Life Expert Centre
METHODOLOGY

Reproductive uterine diagnosis and treatment "Life Expert Centre Method"

Adenomyosis cause of failed implantation

STEPHAN GORDTS

Life Expert Centre
METHODOLOGY

INFERTILITY: DIAGNOSIS AND TREATMENT

Questions:

1. Do we understand raison for implantation failure?

2. Do we understand raison for failure of spontaneous conception?

3. Which is the most accurate method of treatment?

Life Expert Centre
METHODOLOGY

UTERUS HAS BEEN A "NEGLECTED INCUBATOR"

URGENT NEED FOR BETTER UNDERSTANDING

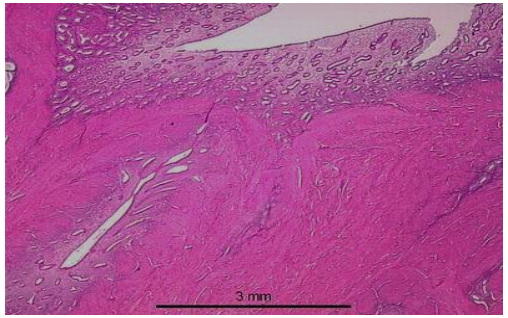
systematic use of indirect and direct methods of visualization

hysteroscopy
ultrasound / MRI
research: endometrium, JZ, contractility, pressure

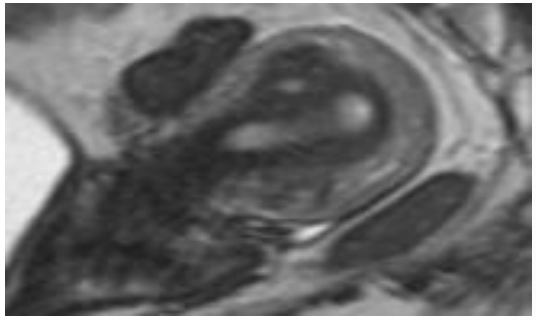
INCIDENCE

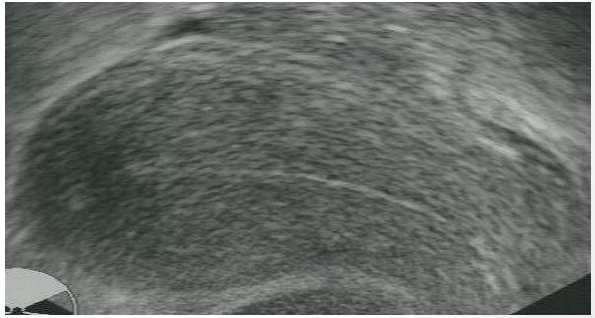
Adenomyosis - Incidence

No real clinical diagnosis
common histological diagnosis



Clinical entitiy
TVS and MRI





Incidence: 5- 70 %
retrospective studies

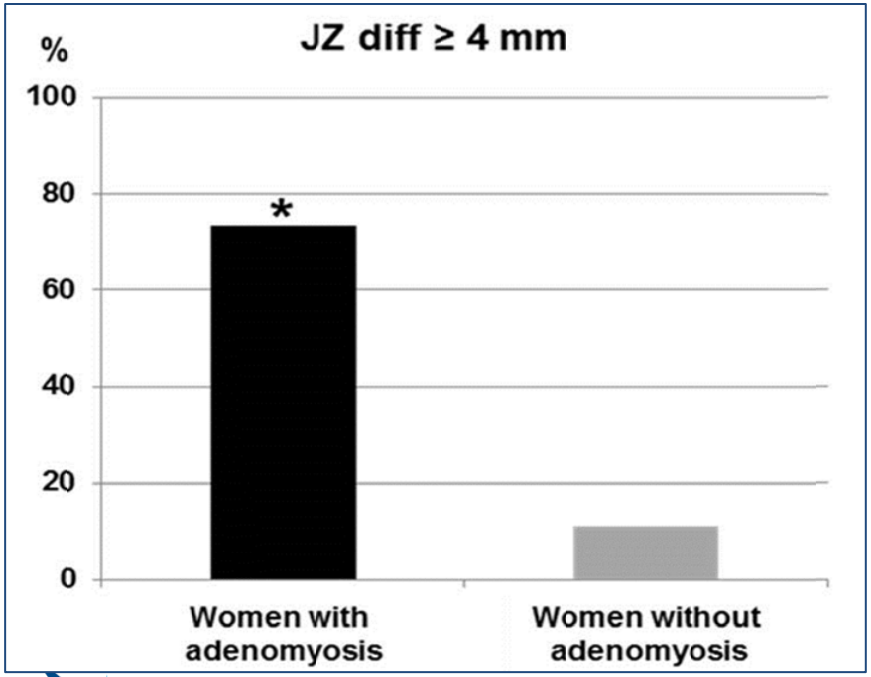
Adenomyosis incidence, prevalence and treatment: United States population based study 2006-2015.

