OBSTETRIC RISKS IN PATIENTS WITH ENDOMETRIOSIS

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Definition

- Presence of endometrial-like tissue outside the uterine cavity
- Hormonal responsiveness similar to functional endometrium
- Pathophysiology, nature and progression are poorly understood
- Delayed diagnosis: 7 years *(Nnoaham et al, 2011)*

- Different types
  - Ovarian
  - Superficial
  - Deep
  - Adenomyosis
- Common symptoms
- Subfertility/infertility
- Pain syndrome

- Common disease among women in reproductive age: 10-15% *(Nothnick and D'Hooghe, 2003)*
- High prevalence in infertile women: 48% *(Strathy et al, 1982)*
- Low "Monthly fecundity rate": 2-10% *(Hughes et al, 1993)*
- High recurrence rate: 10-15% for 1 year, up to 40-50% after 4-5 years follow-up *(Guo, 2009)*

Pathophysiology

- Chronic inflammation
- Angiogenesis
- Adhesion formation
- Perturbed endometrium
- Thickening and dysperistalsis of junctional zone
- Pg resistance

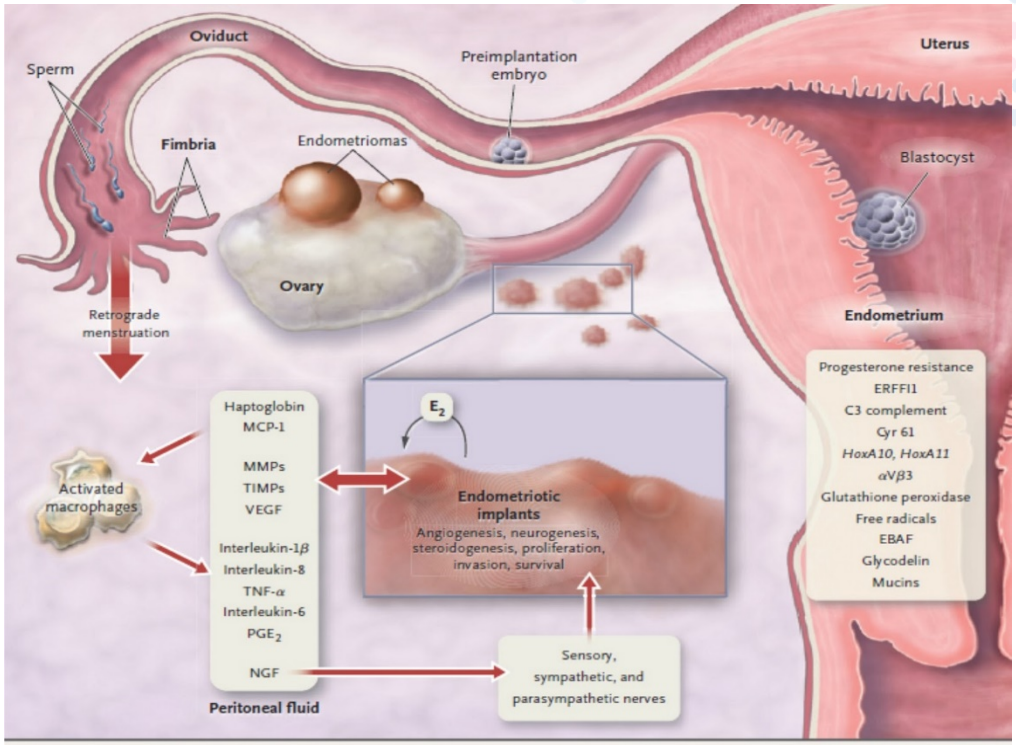


Figure 2. Pathophysiology of Pain and Infertility Associated with Endometriosis.

Inflammation

- Dysfunction of immune-related cells and macrophages within the peritoneum *(Yagmur et al, 2013; Bulun, 2009)*
- Activation of peripheral blood monocytes

