



**Spital Thurgau**

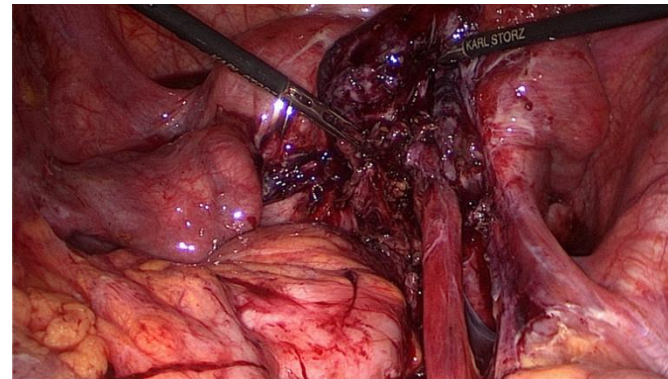
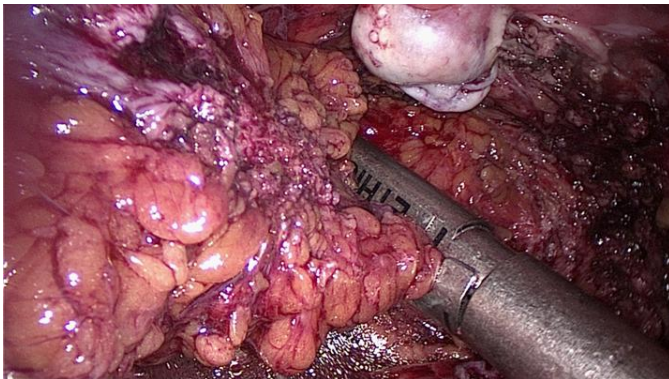
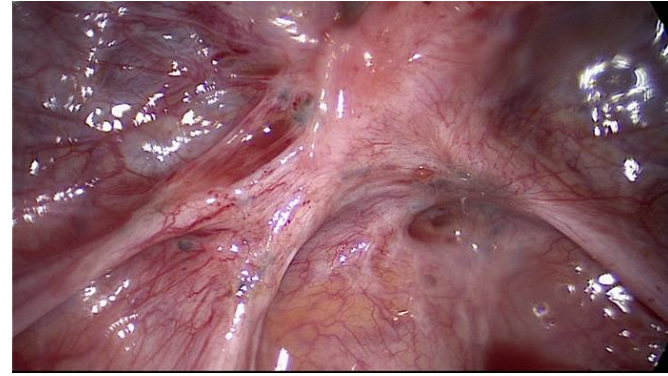
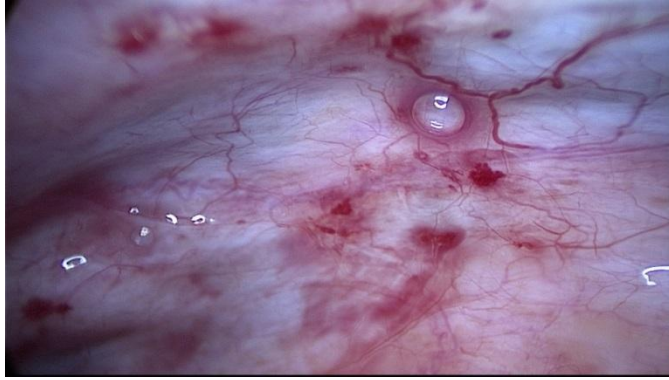
MÜNSTERLINGEN



# **Endometriose**

## aktuelle Aspekte zu Pathophysiologie und Therapie

Priv.-Doz. Dr. Stefan Rimbach  
Frauenklinik, Kantonsspital Münsterlingen





# Fetal endometriosis: a case report

Meike Schuster, D.O. and Dhanya A. Mackeen, M.D., M.P.H.

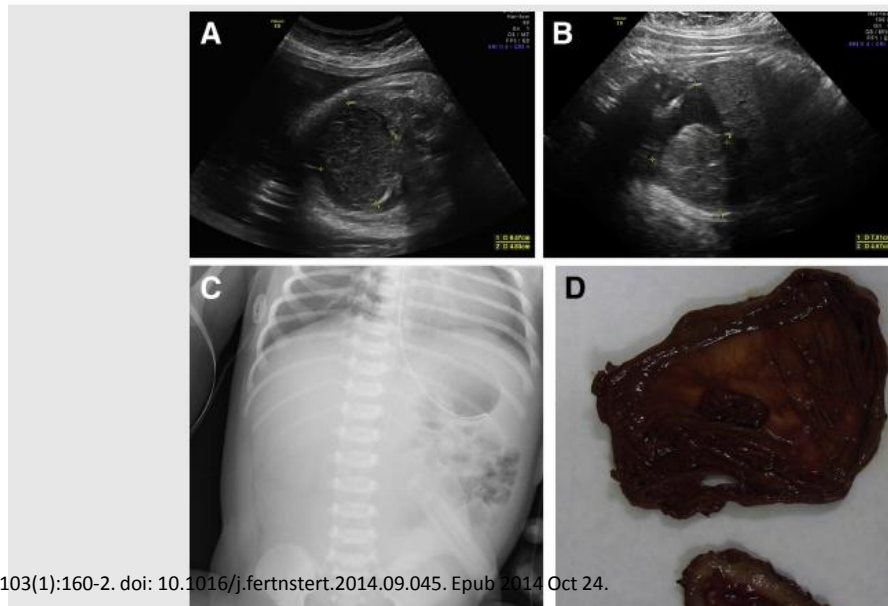
Geisinger Medical Center, Danville, Pennsylvania

**Objective:** To report a case of a large fetal pelvic mass diagnosed at 35 weeks' gestation.

**Design:** Report of a unique case of a fetal abdominal mass, emphasizing the wide range of differential diagnoses. Although rare reports of fetal ovarian cysts exist, even fewer describe endometriosis or endometriomas in infants. As of 2014 there have not been any published reports of fetal endometriosis from the United States.

