

Endoskopie & Kinderwunsch

Conflict of Interest Statement

**Bezüglich des folgenden
Vortragsinhaltes besteht
kein Interessenskonflikt.**

➤ **Endometriose**

➤ **Pathologien an Uterus**

Myome

Polypen

Fehlbildungen

Adenomyosis

Tube

Hydro / Sactosalpinx

Pyosalpinx

Ovar

Zysten

einfache, Endometriose, PCOS

**Jede 10.Frau im reproduktiven
Lebensalter hat Endometriose !**





Endometriose in Österreich

gesamt

172.000

Wien

33.600

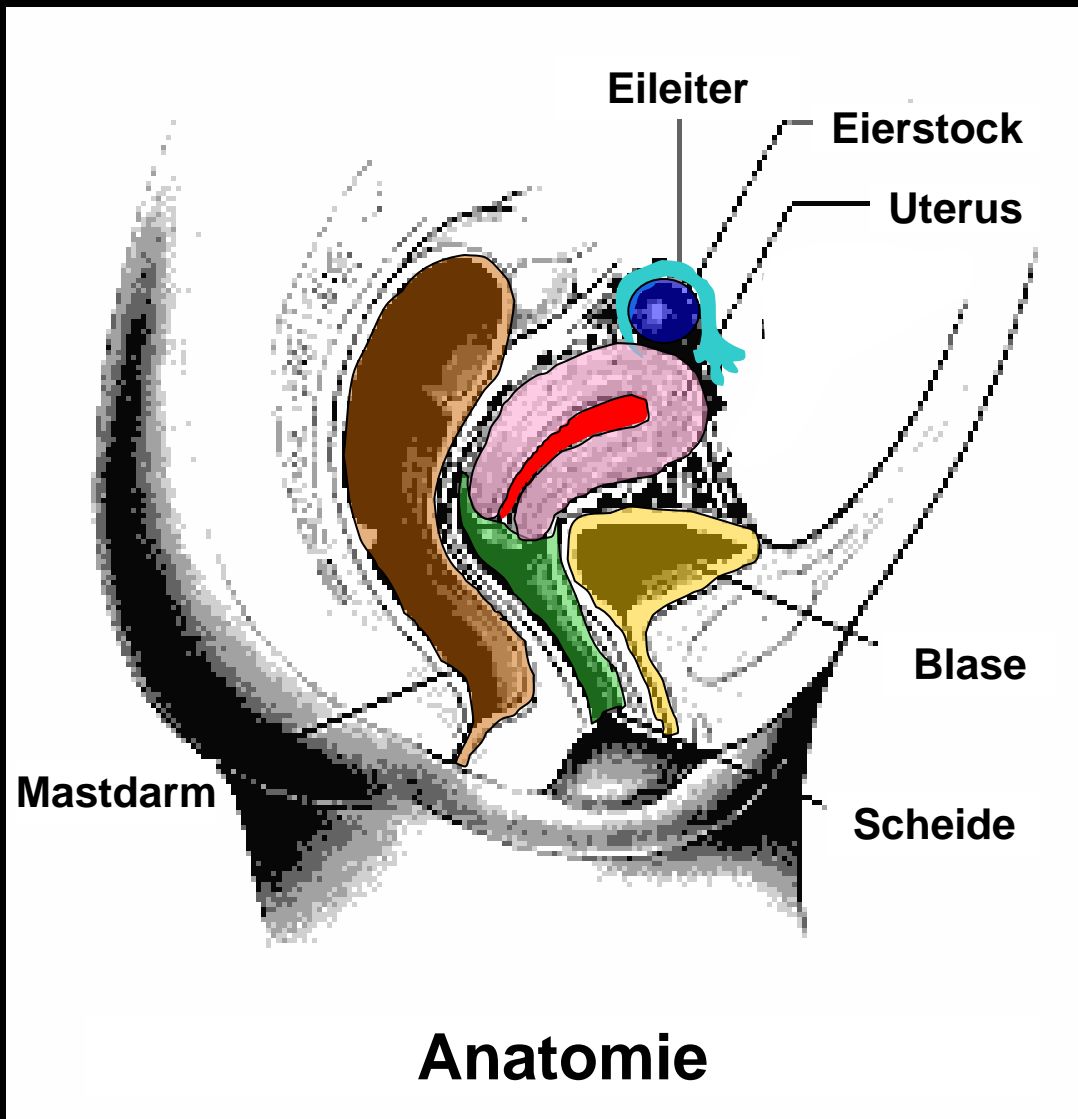


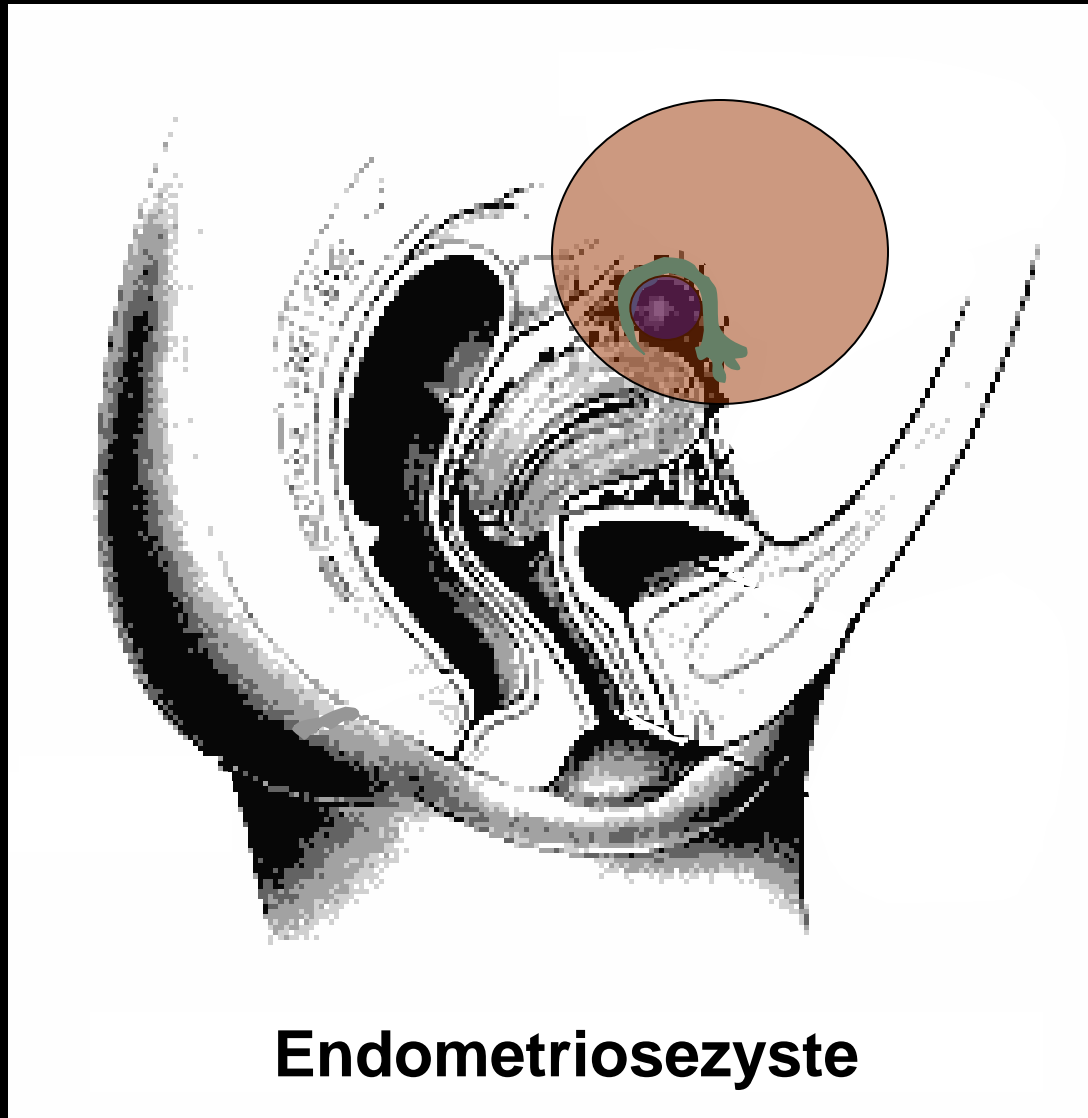
*Statistik Austria
Jahresdurchschnitt 2002
Frauen 15 – 45 Jahre*

Endometriose

Risikofaktoren

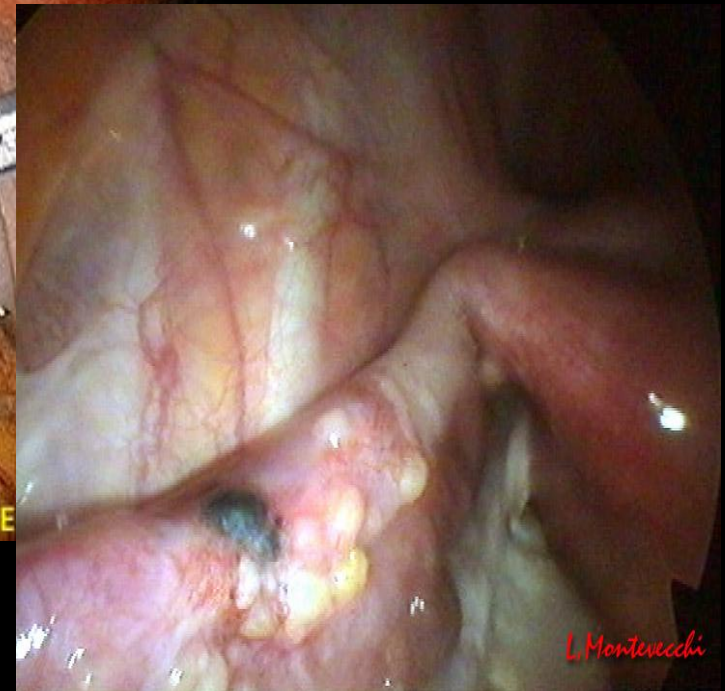
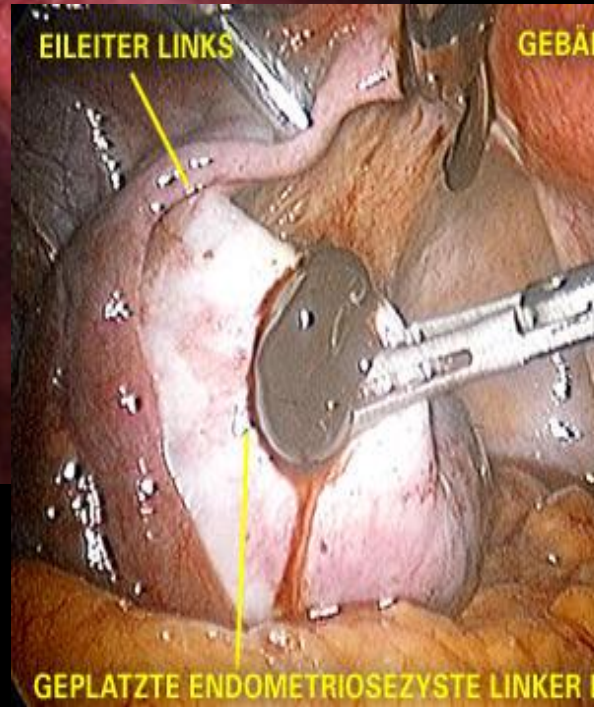
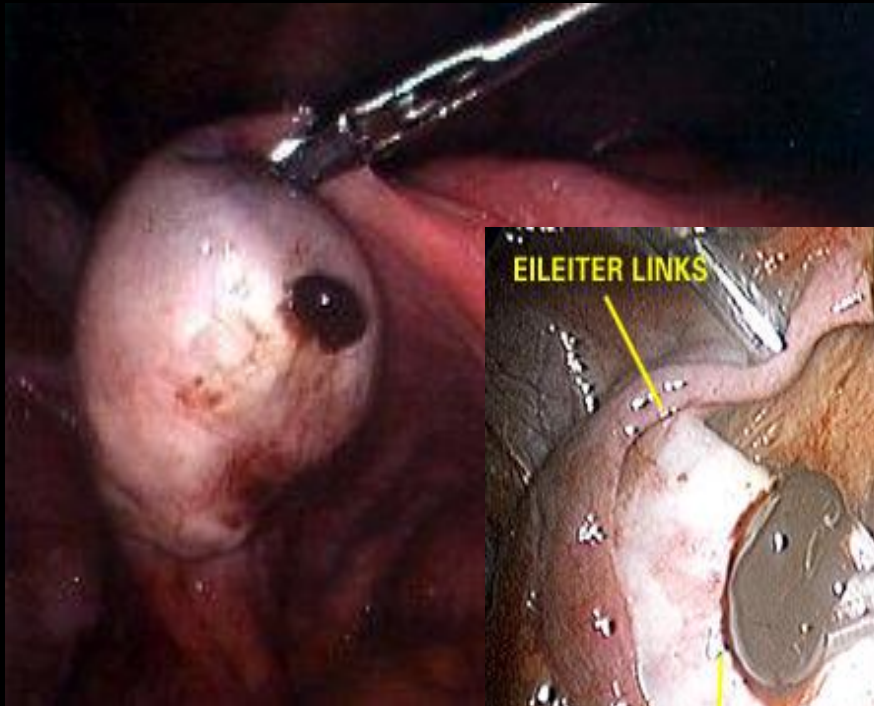
- ⇒ ***Frühe erste Menstruation*** ↑↑
- ⇒ ***Kurze Zyklen*** ↑↑
- ⇒ ***Schmerzhafte Regelblutung*** ↑↑↑
- ⇒ ***Körpergröße*** ↑
- ⇒ ***Alkohol*** ↑
- ⇒ ***Koffein*** ↑
- ⇒ ***Positive Familienanamnese*** ↑
- ⇒ ***Umwelt (Dioxin, PCB)*** ↑

