

**SEUD 2018**

# **NEW TREATMENTS FOR OVARIAN ENDOMETRIOMA**

**Ivo Brosens**

**Giuseppe Benagiano**

**Faculty of Medicine, KU Leuven, Belgium  
Sapienza University, Rome, Italy**

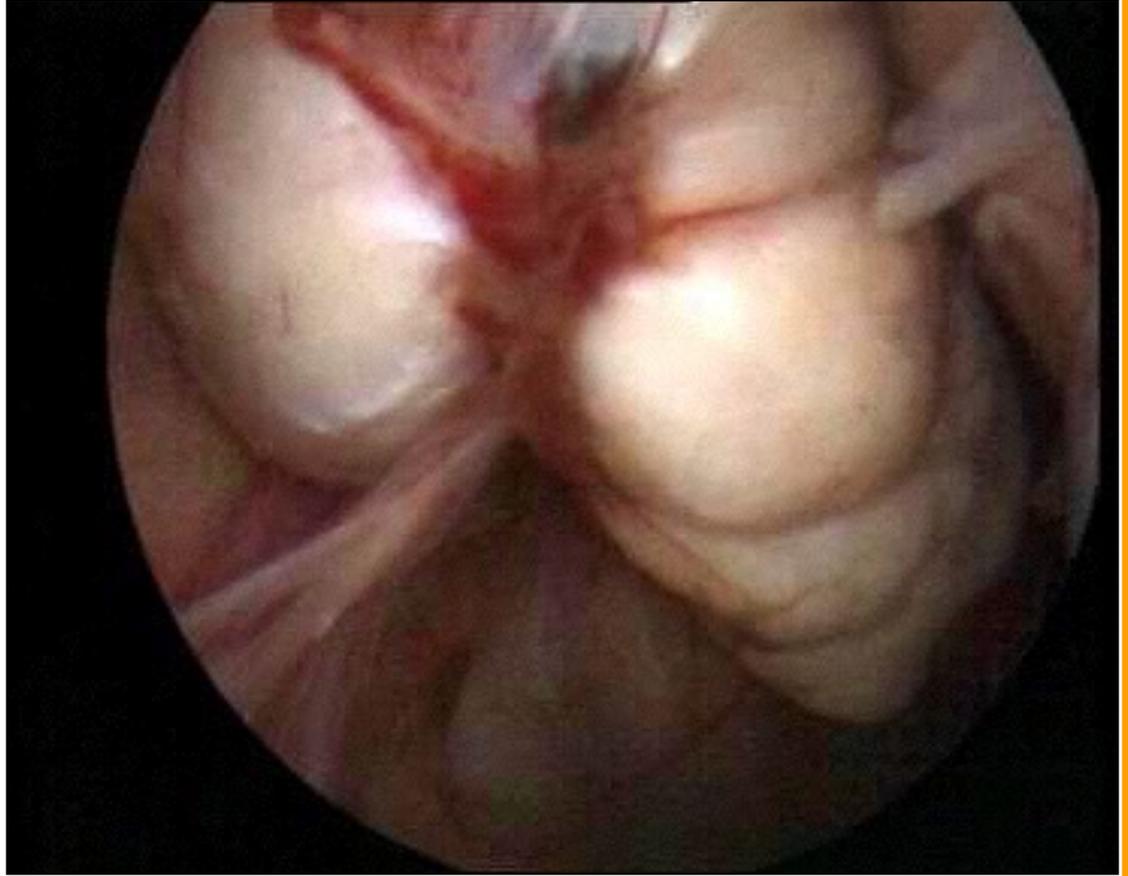
## THE OVARIAN ENDOMETRIOMA

- Invagination of the cortex with endometrial implant and adhesions
- Progressive fibromuscular metaplasia and devascularisation of the “endometrioma bed”