**Setting:** Large tertiary community hospital

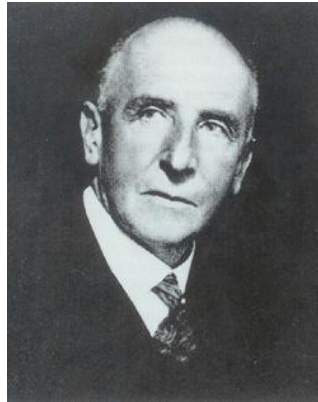
FIGURE 1



# Metaplasietheorie

## Über den Stand der Frage der Adenomyositis und Adenomyome

Zbl Gynäköl 1919



**Robert Meyer (1864-1947)**

# Metastasierungstheorie

**Hysteroadenosis metastatica. Die lymphogene  
Genese der sogenannten Adenofibromatosis  
heterotopica.**

Wien Klin Wschr 1924



**Josef Halban (1870-1937)**



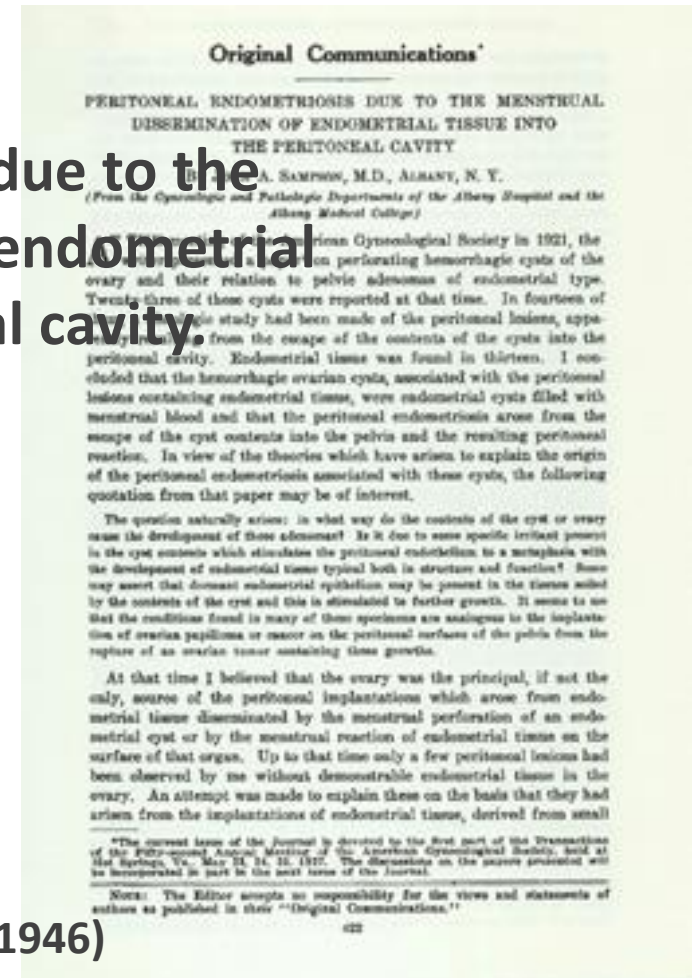
# Implantationstheorie

Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity

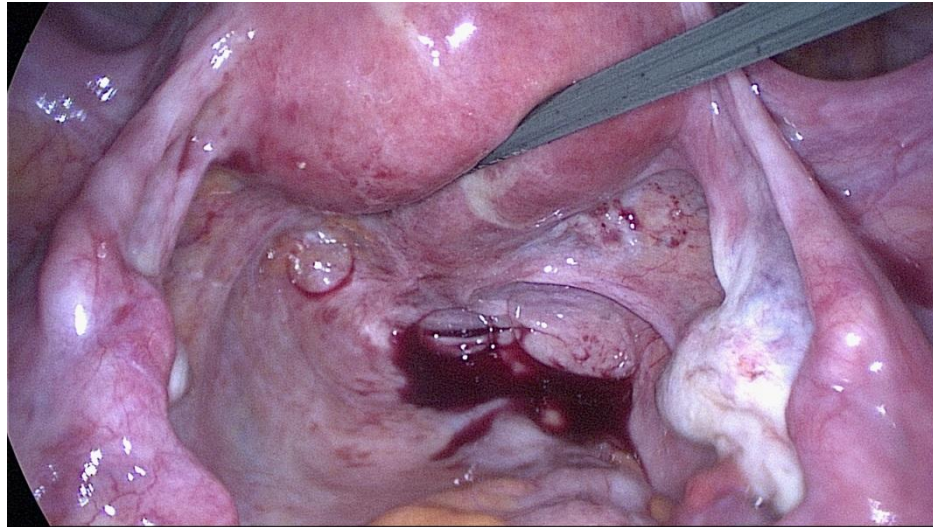
Am J Obstet 1927



John A. Sampson (1873-1946)



# Pathogenese - Retrograde Menstruation ?



# Eutopes und ektopes Endometrium, Gen-Expression

Candidate factors implicated in the pathophysiology of endometriosis.

Gene	Function	Reference
17 $\beta$ -HSD-2	Hydroxysteroid dehydrogenase	(47)
BCL-2	Antiapoptosis	(31)
CYP19	Aromatase enzyme	(102)
HOXA10	Transcription factor	(103)
IL-6	Cytokine	(82)
KRAS	Oncogene	(30)
MMP 3,7	Matrix metalloproteinases	(65)
NF-KB	Transcription factor	(104)
PGE <sub>2</sub>	Prostaglandin	(105)
PTEN	Tumor suppressor gene	(30)
TGF-B	Cytokine	(61)
TNF- $\alpha$	Cytokine	(81)

*Burney. Pathogenesis and pathophysiology of endometriosis. Fertil Steril 2012.*



# Genetik

Khan *et al. Reproductive Biology and Endocrinology* 2012, **10**:84  
<http://www.rbej.com/content/10/1/84>



## RESEARCH

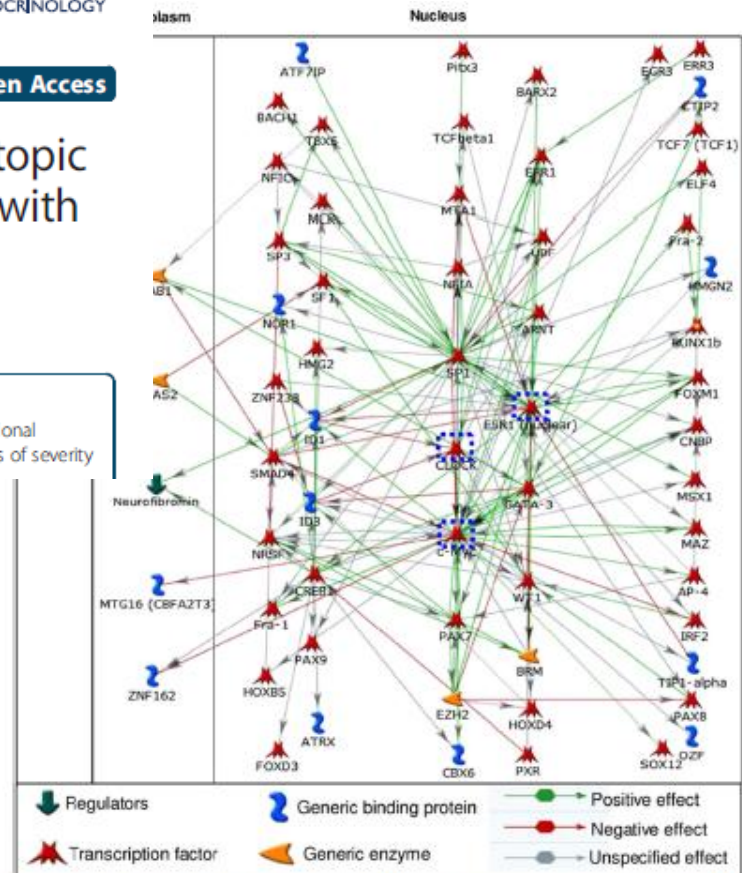
## Open Access

### Genome-wide expressions in autologous eutopic and ectopic endometrium of fertile women with endometriosis

Meraj A Khan<sup>1</sup>, Jayasree Sengupta<sup>1</sup>, Suneeta Mittal<sup>2</sup> and Debabrata Ghosh<sup>1\*</sup>

#### Abstract

**Background:** In order to obtain a lead of the pathophysiology of endometriosis, genome-wide expressional analyses of eutopic and ectopic endometrium have earlier been reported, however, the effects of stages of severity and phases of menstrual cycle on expressional profiles have not been analysed. The effect of genetic



**Figure 5** Knowledge-based construction of the pathways-network of transcription factors putatively associated with pathogenesis of endometriosis. The transcription factors were identified from GSEA implementation on co-expressed genes. It is notable that CLOCK, ESR1, and MYC (shown inside blue dotted rectangle) are differentially co-expressed in endometriosis as shown in Table 5.



# Epigenetik

[Reprod Sci](#). 2015 Mar 27. pii: 1933719115578924. [Epub ahead of print]

## **H3K27me3 is an Epigenetic Mark of Relevance in Endometriosis.**

[Colón-Caraballo M](#)<sup>1</sup>, [Monteiro JB](#)<sup>2</sup>, [Flores J](#)<sup>3</sup>.

### **Author information**

### **Abstract**

Epigenetic mechanisms may play an important role in the etiology of endometriosis. The modification of histones by methylation of lysine residues has been shown to regulate gene expression by changing chromatin structure. We have previously shown that endometriotic lesions had aberrant levels of histone acetylation (lower) and methylation (higher) than control tissues. We aimed to determine the levels of trimethylated histone 3 at lysine residue 27 (H3K27me3), a well-known repressive mark, by immunoassay of fresh tissues and immunohistochemistry (IHC) of an endometriosis focused tissue microarray. Also, we aimed to determine levels of expression of enhancer of zeste homolog 2 (EZH2), the enzyme



# Fetal Programming

[Hum Immunol.](#) 2014 Mar;75(3):208-217. doi: 10.1016/j.humimm.2013.12.012. Epub 2013 Dec 27.

## **Fetal programming theory: Implication for the understanding of endometriosis.**

[Kobayashi H<sup>1</sup>](#), [Iwai K<sup>2</sup>](#), [Niino E<sup>2</sup>](#), [Morioka S<sup>2</sup>](#), [Yamada Y<sup>2</sup>](#).

### **Author information**



### **Abstract**

Comparison of the transcriptomes and proteomes of the decidualization-specific genes that express high vs low levels of the eutopic and ectopic endometrium of women with endometriosis compared with controls, could be useful in understanding the pathogenesis of endometriosis. Genome-wide comparison between decidual tissue and non-decidual tissue identified many genes significantly modulated in the process of decidualization. Comparison of eutopic endometrium and endometriotic sites also revealed up- and down-regulated genes. A combined analysis of the experimental data showed specific genes up-regulated both at the endometriotic site and in the decidualization process, representing a broad diversity of molecular functions, including cell cycle regulation, angiogenesis and adhesion molecules. In contrast, down-regulated genes identified in endometriosis among genes overexpressed in decidualization encode Müllerian embryogenesis, which includes transcription factors, hormonal regulation and cytokine expression. The mechanism responsible for insufficient decidualization in endometriosis may be mediated through down-regulation of the Müllerian embryogenesis-related genes. In conclusion, a range of decidualization resistance has been associated with endometriosis. Future study will identify the putative mechanisms relating epigenetic changes of decidualization susceptibility genes in early life to the risk of developing endometriosis in adulthood.