Yu Onchee et al. AJOG 2020, Jan.

N= 333693

Adenomyosis by transvaginal ultrasonographic features in nulligravid women without endometriosis aged 18-30 years: correlation with symptoms

Pinzauti S et al. RBM online 2020



156 young patients (age: 26,06±2.89)
Nulligravida
No previuous surgery

Incidence:

33.9 % diffuse adenomyosis

73.5 % at least one feature

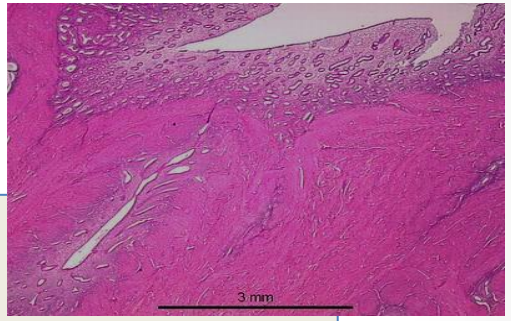
Conclusion:

Diffuse adenomyosis in early life may occur from endometrial-myometrial dysfunction

PATHOGENESIS

Adenomyosis- Pathogenesis

Presence of endometrial glands and stroma deep within the myometrium (>2.5 mm from EJZ)



- TRAUMA

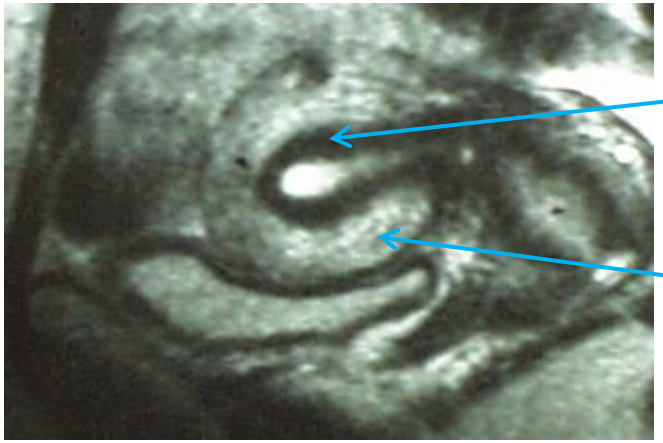
  IATROGENIC: D&C / C-SECTION

  UTERINE SURGERY

- UTERINE PATHOLOGY

MRI
clinical significance of the myometrial architecture

Myometrium has 2 structural and functional different entities



Junctional zone
small central zone of increased density
IMPORTANT IN REPRODUCTION

Outer myometrium
Larger outer hypodenser zone

The Myometrial Junctional zone

JZ myometrium is a distinct uterine structure

More akin to the endometrium than outer myometrium

Like the endometrium, the JZ is of Müllerian origin, while the outer myometrium is of non-müllerian, mesenchymal origin (Noe et al. 1999)

The JZ but not outer myometrium undergoes cycle-dependent changes

Uterine peristaltic activity originates exclusively from the JZ while the outer myometrium remains quiescent throughout the cycle