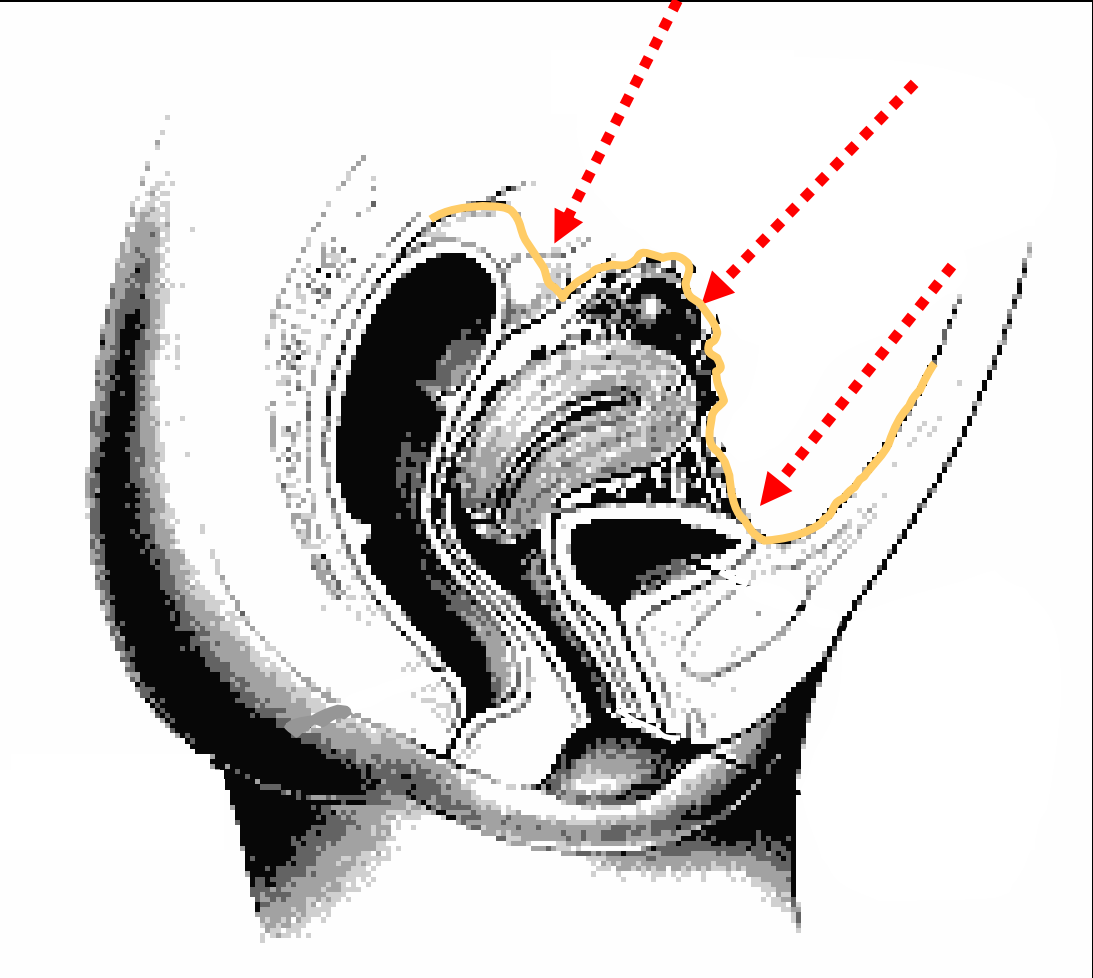




Endometriosezyste

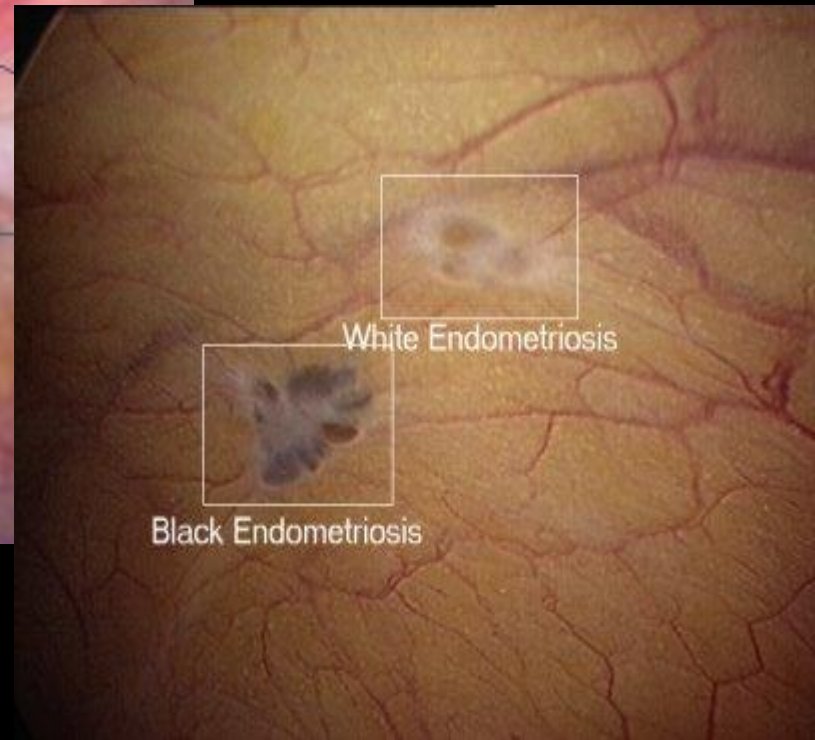
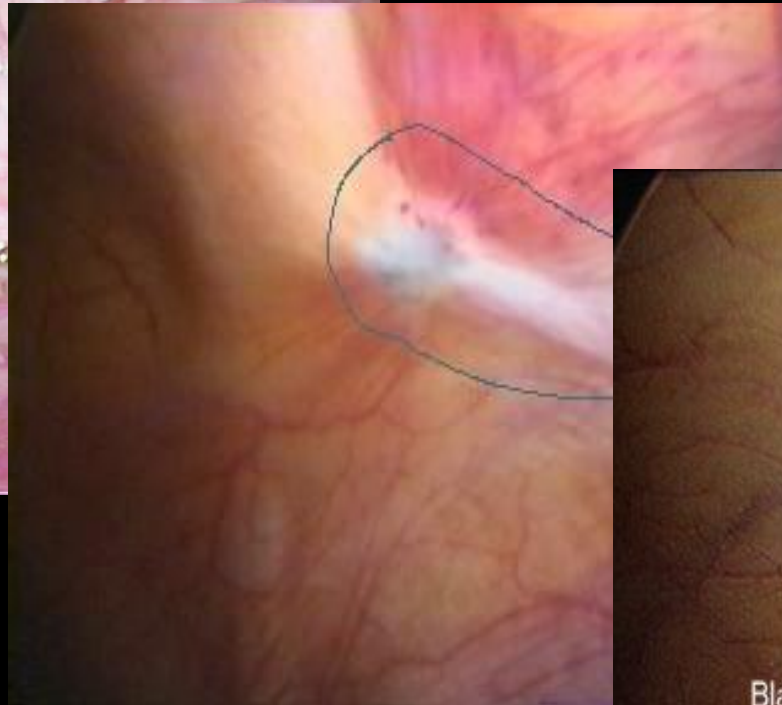
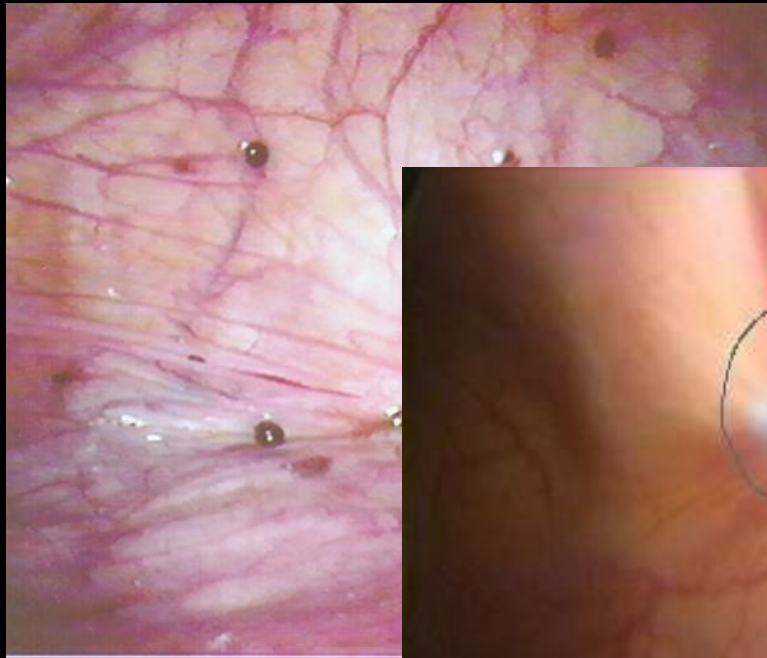
Endometriose am Eierstock / Eileiter