# Stammzellen

Clin Sci (Lond). 2014 Jan;126(2):123-38. doi: 10.1042/CS20130099.

**Genetic, epigenetic and stem cell alterations in endometriosis: new insights and potential therapeutic perspectives.**

Forte A<sup>1</sup>, Cipollaro M, Galderisi U.

**Author information**

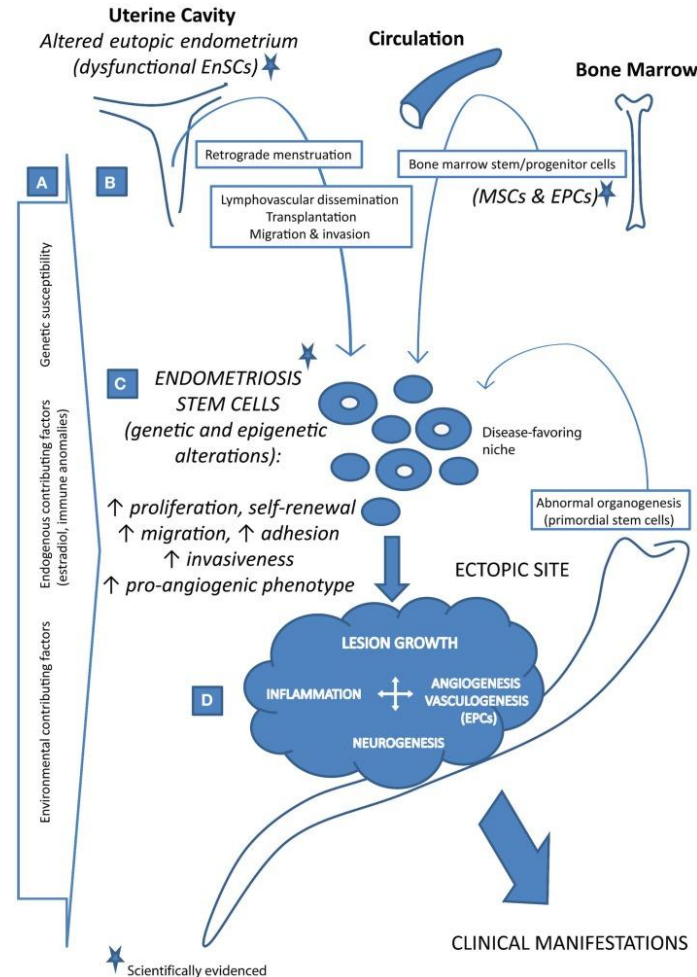
## **Abstract**

Human endometrium is a highly dynamic tissue, undergoing periodic growth and regression at each menstrual cycle. Endometriosis is a frequent



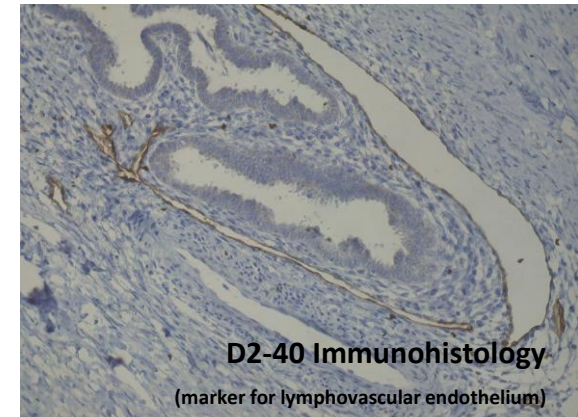
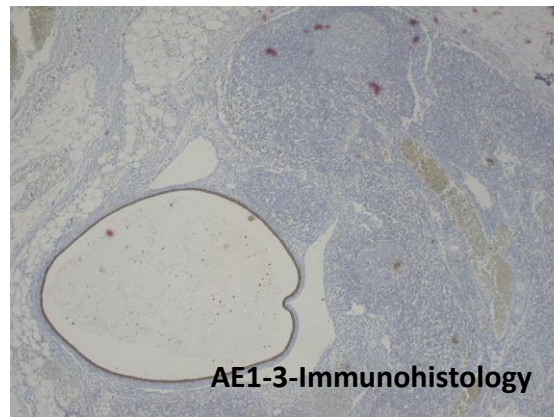
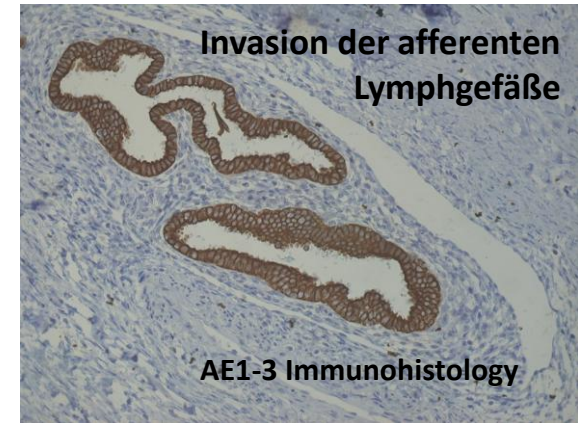
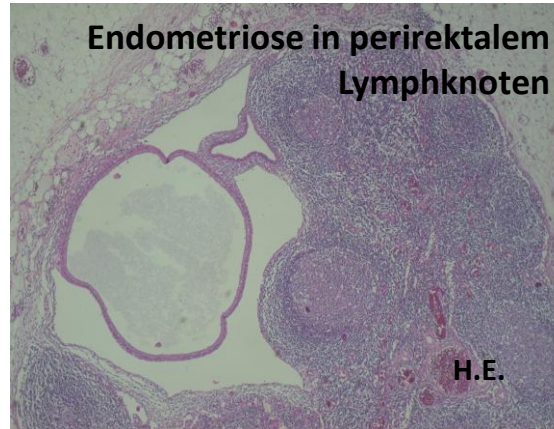
## Somatic stem cells and their dysfunction in endometriosis

Dusan Djokovic<sup>1,2</sup> and Carlos Calhaz-Jorge<sup>3,4,\*</sup>





# Pathogenese - Lymphatische Ausbreitung

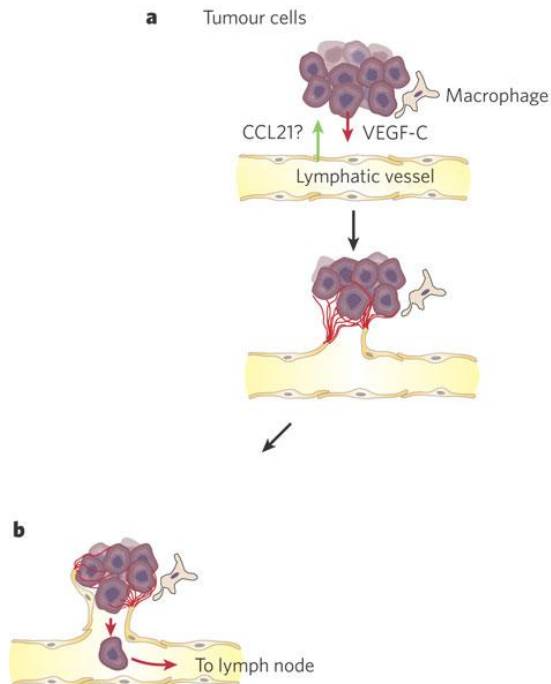


Schlatterer T, Scholz H, Tigges H, Letzkus C, Rimbach S: Endometriosis of perirectal lymph nodes in deep infiltrating endometriosis of the rectosigmoid colon – a new therapeutical consequence to be considered ? Arch Gynecol Obstet 2010

# Pathogenese - Lymphatische Ausbreitung

Author/ Source	design	Disease	LN	Pat	LN +
<b>Mechsner</b> Fertil Steril 2010	retrospective	DIE	incidentally removed	24	8 (33.3%)
<b>Abrao</b> Fertil Steril 2006	prospective	rectosigmoid	perirectal	35 (LN in 19)	5 (26.3%)
<b>Noël</b> Fertil Steril 2008	prospective	rectosigmoid	perirectal	26	11 (42.3%)
<b>Mechsner</b> Hum Reprod 2008	prospective	DIE	pelvic SLN	14 (in 12 SLN detected)	3 (25%)
<b>Tempfer</b> Fertil Steril 2011	prospective	ovarian/ peritoneal	pelvic SLN	23 (in 19 SLN detected)	2 (11%)

# Lymphangiogenese



Reichert U, Keichel S, Barcena de Arellano ML, Chiantera V, Schneider A, Mechsner S.: **High lymph vessel density and expression of lymphatic growth factors in peritoneal endometriosis.** Reprod Sci 2012

Keichel S, Barcena de Arellano ML, Reichelt U, Riedlinger WF, Schneider A, Köhler C, Mechsner S.: **Lymphangiogenesis in deep infiltrating endometriosis.** Hum Reprod 2011

Takehara M, Ueda M, Yamashita Y, Terai Y, Hung YC, Ueki M.: Vascular endothelial growth factor A and C gene expression in endometriosis. Hum Pathol. 2004 Nov;35(11):1369-75.