## Typical ovarian endometrioma

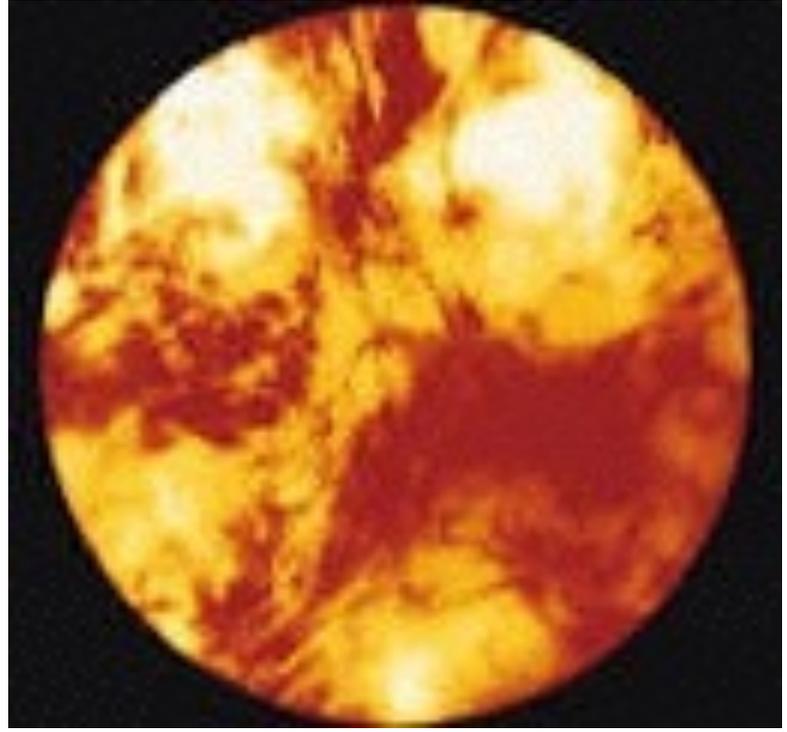
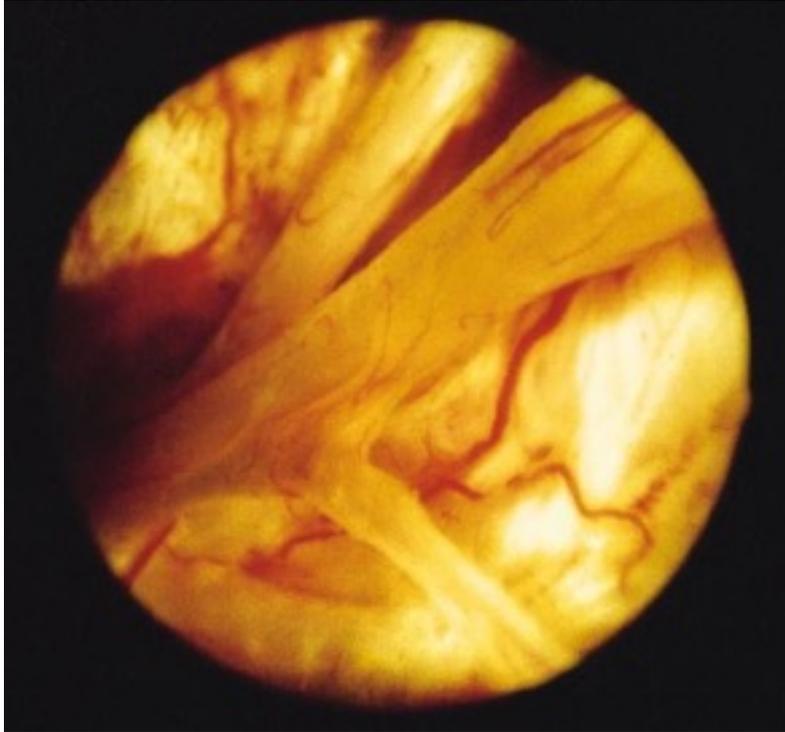
**Site of cortical  
invagination with  
endometriotic implant,  
bleeding and adhesions  
to the fossa ovarica**



# Ovarioscopy

**Left:** cortical retraction towards the site of invagination with the implant

**Right:** haemorrhagic endometrial-like tissue lining the invaginated cortex from the site of invagination



## **New options for the treatment of ovarian endometriomas**

- 1. The adolescent vs. adult phenotype**
- 2. Pathology-based reconstructive surgery**
- 3. New treatments of the ovarian endometrioma**