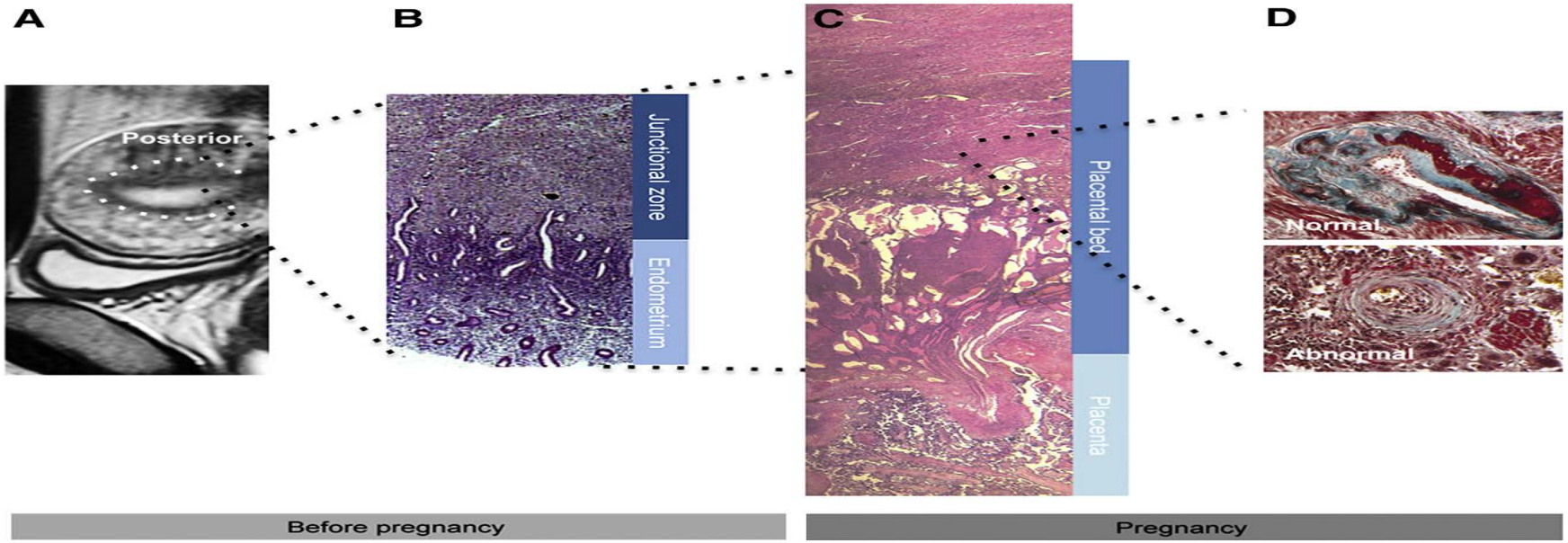
→ Systematic immune alterations

(Carmona et al, 2012)

- Aberant expression of proinflammatory cytokines
- Elevated levels of IL-1β, IL-6, TNFα

Junctional zone

- Strong relationship between pelvic Endo and thickening of the posterior JZ myometrium *(Kunz et al, 2005)*
- Size increases with age, JZ is thick even in young women with adenomyosis



Brosens. Adverse pregnancy outcome in endometriosis. Fertil Steril 2012.

Junctional zone

- Share the same progenitor cells as the endometrial stroma *(Borsens et al, 1072)*
- Thickening in Endo may result as perturbation in the differentiation potential of the basal endometrial layer *(Craven, 1998)*
- Inflammatory cues associated with Endo may impact basal endometrium and JZ

Angiogenesis

- Increased endometrial angiogenesis
- Significantly higher endometrial perfusion rates during the secretory phase of the cycle *(Xavier et al, 2005)*
- Production of VEGF, IL-1,-6,-8 and EGF is enhanced in both eutopic and ectopic endometrium in women with endometriosis *(Taylor et al, 2002)*

Pg resistance

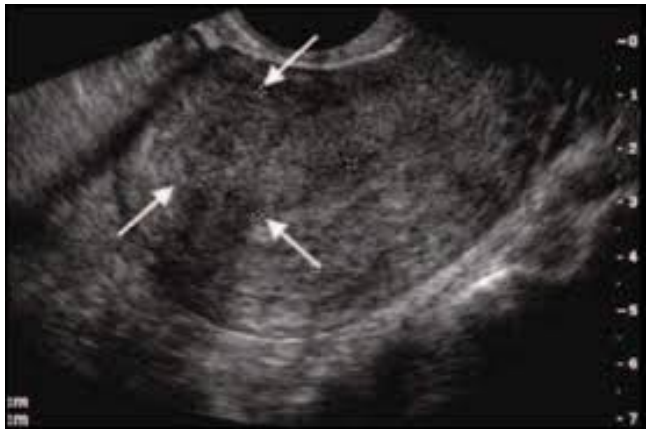
- Reverse decidual phenotype
- Induce gene expression for
  - *Chemokines*
  - *Proinflammatory cytokines*
  - *Matrix metalloproteinases*
  - *Apoptotic factors*