Alitalo K, Tammela T, Petrova TV: **Lymphangiogenesis in development and human disease.** Nature 2005;438:946-53.

# Angiogenese



Xu H, Zhang T, Man GC, May KE, Becker CM, Davis TN, Kung AL, Birsner AE, D'Amato RJ, Wong AW, Wang CC.: Vascular endothelial growth factor C is increased in endometrium and promotes endothelial functions, vascular permeability and angiogenesis and growth of endometriosis. Angiogenesis. 2013 Jan 19. [Epub ahead of print]

Hey-Cunningham AJ, Markham R, Fraser IS, Berbic M.: Dysregulation of Vascular Endothelial Growth Factors and Their Neuropilin Receptors in the Eutopic Endometrium of Women With Endometriosis. Reprod Sci. 2013 Apr 12. [Epub ahead of print]



# Angiogenese

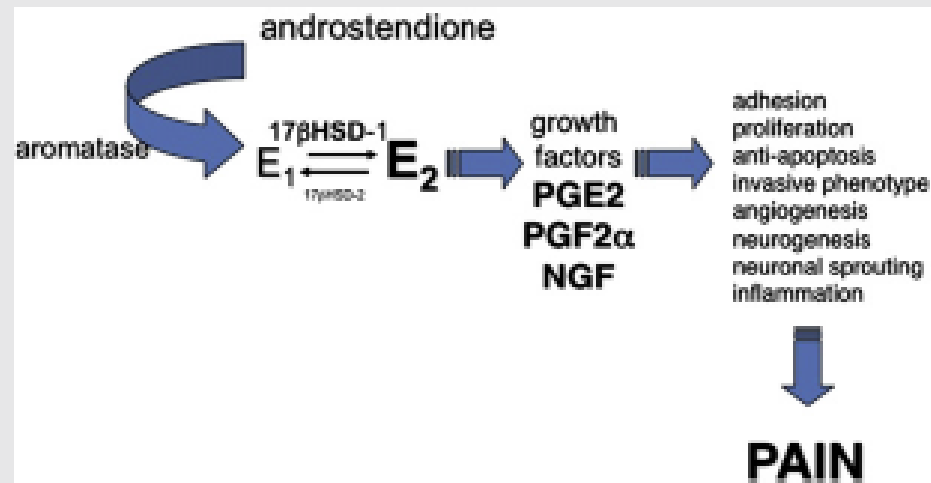


Xu H, Zhang T, Man GC, May KE, Becker CM, Davis TN, Kung AL, Birsner AE, D'Amato RJ, Wong AW, Wang CC.: Vascular endothelial growth factor C is increased in endometrium and promotes endothelial functions, vascular permeability and angiogenesis and growth of endometriosis. Angiogenesis. 2013 Jan 19. [Epub ahead of print]

Hey-Cunningham AJ, Markham R, Fraser IS, Berbic M.: Dysregulation of Vascular Endothelial Growth Factors and Their Neuropilin Receptors in the Eutopic Endometrium of Women With Endometriosis. Reprod Sci. 2013 Apr 12. [Epub ahead of print]



# Pathophysiologie - Schmerz



Local  $E_2$  production in endometriotic lesions and eutopic endometrium, inflammation, and pain.  $17\beta$ -HSD =  $17\beta$ -hydroxysteroid dehydrogenase;  $E_1$  = estrone;  $E_2$  = estradiol;  $PGE_2$  = prostaglandin  $E_2$ ;  $PGF2\alpha$  = prostaglandin  $F_{2\alpha}$ ; NGF = nerve growth factor.

Burney. *Pathogenesis and pathophysiology of endometriosis*. Fertil Steril 2012.

# Pathophysiologie - Sterilität

Minerva Ginecol. 2013 Apr;65(2):181-98.

**From conception to birth - how endometriosis affects the development of each stage of reproductive life.**

Carvalho LF<sup>1</sup>, Rossener R, Azeem A, Malvezzi H, Simões Abrão M, Agarwal A.

**Author information**



## **Abstract**

Increasing evidence suggests that female infertility is associated with endometriosis. Indeed, 40% of women with this disease are infertile. However, a causal relationship has not yet been established, and the possible pathophysiology of infertility in this disease also has not been completely elucidated. In this article, we analyze the mechanisms necessary to achieve a successful live birth in patients with this disease as well as the important steps of fertility, pregnancy and birth that can be impaired in these women. Specifically, we will review new advances in research on folliculogenesis, oocyte quality and sperm quality, egg fertilization, embryo quality, transport through fallopian tube and utero-tubal transport sperm, implantation defects, risk of miscarriage, risk during pregnancy and pre-term delivery. The physiopathology of these alterations and the clinical results of the studies are still very controversial. For these reasons, we can conclude that more research is needed to study the biological pathways of the fertility impairment caused by this disease.

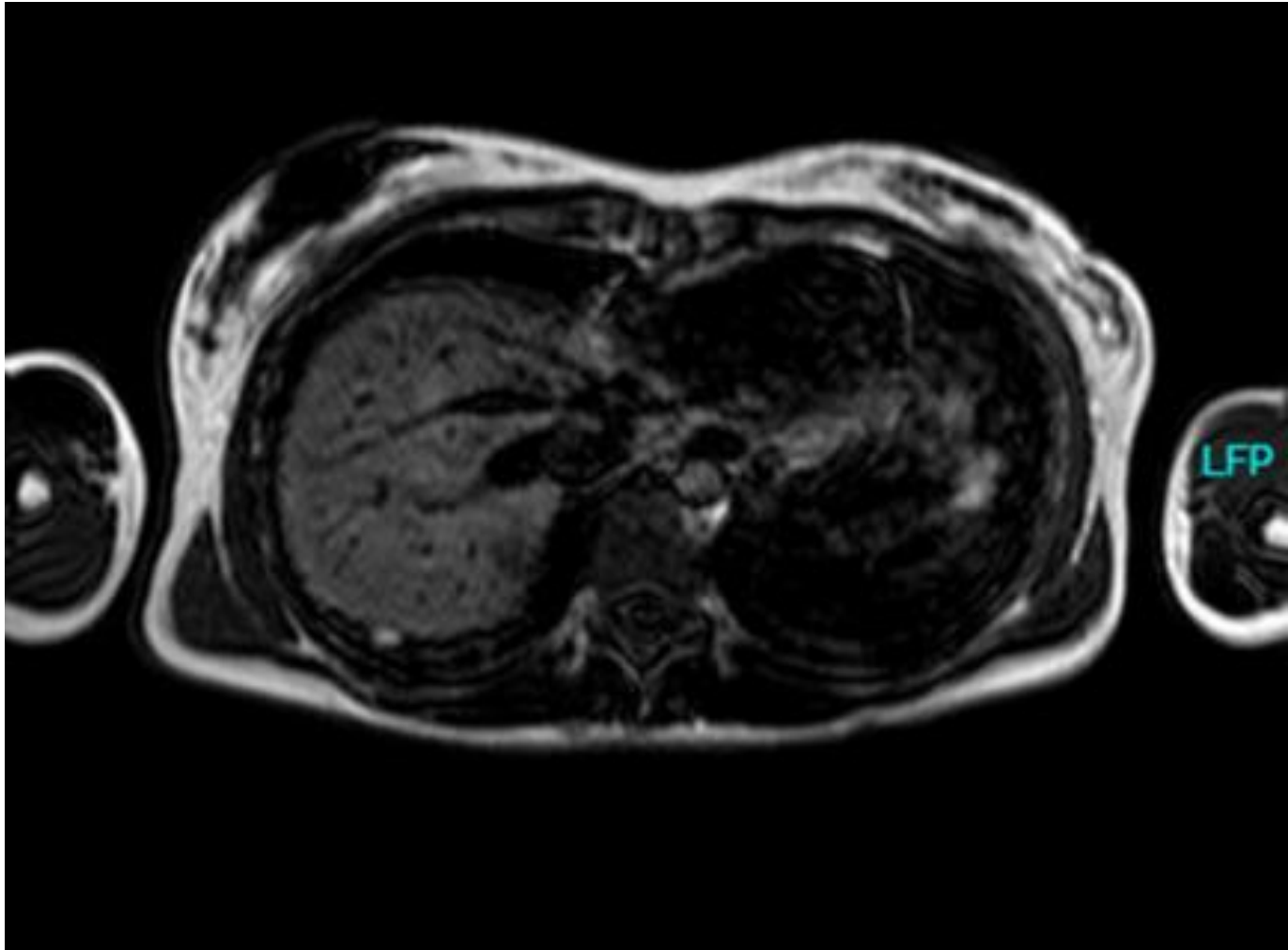
# Diagnostik

- **daran denken**
- **GynU (Spec/Palp)**
- **vag US**
- **US NBKS**
- **MRT**
- **Rekto-Sigmoideoskopie**