## Phenotype of adolescent endometriosis



An angiogenic disease

Bleeding can cause  
adhesions and  
formation of  
endometriomas

*Images observed at  
Transvaginal hydrolaparoscopy*

*Courtesy of Patrick Puttemans*



| <b>Adolescent endometriosis</b>   | <b>Adult endometriosis</b>  |
|---|---|
| Symptoms:<br>- Severe primary dysmenorrhea<br>- Resistant to OCP/NSAID  | Symptoms:<br>- Moderate dysmenorrhea  |
| <b>Peritoneal</b><br>Red, clear or vesicular implants<br>Minimal fibrosis<br><br><b>Ovarian endometrioma</b><br><b>Implant</b><br>Angiogenic adhesions<br>Stigma of inversion<br><b>Invaginated cortex</b><br>Marble white<br>Thin angiogenic mucosal lining<br><b>Endometrioma bed</b><br>Stretched<br><br><b>Deep endometriosis:</b> seldom | <b>Peritoneal</b><br>Black intraperitoneal implants<br>White, fibrotic<br><br><b>Ovarian endometrioma</b><br><b>Implant</b><br>Dense adhesions<br>Stigma of inversion<br><b>Invaginated cortex</b><br>Dark pigmented<br>Endometrial tufts<br><b>Endometrioma bed</b><br>Smooth muscle metaplasia<br>Fibrosis, devascularisation<br><br><b>Deep endometriosis:</b> more frequent |

| Age at onset of symptoms (years) | From first symptoms to seeing a doctor | From seeing a doctor to surgical diagnosis | From first symptoms to diagnosis |
|----------------------------------|--|--|----------------------------------|
| <19                              | 2.1                                    | 9.0  | 12.1                             |
| 20-29                            | 0.5                                    | 4.0  | 4.5                              |
| >30                              | 0.3                                    | 3.0  | 3.3                              |
| p                                | <0.01                                  | <0.01                                      | <0.01                            |

**Unfortunately, the earlier the onset of symptoms, the longer the delay in reaching a diagnosis**

## AWARENESS OF EARLY ONSET ENDOMETRIOSIS

The first and most important sign indicating the possible presence of endometriosis is **treatment-resistant dysmenorrhea**, to the point that it seems possible to predict an increased risk of endometriosis in girls with an early-onset of this symptom.

At the same time, dysmenorrhea alone cannot be sufficient for a proper diagnosis. Therefore, **clinical conditions that may increase the occurrence of neonatal bleeding: preeclampsia, post-maturity, feto-maternal incompatibility and low birth weight at or around term become important.**

*Bianchi et al. MOJ Women's Health 2017*

**Endometriomas in adolescents:  
The new hypothesis on its  
neonatal origin**

Incidence of ovarian endometrioma and deep or rectovaginal endometriosis in adolescents or young women with advanced stage pelvic endometriosis