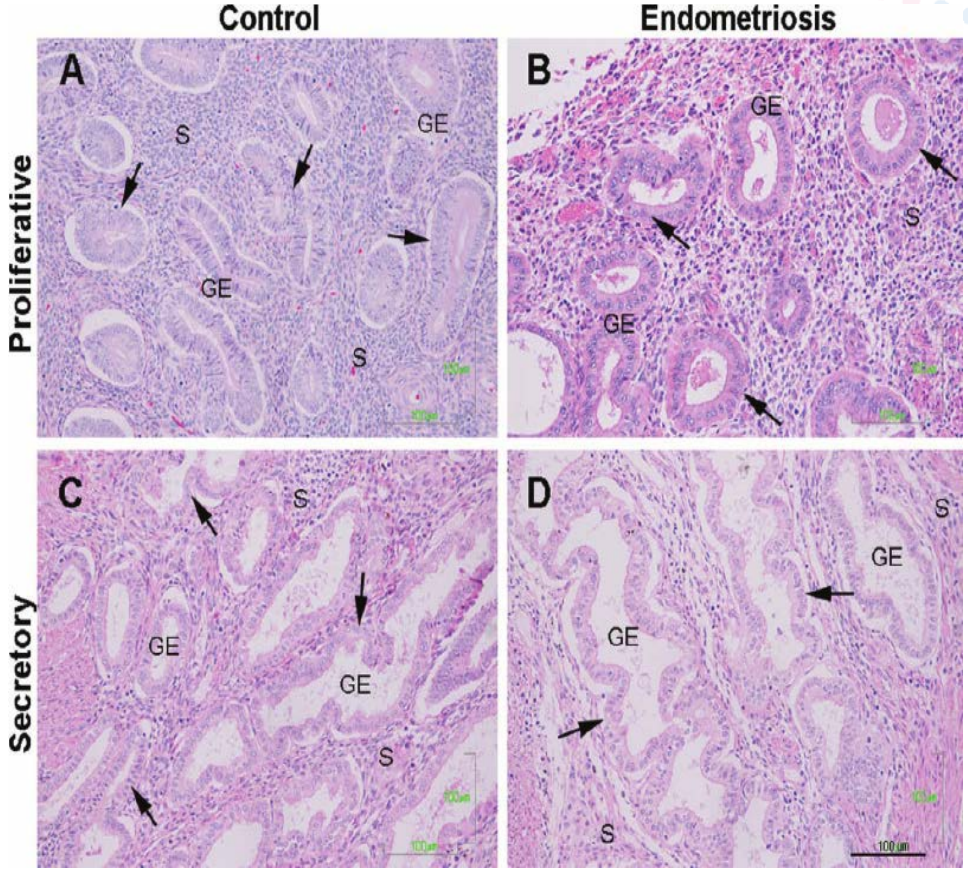
➡ Influx of inflammatory cells, proteolytic breakdown of the extracellular matrix, cell death, bleeding

Findings in endometrium

- Lower peak of endometrial thickness: “proliferative phase defect” *(Bromer, 2009)*
- Delayed maturation
- Altered glycosylation

(Miller et al, 2010)





