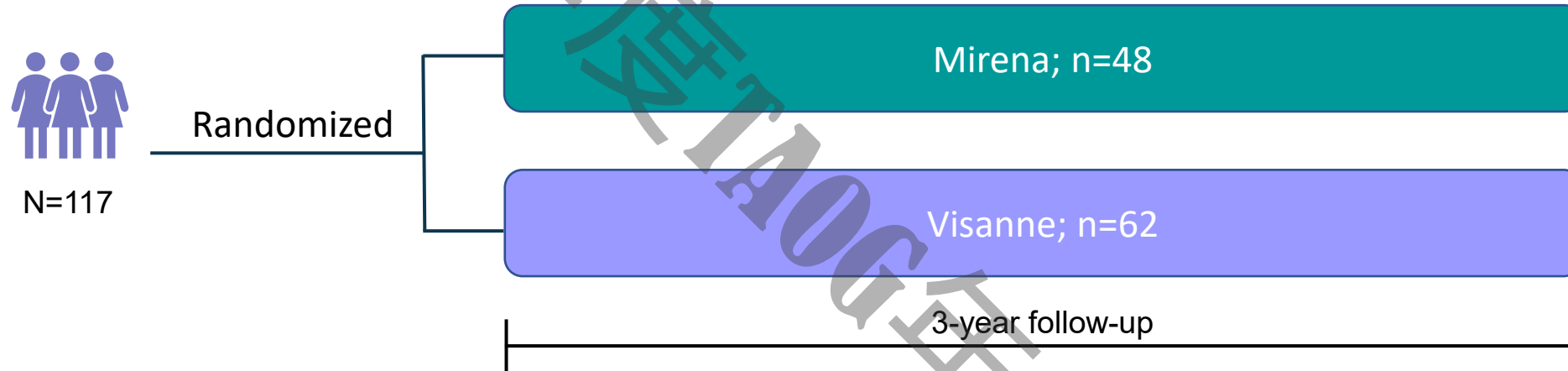
**Findings:** The VAS pain score was significantly decreased in both groups after 3 months of treatment. Three months later, patients receiving DNG reported significantly lower VAS scores compared with those treated with LNG-IUS ( $P < 0.05$ ). Compared with LNG-IUS, DNG effectively controlled uterine volume growth after 12 months of treatment but neither significantly reduced uterine volume. During the treatment period, endometrial thickness in both groups was maintained at 0.4 to 0.7 cm.

**Implications:** Both DNG and LNG-IUS significantly improved adenomyosis-associated pain after 3 months of treatment. Compared with LNG-IUS, DNG was shown to continuously relieve the symptoms of pain and effectively control the growth of uterine volume.



# Study design: Mirena vs Visanne

**Study Purpose:** to examine the efficacy and safety of the levonorgestrel intrauterine system (LNG-IUS) versus dienogest (DNG) in female subjects with symptomatic uterine Endometriosis of uterus



## Inclusion criteria:

- age  $\geq 18$  years
- Regular menstrual cycles of 21 to 38 days
- pain symptoms (progressive dysmenorrhea or chronic pelvic pain)
- Endometriosis of uterus with or without ovarian cyst

## Exclusion criteria:

- active thrombotic disease, moderate to severe anemia, cardiovascular disease, liver and kidney dysfunction, and sex hormone–dependent malignant tumors
- unexplained genital bleeding;
- receipt of hormone therapy within 3 months before the initiation of study treatment





## Characteristic of patients

**Table 1**

Characteristic of the patients in levonorgestrel intrauterine system (LNG-IUS) and dienogest (DNG) groups.

Characteristic	LNG-IUS (n = 48)	DNG (n = 69)	<i>P</i>
Age, y*	39.3 (5.2)	39.7 (6.3)	0.078
BMI, kg/m <sup>2</sup> *	22.5 (2.2)	22.7 (2.7)	0.107
Parity <sup>†</sup>	1 (1–2)	1 (1–2)	0.869
Uterine volume, cm <sup>3</sup> *	157.94 (88.47)	119.31 (37.05)	0.153
Initial VAS*	85.8 (18.2)	81.7 (14.1)	0.141
With endometrioma	17 (35.4%)	31 (44.9%)	0.304 ( $\chi^2 = 1.058$ )

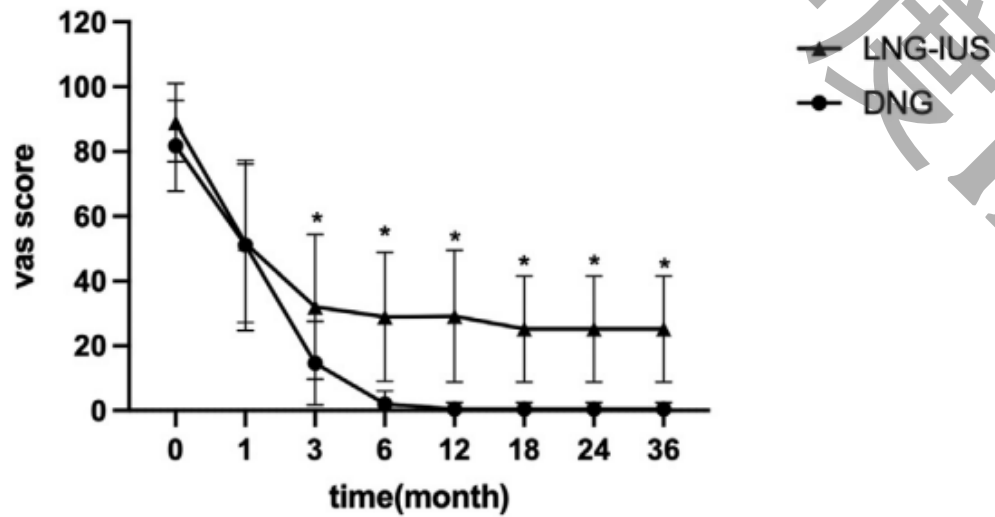
BMI = body mass index; VAS = visual analog scale.

\* Mean (SD).

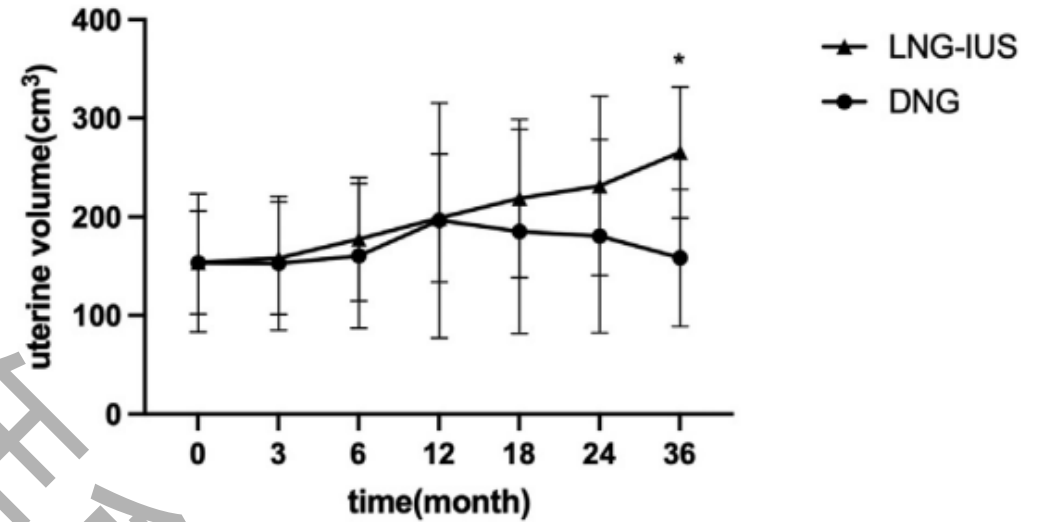
<sup>†</sup> Values are given as median (1/4 quintile–3/4 quintile).



# The efficacy on dysmenorrhea of Visanne is better than Mirena



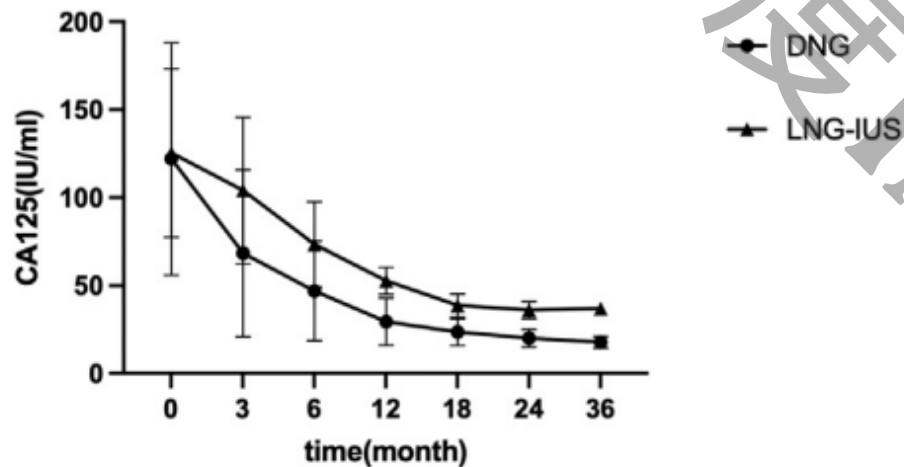
**Figure 1.** Trend of visual analog scale (VAS) score during treatment with the levonorgestrel intrauterine system (LNG-IUS) and dienogest (DNG). \* $P < 0.05$ , LNG-IUS versus DNG at the same point of time.