Uterine peristalsis during the menstrual cycle

Hysterosalpingoscintigraphy
- Classification of Results -

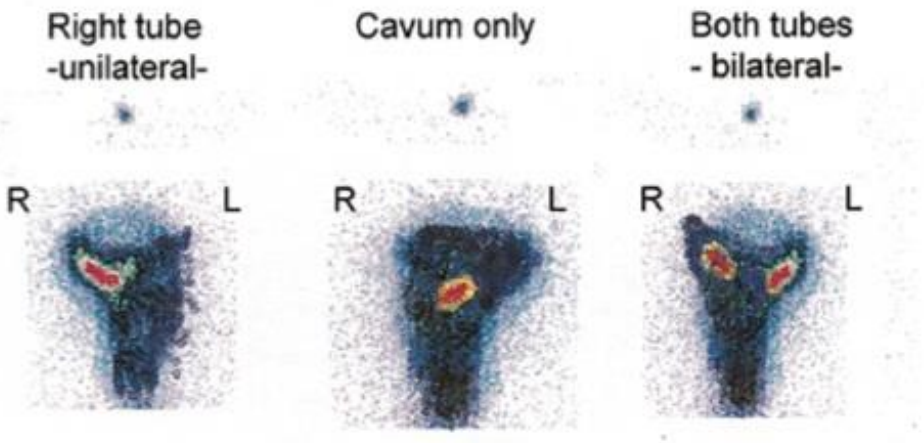


Figure 1. Typical examples of scans taken 10–20 min after application of 10–12 MBq ^{99m}Tc(radioactive Technetium)-labelled microspheres to the posterior vaginal fornix, demonstrating (from left to right) uptake into the uterus and unilateral transport to the right Fallopian tube, uptake into the uterus only and bilateral transport into the oviducts. A marker is placed at half distance between the pubic symphysis and umbilicus.

L. Wildt Hum Reprod Update, 1998, 4: 655-666


IVF

Uterine peristalsis during the menstrual cycle

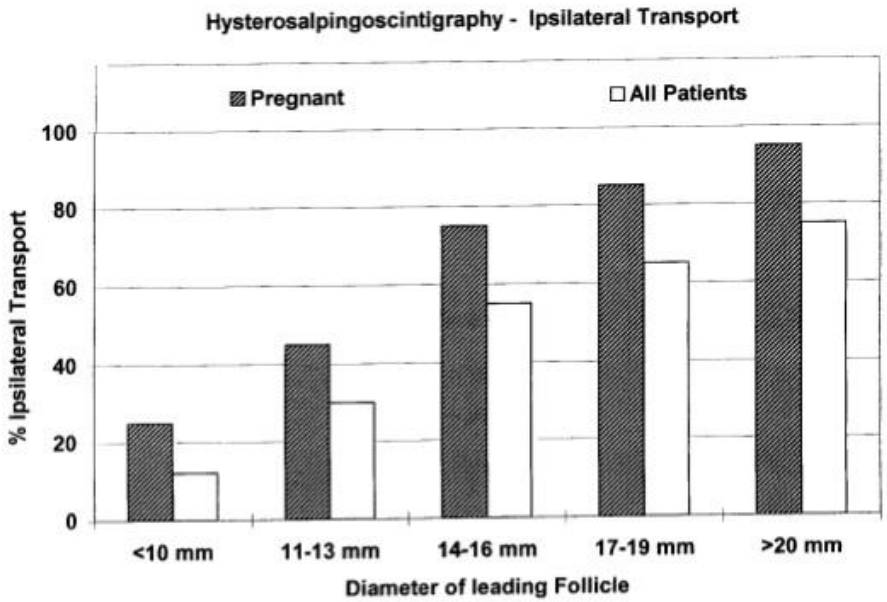


Figure 4. Lateralization of transport of labelled microspheres and size of the leading follicle. With increasing diameter of the dominant follicle, the proportion of patients exhibiting ipsilateral transport to the oviduct leading to the dominant follicle increased progressively. The proportion of patients with ipsilateral transport was higher in those who became pregnant after timed intercourse or intrauterine insemination than in those who did not conceive after this treatment (treatment duration lasting up to six cycles). Up to a follicle size of 13 mm, ipsilateral transport could be diagnosed only in retrospect, at the time when a dominant follicle did appear on the side where radioactivity was concentrated.