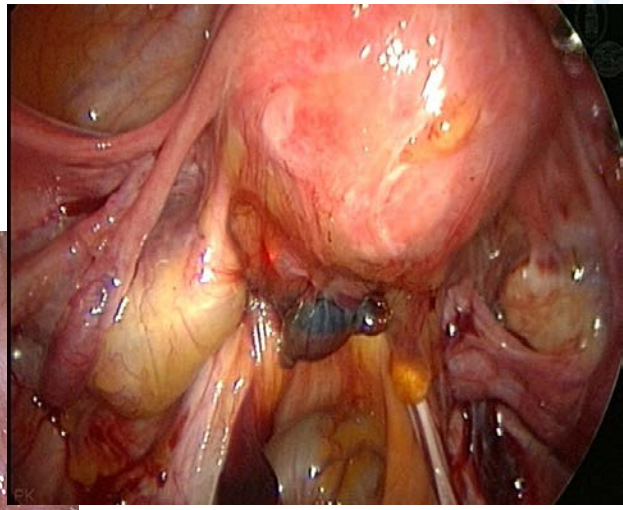
Findings in endometrium

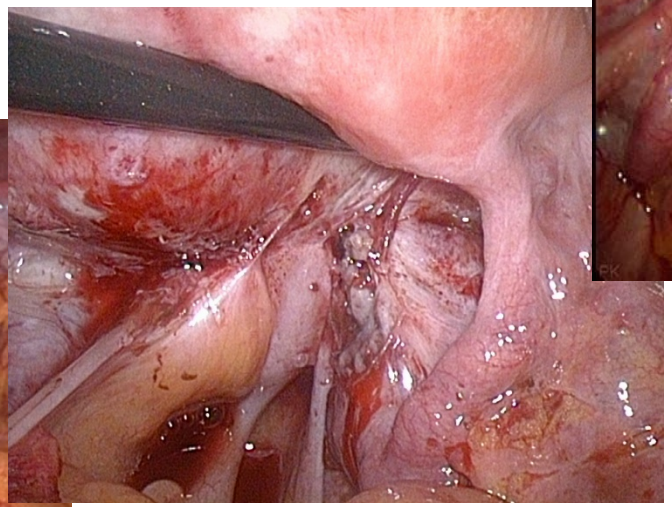
- Molecular abnormalities: local steroid biosynthesis, cell growth, apoptosis, immune cell function, angiogenesis, cell adhesion, cytokine production *(Carvalho et al, 2011; Sharpe-Timms et al, 2010)*
- Perturbed endometrial gene expression *(Giudice, 2004)*

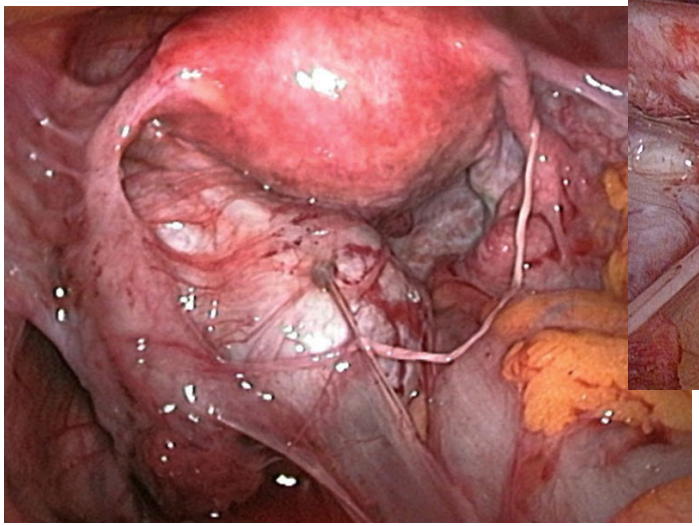
- embryo implantation
- controlled interstitial and endovascular trophoblast invasion
- establishment of functional placenta

Feature of endometriosis patient

- Subfertile
- After one or multiple surgeries
- ART







Feature of endometriosis patient

- Advanced maternal age
- Primiparous
- Distorted pelvic anatomy
- Other pelvic organs affected
- CPID

Endometriosis and pregnancy

- Decidualization preventing progression

- Not confirmed for DIE

BUT:

Decidualization causes invasion of the ectopic endometrium

Endometriosis has impact on controlled interstitial and endovascular trophoblast invasion

Reports for bleeding and progression of the endometriotic lesions

Complications

Women with untreated DIE

TABLE 2

Comparison of pregnancy and delivery complications in women with endometriosis and control group.