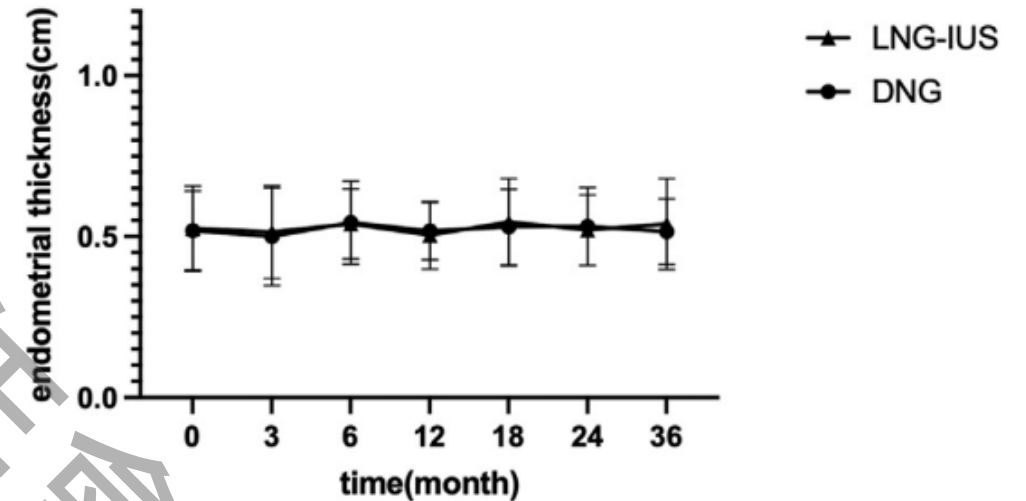
**Figure 2.** Change in uterine volume according to treatment with the levonorgestrel intrauterine system (LNG-IUS) and dienogest (DNG) for 36 months. \* $P < 0.05$ , LNG-IUS vs. DNG at the same point of time.



# In Visanne group, serum CA125 levels decreased more rapidly than Mirena



**Figure 5.** Change in carcinoma antigen 125 (CA125) level according to treatment with the levonorgestrel intrauterine system (LNG-IUS) and dienogest (DNG) for 36 months.



**Figure 3.** Assessment of endometrial thickness by transvaginal or transabdominal ultrasound during treatment with the levonorgestrel intrauterine system (LNG-IUS) and dienogest (DNG).

# What side effect we may meet in initial treatment with Visanne ?





# Common side effects of Visanne

## 不良反應之摘要報告表

使用Visanne時通報的藥物不良反應(ADR)的發生頻率依照MedDRA系統器官分類(MedDRA SOC)彙整於下表。在每個發生頻率類別中，不良反應均依發生頻率遞減的順序排列。發生頻率的定義為常見(≥ 1/100至 < 1/10)以及不常見(≥ 1/1000至 < 1/100)。發生頻率的匯集資料來自於四項臨床試驗，包含332位患者(100.0%)。

表1：第三期臨床試驗之不良反應列表 (共332位患者)。

器官類別	常見	不常見
血液與淋巴系統異常		貧血
新陳代謝與營養異常	體重增加	體重減少 食慾增加
心理失調	情緒憂鬱 睡眠障礙 神經緊張 失去性慾 情緒改變	焦慮 憂鬱 情緒波動
神經系統失調	頭痛 偏頭痛	自律神經系統失調 注意力障礙

眼睛疾病		眼睛乾澀
耳朵與內耳疾病		耳鳴
心臟異常		非特定的循環系統異常 心悸
血管異常		低血壓
呼吸道、胸腔及縱膈膜異常		呼吸困難
胃腸不適	噁心 腹部疼痛 脹氣 腹脹 嘔吐	腹瀉 便秘 腹部不適 胃腸道發炎 齒齦炎
皮膚及皮下組織異常	痤瘡 掉髮	皮膚乾燥 多汗症 搔癢症 多毛症 指甲斷裂 頭皮屑 皮膚炎 毛髮生長異常 光敏感反應 色素沉澱異常

肌肉骨骼及結締組織異常	背痛	骨頭疼痛 肌肉痙攣 四肢疼痛 四肢沉重
腎臟與泌尿異常		泌尿道感染
生殖系統與乳房不適	乳房不適 卵巢囊腫 熱潮紅 子宮/陰道出血，包括點狀出血	陰道念珠菌感染 外陰陰道乾澀 陰道分泌物增加 骨盆腔疼痛 萎縮性外陰陰道炎 乳房腫塊 纖維囊腫性乳房疾病 乳房硬結
全身性異常與用藥部位症狀	衰弱無力 煩躁不安	水腫

# How to manage spotting?

method. A leading cause of unscheduled bleeding with initiation is thought to be secondary to the rapid endometrial thinning effects of progestins. More practically, if women are going from relatively thick endometrium to relatively thin endometrium, it is biologically plausible that unscheduled bleeding/spotting will result.<sup>4</sup> As women continue their method, sustained exposure can lead to endometrial angiogenesis disruption, resulting in the development of a dense venous network that is fragile and prone to bleeding.<sup>5</sup>

The etiology of such bleeding is poorly understood: over the past 35 years, 5 different World Health Organization workshops have attempted to investigate the pathogenesis. Part of the difficulty with identifying the predominant etiology is the multiple contributors to the problem. Unscheduled bleeding is likely influenced by type/dose of progestin, how the progestin is delivered, duration of use, and specific effects to the endometrium because of the mechanism of action.

Expert Reviews ajog.org

**Unscheduled vaginal bleeding with progestin-only contraceptive use**

Rachel E. Zigler, MD; Colleen McNicholas, DO, MSCI

**P**rogestin-only methods of contraception include progestin-only pills (POPs), depot-medroxyprogesterone acetate (DMPA), subdermal etonogestrel (ENG) implants, and levonorgestrel intrauterine devices (LNG IUDs). Use of progestin-only methods is increasing, in part because of growing popularity of long-acting reversible contraceptives (LARC) but also because they are safe in women with other medical comorbidities.

The LARC methods, including intrauterine devices (IUDs) and implants are appealing for their ease of use, long-term protection, noncontraceptive benefits, and relatively few contraindications. Despite the benefits, both LARC and shorter acting progestin methods can result in unscheduled bleeding and spotting, which may lead to dissatisfaction and discontinuation.<sup>1</sup>

Unscheduled bleeding and spotting while on active hormones is subjective but has been defined in the literature as any bleeding requiring the use of a sanitary product. Estimating the prevalence is difficult because the literature has not been consistent. A recent study evaluating reasons for early discontinuation (within 6 months of initiation) among LNG IUD and ENG implant users found irregular/frequent bleeding was reported in 9% and 53% of these women, respectively.<sup>2</sup>

The Contraceptive Choice Project evaluated reasons for discontinuation in

Nearly 20% of women using contraception are using progestin-only contraception, including progestin-only pills, depot-medroxyprogesterone acetate, subdermal etonogestrel implants, and levonorgestrel intrauterine devices. This number will continue to grow with the increased provision of long-acting reversible contraception. Although overall satisfaction among women using progestin-only contraception is high, dissatisfaction and discontinuation may be associated with unscheduled bleeding and spotting. The exact etiology of irregular bleeding associated with progestin-containing contraceptives is not completely understood, yet several mechanisms have been suggested. Several therapies targeting these mechanisms have been evaluated with mixed results. This paper will review the physiology and management of unscheduled bleeding with progestin-containing contraceptives.

**Key words:** irregular bleeding, long-acting reversible contraception, progestin-only contraception, unscheduled bleeding

women who chose the LNG IUD, ENG implant, or DMPA at least once during their study participation. Among discontinuers, 19% of LNG IUD users, 46% of ENG implant users, and 26% of DMPA users listed bleeding changes as their main reason for discontinuation.<sup>3</sup>

Bleeding patterns are not standardized across the different forms of progestin-only contraceptives. Bleeding patterns can range from amenorrhea to unpredictable timing with varying degrees of flow to normal monthly menses. Unscheduled bleeding/spotting has been consistently demonstrated as a side effect for all progestin-only contraceptives.