# Diagnostik



# Diagnostik

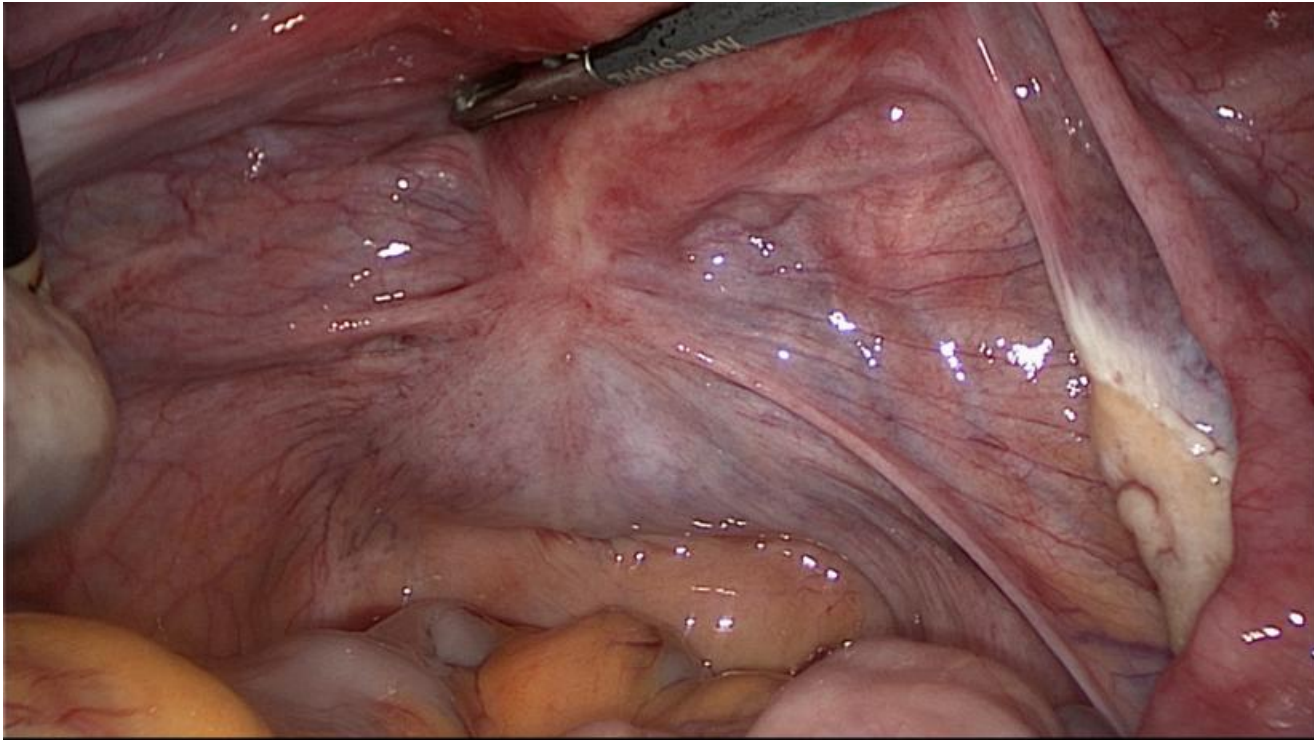




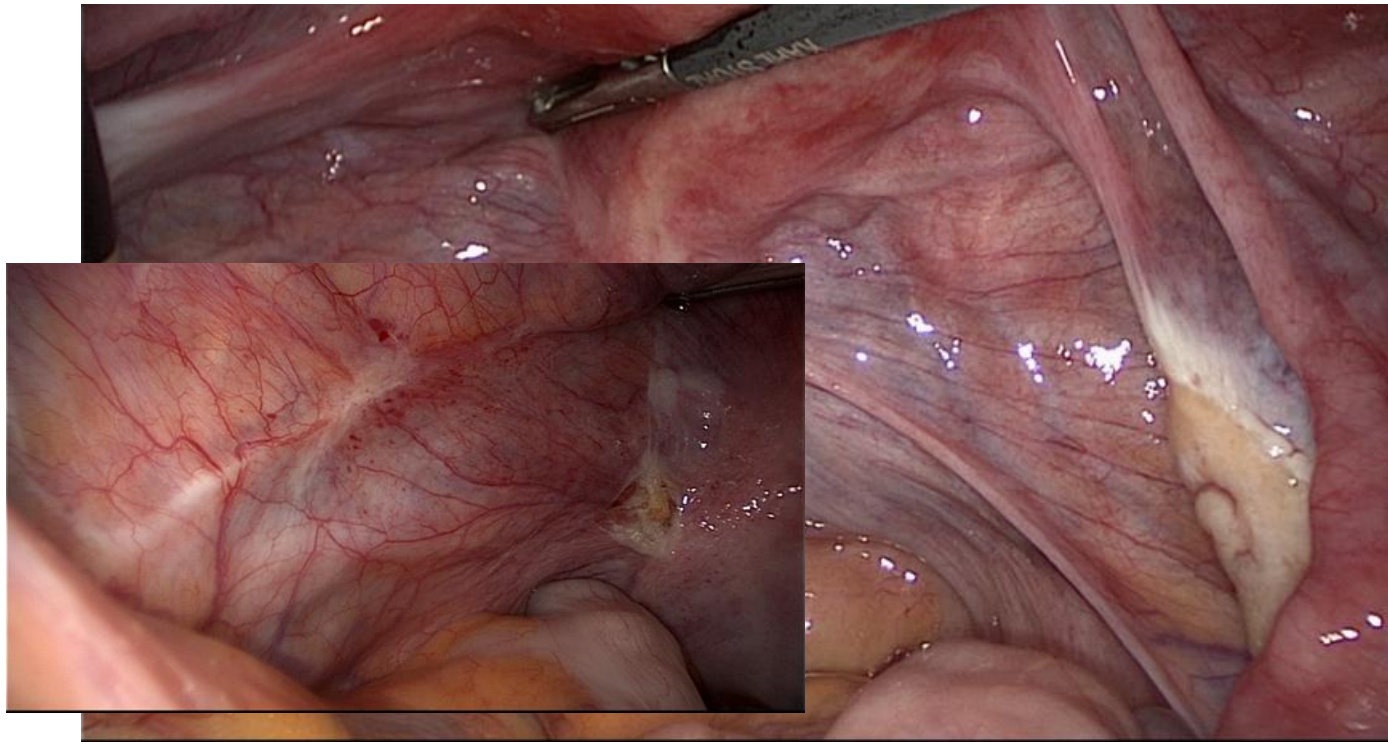
# Diagnostik

- daran denken
- GynU (Spec/Palp)
- vag US
- US NBKS
- MRT
- Rekto-Sigmoideoskopie
- **Laparoskopie**

# Diagnostik



# Diagnostik



# Therapie-Spektrum

- **Dienogest (Visanne<sup>R</sup>)**

# Therapie-Spektrum

- **Dienogest** (Visanne<sup>R</sup>)
- off-label: andere Gestagene, LNG-IUD (Mirena<sup>R</sup>), OH im Longzyklus
- GnRHa (± add back)



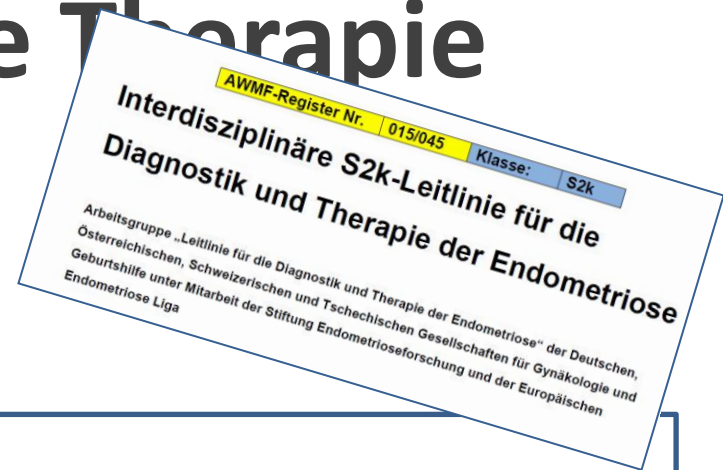
# Therapie-Spektrum

- **Dienogest** (Visanne<sup>R</sup>)
- off-label: andere Gestagene, LNG-IUD (Mirena<sup>R</sup>), OH im Longzyklus
- GnRHa (± add back)
- Studien: Aromataseinhibitoren ?  
Angiogeneseinhibitoren ?