Complications	Posterior DIE n (%)	Control group n (%)	*P* value[a]	OR (95% CI)
During pregnancy (n)	41	300		
Premature delivery <37 wk	13 (31.7)	19 (6.3)	<.0001	6.867 (3.069–15.36)
Premature delivery <32 wk	2 (4.8)	6 (2.0)	.2481	2.513 (0.49–12.89)
Placenta previa	7 (17.8)	1 (0.3)	<.0001	61.56 (7.351–515.5)
Placental abruption	2 (4.8)	1 (0.3)	.0392	15.33 (1.359–173)
Gestational hypertension	6 (14.6)	12 (4.0)	.0129	4.114 (1.453–11.65)
Gestational diabetes	3 (7.3)	8 (2.7)	.1342	2.882 (0.7328–11.33)
Small-for-gestational-age fetuses	4 (9.8)	17 (5.7)	.2985	1.8 (0.5745–5.637)
Delivery route				
Vaginal	12 (29.3)	151 (50.3)	.0124	0.4083 (0.200–0.830)
Vaginal operative	1 (2.4)	19 (6.4)	.4881	0.3697 (0.04817–2.838)
Cesarean section	28 (68.3)	130 (43.3)	.0041	2.817 (1.404–5.651)
During cesarean delivery (n)	28	130		
Hysterectomy	2 (7.1)	0 (0)	.0305	24.62 (1.149–527.7)
Hemoperitoneum	2 (7.1)	0 (0)	.0305	24.62 (1.149–527.7)
Bowel resection	1 (3.6)	0 (0)	.1772	14.24 (0.5649–358.8)
Bladder injury	2 (7.1)	0 (0)	.0305	24.62 (1.149–527.7)
During vaginal delivery (n)	13	170		
Extend vaginal laceration	1 (7.7)	1 (0.6)	.1374	14.08 (0.8286–239.4)
Uterine atonia	1 (7.7)	1 (0.6)	.1374	14.08 (0.8286–239.4)
Cervical lesion	1 (7.7)	0 (0)	.0710	40.92 (1.584–1057)

Note: $P < .05$ was considered statistically significant. CI = confidence interval; DIE = deep infiltrating endometriosis; OR = odds ratio.
[a] Posterior DIE vs. control group.

Exacoustos. Posterior DIE and pregnancy complications. Fertil Steril 2016.

Obstetrical bleeding

- Antepartal haemorrhage incl. placental disorders are up to 80% higher *(Stephansson et al, 2009)*

- Placenta praevia: 1.7-fold increase incidence *(Healy et al, 2010)*

- Almost 10 times higher in women with DIE *(Exacoustos et al, 2016)*

- Placental abruption: higher incidence in women with DIE *(Exacoustos et al, 2016)*

- Postpartal bleeding: 1.3-fold risk *(Healy et al,2009)*

Obstetrical bleeding

- Possible explanation:
- Anomalous blastocyst implantation due to:

1. Altered JZ

The uterine JZ becomes the site of the placental bed in pregnancy *(Pijnenborg et al, 2011)*

2. Uterine dysperistalsis

3. Fixed abnormal uterine position

4. Local inflammation

5. Adenomyosis may act as confounder

Preterm birth

- Doubling the incidence of preterm birth comparing to control group in women with ovarian endometrioma *(Fernando et al, 2009)*
- Inflammation: local and systematic
  - ⟹ Activation of PGE2, COX-2, IL-8
  - ⟹ Myometrial contractility
- Endometriosis: increased levels of PGs and cytokines in peritoneal fluid

Preterm birth

- Adenomyosis *(Juang et al, 2007)*

  - 1.84-fold risk of preterm birth

  - 1.98-fold risk of preterm premature rupure of mambranes

- Possible cause: chorioamniotic or systematic inflammation
- Increased uterine pressure *(Ferenczy, 1998)*

Small for gestational age baby

- Endometriosis is associated with two times higher rate of SGA newborns *(Conti et al, 2015; Fernando et al, 2009)*