The etiology of such bleeding is poorly understood: over the past 35 years, 5 different World Health Organization workshops have attempted to investigate the pathogenesis. Part of the difficulty with identifying the predominant etiology is the multiple contributors to the problem. Unscheduled bleeding is likely influenced by type/dose of progestin, how the progestin is delivered, duration of use, and specific effects to the endometrium because of the mechanism of action.

The quantity/duration of bleeding may change between the initiation of a method and continuation of that

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<http://dx.doi.org/10.1016/j.ajog.2016.12.008>

**Progestin-containing contraceptive methods**

**Progestin-only pills**  
Progestin-only pills, or POPs, are available in the United States in 1 formulation: norethindrone 0.35 mg tablets.

MAY 2017 American Journal of Obstetrics & Gynecology 443



# NSAID

113

## Medical therapy: nonsteroidal antiinflammatory

Nonsteroidal antiinflammatory (NSAID) medications primarily act by inhibiting cyclooxygenase, which is a prostaglandin synthase. Given that some women with irregular bleeding have been shown to have elevated levels of prostaglandin (PGE<sub>2</sub> and PGF<sub>2a</sub> increase during the secretory phase), short courses of NSAIDs could plausibly have an impact on this particular mechanism (Table 1).<sup>37,38</sup>

TABLE 1

Previous studies of nonsteroidal antiinflammatory medications

Contraceptive	Medical therapy
DMPA	Mefenamic acid 500 mg 2 times per day × 5 days <sup>38</sup>
	Valdecoxib 40 mg daily × 5 days <sup>39</sup>
ENG implant (Implanon)	Mefenamic acid 500 mg 3 times per day × 5 days <sup>40</sup>
LNG implants (Norplant <sup>a</sup> ; Jadelle <sup>b</sup> )	Ibuprofen 800 mg 3 times per day × 5 days <sup>41</sup>
	Ibuprofen 800 mg 2 times per day × 5 days <sup>42</sup>
	Mefenamic acid 500 mg 2 times per day × 5 days <sup>43</sup>
	Aspirin 80 mg daily × 10 days <sup>44</sup>
	Celecoxib 200 mg daily × 5 days <sup>45</sup>
LNG IUD	Naproxen 500 mg 2 times per day × 5 days <sup>46</sup>

DMPA, depot-medroxyprogesterone acetate; ENG, etonogestrel; LNG, levonorgestrel; LNG IUD, levonorgestrel intrauterine device.

<sup>a</sup> No longer available in the United States; <sup>b</sup> Available internationally but not in the United States.

Zigler. *Unscheduled bleeding with progestin-only contraception. Am J Obstet Gynecol* 2017.



# Estrogen

## Medical therapy: estrogen

Estrogen, whether given by itself or as a COC, may be an option for some

women. Exogenous estrogen may aid in tissue repair and stabilization of the endometrial lining (Table 2).

**TABLE 2**  
**Previous studies of estrogen**

Contraceptive	Medical therapy
DMPA	EE 50 $\mu$ g daily $\times$ 14 days <sup>47</sup>
ENG implant	LNG 150 $\mu$ g/EE 30 $\mu$ g daily $\times$ 4 weeks <sup>48</sup>
	LNG 150 $\mu$ g/EE 30 $\mu$ g daily $\times$ 14 days <sup>26</sup>
LNG implant (Norplant)	EE 50 $\mu$ g daily $\times$ 20 days <sup>41,49</sup>
	EE 20 $\mu$ g daily $\times$ 10 days <sup>42</sup>
	LNG 250 $\mu$ g/EE 50 $\mu$ g daily $\times$ 20 days <sup>49</sup>
LNG IUD	Estradiol patch 0.1 mg/d $\times$ 6 weeks <sup>50</sup>
	Estradiol patch 0.1 mg weekly $\times$ 12 weeks <sup>46</sup>

DMPA, depot-medroxyprogesterone acetate; EE, ethinyl estradiol; ENG, etonogestrel; LNG, levonorgestrel; LNG IUD, levonorgestrel intrauterine device.

Zigler. *Unscheduled bleeding with progestin-only contraception. Am J Obstet Gynecol* 2017.





# Doxycycline

## Medical therapy: doxycycline

At subantimicrobial doses, doxycycline inhibits matrix-metalloproteinase (MMP) activity. MMPs play an important role in tissue remodeling, and it is thought that increased MMP activity within the endometrium is a cause for unscheduled bleeding (Table 3).

**TABLE 3**

### Previous studies of doxycycline

Contraceptive	Medical therapy
DMPA	Doxycycline 100 mg 2 times per day × 5 days <sup>51</sup>
ENG implant	Doxycycline 100 mg 2 times per day × 5 days <sup>52,53</sup>

*DMPA*, depot-medroxyprogesterone acetate; *ENG*, etonogestrel.

Zigler. *Unscheduled bleeding with progestin-only contraception. Am J Obstet Gynecol* 2017.



# Tranexamic acid (TXA)

## Medical therapy: tranexamic acid

Tranexamic acid (TXA) is an anti-fibrinolytic medication that has been previously used for heavy menstrual bleeding. It aids in decreasing clot breakdown, thus decreasing bleeding (Table 4).

**TABLE 4**  
**Previous studies of tranexamic acid**

Contraceptive	Medical therapy
DMPA	TXA 250 mg 4 times per day × 5 days <sup>54</sup>
LNG implant	TXA 500 mg 2 times per day × 5 days <sup>55</sup>
LNG IUD	TXA 500 mg 3 times per day from bleeding onset until day after bleeding cessation <sup>56</sup>

*DMPA*, depot-medroxyprogesterone acetate; *LNG*, levonorgestrel; *LNG IUD*, levonorgestrel intrauterine device; *TXA*, tranexamic acid.

*Zigler. Unscheduled bleeding with progestin-only contraception. Am J Obstet Gynecol 2017.*



# Mifepristone

## Medical therapy: mifepristone

Mifepristone is an antiprogestin that may lead to the up-regulation of estrogen receptors within the endometrium, thus stabilizing the endometrium (Table 5).<sup>20</sup>

**TABLE 5**

### Previous studies of mifepristone

Contraceptive	Medical therapy
DMPA	Mifepristone 50 mg × 1 every 14 days <sup>57</sup>
ENG implant	Mifepristone 25 mg 2 times daily × 1 day <sup>53</sup>
LNG implant	Mifepristone 100 mg daily × 2 days <sup>58</sup>

*DMPA*, depot-medroxyprogesterone acetate; *ENG*, etonogestrel; *LNG*, levonorgestrel.

Zigler. *Unscheduled bleeding with progestin-only contraception. Am J Obstet Gynecol* 2017.



# Tamoxifen

## Medical therapy: tamoxifen

Tamoxifen, a selective estrogen receptor modulator, may work by antagonizing the angiogenic effect of estrogen (Table 6).<sup>22</sup>

**TABLE 6**  
**Previous studies of tamoxifen**

Contraceptive	Medical therapy
ENG implant	Tamoxifen 10 mg 2 times per day × 7 days <sup>59</sup>
LNG implant	Tamoxifen 10 mg 2 times per day × 10 days <sup>60</sup>

ENG, etonogestrel; LNG, levonorgestrel.

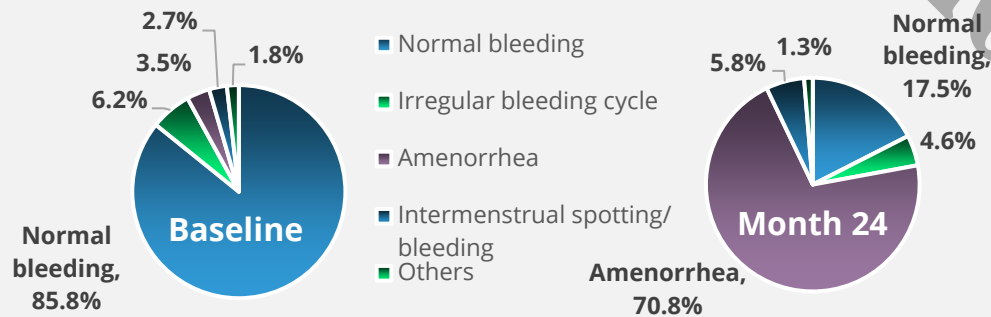
Zigler. *Unscheduled bleeding with progestin-only contraception. Am J Obstet Gynecol* 2017.