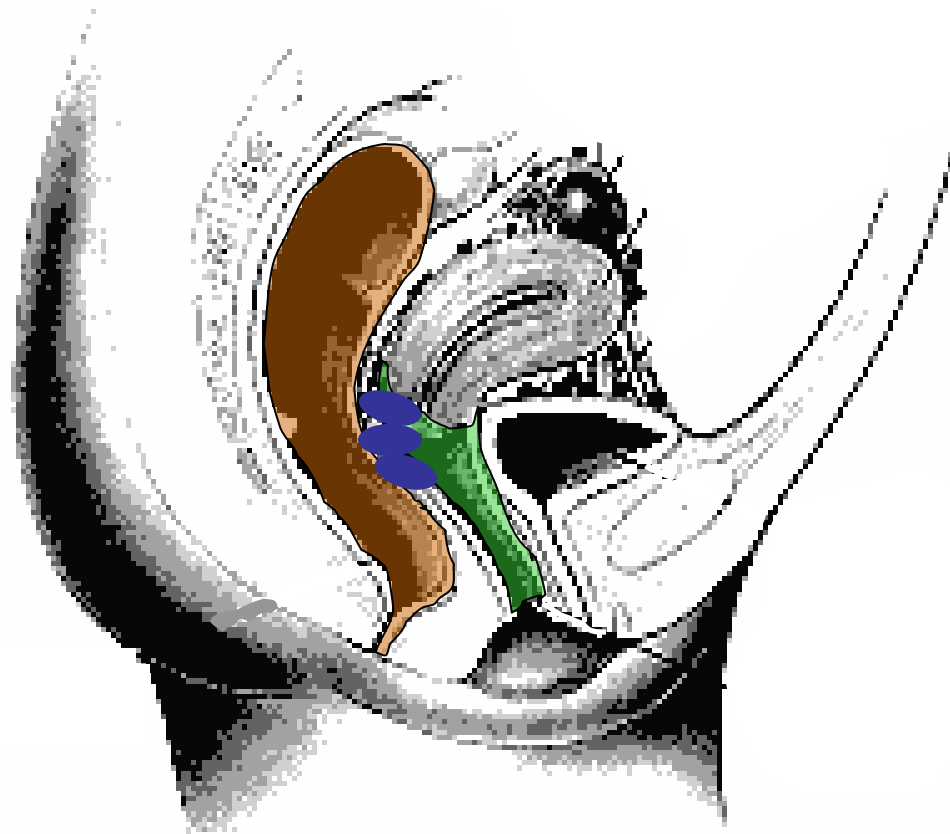




Peritoneale Endometriose

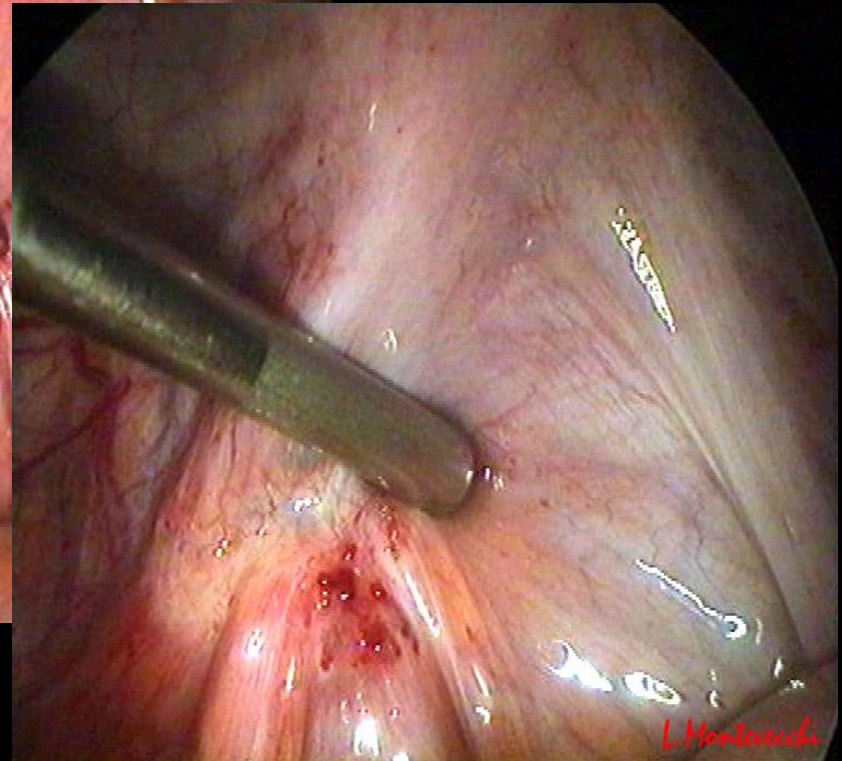
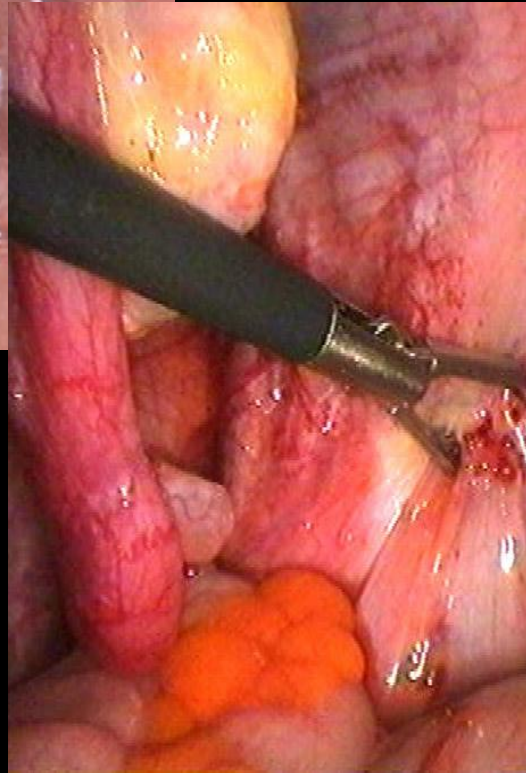
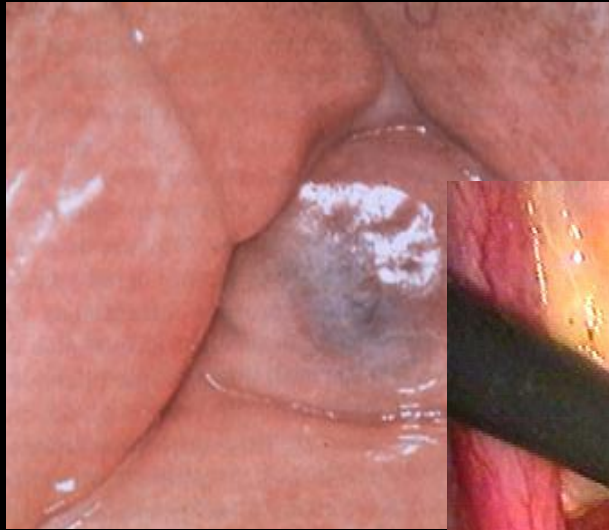
Typische Endo-Herde am Bauchfell

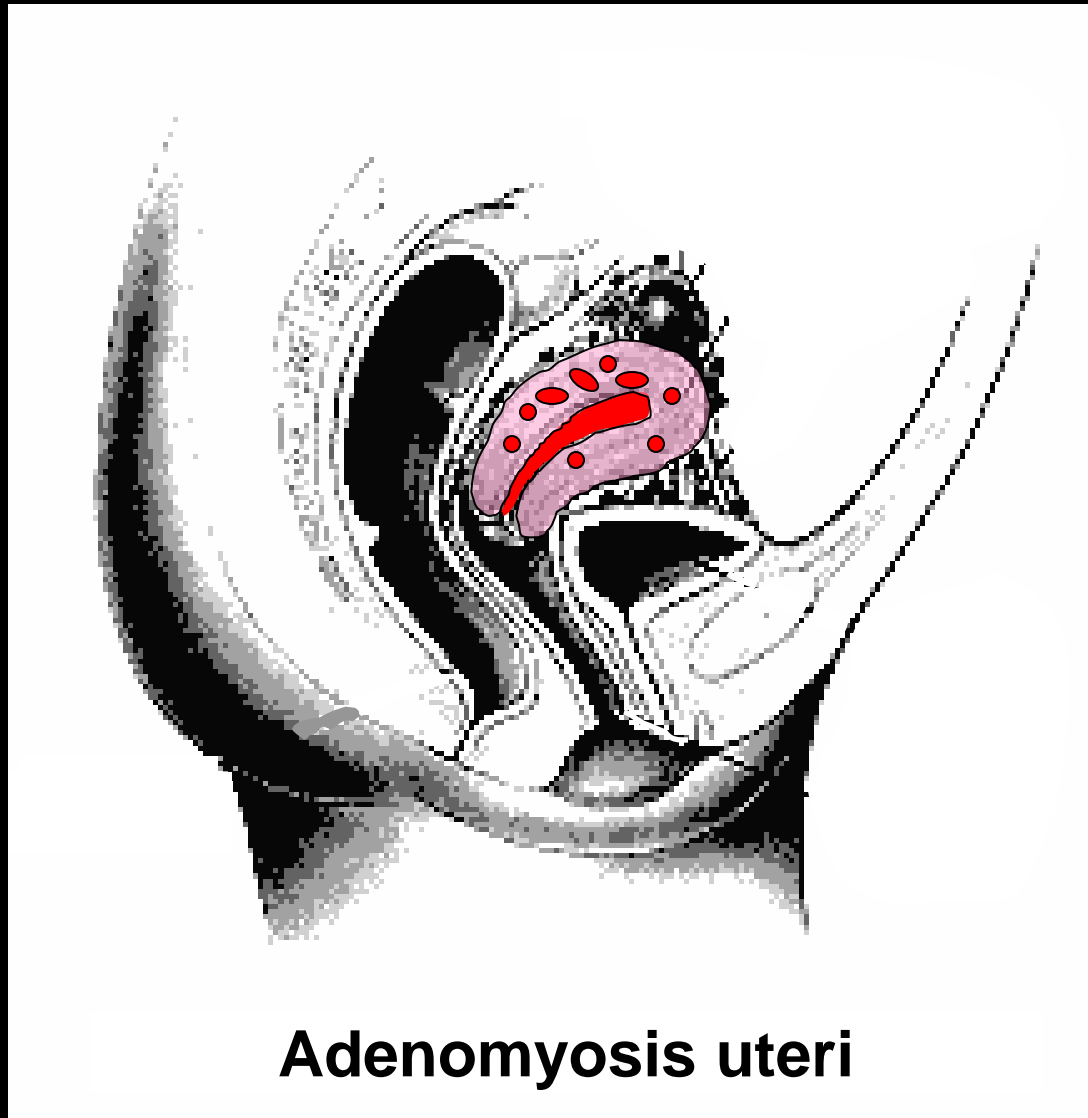




Rectovaginale Endometriose

Rectovaginale Endometriose

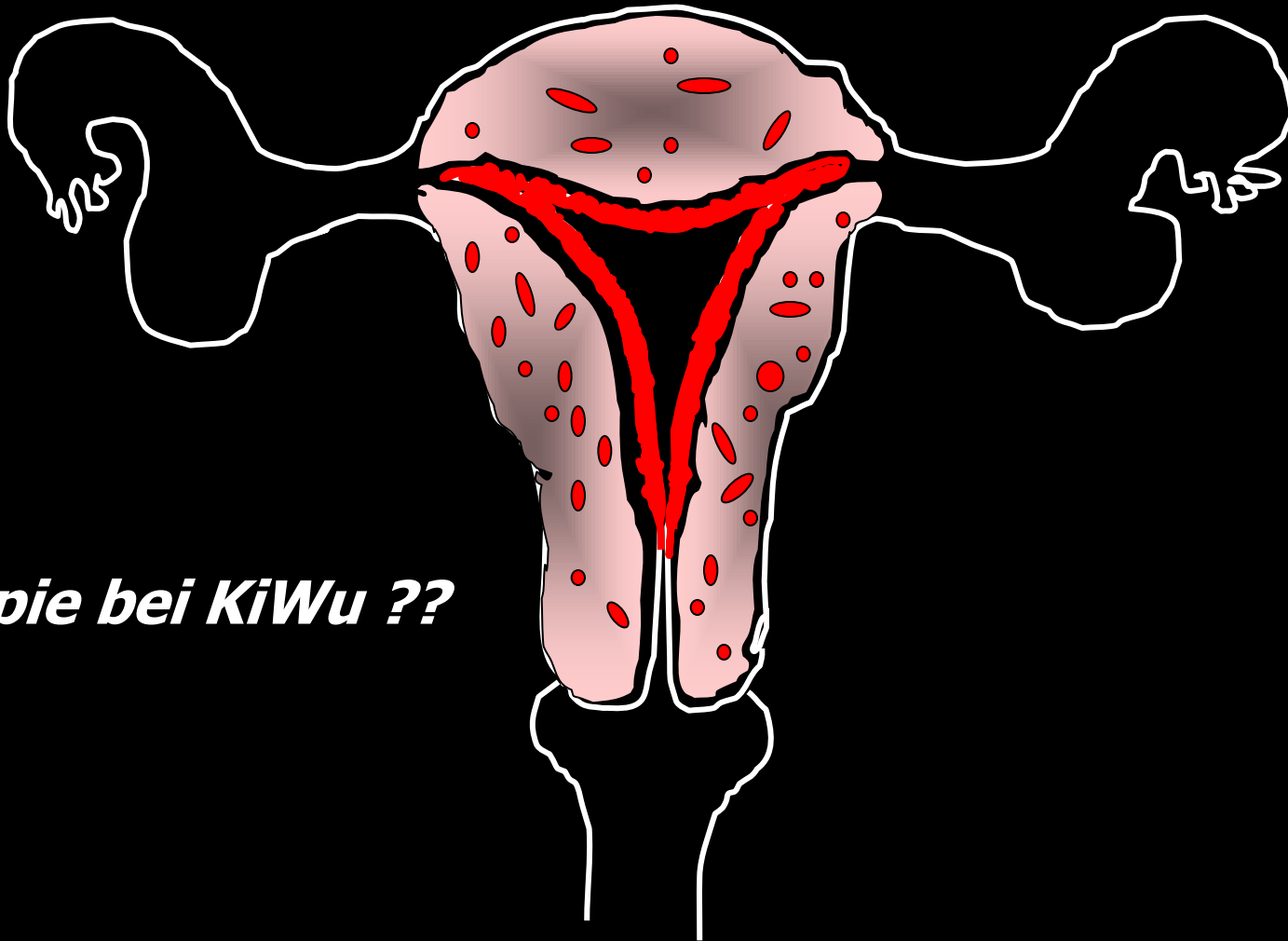




Adenomyosis uteri

„Innere“ Endometriose

Adenomyosis uteri = Endometriosis genitalis interna



Therapie bei KiWu ??