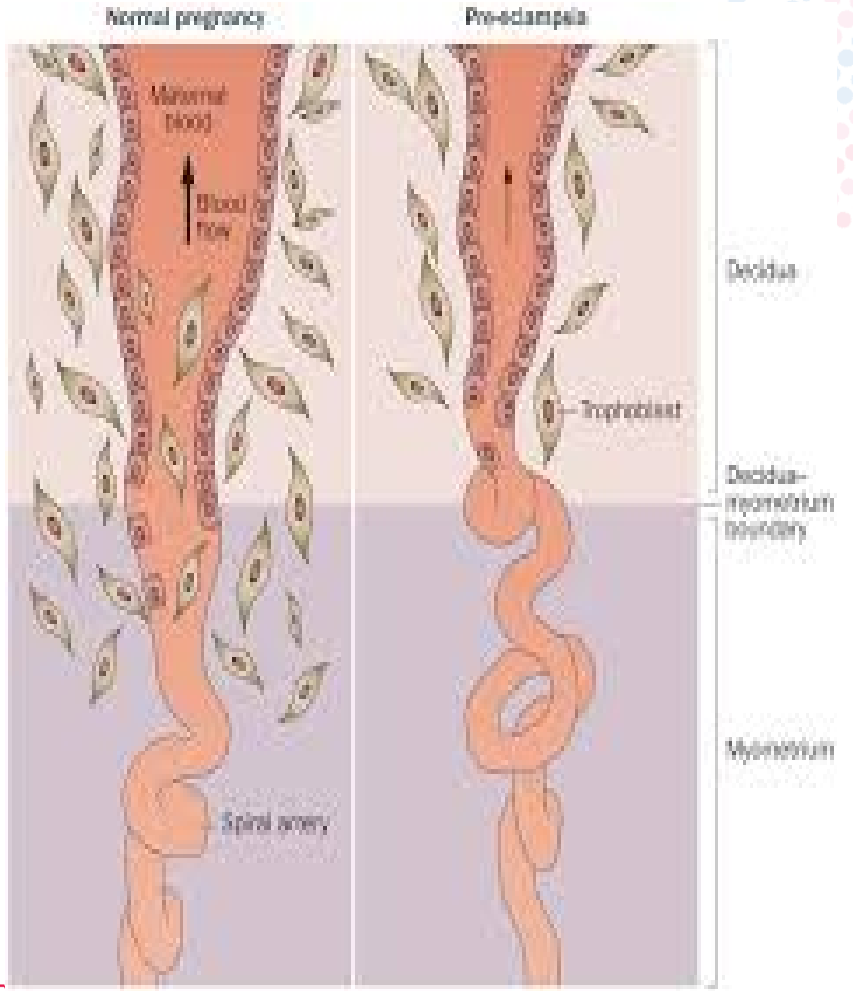
  - Impaired placentation due to abnormal endometrium *(Fernando et al, 2009)*

- Larger studies show no difference between endometriosis and control group in rate of SGA babies *(Exacoustos et al, 2016; Stephansson et al, 2009)*

Preeclampsia

- Preeclampsia is a model of angiogenic disorder, resulting in endothelial-cell disfunction, vessel malformation or regression and impaired re-vascularization *(Carmeliet, 2005)*

- Defective spiral arteries remodeling in JZ *(Brosens et al, 2011)*



Preeclampsia

- There is no link between endometriosis and risk of preeclampsia *(Mekaru et al, 2013; Brosens et al, 2007)*
- No differences according to stage of endometriosis *(Hadfield et al, 2009)*

Table 2: Incidence of pre-eclampsia according to the place of delivery

Place of delivery	Case group (%)	Control group (%)	*P*-value
Ghent, Belgium[a]	0/90 (0.0)	3/62 (4.8)	0.07
Belgium[b]	1/100 (1)	4/61 (6.6)	0.07
The Netherlands	1/47 (2.2)	9/145 (6.3)	0.5

[a]Deliveries at the University Hospital of Ghent.
[b]In centres elsewhere in Belgium.

Brosens. Endometriosis is associated with a decreased risk of preeclapmsia, Hum Reprod 2007

Preeclampsia

- Level of angiogenesis at the feto-maternal interface in early pregnancy is important predictor for obstetric outcome *(Makikallio et al, 2004)*

- Endometriosis features

- Higher endometrial perfusion rates
- Excessive angiogenesis
- High levels of angiogenic factors

Preeclampsia

- Endometriosis is a significant risk for preeclampsia and PIH *(Stephansson et al, 2009, Exacoustos et al, 2016)*
- The high risk arises from relation between endometriosis and dysregulation of the JZ *(Leyendecker et al, 2004)*

→ defective remodeling of the junctional zone myometrial spiral arteries in placental bed

C-section

- Women with endometriosis deliver 1.5-2 times more frequently with C-section than control group *(Exacoustos et al, 2016, Stephansson et al, 2009)*

- Specific complications: higher risk of hemoperitoneum due to bleeding of endometriotic bowel lesions, bladder injuries and hysterectomy

Spontaneous hemoperitoneum

- Rare but life-threatening complication
- Second half of pregnancy
- Early postpartum period
- Major symptoms:
- Acute or subacute abdominal pain
- Hypovolemic shock
- Fetal distress
- Maternal mortality decreased but fetal mortality remain constantly high as 36% *(Brosens et al, 2009)*

Spontaneous hemoperitoneum

- US failed to diagnose intraperitoneal bleeding
- Diagnose set on laparotomy for maternal (shock, anemia), fetal (distress) or combined reasons
- 80% of cases – venous bleeding
- Bleeding sites – posterior uterine wall or parametrium
- Biopsy show decidualized endometriotic lesions