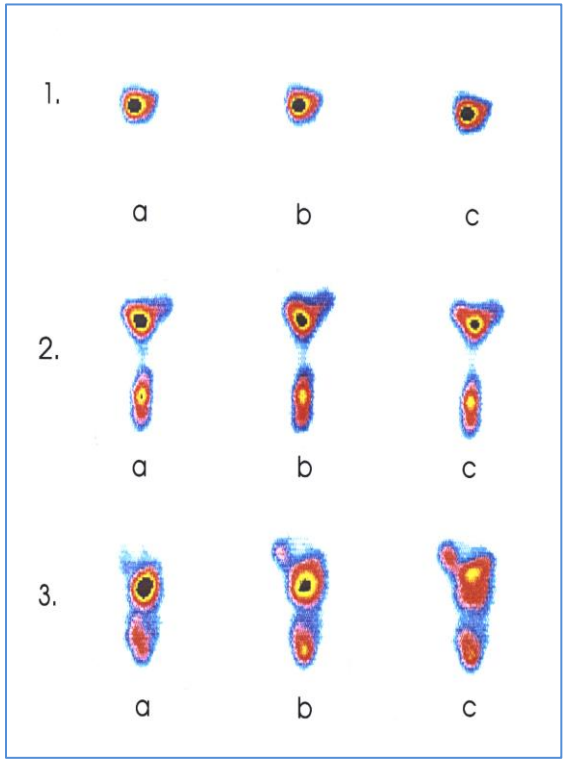
L. Wildt Hum Reprod Update, 1998, 4: 655-666