➤ **Schmerzen**

➤ **Infertilität**

Endometriose

Diagnose & Therapie

Laparoskopie

Operative vs. Diagnostische LSK+Observatio

SS-Raten

| | |
|------------------------------|--------------------|
| Elsheikh¹ | 37% vs. 21% |
| Marcoux² | 31% vs. 18% |
| Parazzini³ | 20% vs. 22% |

Keine Daten für Stadium III – IV !



¹Ann NY Acad Sci 2003 n = 151
²NEJM 1997 n = 341
³Hum Reprod 1999 n = 101

**Laparoscopic surgery in the
treatment of minimal and
mild endometriosis improves
infertility.**

The Cochrane Database of Systematic Reviews 2006

Die Chance schwanger zu werden erhöht sich 7-8 fach !

Marcoux, NEJM;Parazzini, Hum Reprod

Endometriose & Kinderwunsch

**Wie effektiv ist die
chirurgische Sanierung
im Hinblick auf die
Infertilität ?**

Surgery for endometriosis- associated infertility: a pragmatic approach

Vercellini et al., Vol.24, No.2, pp. 254-269

Hum Reprod 2009

Endometriose & Kinderwunsch

The absolute **benefit** increase
in terms of enhancement
of pregnancy rates **seems lower**
than previously suggested 38%
being reasonably **between 10 and 25%**.

Surgery for endometriosis-associated infertility: a pragmatic approach

Vercellini et al., Hum Reprod 2009

Endometriose & Kinderwunsch

The effect of surgery for
peritoneal disease is small.

Surgery for endometriosis-associated infertility: a pragmatic approach

Vercellini et al., Hum Reprod 2009

**Excision of
rectovaginal lesions
is of doubtful value and
associated with
severe morbidity.**

Endometriose & Kinderwunsch

First line surgery for large **ovarian endometriomas** seems to be the procedure with the most favourable balance between benefits, harm and costs.

Endometriose & Kinderwunsch

A practical advantage of surgery
is **temporary pain relief**.
This may render feasible
spontaneous attempts at
conception in women who refuse
or prefer to postpone IVF.

Endometriose & Kinderwunsch & Laparoskopie

OP-Indikationen

1. Klinische Symptomatik

2. Endometriose-Zysten > 3cm

Hormone

- Pille
- Gestagene
- Medroxyprogesteronacetat (MPA)
- Danazol
- Aromatasehemmer
- GnRH-Analoga



Ziel der Hormontherapie

*Blockade oder komplette Unterdrückung
der Östrogenproduktion in den Eierstöcken !*

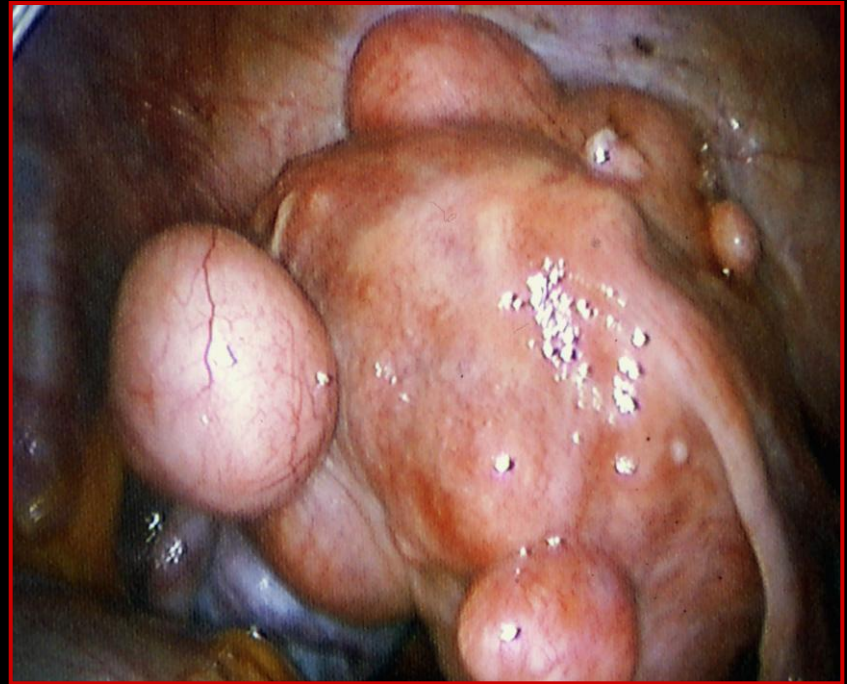
Hormontherapie hat keinen therapeutischen Effekt auf die Schwangerschaftsrate, sondern verlängert lediglich das Intervall bis zum Eintritt einer möglichen Schwangerschaft!



Uterus

Pathologie am Uterus

Myome

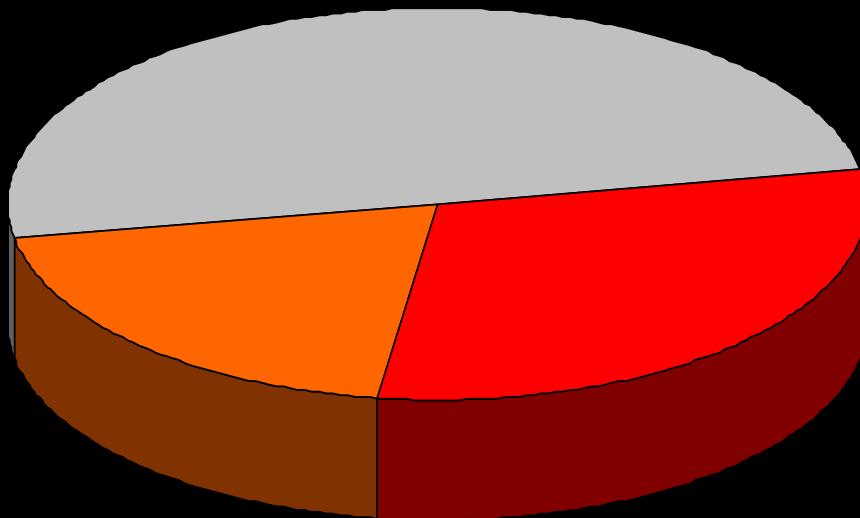


Myome als Sterilitätsfaktor

- ⇒ **Störung der myometranen Integrität**
- ⇒ **Störung der rhythmischen uterinen Kontraktilität**
- ⇒ **Verminderte Expression des TF**
- ⇒ **Gestörte Dezidualisierung**
- ⇒ **Gestörte Hämostase**
 - **Anovulation**
 - **Nidationsstörung**
 - **Konzeptionsstörung**
 - **Prolongierte Spermienaszension**
 - **Mechanische Faktoren**
 - **Höhere Abort-Frequenz, Ab.habitualis**
 - **Gestörte Hämodynamik im Myometrium**

Inzidenz von Myomen

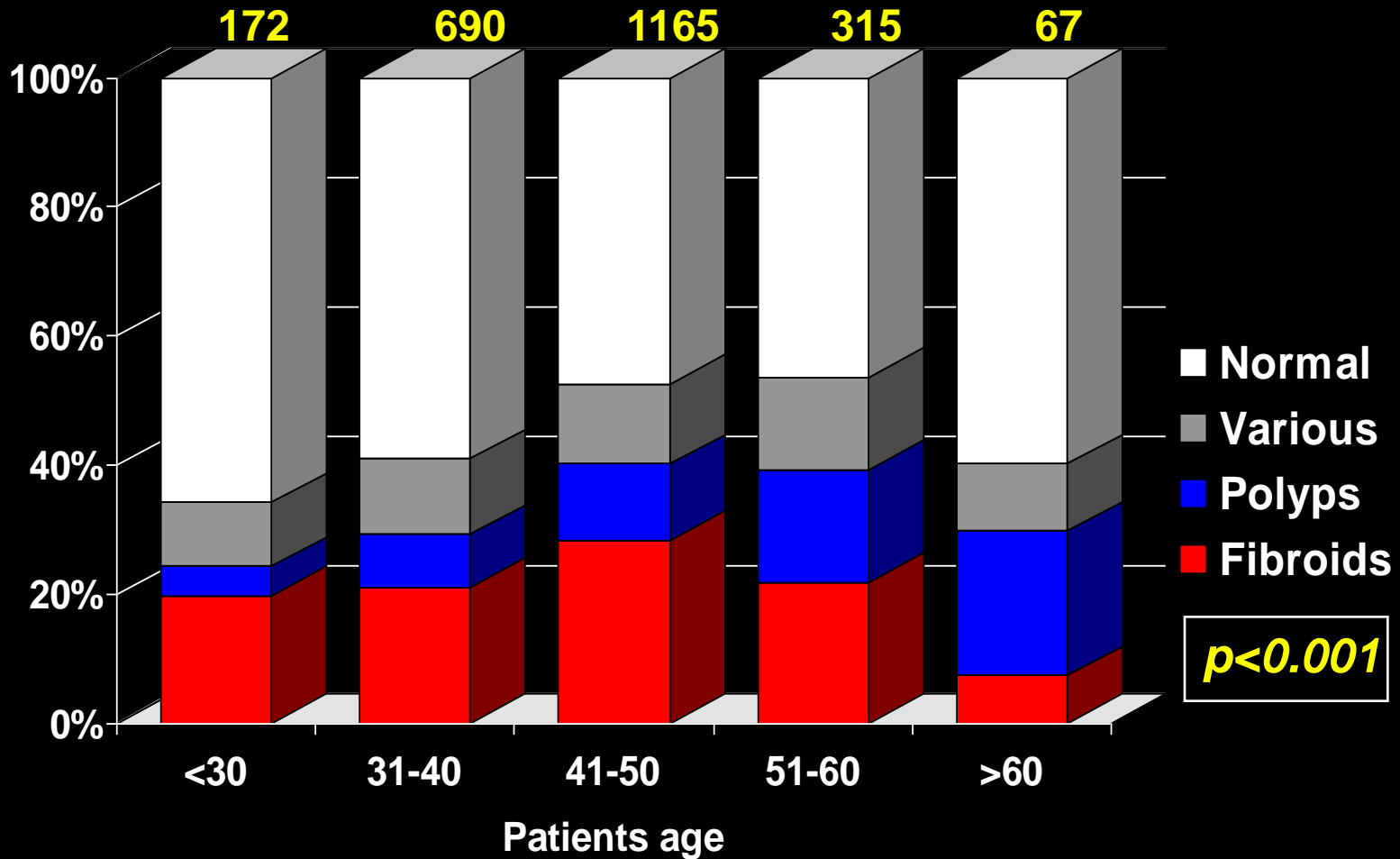
> 30 Jahre



20 - 50%

Frank 1949
Robbins&Cotran 1979
Novak&Woodruff 1979
Merrill&Creasman 1980
Wallach 1992

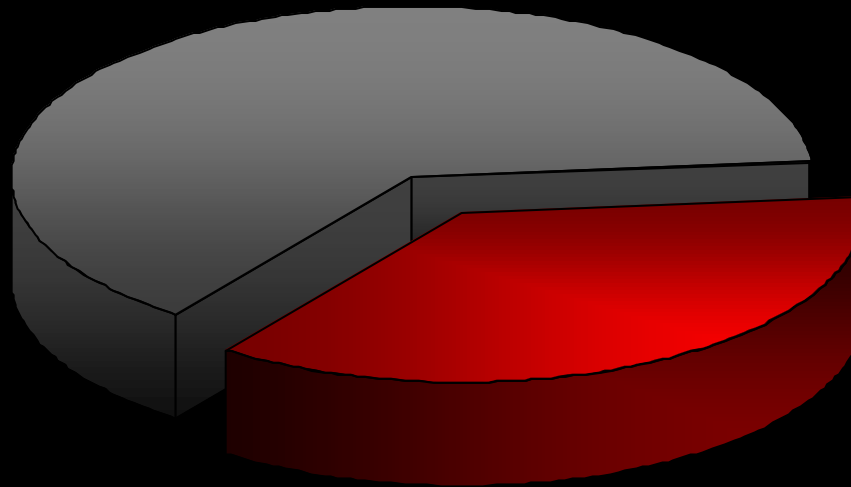
Distribution of intra-uterine pathology *by age*