# Real-world data analysis of **bleeding patterns** after Visanne treatment confirms that menstrual blood volume **decreases with treatment time** and there are **no anemia-related** adverse reactions

## ENVISIOeN study<sup>1</sup>

To assess HRQoL in dienogest-treated patients in real-world setting, ENVISIOeN study enrolled 895 Asian women with endometriosis, presence of EAPP from Apr 2015 to Aug 2016

### Bleeding patterns



### Normal bleeding decreased

From baseline to month 24  
**85.8% → 17.5%**

## VIPOS study<sup>2</sup>

VIPOS study was conducted between 2010 and 2018 and consisted of women starting a new hormonal endometriosis treatment. Total follow-up time was up to 84 months. Out of all participants, 11.4% used dienogest, 12.8% used other approved endometriosis medications and 75.7% used hormonal treatments not approved but frequently used for endometriosis treatment

### No safety signal regarding anemia for dienogest users could be detected

Adjusted **HRs for anemia** for dienogest vs. other approved endometriosis medications

HRs **1.1**  
(95% CI: 0.4–2.6)

## Taiwanese expert experience:

Dienogest treatment for the first 3 months may affect bleeding patterns, and menstrual blood volume will decrease with treatment time

### Taiwan Expert Opinion

Dienogest 可能影響出血型態  
多半在用藥

前 3 個月出現

不規則出血

經血量隨治療時間而減少

也有造成無月經現象的可能性

### Taiwan Expert Opinion

出血型態變化可能影響  
日常生活與性生活

實務上仍須考量  
病人個別狀況

提供衛教諮詢

# Taiwanese expert experience:

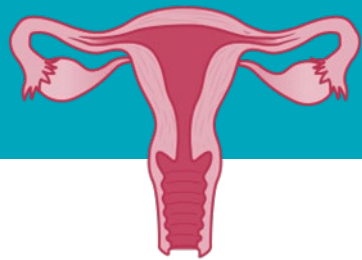
## Recommendations for managing bleeding problems related to Dienogest, including assessment of endometrial thickness in advance

### Taiwan Expert Opinion

用藥前建議以超音波評估子宮內膜狀態

若內膜過薄  
建議併用低劑量 ( 1 mg )  
雌激素 7 天

以穩定內膜



### Dienogest 相關出血問題的處置方式 ( 臺灣臨床經驗 )

- 加入 **低劑量雌激素**
- 出血風險高的子宮內膜異位症與子宮腺肌症病人，在 dienogest 治療前

**先使用 GnRHa 治療 1-3 個月**

血量穩定後即可接續長期 dienogest 治療

- 若持續子宮不正常出血，**建議子宮鏡檢查** 或超音波檢查，以確認是否有子宮內膜異位症外的其他子宮疾病

# Is it true that medical treatment will reduce surgical cases?







# 討論

- 該手術還是手術, 術後記得藥物治療至少2yrs預防復發
- 選擇藥物治療, 把它視為長期慢性病 (按時回診追蹤, 3個月)

# How long we should recommend patient to take Visanne?



# Post-surgery patient





# ESHRE 2022 suggests long-term hormone treatment for prevention of endometriosis recurrence

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

avoid

From

## Endometriosis recurrence

Chapter IV

### Prevention of recurrence of endometriosis

64	When surgery is indicated in women with an endometrioma, clinicians should perform ovarian cystectomy, instead of drainage and electrocoagulation, for the secondary prevention of endometriosis-associated dysmenorrhea, dyspareunia, and non-menstrual pelvic pain. However, the risk of reduced ovarian reserve should be taken into account.	⊕⊕○○	Strong recommendation
65	Clinicians should consider prescribing the <b>postoperative use</b> of a levonorgestrel-releasing intrauterine system (52 mg LNG-IUS) or a combined hormonal contraceptive for <b>at least 18–24 months</b> for the secondary prevention of endometriosis-associated dysmenorrhea.	⊕⊕○○	Strong recommendation
66	After surgical management of ovarian endometrioma in women not immediately seeking conception, clinicians are recommended to offer long-term hormone treatment (e.g. combined hormonal contraceptives) for the secondary prevention of endometrioma and endometriosis-associated related symptom recurrence.	⊕○○○	Strong recommendation

ION

es and additional  
ent is required.<sup>2,3</sup>

Continuing high-dose treatment or after  
cessation of medical therapy,  
continuous, long-term hormonal control is suggested.<sup>4</sup>

113年醫學博士學位論文  
113年醫學博士學位論文

# Clinical diagnosis patient



- Clinical diagnosis?

- ✓ 套用術後, 病灶消除最小後用藥物2年
- ✓ 臨床診斷也應使用到症狀不見後2年

# Endometriosis of uterus (adenomyosis)



# Chapron et al. suggests to rethink the endometriosis management to optimize medical treatment to reduce the number of unnecessary and/or inappropriate surgeries for endometriosis

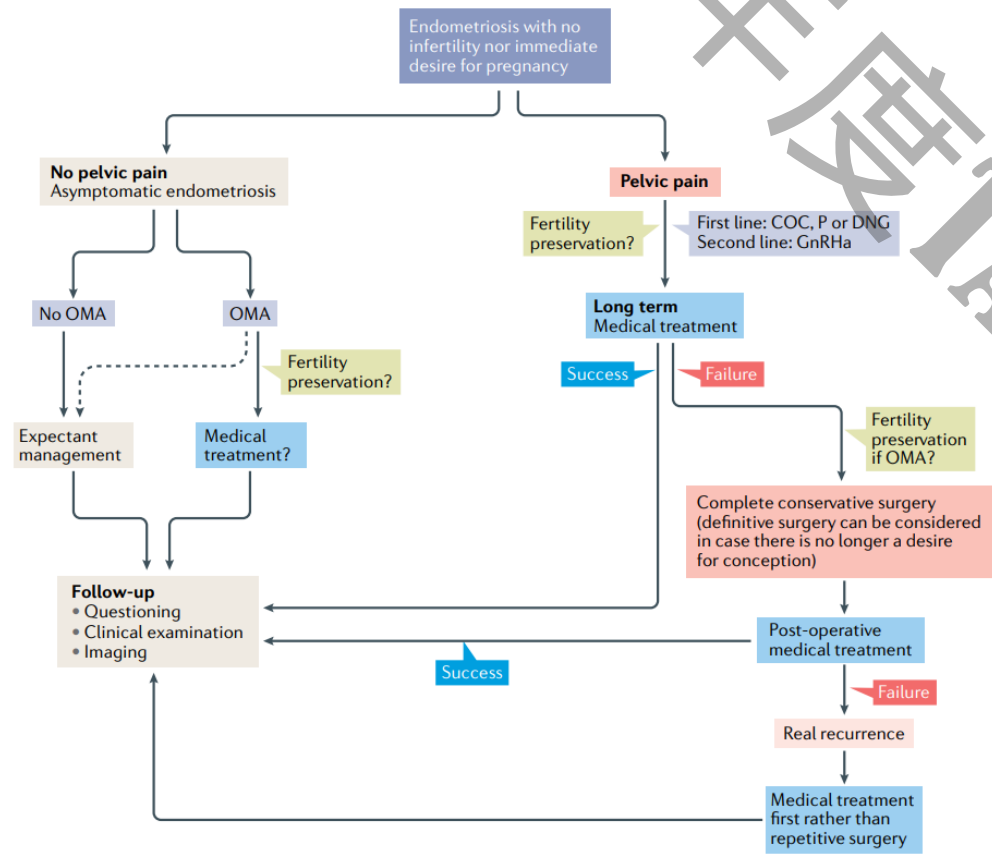
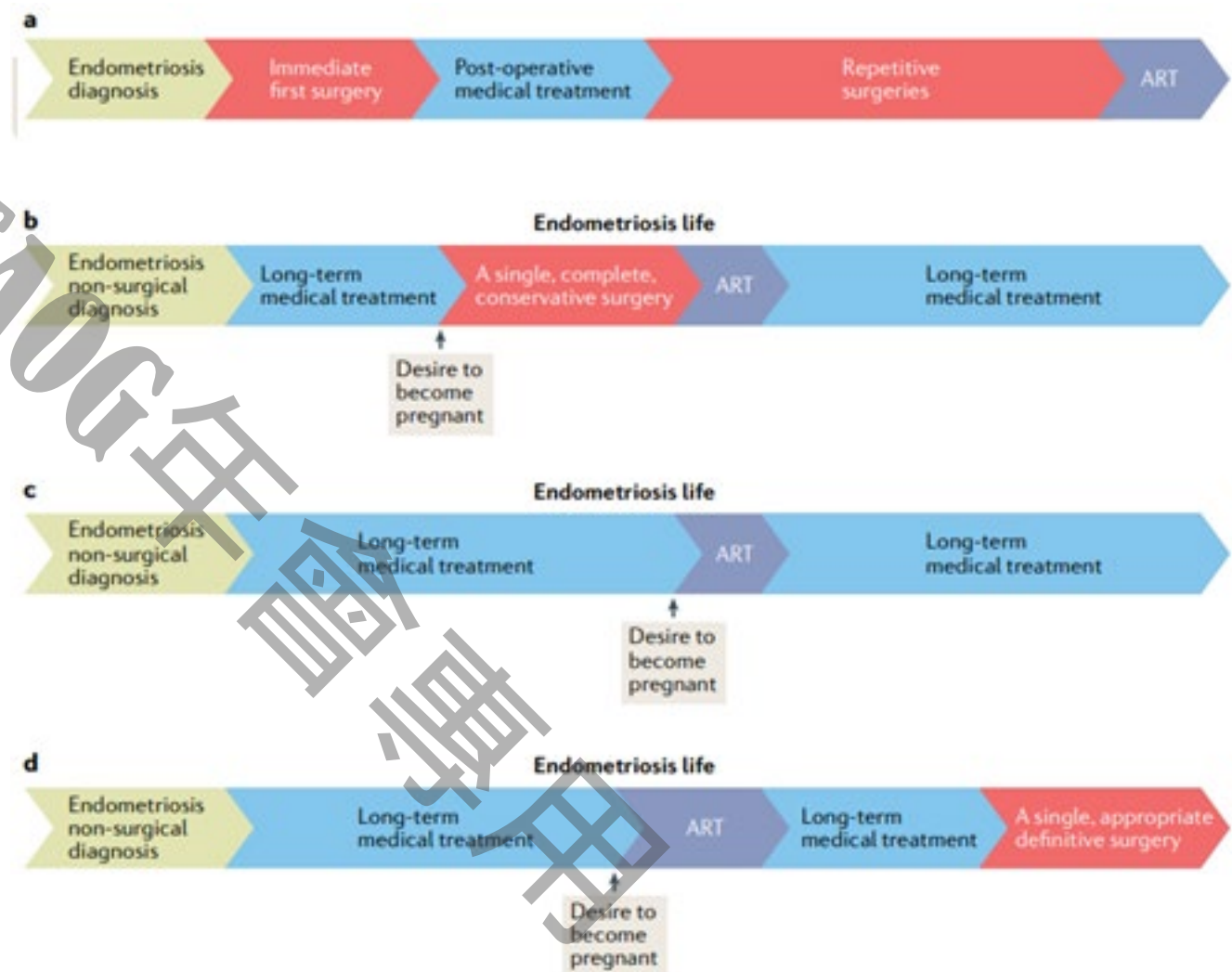