# Therapie-Spektrum

- **Dienogest** (Visanne<sup>R</sup>)
- off-label: andere Gestagene, LNG-IUD (Mirena<sup>R</sup>), OH im Longzyklus
- GnRHa (± add back)
- Studien: Aromataseinhibitoren ?  
Angiogeneseinhibitoren ?
- **Operative Therapie**

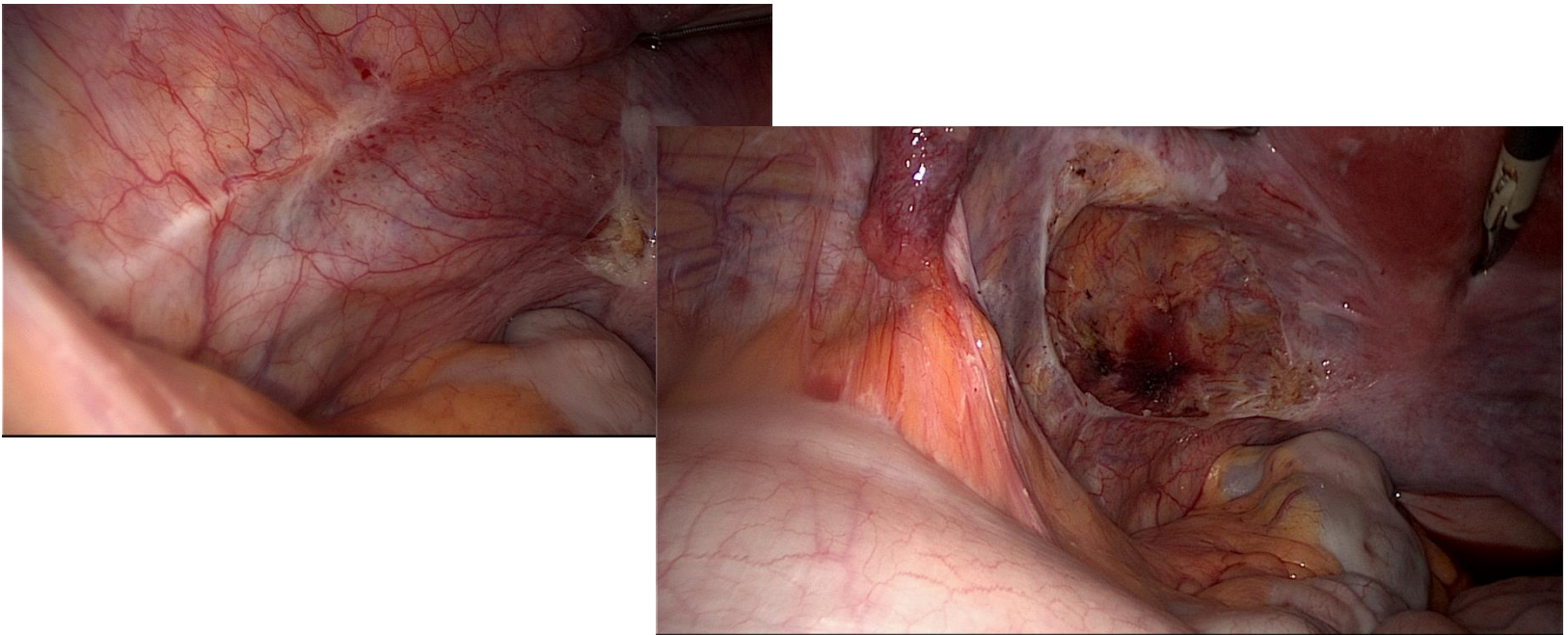
# Leitlinie: operative Therapie



## Empfehlungen:

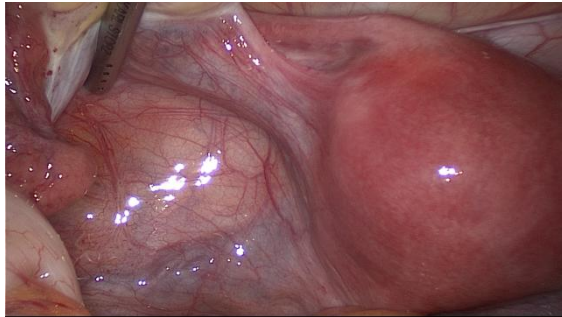
a) Therapeutisch sollte die **Resektion in sano** erfolgen. Gleichwohl sind dabei wegen des oft gebotenen Erhalts der Fertilität Kompromisse einzugehen. Der Umfang der Resektion soll vor dem Hintergrund einer benignen Erkrankung und relevanter möglicher Komplikationen gut mit der Patientin abgestimmt werden.

# Peritoneale Endometriose

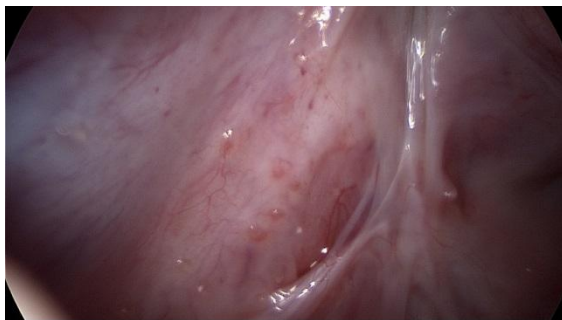


**Exstirpation im Gesunden**

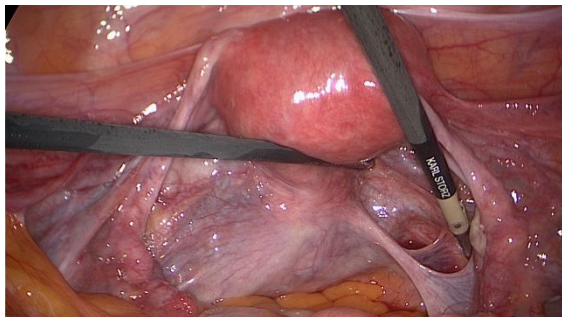
# Peritoneale Endometriose



winzige Herde – massive  
Symptome



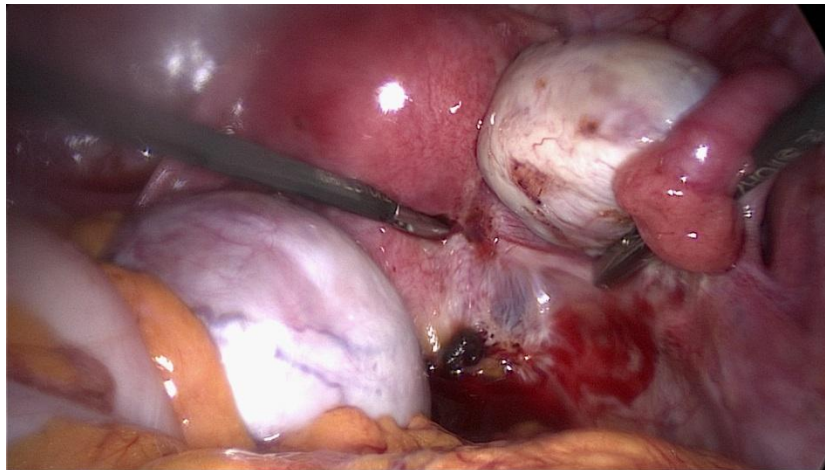
peritoneale Bläschen



Peritonealdefekte (Allen-  
Masters-Läsionen)

# Ovarial - Endometriose

- 100 % Ovarialstroma im Präparat nachweisbar
- 68.9 % Primordialfollikel (1-25, mean 6.6)
- Gefahr Beeinträchtigung der Ovarialfunktion



Brosens IA, Puttemans PJ, Deprest J (1994) Fertil Steril 61, 1034-8.

Donnez J, Nisolle M, Gillet N (1996) Human Reprod 11, 641-6.