Submuköse Myome

Inzidenz

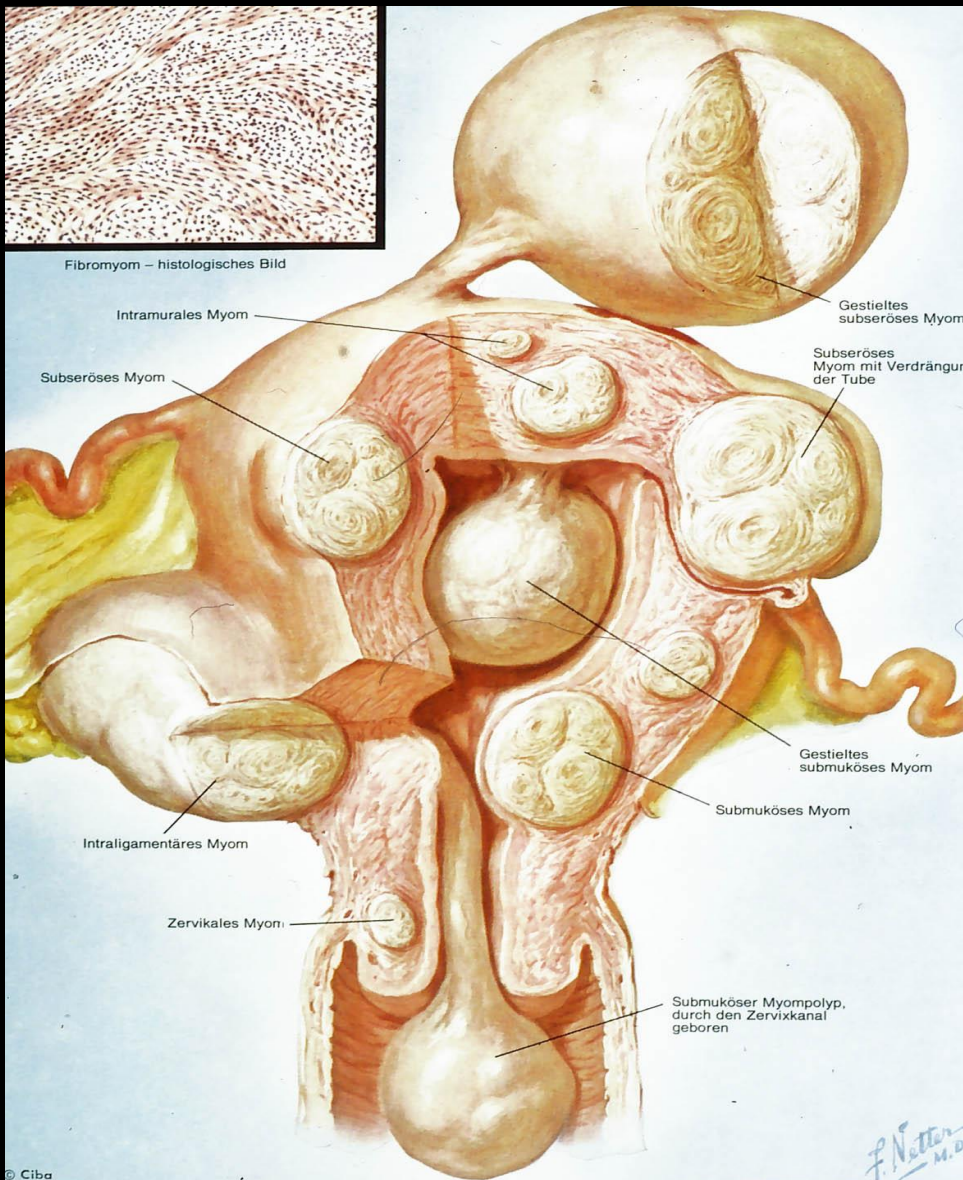
ESH II
64%



ESH 0 & I
36%

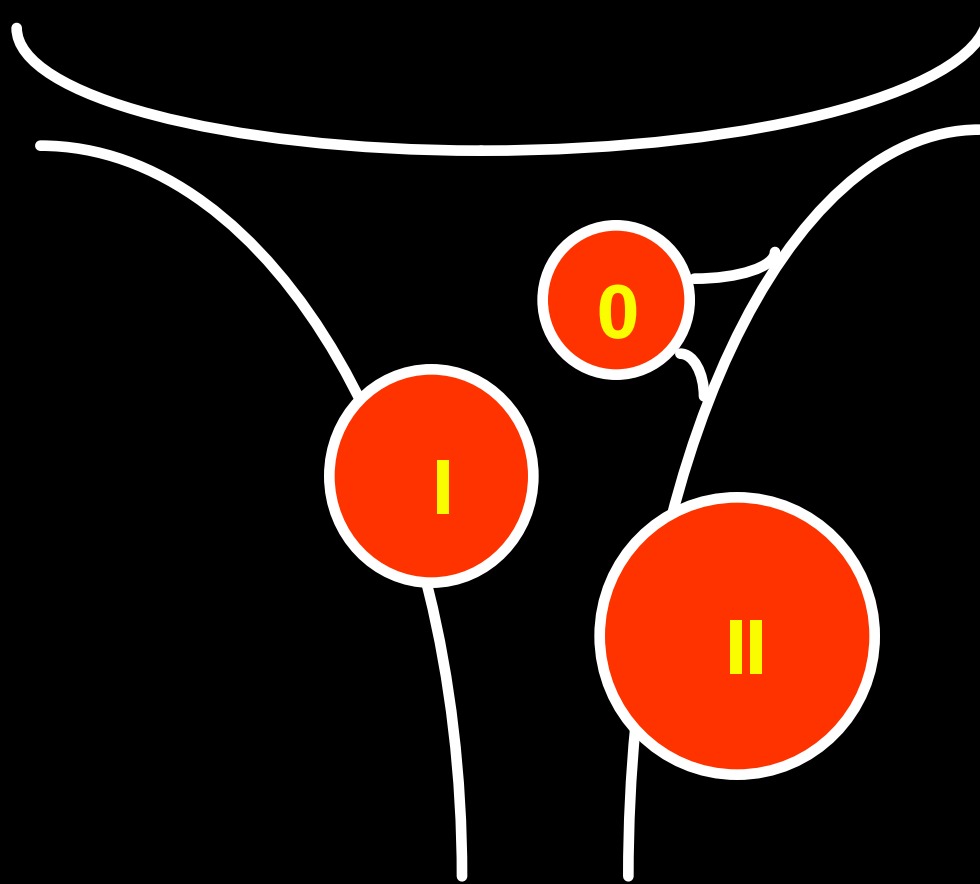
585/2409 (24.3%)

Myome - Lokalisation



ESH-Klassifikation

Intra-uterine Myome



nach Wamsteker 1993

Meta-analysis of pregnancy rates (PR%) in women with fibroids distorting the cavity, not distorting the cavity, and in a control group without myomas

Myomas and IVF

| | Distorted cavity | | Not distorted cavity | | Control group | |
|------------------|------------------|-------------|----------------------|----------------|---------------|-----------------|
| | PR% | n | PR% | n | PR% | n |
| Eldgar-Geva 1998 | 10 | 1/10 | 16.4 | 9/55 | 30 | 98/318 |
| Stovall 1998 | 37 | 34/91 | 53 | 48/91 | | |
| Farhi 1995 | 9 | 5/55 | 29 | 25/88 | 25 | 32/127 |
| Ramzy 1998 | 39 | 15/39 | 34 | 123/367 | | |
| Surrey 2001 | 50.7 | 37/73 | 58.4 | 191/327 | | |
| Jun 2001 | 30.5 | 43/141 | 41.6 | 169/406 | | |
| Total | 9 | 6/65 | 33.5 | 163/487 | 40.4 | 661/1636 |

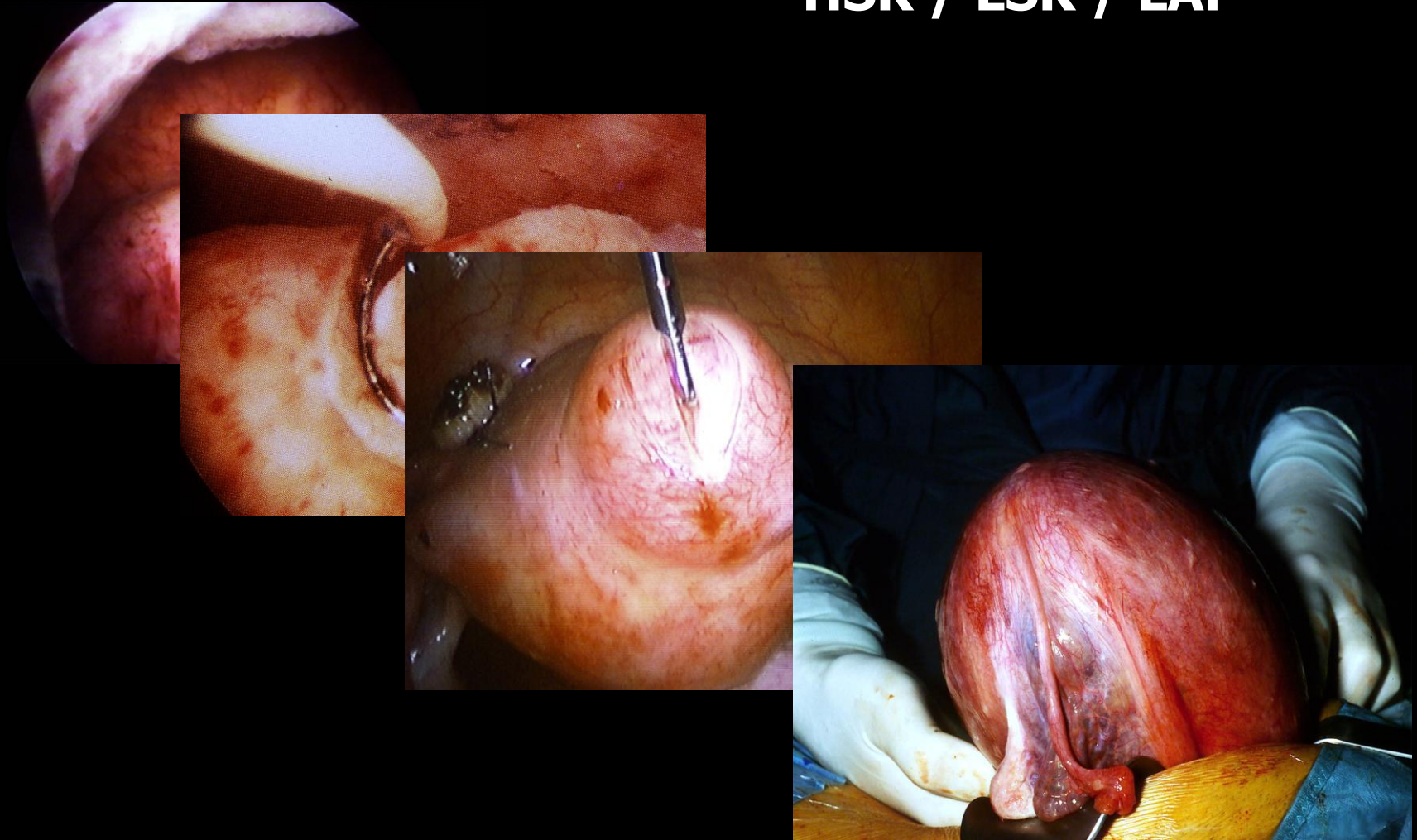
**What are the implications of myomas on fertility?
Donnez and Jadoul, Hum Reprod 2002**

Meta-analyses on the influence of fibroids on IVF outcome according to the localization of the lesions

| Localization | Number of Studies | OR (95% CI) |
|--------------------------------|--------------------------|----------------------|
| Clinical pregnancy rate | | |
| Submucosal | 2 | 0.3 (0.1-0.7) |
| Intramural | 7 | 0.8 (0.6-0.9) |
| Subserosal | 3 | 1.2 (0.8-1.7) |
| Intramural a/o subserosal | 11 | 1.0 (0.8-1.2) |
| All types | 16 | 0.8 (0.7-1.0) |
| Delivery rate | | |
| Submucosal | 2 | 0.3 (0.1-0.8) |
| Intramural | 7 | 0.7 (0.5-0.8) |
| Subserosal | 3 | 1.0 (0.7-1.5) |
| Intramural a/o subserosal | 11 | 0.9 (0.7-1.1) |
| All types | 16 | 0.8 (0.6-0.9) |