Fig. 5 | Endometriosis management algorithm for patients without an immediate desire for pregnancy. This novel algorithm can be used by health-care professionals for the management of patients with endometriosis who have no immediate desire for pregnancy. COC, combined oral contraceptive; DNG, dienogest; GnRHa, gonadotropin-releasing hormone analogues; OMA, ovarian endometriomas; P, progestins.







# Any safety issue we should care when we use Visanne over than 2 years?



# Synthetic progestins (such as MPA), not Visanne, may bind to other receptors to produce off-target effects

- 合成黃體素除了與 PR 結合，同時也會與其他類固醇受體（包括 AR、GR、MR）結合產生脫靶效應（off-target effect），導致乳癌等風險。

Glucocorticoid activity	
Dienogest	—
MPA	+

+ , effective; — , not effective; ? , literature inconsistent.

Dienogest 專一性較高，不具備 GR 結合活動

MPA 專一性較低，具有 GR 結合力，而乳癌細胞內 GR 表現增加，被認為與乳癌相關



# Taiwanese experts suggest that there is currently **no direct evidence** that long-term use of Dienogest increases the risk of breast cancer

## 國健署乳癌篩檢政策<sup>1</sup>

- ✓ 45-69 歲婦女
- ✓ 40-44 歲具乳癌家族史<sup>§</sup>婦女

### 建議

每 2 年 1 次

乳房 X 光攝影檢查

<sup>§</sup>指祖母、外婆、母親、女兒、姊妹曾有人罹患乳癌。

## No direct evidence of additional breast cancer risk with dienogest treatment

Expert opinion



The use of **progestins** for contraception has **never** been associated with an **increased risk of breast cancer**<sup>2</sup>

54 studies in 25 countries



There is no evidence of increased breast cancer risk with duration of hormonal contraceptives use<sup>3</sup>

Systematic review



No association between progestin-only formulations and breast cancer risk<sup>4</sup>

3593 cases of breast cancer were identified and compared with 9098 controls



The adjusted **odds ratio** estimate for **breast cancer** associated with **dienogest use** was **0.9** (95% CI: 0.2-3.4)<sup>5</sup>

21 women with endometriosis treated with dienogest 20 mg daily for 24 weeks\*



Non-significant change of the maximum diameter of the ducts and the portion of the fatty tissue<sup>6</sup>

\* 此用法僅限於本試驗觀察短時間高劑量 dienogest 對乳房的影響，非仿單建議之用法用量，臨床使用請參照仿單建議。

CI, confidence interval.

1. 衛生福利部國民健康署 / 乳癌防治 <https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=614&pid=1124> (Accessed in July 2022). 2. Berlanda N, et al. Expert Opin Drug Saf 2016;15:21-30. 3. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 1996;347:1713-27. 4. Samson M, et al. Breast Cancer Res Treat 2016;155:3-12. 5. Dinger JC, et al. BMC Womens Health 2006;6:13. 6. Schindler AE, et al. Gynecol Endocrinol 2009;25:472-4.

# Long term use with Visanne will not increase risk of breast cancer in Cohort Study of Taiwan

Received: 4 February 2023 | Revised: 24 May 2023 | Accepted: 28 May 2023  
DOI: 10.1002/ijgo.14930

BRIEF COMMUNICATION  
Gynecology



## Effects of Dienogest on breasts of women of reproductive age and women in menopausal transition: A cohort study

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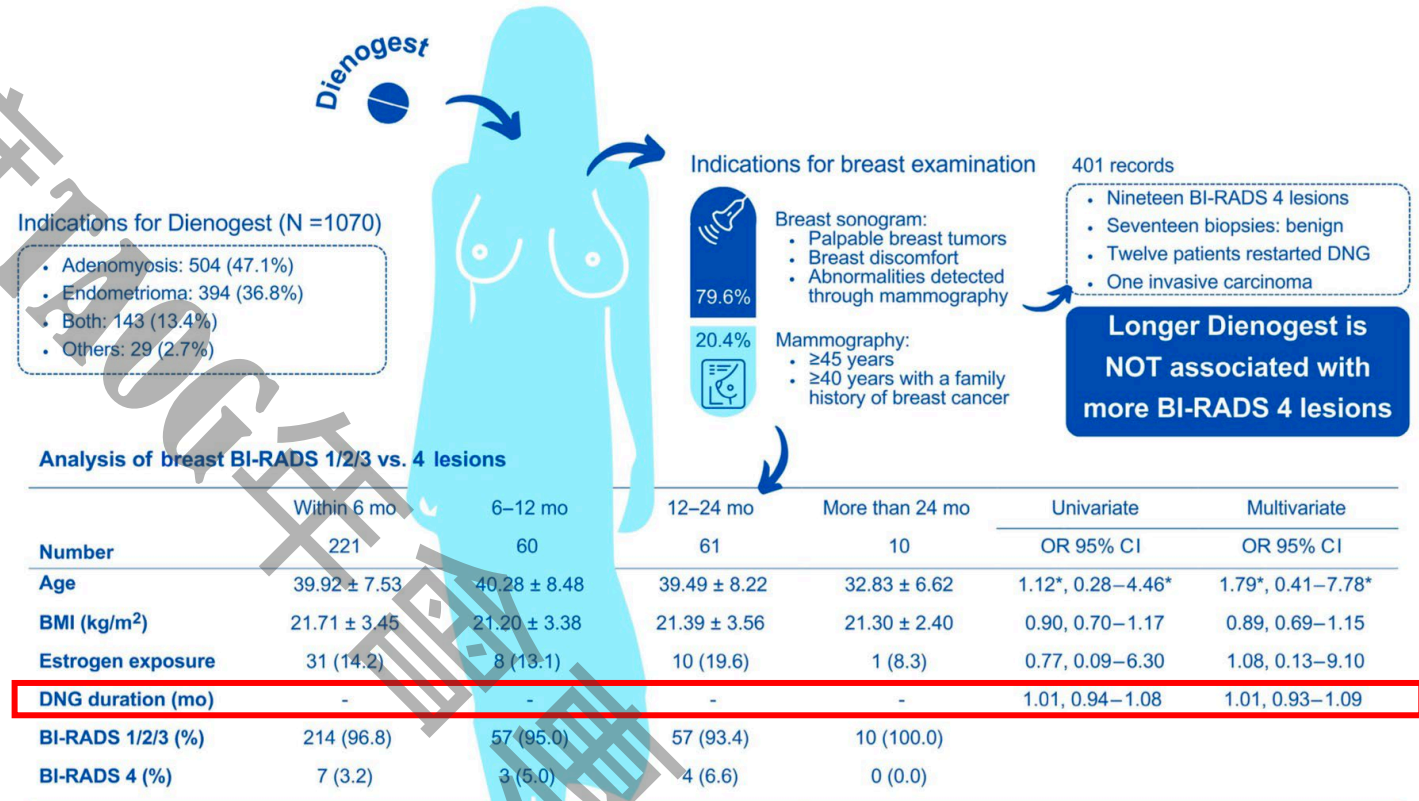
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KEYWORDS