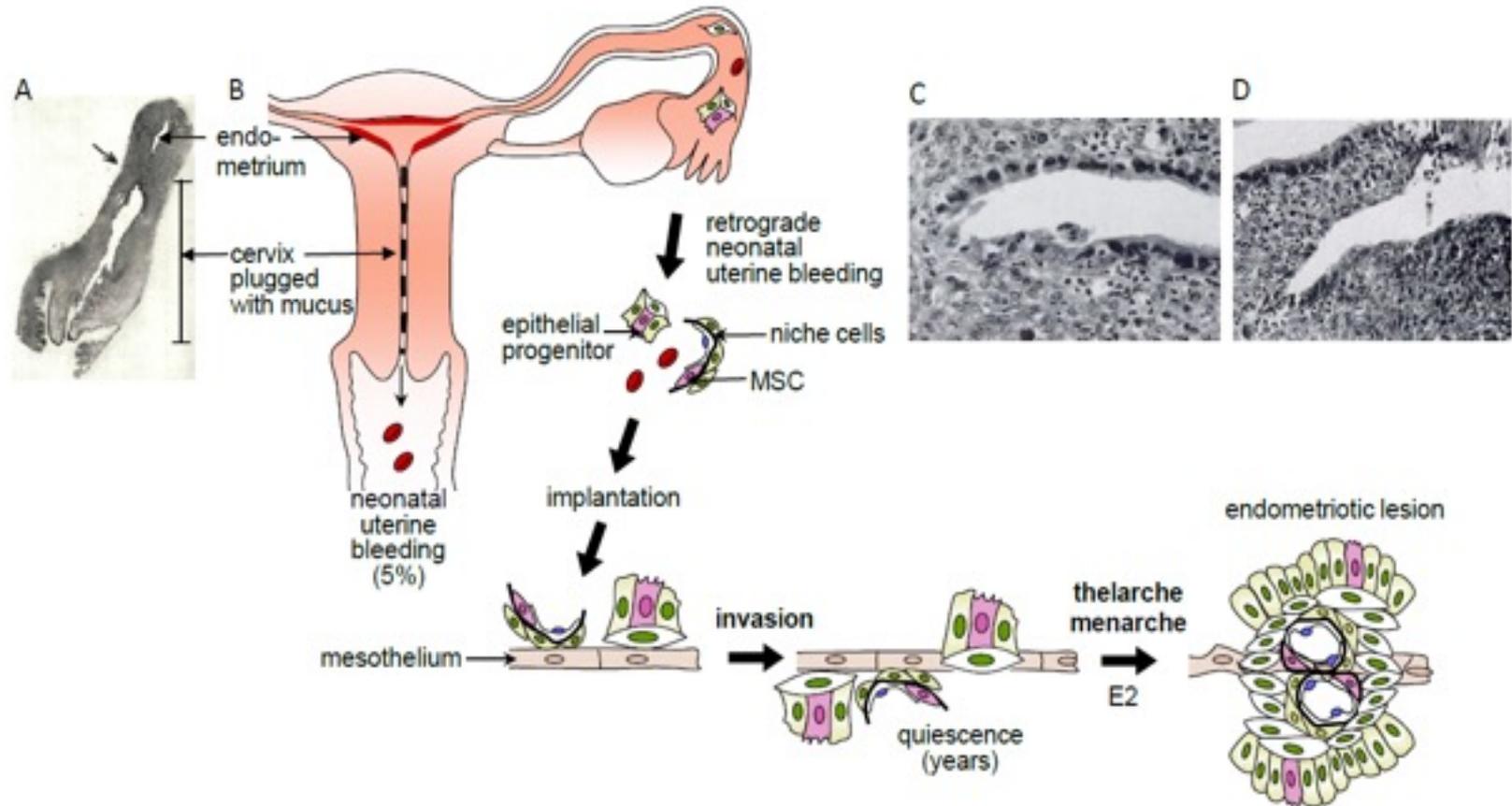
| Normal GT              | Age (years) | Stage III-IV (n) | Endometrioma | Deep or RV |
|------------------------|-------------|------------------|--------------|------------|
| Vicino <sup>37</sup>   | ≤ 21        | 26               | 26 (100%)    | 0 (0%)     |
| Yang <sup>38</sup>     | ≤ 21        | 48               | 40 (83%)     | 18 (40%)   |
| Lee <sup>39</sup>      | ≤ 20        | 35               | 35 (100%)    | 0 (0%)     |
| Smorgick <sup>40</sup> | ≤ 22        | 20               | 14 (70%)     | 1 (5%)     |
| Audebert <sup>41</sup> | 12-19       | 24               | 18 (75%)     | 6 (25%)    |
| GT obstruction         | Age         | Number           | Endometrioma | Deep or RV |
| Yang <sup>38</sup>     | ≤21         | 15               | 14 (93%)     | 2 (13%)    |
| Tong <sup>34</sup>     |             |                  |              |            |
| Complete:              | < 20        | 10               | 10 (100%)    | 0 (0%)     |
| Incomplete:            | < 37        | 8                | 8 (100%)     | 0 (0%)     |

GT: genital tract; Deep or RV: deep or rectovaginal endometriosis.