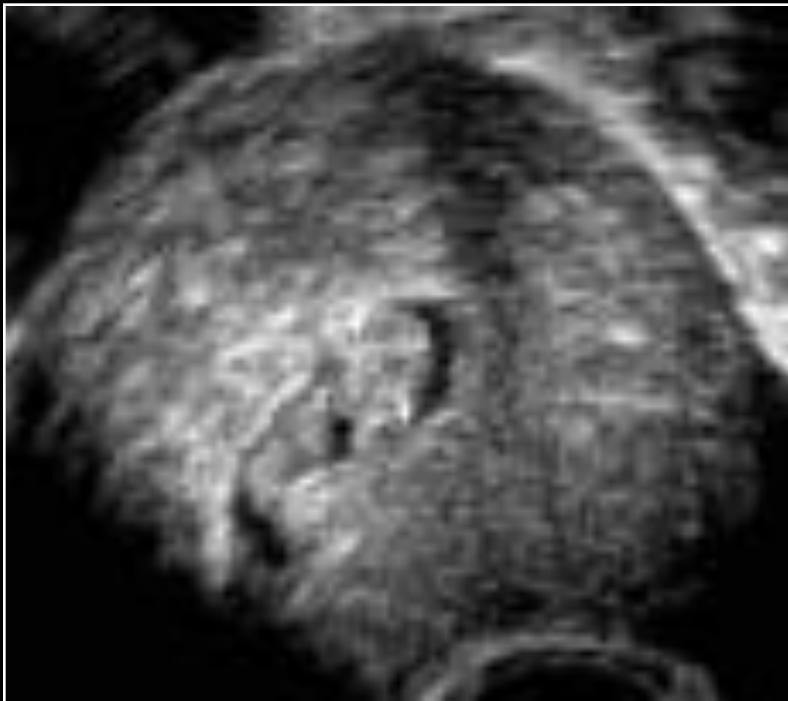
Conclusio: Intracavitäre Myome und intramurale Myome mit Cavumimpression = OP-Indikation

HSK / LSK / LAP



Pathologie am Uterus

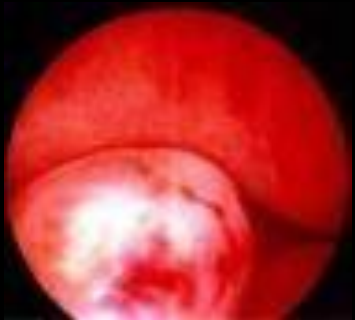
EM-Polyp



Hysteroscopic polyp resection

n=240, follow-up 9yrs

- **0% recurrence (resectoscope)**
- **Ind. AUB: 93% Eumenorrhoea**
- **Ind. Sterility: 42% cum. pregnancy rate**
- **Success rate depending on Size of polyps and complete resection, respectively**

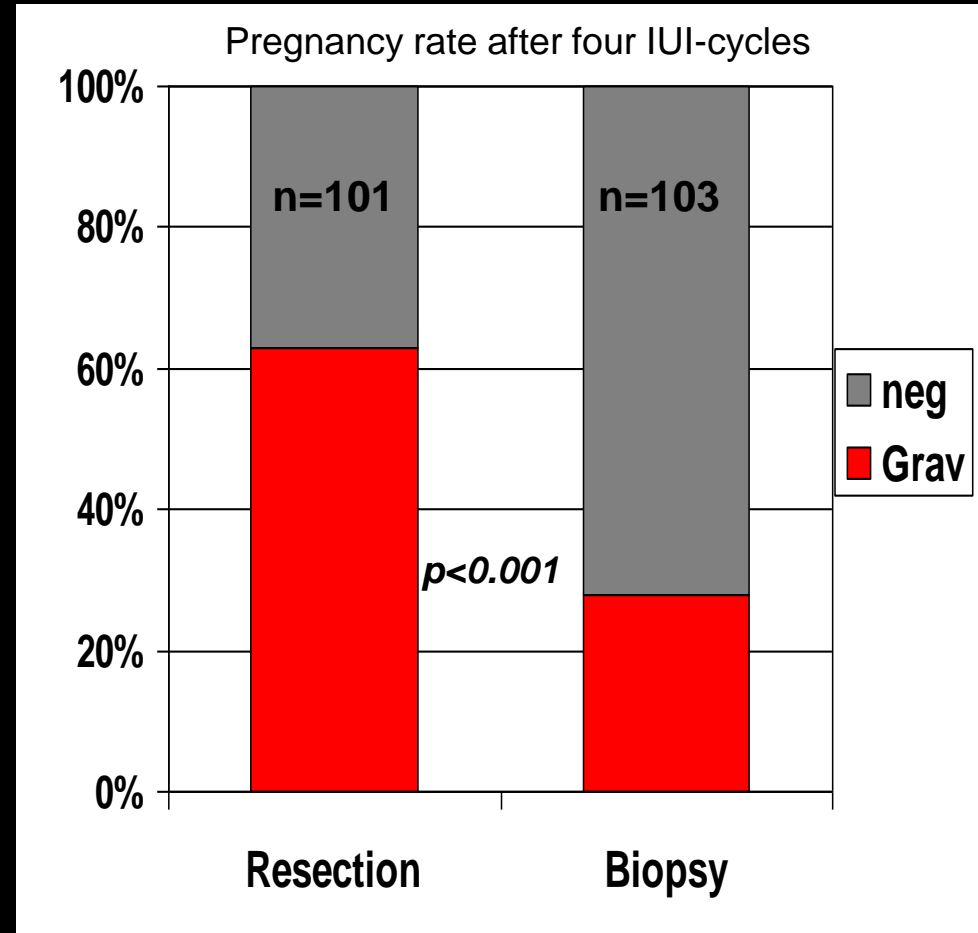
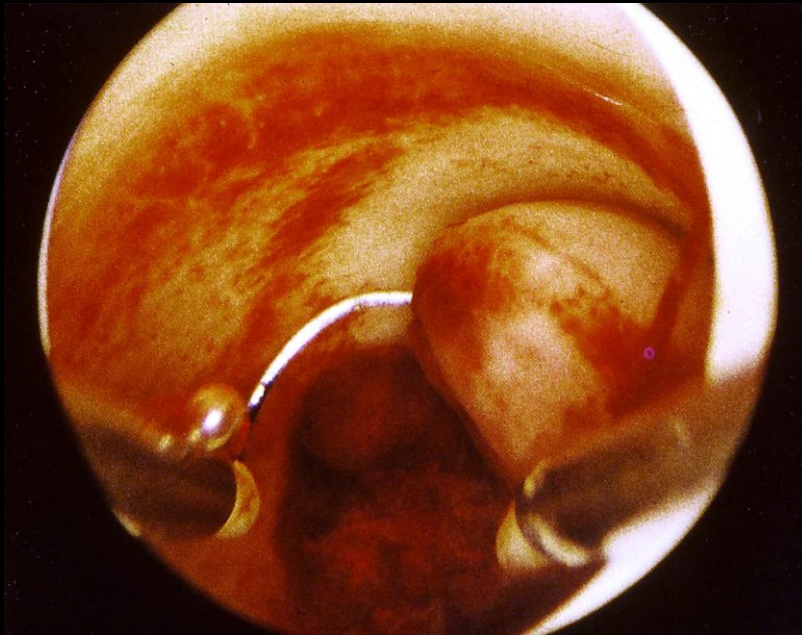


Preutthipan et al., Fertil Steril 2005

Polyp resection & Intrauterine insemination

RCT: Resectoscope vs. HSC+Biopsy only

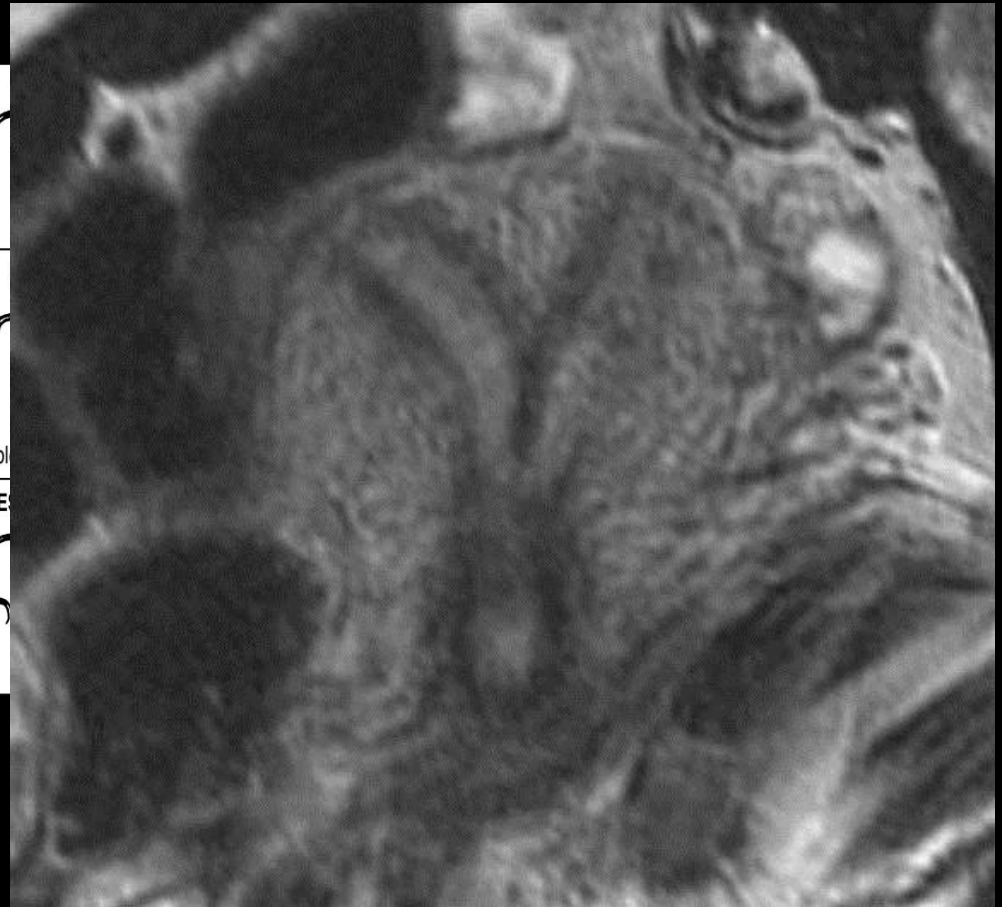
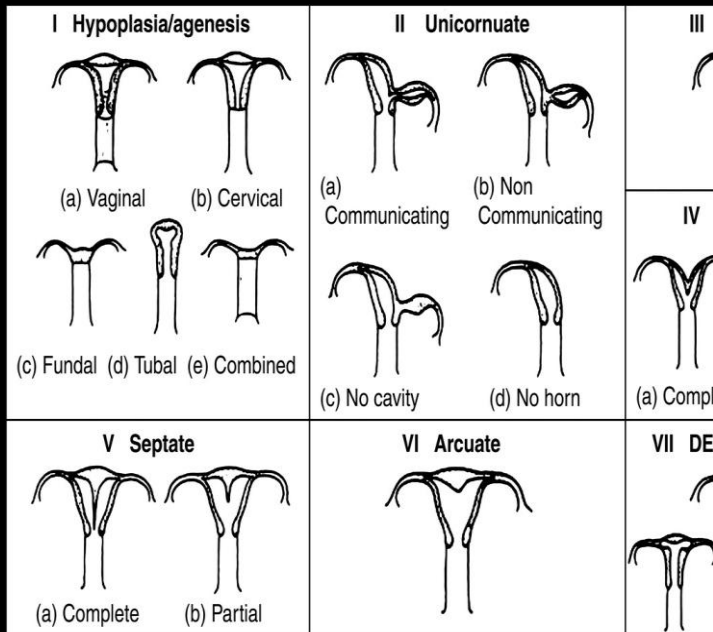
Study group:
65% pregnancies before 1.IUI



Perez-Medina et al., Hum Reprod 2005

Pathologie am Uterus

Uterus subseptus



Abortion is related to septal implantation of the pregnancy, insufficient vascular supply at this sites being the most attractive hypothesis for this disorder.