breast, Dienogest, mammography, ultrasonography



# Can I prescribe Visanne to teenager of endometriosis?





# Visanne can be use in teenage who already had menstruation

## 異位寧 2毫克 Visanne 2 mg tablet

衛部藥輸字第 027029 號  
本藥須由醫師處方使用



### 1. 品名

異位寧 2毫克

### 2. 成分含量

每類藥錠含有2 mg dienogest。  
完整的賦形劑列表，請參閱「賦形劑列表」一節。

### 3. 藥物劑型

錠劑  
白色至灰白色、圓形、平面、邊緣斜切之錠劑，一面標示有「B」字樣，直徑為7 mm

### 4. 臨床特性

#### 4.1 適應症

治療子宮內膜異位症伴隨之骨盆腔疼痛

#### 4.2 用量及使用方法

##### 4.2.1 使用方法

口服使用。

##### 4.2.2 用法用量

Visanne的劑量為每日一錠，持續不斷斷，最好於每天同一時間服藥，並視需要搭配飲水。可於飯前或飯後服用。無論是否發生陰道出血，均必須連續服藥。當服完一份包裝的藥物後，應開始服用下一份藥物，不可中斷。

可於月經週期的任一天開始服藥。

任何的荷爾蒙避孕法均必須在開始Visanne治療前停用。若有避孕需要，應使用非荷爾蒙類的避孕方法(例如：阻隔式避孕)。

#### 漏服藥錠的處置方式

如果漏服藥錠、嘔吐以及/或腹瀉(若發生於服藥後3小時-4小時內)，可能會降低Visanne的療效。若漏服藥錠，應於想起來時儘快服用一顆藥錠(僅可服用一顆)，並應於隔天依照平常的時間繼續服藥。如果因嘔吐或腹瀉而無法吸收藥錠，同樣也應補服一顆藥錠。

#### 特殊族群的額外資訊

##### 小兒病患

Visanne不適用於初經前的兒童。

#### 青少年女性的骨質密度

青少年(12歲至18歲)使用Visanne治療12個月期間，與腰椎的骨質密度(BMD)平均下降1.2%有關。針對BMD降低的子群組，在治療之後6個月進行追蹤測量，結果顯示BMD平均增加至-0.6%。停止治療之後，大部分患者的BMD會再度增加。

103位青少年(12至18歲)使用Visanne治療52週，在52週治療結束時，腰椎(L2-L4)的骨質密度(BMD)較基礎線平均下降1.2%。在全部患者中，有1%的患者其骨質密度較基礎線下降6%以上，有10.7%的患者較基礎線下降4%至6%之間，有24.3%的患者較基礎線下降2%至4%之間，有35.9%的患者較基礎線下降0%至2%之間。

在青少年族群中，使用Visanne與BMD不變或減少有關，這些變化並非完全可逆。青少年與成年早期階段需特別注意BMD是否降低，此階段為骨質增加的關鍵時期。

隨著使用時間增長，BMD減少可能增加。目前不清楚此族群的BMD降低現象是否會降低高峰骨量，以及是否會增加之後的骨折風險。

因此治療醫師應權衡個別青少年使用Visanne的效益與可能風險，並定期予以再評估。(請參閱「兒童病患」與「藥效學特性」二節)。

在骨質疏鬆風險偏高的病患中，應於開始Visanne治療前進行詳細的風險與效益評估，因Visanne治療期間內源性雌激素濃度會有中度的降低(請參閱「藥效學特性」)。

所有年齡的女性均應該自飲食或補充劑中攝取足量的鈣質和維生素D。

#### 其他情形

應小心觀察具有憂鬱症病史的患者，如果復發嚴重程度的憂鬱症，應停用藥物。

血壓正常的女性使用Visanne通常不會出現血壓影響。不過，如果於Visanne使用期間出現持續且具臨床顯著的高血壓，建議停用Visanne並治療高血壓。

若於Visanne使用期間復發膽汁鬱積性黃疸及/或瘙癢(其於懷孕期間或先前使用性類固醇時首次發生)，必須停用Visanne。

Visanne可能對於周邊胰島素抗性以及葡萄糖耐受性有略微的影響。糖尿病女性(尤其是有妊娠期糖尿病病史者)服用Visanne的期間應小心監測。

## 特殊族群的額外資訊

### 小兒病患

Visanne不適用於初經前的兒童。

# Efficacy of Dienogest in Adolescent Endometriosis: A Narrative Review

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## Abstract

Teenage endometriosis is seen as a chronic condition that can worsen if untreated. Treatment objectives include relief of symptoms, prevention of disease development, and preservation of future fertility. In many regions, dienogest (DNG), an oral progestin, has emerged as a key treatment in suppressing endometriosis. The usage of DNG for endometriosis in adolescents was researched in papers published between 2015 and 2022 using PubMed and Google Scholar. A thorough search of all identified studies' reference lists and previously published literature reviews was carried out. The study's nature and geographic scope were not restricted. After reviewing these publications, the authors decided on which ones were the most pertinent in light of their personal experiences. The final study consisted of 14 studies that satisfied inclusion requirements. The trials showed that taking DNG 2 mg daily efficiently lowers endometriotic lesions, eases painful endometriosis symptoms, and improves quality-of-life indicators. In most of these investigations, DNG was shown to be safe and tolerated, with predictable and moderate side effects, good patient compliance rates, and low withdrawal rates. Although endometrioma did not enlarge while receiving treatment, significant regression was not typical. Overall, the studies found that DNG is safe and effective in reducing symptoms of endometriosis in adolescents.

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**Categories:** Obstetrics/Gynecology

**Keywords:** endometriosis, severe dysmenorrhea, pelvic pain, dienogest, adolescents

Sr. No.	Study	Design	Sample size	Intervention	Duration	Comments
1.	Ebert et al., 2017 [6]	Open-label, single-arm study	111	DNG, 2 mg/day	52 weeks	Endometriosis-associated pain was substantially reduced during treatment, but it was discovered that DNG 2 mg was connected to a decline in lumbar BMD, which was followed by a partial recovery following treatment cessation
2.	Malik and Mann, 2021 [9]	Short-term single-centre study	56	DNG, 2 mg/day	3 months	DNG is a well-tolerated drug for endometriosis showing significant relief of pain with no major side effects. Although endometrioma did not enlarge throughout treatment, it was shown that significant regression was rare
3.	Techatraisak et al., 2022 [15]	Prospective, non-interventional study	887	DNG, 2 mg/day	24 months	From baseline to month 24, rates of normal bleeding decreased while rates of amenorrhea increased. Most patients and doctors expressed satisfaction with DNG. More than 80% of patients said their symptoms had improved. Drug-related treatment-emergent side effects, such as vaginal bleeding (10.4%), metrorrhagia (7.3%), and amenorrhea (6.4%), were experienced by 39.9% of patients
4.	Ota et al., 2021 [8]	Retrospective cohort study	321	DNG, 1 mg/day	3 months	In young women's bone-growth phase, DNG 1 mg/day treatment had no appreciable impact on bone turnover after three months
5.	Yu et al., 2018 [7]	Open-label extension study	220	DNG, 2 mg/day	28 weeks	Initiation of the DNG was related to longer but fewer spotting/bleeding episodes. As the medication was continued, the frequency and severity of bleeding gradually decreased. Treatment-emergent AEs, typically mild or moderate, resulted in discontinuation in the open-label study, and the DNG had no effect on BMD





6.	Luisi et al., 2015 [10]	Prospective observational multicentre study	142	DNG, 2 mg/day	90 days	The mean VAS in women with endometriosis significantly decreased at the end of the study. Mental index score values increased and the physical index increased. The most prevalent AEs during the treatment period were headaches, followed by bleeding, depression, breast soreness, and acne; however, none of these were persistent enough to cause study discontinuation
7.	Vignali et al., 2020 [16]	Prospective observational study	70	DNG, 2 mg/day	12 months	After a year, the mean volume had decreased by 76.19%. Dysmenorrhea decreased by 74.05% after six months and by 96.55% after a year. Patients reported reductions in dyspareunia and chronic pelvic pain of 42.71%, 48.91%, and 51.93%, respectively, after 6 and 12 months. DNG results in a statistically significant decrease in the size and discomfort of endometriomas
8.	Uludag et al., 2021 [11]	Prospective study	30	DNG, 2 mg/day	6 months	At six months into treatment, the VAS score for pelvic discomfort considerably decreased from 7.50 to 3.00 ( $p < .001$ ). Inconsistencies in menstruation were the most frequent negative effects. The study's parameters for the lab remained constant. DNG was thought to have a favourable safety and tolerability profile and be effective for 6 months in reducing the size of endometriomas and the pain associated with endometriosis