CLASSIFICATION OF CHANGES SEEN IN ENDOMETRIA  
OF 169 NEONATAL INFANTS

|  |     |       |
|--|-----|-------|
| <i>Proliferative endometrium</i>           | 116 | (68%) |
| No change (resting phase)                  | 60  |       |
| Stromal loosening                          | 44  |       |
| Hyperemia                                  | 35  |       |
| Petechial hemorrhage                       | 21  |       |
| Increased glandular tortuosity             | 17  |       |
| <i>Secretory endometrium</i>               | 45  | (27%) |
| Subnuclear vacuolation                     | 37  |       |
| Subnuclear and supranuclear<br>vacuolation | 8   |       |
| Secretion in glandular lumina              | 12  |       |
| Hyperemia and/or petechial<br>hemorrhage   | 5   |       |
| <i>Progestational endometrium</i>          | 8   | (5%)  |
| Decidual transformation                    | 3   |       |
| Menstrual changes                          | 5   |       |
|  | 169 |       |

# Pathogenesis of EOE (Gargett et al. 2014)



## Endometrioma Phenotypes

| Age group      | Fossa adherence | Cortex invagination | Subcortical metaplasia |
|----------------|-----------------|---------------------|------------------------|
| Perimenarcheal | present         | present             | absent                 |
| Adolescent     | present         | present             | absent                 |
| Adult          | present         | present             | present                |

## **Endometrioma in adolescence**

**Are the 2013 WES Consensus statements on the management of ovarian endometrioma applicable to the adolescent?**

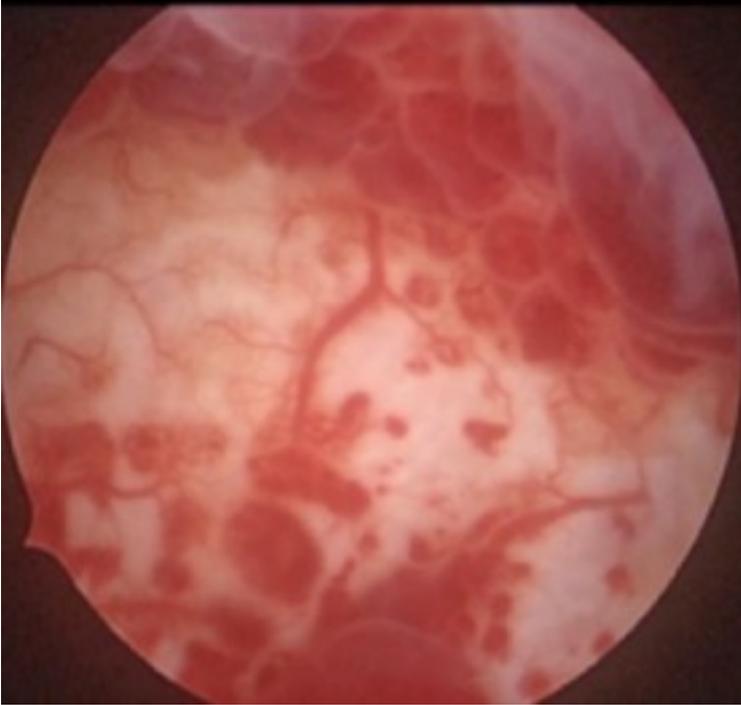
- **Laparoscopic excision (cystectomy) for ovarian endometriomas is preferred where possible.**
- **Laparoscopic excision (cystectomy) where possible is preferred to laparoscopic ablation.**
- **The combined oral contraceptive pill is a simple and effective medical treatment to minimise endometrioma recurrence rate after surgical removal.**