Fedele 1988

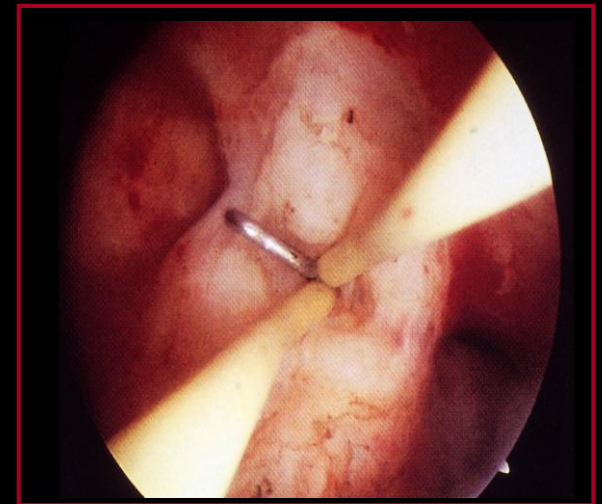


Pregnancy rates following hysteroscopic metroplasty

| | |
|-----------------------|------------|
| Perino 1987 | 63% |
| Fayez 1986 | 71% |
| Daly 1989 | 47% |
| Querleu 1990 | 67% |
| Marabini 1994 | 44% |
| Pabuccu 1995 | 63% |
| Colacurci 1996 | 29% |
| Total | 48% |

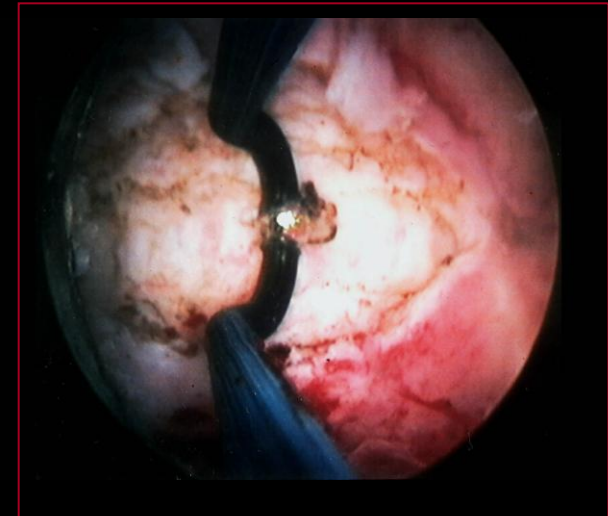
... uterine septum in otherwise unexplained infertility ...

- **Conception rate 25/61 (41%) within 12 months**
- **Life-birth-rate 18/65 (30%)**
- **CS 12/18 (67%)**



Reproductive outcome of septate uterus after hysteroscopic metroplasty

- **n=361**
- **follow-up 10yrs**
- **180 Pregnancies (50%)**
- **151 Live-birth-rate (42%)**



Tube & Ovar

Tubenfaktor

- **Low embryo implantation rate**
- **Increased risk for early pregnancy loss**
- **Bathing of intrauterine environment with toxic fluid within hydrosalpinx**
- **May reduce receptive capabilities of endometrium**
- **Direct embryo toxicity**
- **Negative influence on oocytes**



Surgical treatment for tubal disease in women due to undergo in vitro fertilisation, Cochrane Database Syst Rev 2004

Comparison of laparoscopic surgery on the fallopian tube VERSUS no surgery on the fallopian tube, Outcome: **Live birth rate**

| Treatment | Control | Odds Ratio |
|------------------|----------------|-------------------|
| n | n | |
| 161 | 134 | 2.13 |



- 1 Laparoscopic bilateral salpingectomy and adhesiolysis versus laparoscopic adhesiolysis, Dechaud 1998
- 2 Laparoscopic salpingectomy versus no intervention, Strandell 1999
- 3 Laparoscopic selective salpingostomy-salpingectomy versus progesterone medical treatment, Goldstein 1998

Surgical treatment for tubal disease in women due to undergo in vitro fertilisation, Cochrane Database Syst Rev 2004

Comparison of laparoscopic surgery on the fallopian tube VERSUS no surgery on the fallopian tube, Outcome: **Total pregnancy rate**

| Treatment | Control | Odds Ratio |
|------------------|----------------|-------------------|
| n | n | |
| 161 | 134 | 1.75 |



- 1 Laparoscopic bilateral salpingectomy and adhesiolysis versus laparoscopic adhesiolysis, Dechaud 1998
- 2 Laparoscopic salpingectomy versus no intervention, Strandell 1999
- 3 Laparoscopic selective salpingostomy-salpingectomy versus progesterone medical treatment, Goldstein 1998

Surgical treatment for tubal disease in women due to undergo in vitro fertilisation, Cochrane Database Syst Rev 2004

Comparison of laparoscopic surgery on the fallopian tube VERSUS no surgery on the fallopian tube, Outcome: **Ectopic pregnancy rate**

| Treatment | Control | Odds Ratio |
|------------------|----------------|-------------------|
| n | n | |
| 161 | 134 | 0.42 |



1 Laparoscopic bilateral salpingectomy and adhesiolysis versus laparoscopic adhesiolysis, Dechaud 1998

2 Laparoscopic salpingectomy versus no intervention, Strandell 1999

3 Laparoscopic selective salpingostomy-salpingectomy versus progesterone medical treatment, Goldstein 1998

Surgical treatment for tubal disease in women due to undergo in vitro fertilisation, Cochrane Database Syst Rev 2004

Comparison of laparoscopic surgery on the fallopian tube VERSUS no surgery on the fallopian tube, Outcome: **Miscarriage rate**

| Treatment | Control | Odds Ratio |
|------------------|----------------|-------------------|
| n | n | |
| 161 | 134 | 0.49 |



1 Laparoscopic bilateral salpingectomy and adhesiolysis versus laparoscopic adhesiolysis, Dechaud 1998

2 Laparoscopic salpingectomy versus no intervention, Strandell 1999

3 Laparoscopic selective salpingostomy-salpingectomy versus progesterone medical treatment, Goldstein 1998

PCOS

Stein & Leventhal 1935

- **Amenorrhea**
- **Hirsutism**
- **Obesity**
- **Enlarged polycystic ovaries**



PCOS

Revised diagnostic criteria of PCOS

- 1. Oligo- or anovulation**
- 2. Clinical and/or biochemical signs of hyperandrogenism**
- 3. Polycystic ovaries**
and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing´s syndrome)

PCOS

1. Oligo- or anovulation



PCOS

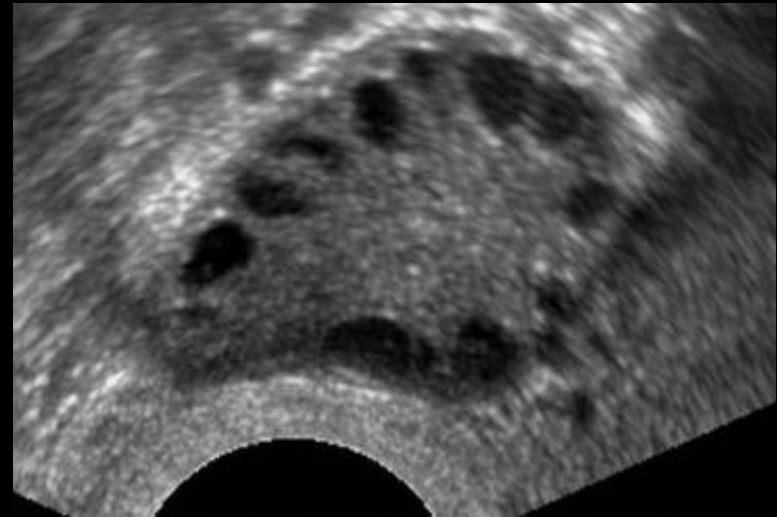
Hyperandrogenism

- **Clinical signs**
 - **hirsutism, acne**
- **Biochemical signs**
 - **free T, DHEAS**



PCOS

- **Presence of 12 or more follicles in each ovary measuring 2-9mm in diameter, and/or increased ovarian volume (>10ml)**



***Polyzstisches Ovar* ≠ PCOS**

25% of normal ovulating women without hyperandrogenism also have polycystic ovaries at sonography !!!



Table 1. Conditions for Exclusion in the Diagnosis of the Polycystic Ovary Syndrome.

| Condition | Hyperandrogenemia, Hyperandrogenism, or Both | Oligomenorrhea or Amenorrhea | Distinguishing Features | |
|---|--|------------------------------|---|---|
| | | | Clinical | Hormonal or Biochemical |
| Nonclassic congenital adrenal hyperplasia due to deficiency of 21-hydroxylase | Yes | Not often | Family history of infertility, hirsutism, or both; common in Ashkenazi Jews | Elevated (basal) level of 17-hydroxyprogesterone in the morning or on stimulation |
| Cushing's syndrome | Yes | Yes | Hypertension, striae, easy bruising | Elevated 24-hr urinary free cortisol level |
| Hyperprolactinemia or prolactinoma | None or mild | Yes | Galactorrhea | Elevated plasma prolactin level |
| Primary hypothyroidism | None or mild | May be present | Goiter may be present | Elevated plasma thyrotropin and subnormal plasma thyroxine level; prolactin level may also be increased |
| Acromegaly | None or mild | Often | Acral enlargement, coarse features, prognathism | Increased plasma insulin-like growth factor I |
| Premature ovarian failure | None | Yes | May be associated with other autoimmune endocrinopathies | Elevated plasma follicle-stimulating hormone and normal or subnormal estradiol level |
| Simple obesity | Often | Not often | Diagnosed by exclusion | None |
| Virilizing adrenal or ovarian neoplasm | Yes | Yes | Clitorimegaly, extreme hirsutism, or male-pattern alopecia | Extremely elevated plasma androgen level |
| Drug-related condition* | Often | Variably | Evidence provided by history | None |

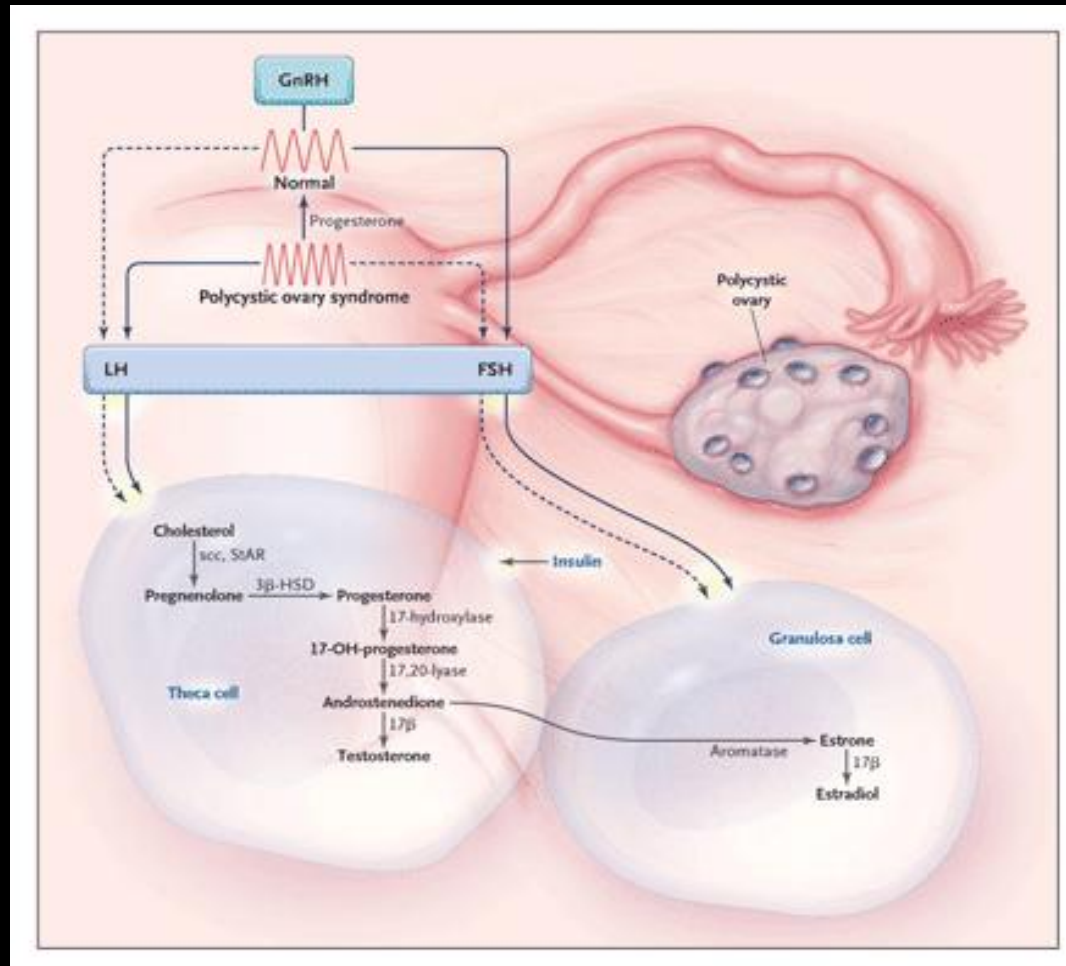
* A drug-related condition is a condition due to the use of androgens, valproic acid, cyclosporine, or other drugs.