9.	Kizilkaya et al., 2020 [17]	Prospective cohort study	37	DNG, 2 mg/day	3 months	The mean endometrioma volume was significantly reduced compared to the pre-treatment volume. <b>Dysmenorrhea, dyspareunia, and persistent pelvic pain post-treatment VAS values all showed a significant reduction.</b> The mean physical function score and mental health score significantly increased. They discovered that DNG treatment at a oral dose of 2 mg/day for 3 months significantly decreased endometrioma size, pain intensity, and quality of life in women with endometriosis
10.	Ji et al., 2022 [18]	Cohort study	127	The first group DNG 2 mg/day; second group received goserelin acetate (GS) (3.6 mg/4 weeks)	12 weeks	In individuals with <b>adenomyosis, DNG efficiently reduces the symptoms of dysmenorrhea,</b> but it is unable to relieve anaemia or shrink the size of the uterus
11.	Miao et al., 2022 [12]	Retrospective observational study	104	52 group 2 (maximum uterine dimension, 100.0 mm): DNG without prior GnRH-a treatment; 52 group 1 (maximum uterine dimension, 100.0 mm): DNG after 4 months of GnRH-a administration	24 months	After 24 months of DNG treatment, the mean uterine volume marginally dropped from 157.9 to 153.3 ml ( $p > .05$ ). All laboratory measurements fell within the expected range. <b>As a long-term treatment for symptomatic adenomyosis, DNG is efficient and well tolerated.</b> It can also be used as maintenance therapy following the cessation of GnRH-a administration
12.	Angioni et al., 2020 [19]	Prospective study	81	40 were given (DNG 2 mg/day); 41 were given ethinyl estradiol 30 mg [EE] with DNG 2 mg (DNG + EE)	6 months	<b>The size of the endometrioma cysts was significantly reduced in the DNG group.</b> The mean cyst diameter was $52 \pm 22$ mm at baseline and $32 \pm 12$ mm after six months of treatment ( $p < .001$ )

13.	Muzii et al., 2020 [20]	Prospective study	32	DNG, 2 mg/day	6 months	Medical treatment with DNG significantly reduced the endometrioma diameter and associated pain, whereas the ovarian reserve appears to be preserved, with a significant improvement of AFC and no significant change in AMH
14.	Angioni et al., 2015 [21]	Pilot study	6	DNG, 2 mg/day	12 months	Pain symptoms get better, and the nodule size gets smaller

### Conclusion

**Visanne** is effective medical treatment **in teenage of endometriosis**. Few data show that Visanne may have impact on **BMD and it can be recovered after cessation**. We can have regular monitoring when we start Visanne for teenage.



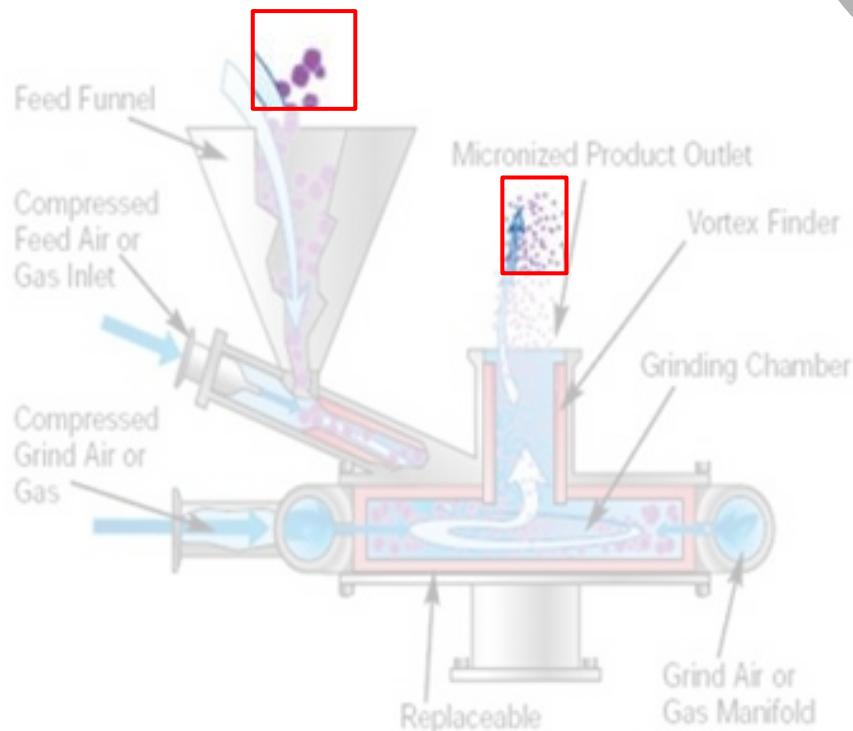
# What is the difference in the ingredient between branded medicine and generic medicine?



# 氣流研磨技術解決DNG不易溶解的問題

## Jet milling manufacturing process

Jet milling is a particle size reduction method – also known as micronisation – to enhance dissolution rate in the gastrointestinal tract. This is a unique and valuable approach to improve digestive absorption, and consequently the bioavailability and clinical efficacy of oral formulations.



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### MICRONIZATION: AN EFFICIENT TOOL FOR DISSOLUTION ENHANCEMENT OF DIENOGEST

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**Table 1:** Particle size analysis of Dienogest (before and after micronization)

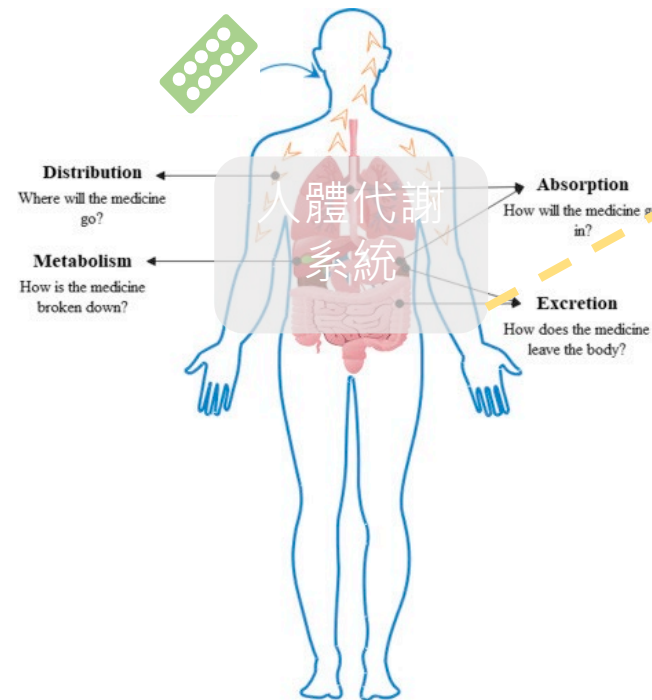
Particle Size	Unmicronized Dienogest (Batch No. SD/DNG/170)	Micronized Dienogest (Batch No. SD/DNG/179)
d (0.1)	1.95 $\mu$	0.75 $\mu$
d (0.5)	10.90 $\mu$	1.80 $\mu$
d (0.9)	45.97 $\mu$	6.50 $\mu$

**Table 5:** Comparative of dissolution profile of formulations and Reference product

Time (Minutes)	Cumulative Percent Drug Release		
	Reference	F1	F2
10	97 $\pm$ 2.3	98 $\pm$ 2.5	66 $\pm$ 2.4
15	97 $\pm$ 2.2	98 $\pm$ 2.1	74 $\pm$ 2.5
20	98 $\pm$ 2.4	99 $\pm$ 2.3	83 $\pm$ 2.2
30	98 $\pm$ 2.1	99 $\pm$ 2.8	89 $\pm$ 2.6
45	98 $\pm$ 2.2	99 $\pm$ 2.4	92 $\pm$ 2.8
60	99 $\pm$ 2.7	99 $\pm$ 2.5	94 $\pm$ 2.4

# Drugs can be put on the market within the tolerance of the bioavailability/bioequivalence test (BA/BE)

學名藥的BA/BE試驗只與藥效藥劑動力學有關，與臨床治療藥效沒有直接關係。  
原廠藥與學名藥存在賦形劑差異，導致藥物吸收差異。



受試者必須至少12名



80%~125%

藥物  
體內濃度

=

原廠藥  
藥物體內濃度

賦形劑雖然非活性，卻可能增加或減少藥物吸收的  
Drug Absorption, 2021  
(<https://www.ncbi.nlm.nih.gov/books/NBK557405/>)