## **New options for the treatment of ovarian endometriomas**

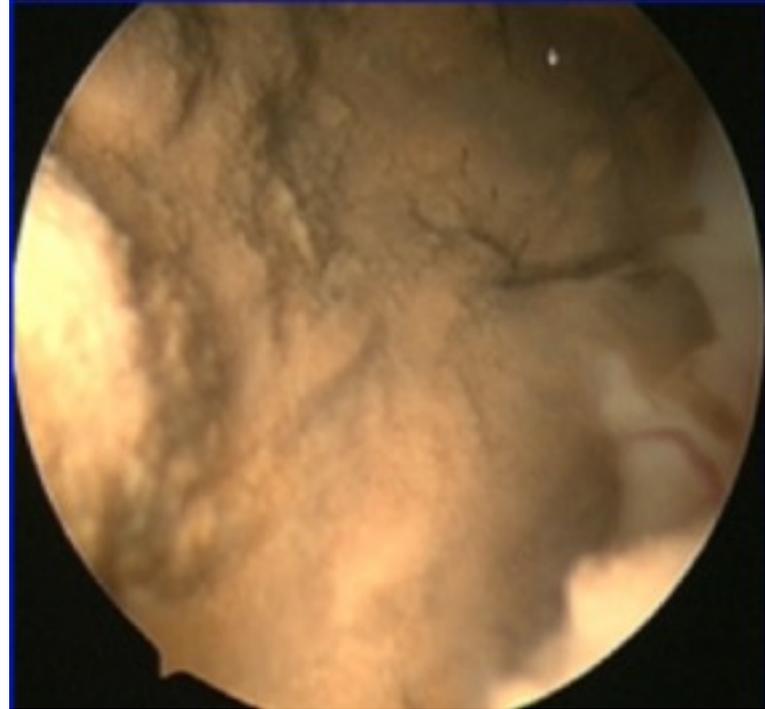
- 1. The adolescent vs. adult phenotype**
- 2. Pathology-based reconstructive surgery**
- 3. New treatments of the ovarian endometrioma**

**Endometrioma aging :**  
from “red” to “brown-black”

**Endometrial-like lining of the cortex**



**Devascularisation and fibrosis**



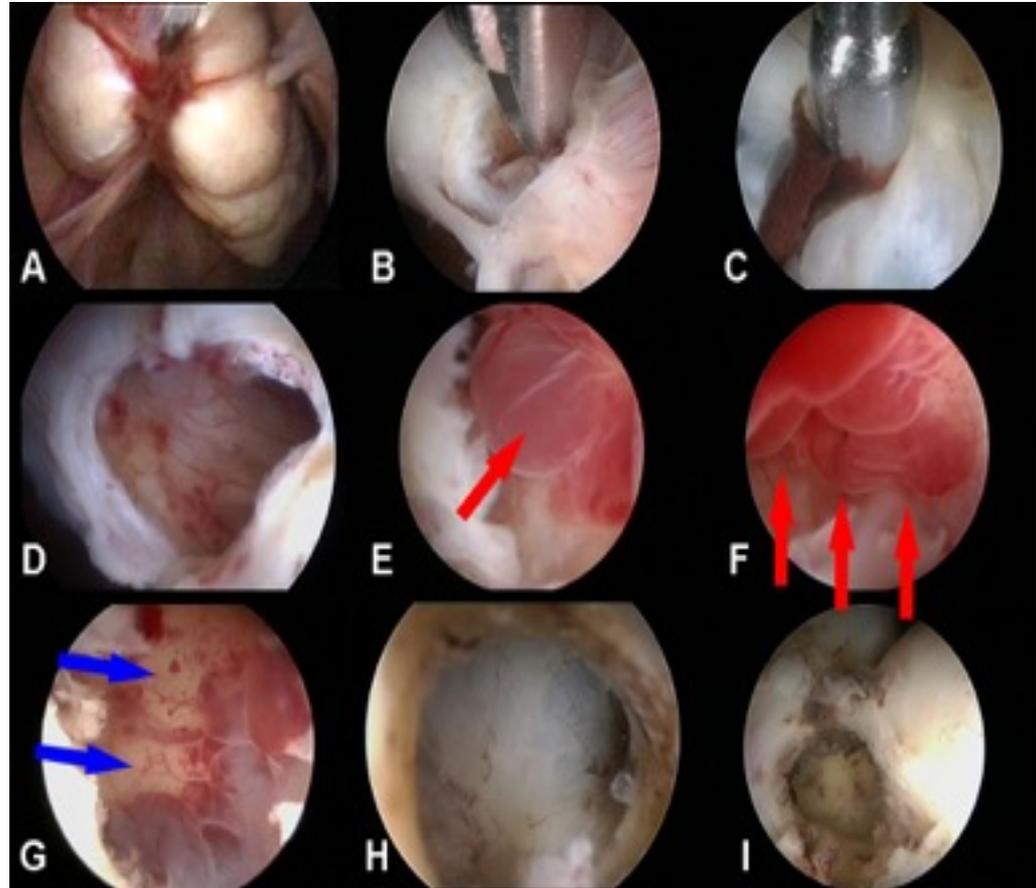
# RECONSTRUCTIVE SURGERY OF THE NON-FIBROTIC ENDOMETRIOMA (up to 3cm)