Hachisuga T, Kawarabayashi T (2002) Human Reprod 17, 432-5.



# Ovarial - Endometriose

n=1785

***ausschließlich*** Ovarial-  
Endometriose nur in 1.06 %

- Marker für weitere Lokalisationen
- Untertherapie vermeiden





# Tief Infiltrierende Endometriose

918 GebFra Science

## Surgical Therapy of Endometriosis: Challenges and Controversies

Herausforderungen und Kontroversen bei der operativen Therapie  
der Endometriose

### Authors

S. Rimbach<sup>1</sup>, U. Ulrich<sup>2</sup>, K. W. Schweppe<sup>3</sup>

### Affiliations

<sup>1</sup> Gynäkologie und Geburtshilfe, Landeskrankenhaus Feldkirch, Feldkirch, Austria  
<sup>2</sup> Klinik für Gynäkologie und Geburtshilfe, Martin-Luther-Krankenhaus, Berlin  
<sup>3</sup> Endometriose-Zentrum Ammerland, Westerstede

### Key words

○ reproductive medicine  
○ dyspareunia  
○ endometriosis  
○ gynaecology  
○ infertility  
○ mvar v

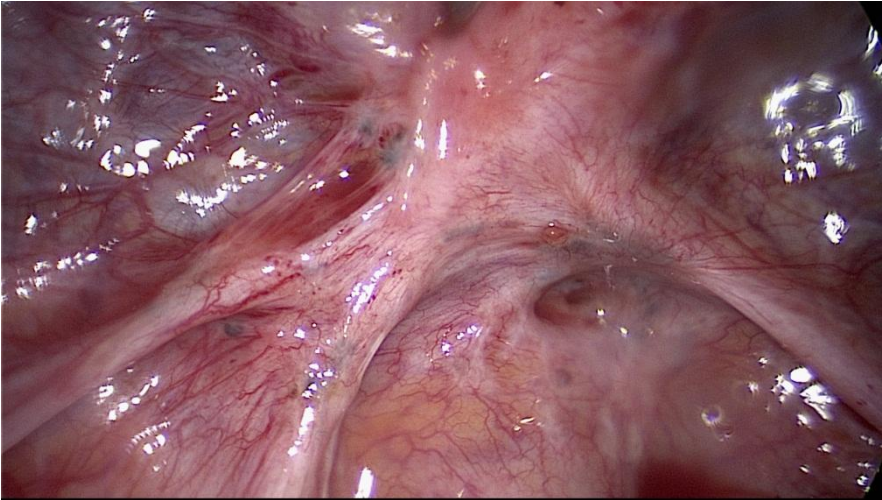
### Abstract

▼  
Endometriosis is one of the most common disorders encountered in surgical gynaecology. The laparoscopic technique, the planning of the surgical intervention, the extent of information pro-

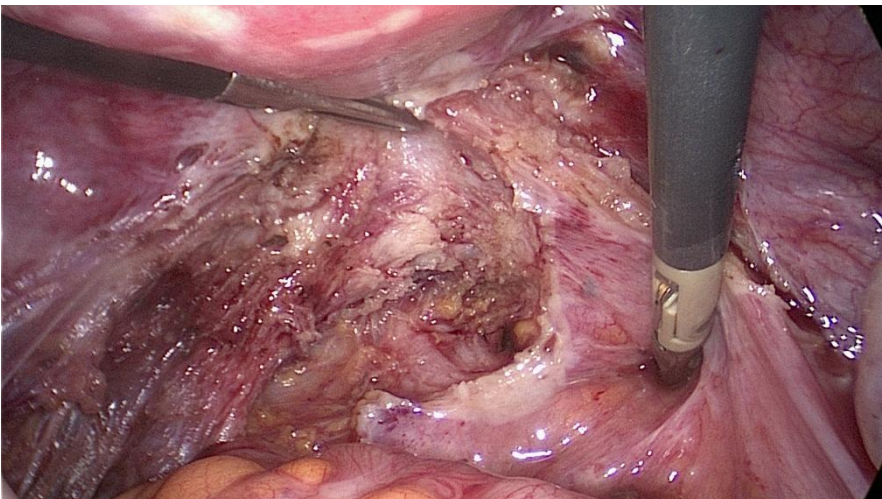
### Zusammenfassung

▼  
Die Endometriose gehört zu den häufigsten Krankheitsbildern in der operativen Gynäkologie mit erheblichen Herausforderungen an die laparoskopische Technik, aber auch die OP-Planung,

# Tief Infiltrierende Endometriose



Ligg. sacro-ut.



# Tief Infiltrierende Endometriose

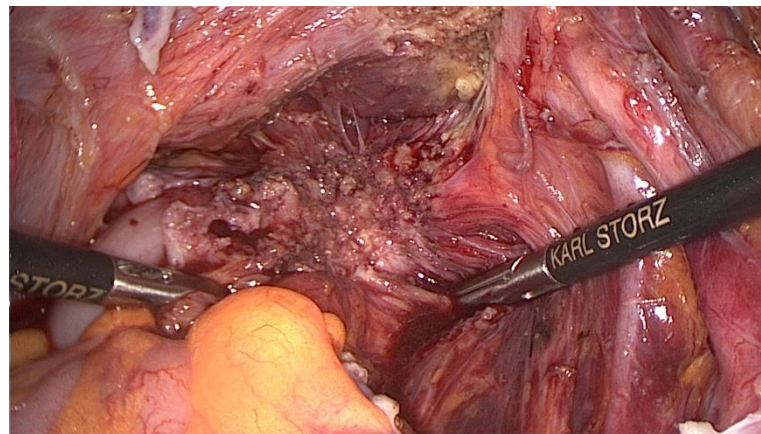
*cave*

**Plexus hypogastricus inf.  
Nn. Splanchnici pelv.**

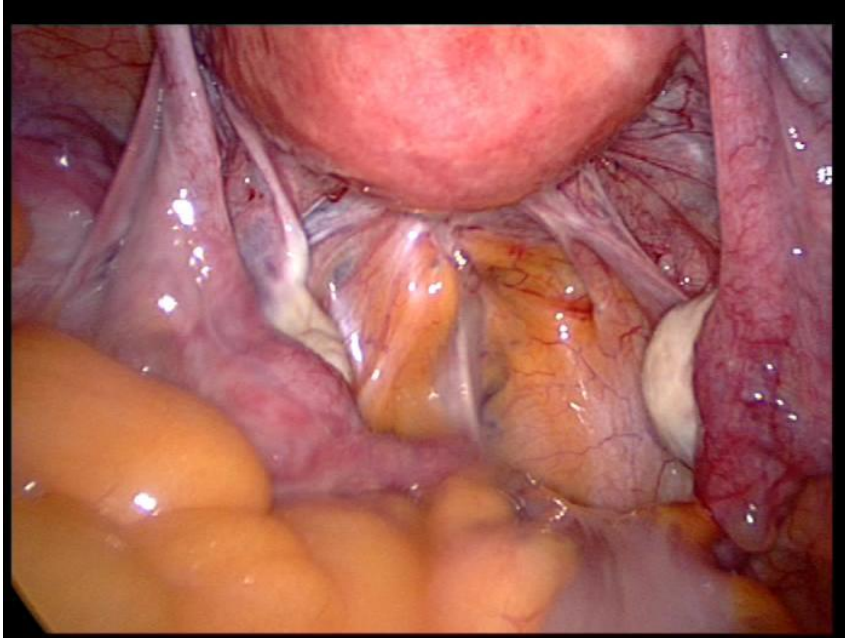
**Blasenfunktionsstörungen    15 – 30 %**