“學名藥與原廠藥的賦形劑往往不相同，雖然這些成分都是被FDA核可的成分，但是缺乏了影響藥物主成分吸收的相關研究”

美國食品藥物管理局

# Branded VS Generic

	Visanne (Dienogest)	學名藥 (Dienogest)
賦形劑	Lactose monohydrate, <u>Potato starch</u> , Microcrystalline cellulose, <u>Povidone K-25</u> , Talc, Crospovidone, Magnesium stearate	Lactose, Microcrystalline cellulose, Crospovidone, <u>Povidone K-30</u> , <u>Pregelatinized starch</u> , Talc, Magnesium stearate.
服用後血液雌激素濃度	39pg/ml 子宮內膜異位症最佳治療區間	?
使用經驗	>13年 使用經驗	?
上市後長期使用 安全性研究	最高長達7年 長期使用的安全性 貧血、憂鬱、骨密度 肝功能監測 脂質代謝	?
臨床文獻發表	>21篇	?
Remark		僅BA/BE證實與原廠藥相似性 (80-125% 的血中濃度範圍)

# Take Home Message

## 子宮內膜異位症疾病

- 子宮內膜異位症為全身性發炎疾病且復發率高，應視為慢性病進行長期控制<sup>1</sup>。

## Visanne的使用

- 術後患者- 至少18~24月以上
- 臨床診斷患者- 症狀消失後比照術後
- 腺肌症患者- 長期使用

## 黃體素造成出血處理

- NSAID/Estrogen/OC/TXA
- GnRH $\alpha$

## Visanne長期安全性

- 目前證據無增加乳癌風險
- VIPOS 7年試驗: 長期vs短期使用Visanne不會增加不良反應風險

## Visanne用在青少年

- 安全且有效, 如有疑慮可定期監測BMD





# Visanne® 異位寧® 簡易處方資訊

**適應症：**治療子宮內膜異位症伴隨之骨盆腔疼痛      **品名：**Visanne® 2mg tablet 異位寧® 2毫克      **成分含量：**每顆藥錠含有 2 mg dienogest

**用法與用量《本藥須由醫師處方使用》：**劑量為每日一錠，持續不間斷，最好於每天同一時間服藥，並視需要搭配飲水。可於飯前或飯後服用。無論是否發生陰道出血，均必須連續服藥。當服完一份包裝的藥物後，應開始服用下一份藥物，不可中斷。可於月經週期的任一天開始服藥。任何的荷爾蒙避孕法均必須在開始Visanne治療前停用。若有避孕需要，應使用非荷爾蒙類的避孕方法(例如：阻隔式避孕)。漏服藥錠的處置方式: 如果漏服藥錠、嘔吐以及/或腹瀉(若發生於服藥後3小時-4小時內)，可能會降低Visanne的療效。若漏服藥錠，應於想起來時儘快服用一顆藥錠(僅可服用一顆)，並應於隔天依照平常的時間繼續服藥。如果因嘔吐或腹瀉而無法吸收藥錠，同樣也應補服一顆藥錠。

**禁忌：**Visanne不應使用於有下列任何病症(部分來自於其他僅含黃體素之製劑的相關資訊)的患者。如果Visanne使用期間出現下列任何病症，必須立即停藥。活性期靜脈血栓栓塞疾病，目前罹患動脈及心血管疾病或有其病史(例如心肌梗塞、腦中風、缺血性心臟病)，合併血管相關併發症之糖尿病，現有或曾患嚴重肝臟疾病且肝功能的各項數值未回復至正常值，現有或曾有肝臟腫瘤(良性或惡性)，已知或疑似罹患性荷爾蒙依賴型惡性腫瘤，未經診斷的陰道出血，對本品主成分或任一賦形劑過敏者。

**警語及注意事項：**雖然並非所有的警語及注意事項均根據Visanne臨床試驗的個別結果，不過由於Visanne是僅含黃體素的製劑，因此可以推論其他僅含黃體素之製劑的特殊警語及使用注意事項也適用於Visanne。如果以下任何情況/風險因素出現或惡化，在開始或繼續服用Visanne之前應先權衡效益與風險。

**嚴重子宮出血：**使用Visanne可能會加重子宮出血(如：罹患子宮肌腺症或子宮肌瘤的女性)。如果出血大量且持續，可能會導致貧血。若發生貧血，應考慮停用Visanne。**出血型態改變：**大多數接受Visanne治療的病患發生經期出血型態改變。**循環障礙：**根據流行病學試驗，很少證據顯示僅含黃體素之製劑與心肌梗塞或腦部血栓栓塞的風險增加有關。此心血管與腦部事件的風險與年齡增加、高血壓及吸菸更相關。高血壓女性使用僅含黃體素之製劑時，會略微增加中風的風險。雖不具統計上的顯著性，有些試驗顯示使用僅含黃體素之製劑可能會略微增加靜脈血栓栓塞的風險(深層靜脈血栓、肺栓塞)。一般認定的靜脈血栓栓塞(VTE)風險因子包括具有個人或家族史(兄弟姐妹或父母在相對較早的年齡發生VTE)、年齡、肥胖、長期臥床、重大手術或重大創傷。若需要長期臥床，建議中止使用Visanne(若為排程手術，則至少提前4週)，並在完全恢復行動能力2週後再重新開始治療。必須考慮到產後期間血栓栓塞風險升高的問題。如果出現(或疑似出現)動脈或靜脈血栓事件的症狀，應立即停止治療。**腫瘤：**一份針對54篇流行病學研究的整合分析報告指出，正在使用口服避孕藥(OC)(主要為雌激素-黃體素製劑)的女性中診斷出乳癌的相對風險(RR = 1.24)略微升高。此現象會在停藥10年內逐漸消失。由於乳癌在40歲以下的女性中很罕見，於正使用及剛使用過口服避孕藥的婦女中診斷出乳癌的數目相對於乳癌發生總數是很小的，這些研究並不足以提供因果證據。使用僅含黃體素製劑的婦女診斷出乳癌的風險幅度可能與使用複合型口服避孕藥者相似。僅含黃體素製劑的證據是根據較小的使用者族群，因此，比起複合型口服避孕藥的證據較無定論，這些研究並未提供因果證據。所觀察到危險性的增加可能是口服避孕藥使用者提早診斷出乳癌，口服避孕藥的生理效應或兩者合併的結果。曾使用口服避孕藥者診斷出的乳癌臨床上比未曾使用者傾向屬較初期病情。在罕見情況下，有荷爾蒙物質(例如Visanne中所含的荷爾蒙)使用者出現良性肝臟腫瘤，而在更罕見的情況下，曾通報惡性肝臟腫瘤。在偶發案例中，這些腫瘤曾導致危及生命的腹內出血。當服用Visanne的女性出現嚴重上腹痛、肝腫大或腹內出血的徵兆時，在鑑別診斷中應考量肝臟腫瘤的可能性。**骨質疏鬆症：**成年女性的骨質密度，Visanne治療期間內源性雌激素濃度會有中度的降低。目前尚無關於Visanne使用者之骨質密度(BMD)與骨折風險的長期資料。青少年女性的BMD，青少年(12歲至18歲)使用Visanne治療12個月期間，與腰椎的BMD平均下降1.2%有關。針對BMD降低的子群組，在治療之後6個月進行追蹤測量，結果顯示BMD增加至-0.6%。停止治療之後，大部分患者的BMD會再度增加。在青少年族群中，使用Visanne與BMD不變或減少有關，這些變化並非完全可逆。青少年與成年早期階段需特別注意BMD是否降低，此階段為骨質增加的關鍵時期。隨著使用時間增長，BMD減少可能增加。目前不清楚此族群的BMD降低現象是否會降低高峰骨量，以及是否會增加之後的骨折風險。因此治療醫師應權衡個別青少年使用Visanne的效益與可能風險，並定期予以再評估。在骨質疏鬆風險偏高的病患中，應於開始Visanne治療前進行詳細的風險與效益評估，因Visanne治療期間內源性雌激素濃度會有中度的降低。

**常見藥物不良反應：**體重增加、情緒憂鬱、睡眠障礙、神經緊張、失去性慾、情緒改變、頭痛、偏頭痛、噁心、腹部疼痛、脹氣、腹脹、嘔吐、瘙癢、掉髮、背痛、乳房不適、卵巢囊腫、熱潮紅、子宮/陰道出血(包括點狀出血)、衰弱無力、煩躁不安。不良反應較常出現於開始服用Visanne之後第一個月，隨著治療時間而消退。

- 許可證字號：衛部藥輸字第027029號
- 詳細產品資訊請參考衛生福利部核准之產品說明書：Visanne 2mg Tablet / CCDS06 / Sep 2014 / TW01