**A-C: Access via stigma  
of invagination**

**D-F: Exploration of  
cavity with mucosal  
lining**

**G-F: Ablation of  
endometrial lining**



## The large endometrioma

**Donnez et al (1996)** proposed a combined therapy using gonadotrophin-releasing hormone agonist (GnRHa) and carbon dioxide laser laparoscopy. Drainage and GnRHa for 12 weeks provoked a reduction of the endometrioma size up to 50% of the initial value. A recurrence rate of 8% was observed.

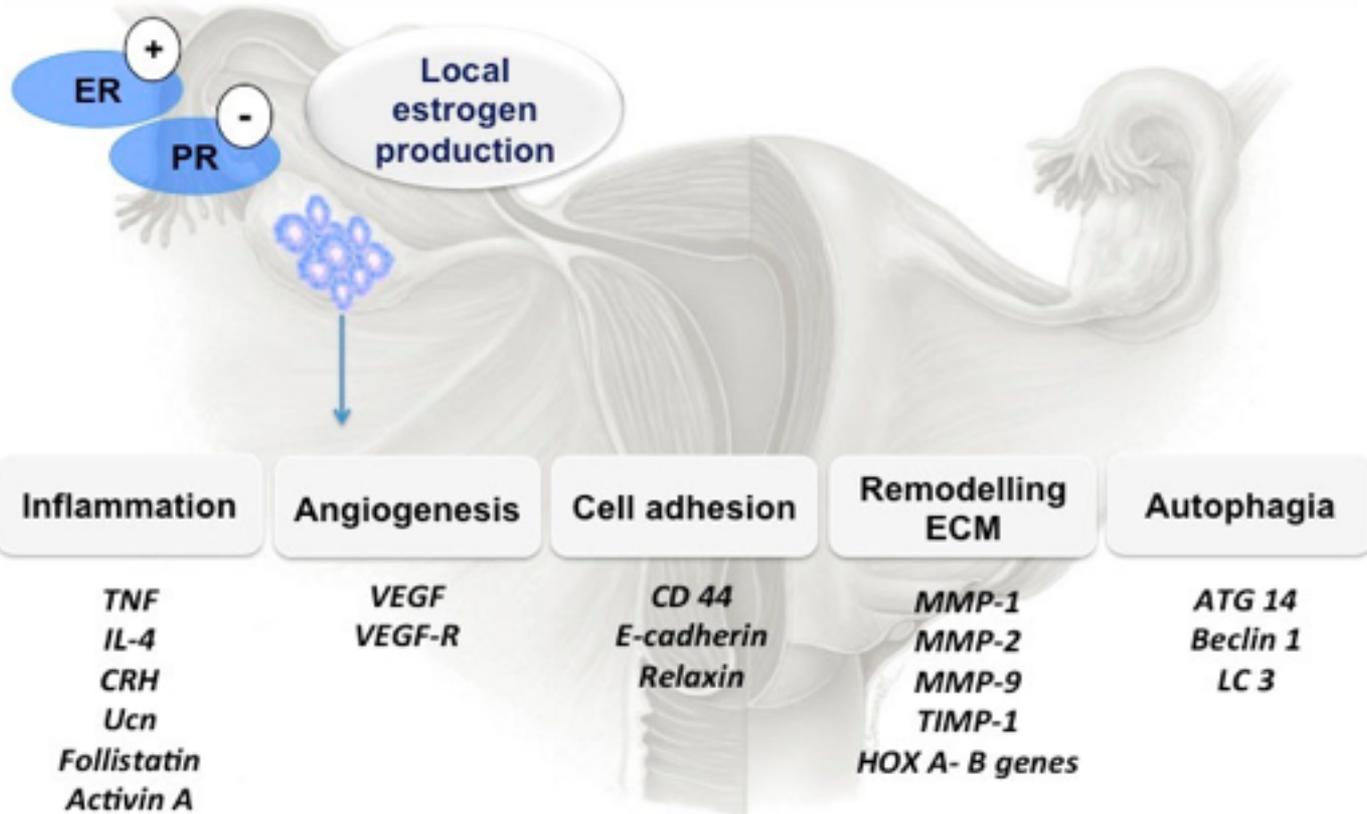
**Brosens et al (1996)** proposed a two-step procedure including first an operative step allowing involution of the pseudocyst and 2-3 months later a second step with adhesiolysis and coagulation of the endometriotic cortical lining.