Deffleux 2007, Dubernard 2007, Ceccaroni 2013

➤ **Nervenschonende Präparation**



# Tief Infiltrierende Endometriose



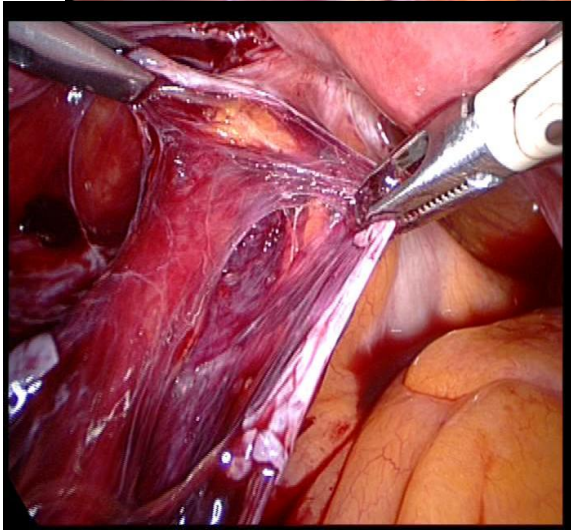
Septum recto-vaginale



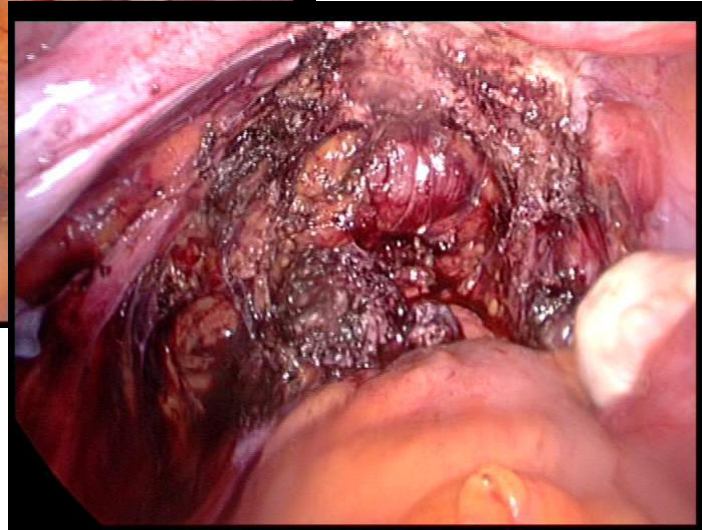
# Tief Infiltrierende Endometriose



Septum recto-vaginale



Ureterolyse

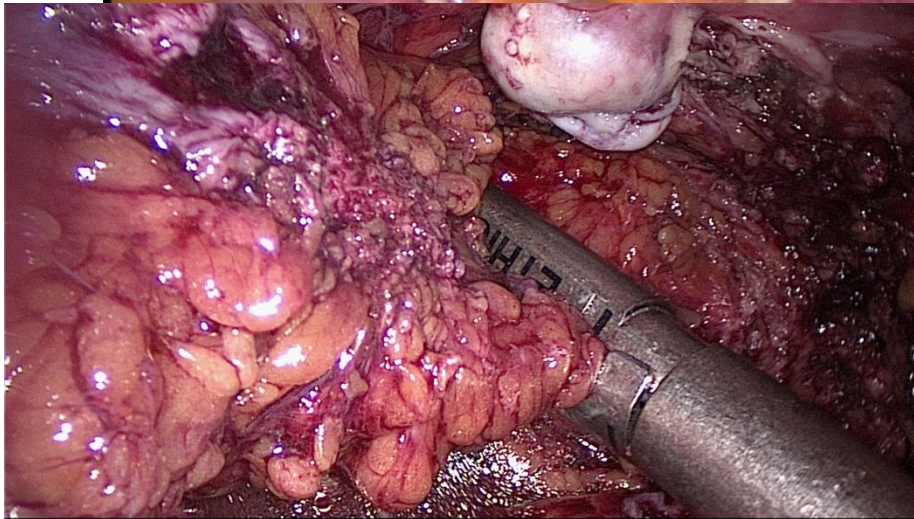


Darstellung des Septum rekto-vag.

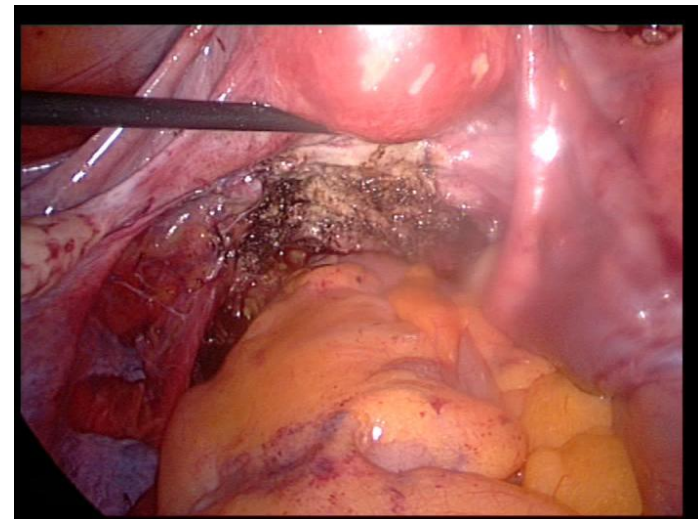
# Tief Infiltrierende Endometriose



Septum recto-vaginale



ggfls Rekto-Sigmoid-Resektion



Stapler-Anastomose



# Tief Infiltrierende Endometriose

**Ziel: komplette Resektion**

	Rezidivrate
<b>Rectum dissection</b>	<b>22.2 %</b>
<i>sign. (<math>p &lt; 0.007</math>) vs.</i>	
<b>Rectal wall excision</b>	<b>5.2 %</b>
<b>Segmental resection</b>	<b>2.2 %</b>
Brouwer, Woods 2007	

# Tief Infiltrierende Endometriose

*cave*

<b>Anus praeter</b>	<b>3 – 14.5 %</b>
<b>Defäkationsprobleme</b>	<b>bis 53 %</b>
<b>Anastomoseninsuffizienz</b>	<b>0.7 – 3 %</b>

Ruffo 2012  
Brouwer 2007  
Roman 2010

<b>Darmfunktionsstörung</b>	<b>52 vs 19 %</b>
<b>Segmentresektion vs.</b>	
<b>„Nodule resection“</b>	

Human Reproduction, Vol.25, No.4 pp. 890–899, 2010  
Advanced Access publication on January 26, 2010 doi:10.1093/humrep/dg407

human  
reproduction

ORIGINAL ARTICLE **Gynaecology**

**Delayed functional outcomes  
associated with surgical management  
of deep rectovaginal endometriosis  
with rectal involvement: giving patients  
an informed choice**

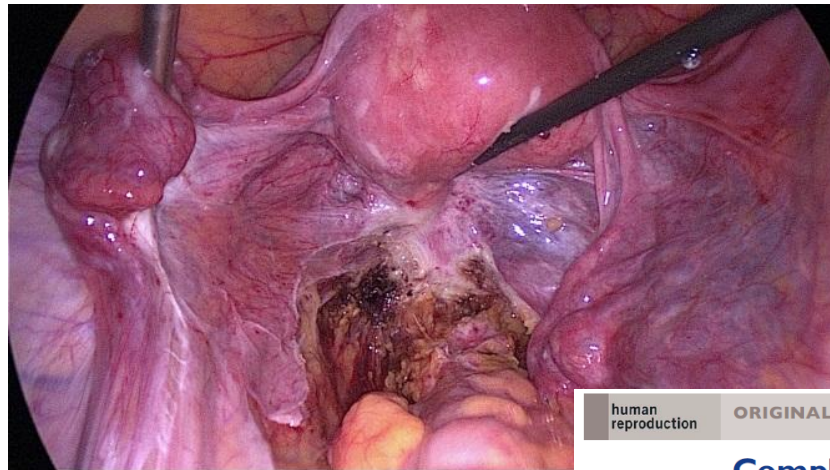
**Horace Roman<sup>1,5</sup>, Cecile Loisel<sup>1</sup>, Benoit Resch<sup>1</sup>, Jean Jacques Tuech<sup>2</sup>,  
Patrick Hochain<sup>3</sup>, Anne Marie Leroi<sup>4</sup>, and Loïc Marpeau<sup>1</sup>**

<sup>1</sup>Department of Gynecology and Obstetrics, Rouen University Hospital, Rouen, France; <sup>2</sup>Department of Digestive Surgery, Rouen University Hospital, Rouen, France; <sup>3</sup>Gastroenterology, Clinique du Cœur, Bois-Guilbert, France; <sup>4</sup>Department of Physiology, Rouen University Hospital, Rouen, France

<sup>5</sup>Correspondence address: Clinique Gynécologique et Obstétricale, CHU « Charles Nicolle », 1 rue de Germont, 76031 Rouen, France.  
Tel: +33 2 328 887 54; Fax: +33 2 329 811 49; E-mail: horaceroman@gmail.com

# Tief Infiltrierende Endometriose

- „Tailoring“ Shaving
- Nodule resection
- Segmentresektion



human  
reproduction

ORIGINAL ARTICLE *Gynaecology*

**Complications, pregnancy and recurrence in a prospective series of 500 patients operated on by the shaving technique for deep rectovaginal endometriotic nodules**

Jacques Donnez<sup>\*</sup> and Jean Squifflet

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# Endometriose

- **Komplexes Erkrankungsbild**
- **Pathogenese weiterhin unklar**
- **Genetik/Epigenetik/Stammzellforschung**
- **Zukünftig neue Therapiekonzepte ?**
- **Operative Therapie aktuell wichtigster Ansatz**