- Pulsatile LH-Sekretion: Frequenz ↑ , Amplitude ↑
 - Theka-Zelle: Androgene ↑
 - Fettzelle: Androgene – Aromatase – Östrogene → LH ↑
 - Granulosazelle: Östrogene ↑ → LH ↑
- Insulin: LH-Agonist
 - Ovar: Androgene ↑
 - NN: Androgene ↑
 - Leber: SHBG ↓

- Hyperandrogenämie
- LH/FSH-Ratio > 2

PCOS

Pathogenesis



PCOS is associated with a significantly increased risk of:

- **Maternal**

- Gestational diabetes
- Pregnancy induced hypertension
- Preeclampsia
- Delivery by C-section

- **Neonatal**

- Admission to a Neonatal Intensive Care Unit
- Perinatal mortality
- Premature deliveries

PCOS

Long-Term Health Risks

- **Type II DM (3-7 times)**
- **CVD**
- **Endometrial cancer**

PCOS & Obesity

- **Weight loss** of 7%
- **Lifestyle** intervention



- Physical activity 150min/week

*Reduces incidence of DM type II by **58%***

- **Metformin** 2x850mg



*Reduces incidence of DM type II by **31%***

PCOS & Obesity

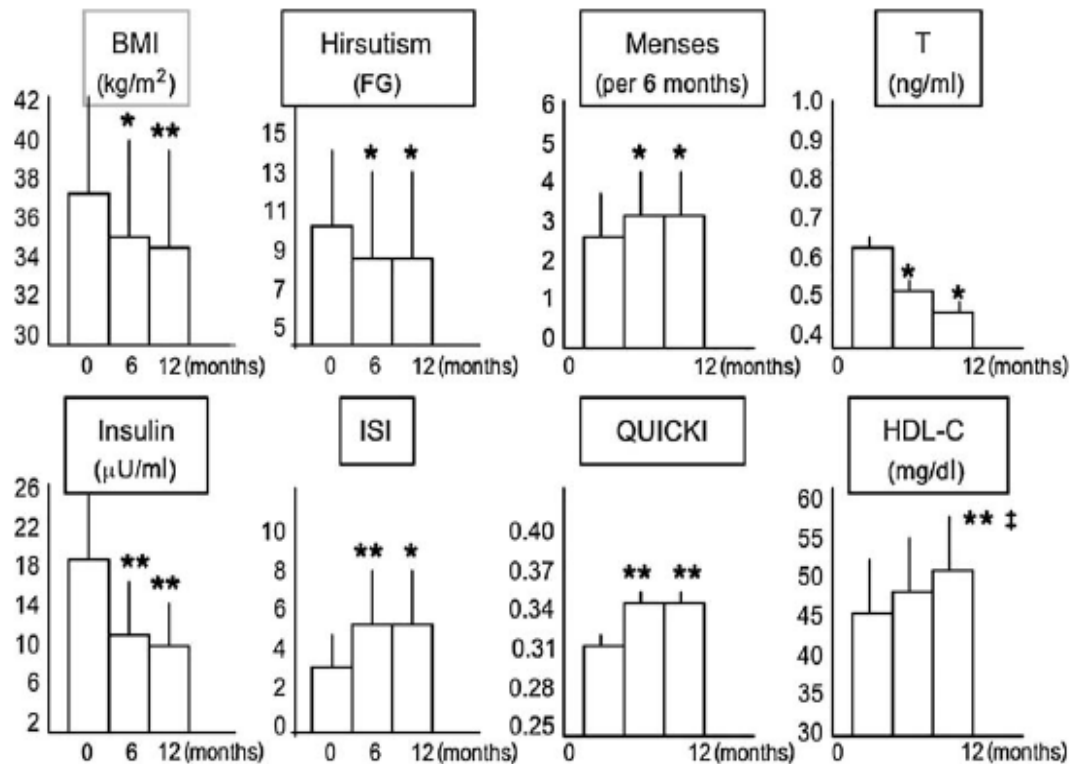


Figure 2. Effect of lifestyle intervention on hirsutism, menses, testosterone and metabolic parameters in a group of obese women with PCOS treated with hypocaloric diet for 1 year (A. Gambineri *et al.*, unpubl. obs.). T, testosterone; QUICKI, quantitative insulin-sensitivity check index; ISI, insulin sensitivity index; HDL-C, HDL cholesterol.^{52,74} * $P < 0.05$; ** $P < 0.01$ versus baseline; ‡ $P < 0.05$ versus sixth month.

PCOS & Hirsutism

Treatment

Specific regimens

Weight loss

Hormonal suppression

OCP
MPA
GnRH-analogs
Glucocorticoids

5^α-reductase inhibitors

Finasterid

Antiandrogens

Cyproterone acetate
Spironolactone
Flutamide

Mechanical

Temporary
LOD

- **First choice for induction of ovulation**
- **50-150mg per day for 5 days**
- **Ovulation rate 75-80%^{1,2}**
- **Pregnancy rate up to 22% per cycle^{3,4,5}**
- **Treatment limited to 6 cycles^{1,3}**
- **Cum. live-birth rate 50-60% for 6 cycles⁵**
- **Adverse effects**
 - Hot flushes, headache
 - Multiple pregnancies < 10%
 - OHSS rare

1 Homburg 2005

2 Messinis 2005

3 Eijkemans et al. 2003

4 Hammond et al. 1983

5 Kousta et al. 1997

PCOS

| Variable | <i>Clomiphene</i> n=209 | <i>Metformin</i> n=208 | <i>COMB.C+M</i> n=209 | <i>C vs. M</i> p-Value | <i>C vs. COMB.</i> p-Value | <i>Met vs. COMB</i> p-Value |
|-------------------|----------------------------|---------------------------|--------------------------|---------------------------|-------------------------------|--------------------------------|
| Ovulation | 49% | 29% | 60% | <0.001 | 0.003 | <0.001 |
| Conception | 30% | 12% | 38% | <0.001 | 0.06 | <0.001 |
| Pregnancy | 24% | 9% | 31% | <0.001 | 0.10 | <0.001 |
| Live birth | 23% | 7% | 27% | <0.001 | 0.31 | <0.001 |
| Multiple | 3 | 0 | 2 | - | - | - |

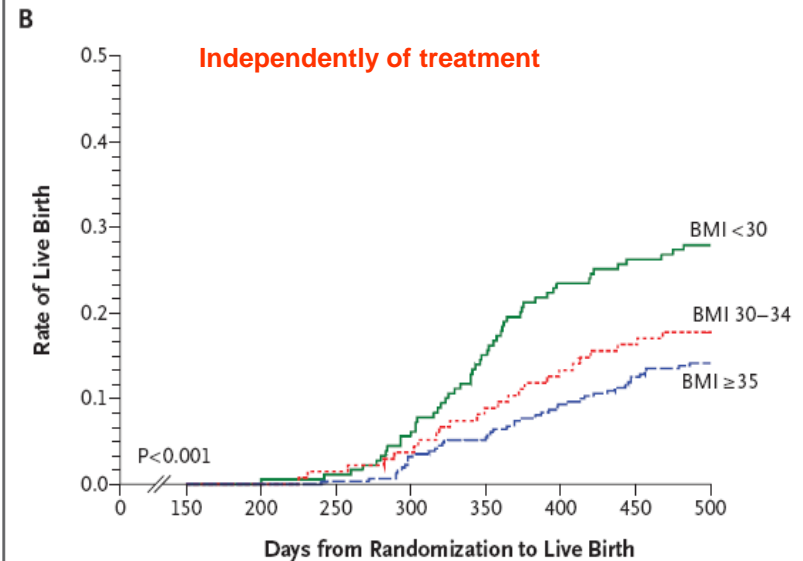
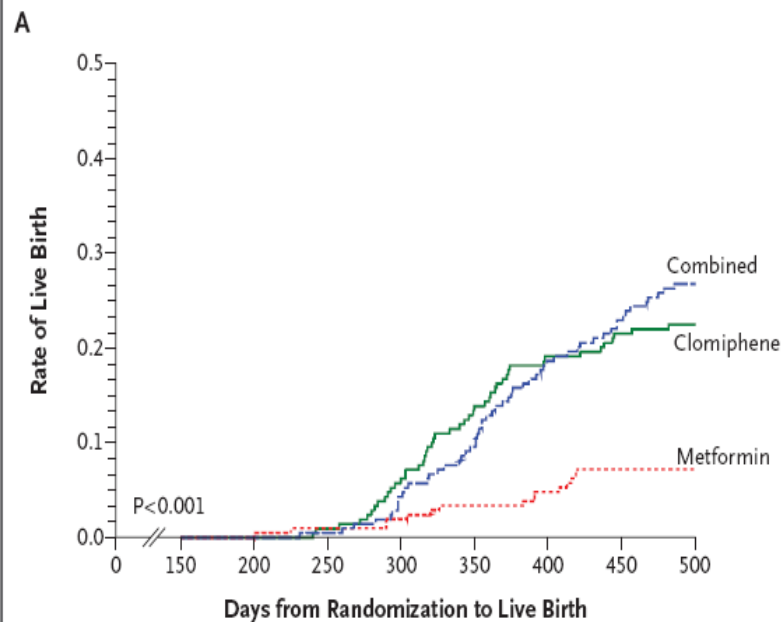


Figure 2. Kaplan–Meier Curves for Live Birth, According to Study Group (Panel A) and Body-Mass Index (BMI) (Panel B).

Chirurgie Oligo-/Anovulation – Infertilität

- **Wedge resection** *(Stein & Leventhal 1935)*
 - 1/3 Resektion per Lap/LSK
 - » verlassen – Adhäsionen, POF
- **Alternativen**
 - Clomiphen, Gonadotropine
 - » OHSS, multiple births
- **Laparoscopic ovarian drilling (LOD)**

Mechanismus



- **Thekazellen zerstört**
- **Reduktion der Androgenproduktion**
- **tTES: -40%; fTES -50%** (*Rossmann 1991*)
 - **Volumen steigt – sinkt** (*Sakata 1990*)
 - **LH steigt – sinkt** (*Liguori 1996*)
 - **Pulsamplitude sinkt, Pulsfrequenz bleibt gleich**
 - **FSH steigt – normalisiert LH/FSH Ratio**

PCOS *Laparoscopic Ovarian Drilling*(**LOD**)

Systematischer review - OD *(Pirwany & Tulandi 2003)*

- Ovulation (10-20 Krater 2-4mm tief): 70-90%
- Dauer?; n=165
n=51 >10a follow-up: 74% nach 10a *(Gjönaess 1998)*
- Pregnancy rate
 - n=111, 54%, 62% (12/18 mos) *(Li 1998)*
 - n=112, 54%, 68% (12/18 mos) *(Felemban 2000)*
- Miscarriage
 - Hypothese: hohes LH
 - 30-50% mehr Aborte bei PCOS *(Kovacs 1991)*
 - Reduktion um 21% *(Abdel 1990)*
 - Reduktion um 37% *(Amer 2002)*



➤ Effectiveness, safety, clomiphene-res. PCOS

– 6 RCTs (*Farquhar 2001*)

- drilling vs. gonadotropins (3-6 cycles)

- outcome: ovulation, pregnancy

 - secondary outcomes : miscarriage, OHSS, multiple births

 - 6-12 mo follow-up

➤ Resultat

- kein Unterschied Schwangerschaftsrate

- pooled OR 1.27 (95% CI 0.8-1.9)

- weniger OHSS, weniger Mehrlinge (OR 0.16)

- Abortraten gleich

- Life style, weight reduction and exercise in overweight women, smoking and alcohol consumption
- Clomiphene citrate (CC) first-line treatment for ovulation induction
- Second-line intervention, should CC fail to result in pregnancy, is either exogenous gonadotrophins or LOD
- Third-line treatment is IVF
- Metformin restricted to women with glucose intolerance. Routine use of this drug for ovulation induction not recommended.
- Insufficient evidence to recommend the clinical use of aromatase inhibitors for routine ovulation induction.
- Even singleton pregnancies in PCOS are associated with increased health risk for both the mother and the fetus.

DANKE !