***Caveat: the large endometrioma can represent an endometrioma combined with a luteal cyst.***

# **New options for the treatment of ovarian endometriomas**

- 1. The adolescent vs. adult phenotype**
- 2. Pathology-based reconstructive surgery**
- 3. New treatments of the ovarian endometrioma**

## Genetic / epigenetic changes



## Currently available drugs labelled for endometrioma treatment

### GnRH agonists

- have a direct anti-proliferative action that may achieve regression
- **beneficial impact on the recurrence rate after conservative laparoscopic surgery;**

### Cabergoline (dopamine agonist)

Yields better results in decreasing the size of the endometrioma, compared to LHRH-agonist (triptorelin acetate) **by exerting antiangiogenic effects** through vascular endothelial growth factor receptor-2 (VEGFR-2) inactivation (*Hamid 2014*)

## Progestins

Information abounds on the use of progestins in the medical treatment of peritoneal endometriosis, with **little data on the specific application to ovarian endometriomas.**

Classically, **norethisterone acetate** has been the progestin of choice. More recently, **dienogest** has been preferred as it **affects endometriotic stromal cells causing high decidualisation and reduced inflammatory reaction.**



### **Oral contraceptives:**

Long-term cyclic or continuous use can prevent recurrences after laparoscopic cystectomy.

### **Mirena (LNG-IUS):**

Its insertion may also prevent recurrence.

### **Subcutaneous Implanon insertion:**

No study on endometrioma yet available.

### **Anti-oestrogens (Aromatase P450 inhibitors):**

Their use yet to be validated

*In principle, the same drugs can be used in adolescent and adult patients.  
The critical issue, however, is the progressive and dynamic nature of endometriosis.*

### **GnRH antagonists:**

Awaiting studies on endometrioma

### **Selective Progesterone Receptor Modulators (SPRMs or PRMs):**

Little is known on endometriomas

### **Quinagolide (a dopamine receptor agonist):**

In a small study it led to the reduction of peritoneal lesions in 2/3 of cases, and elimination in the residual 1/3.

### **Antiangiogenic agents**

### **Valproic acid**

## Intracystic drug administration

Ultrasound-guided alcoholic sclerotherapy of the endometriotic ovarian cysts is effective and safe.

It has been proposed that endometrial growth in the endometrioma is suppressed by intra-cystic application of **progestins**, such as levonorgestrel or danazol or **SPRMs**, such as mifepristone, ulipristal or asoprisnil, without affecting ovarian activity.

## **Intracystic drug administration**

**Is intracystic decidualisation of the ovarian endometrioma in the adolescent the future?**

**We need controlled trials to obtain the answer**

## Conclusions

Ovarian endometriomas are increasingly diagnosed at an earlier stage when the endometrioma may be small, less fibrotic and more responsive to medical treatment,

Today, reliable, non-invasive diagnostic procedures to identify an ovarian endometrioma are available and should be utilized to identify its presence and its type also in young patients.

Classic medical therapies, such as oral contraceptives and synthetic progestins, should be tried first to alleviate symptoms. When surgery is indicated, minimally invasive procedures should be envisaged.

Following endoscopic surgery, adjuvant medical treatment may reduce recurrence of both symptoms and the lesion.