Peritonitis

- Rare, 12 case reports *(Setubal et al, 2014)*
- Second half of pregnancy or early postpartal period
- Presented as acute abdomen
- No indication that could predict the condition
- Possible causes:

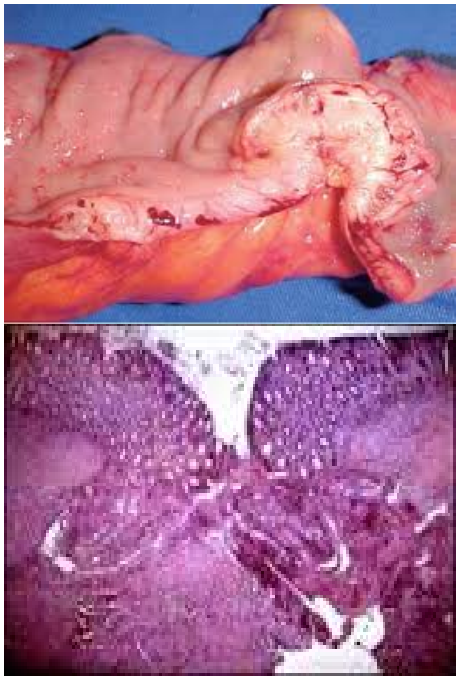
- Bowel wall perforation from decidualized growing endometrial lesion
- Tissue trauma because of uterine growing caused of pelvic adhesion

Peritonitis

- Pregnancy complicates diagnosis during laparotomy-sometimes needed repeated laparotomy
- Pathology reported depostits of endometriosis on the bowel
- Can affect small intestine, caecum

appendix, rectosigmoid colon

- 1 of 4 cases had previous history of endometriosis



Prompt diagnosis

Miscarriage

- Endometriosis cause high incidence of miscarriage *(Naples et al, 1981; Wheeler, 1983)*
- Uncontrolled studies
- 7,4% - No Endo vs. 5,7% - Endo, no relationship between stage and miscarriage rate *(Matorras et al, 1998l Balash et al, 1988)*
- No difference in women with minimal to mild Endo compared to controls *(Marcoux et al, 1997; Gruppo Italiano, 1999)*

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human reproduction ORIGINAL ARTICLE *Gynaecology*

Increased rate of spontaneous miscarriages in endometriosis-affected women

Table II Rates of previous miscarriages.

	Controls		Endometriosis		
	n	Rate % (95% CI)	*n*	Rate % (95% CI)	*P*-value
Total	187/964	19.4 (16.1–22.7)	139/478	29.1 (23.9–34.3)	0.0014
Fertile women	72/583	12.3 (8.9–15.8)	67/341	19.6 (14.0–25.3)	0.014
Infertile women	115/381	30.2 (24.0–36.4)	72/137	52.6 (43.1–62.0)	0.0002
Previous ART treatment for infertility	41/123	33.3 (23.1–43.5)	50/86	58.1 (45.9–70.3)	0.008

Rates of previous miscarriages according to the surgical classification

Controls		SUP		OMA		DIE		
n	Rate (95% CI)	*n*	Rate (95% CI)	*n*	Rate (95% CI)	*n*	Rate (95% CI)	*P*-value
187/964	19.4 (16.1–22.7)	33/87	37.9 (25.4–50.5)	28/104	26.9 (16.3–37.6)	78/287	27.2 (20.4–34.0)	0.005

Rates of previous miscarriages according to rAFS stage

Controls		Stages I–II		Stages III–IV		
n	Rate (95% CI)	*n*	Rate (95% CI)	*n*	Rate (95% CI)	*P*-value
187/964	19.4 (16.1–22.7)	62/215	28.8 (21.9–35.8)	77/263	29.3 (21.7–36.9)	0.006

n, number of pregnancies; SUP, superficial endometriosis; OMA, endometrioma; DIE, deep infiltrating endometriosis; rAFS, according to The Revised American Fertility Society Classification of Endometriosis.

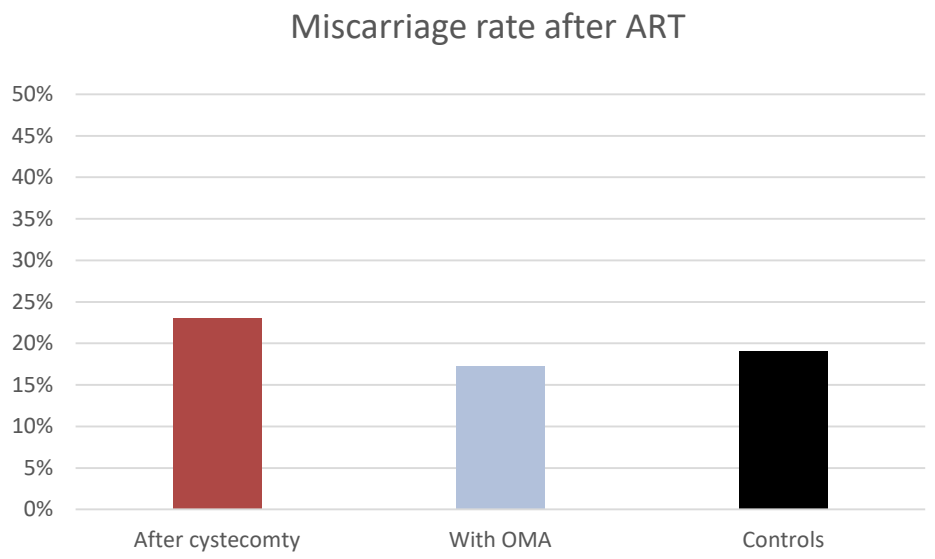
Our data

- IVF: 85 women with ovarian endometrioma

- 50 pregnancies after LS- cystectomy

- 35 pregnancies with presence of OMA

- Control group: 76 pregnant women with tubal factor after IVF-ET



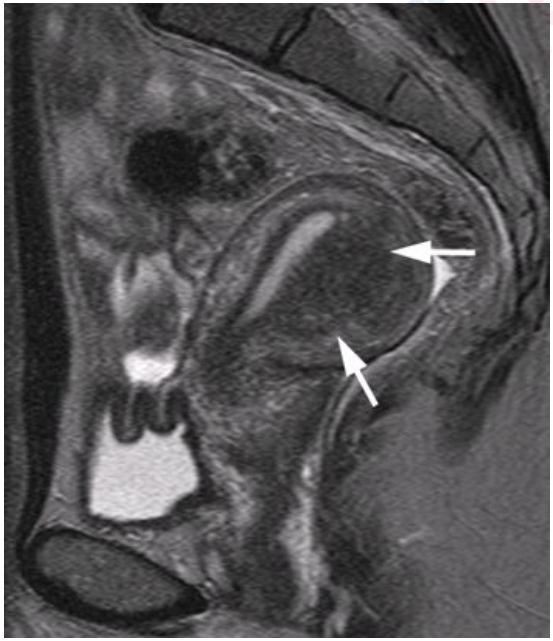
Role of ART

- ART does not increase preterm births in presence of endometriosis *(Stephansson et al, 2009)*
- No difference among patients with endometriosis for placental disorders, preeclampsia, C-section and obstetric hemorrhage *(Exacoustos et al, 2016)*
- Twin pregnancies

Adenomyosis

- Smooth muscle hyperplasia and disorganization in the inner myometrium (JZ)
- Failure of trophoblast-mediated remodeling of JZ spiral arteries
- Inadequate uterine contractility

→ Spectrum of Ob-syndroms: from preterm birth to SGA babies and preeclampsia



Endometriosis and pregnancy

- Incidence of ovarian endometriosis and pregnancy is quadrupled over the last 12 years *(Ueda et al, 2010)*
- Size of the lesion increased during pregnancy in 20% of cases

- Decidualization
- Hemorrhage of the ectopic endometrium

- Risk factor for rupture or abscess formation

Surgical treatment

- No effect on decreasing of miscarriage incidence after LS surgical treatment *(Marcoux et al, 1997; Jacobson et al, 2010)*
- Reduction of miscarriage rate from 63% to 0% *(Metzger et al, 1986; Wheeler et al, 1983; Pittaway et al, 1988)*
- Possible positive role of endometrial lesions resection *(Omland et al, 2005; Centini et al, 2016)*
- Decision should be *individualized*

Conclusions

- Need for prompt diagnosis – preconception
- Proper treatment of the disease
- Counseling the patient
- Awareness of potential complications
- Future research trend – etiologic treatment

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THANK YOU

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