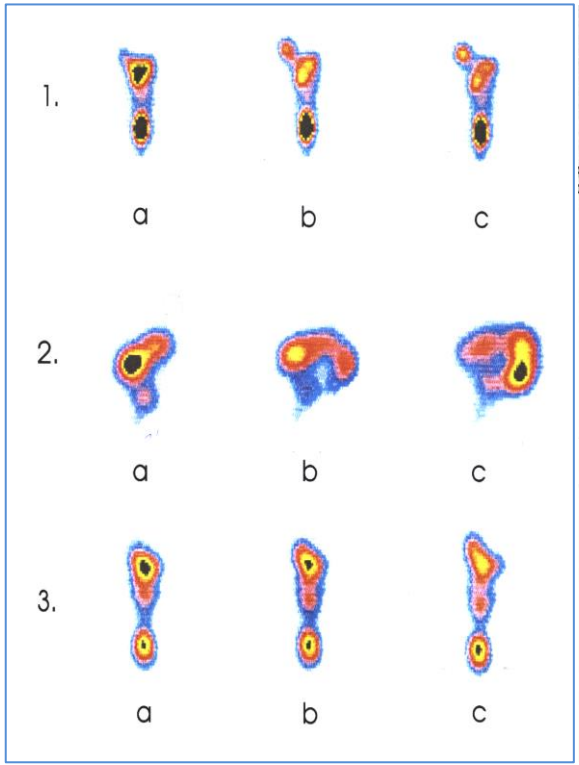
Uterine sperm transport

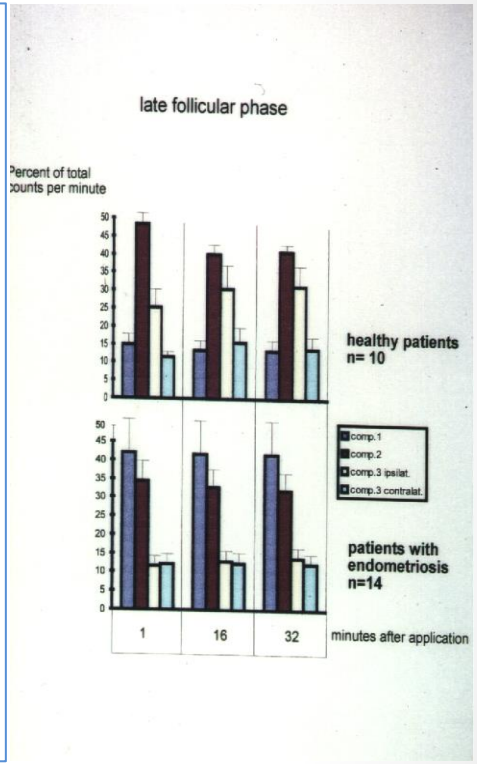
Healthy

Endometriosis

HSSG

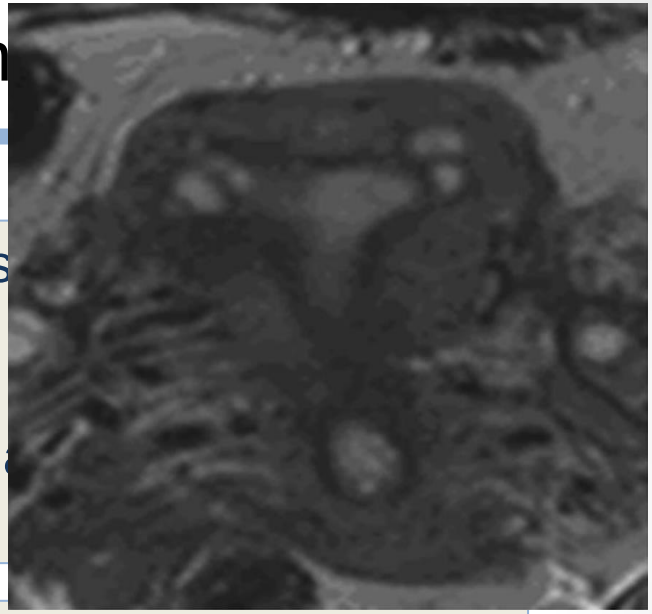






Kunz et al.

Uterine autotraumatization



Uterine peristalsis and hyperperis

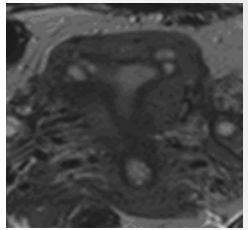
- 4-5 contractions / 10 min
- 1000 single contractions
  ovulatory cycle

Results in local inflammation and proliferation of basal endometrium into the uterine wall.

Intra uterine cystic adenomyosis: displacements of endometrial fragments: at MRI surrounded by their own junctional zone

Leyendecker G. et al. Arch Gynecol Obstet 2014

Uterine autotraumatization



Uterine peristalsis and hyperperistalsis constitutes the main mechanism.

Strongest power at the upper level of the uterine cavity.

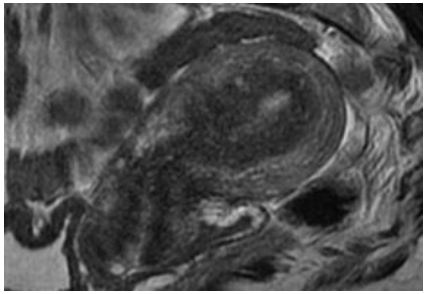
Highest density of OTR (oxytocin receptors)

Most frequent localization of adenomyotic lesions in upper two thirds of uterine cavity

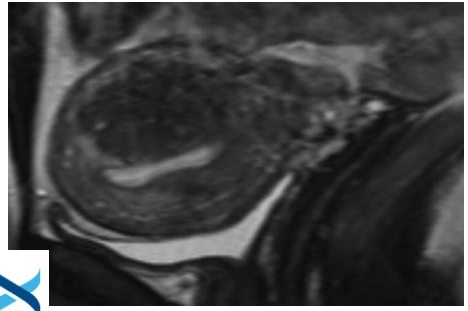
Leyendecker G. et al. Arch Gynecol Obstet 2014

MRI: Adenomyosis - Characteristics

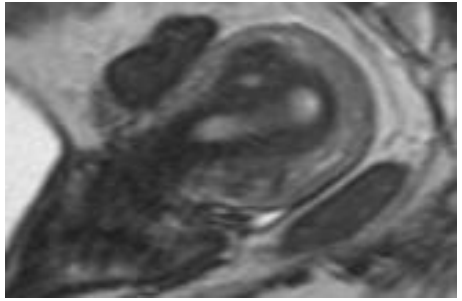
Diffuse lesion



Hyperplasia



Adenomyoma



Focal lesion

Cystic lesion

Symptoms and classification of uterine adenomyosis, including the place of hysteroscopy in diagnosis

Stephan Gordts, M.D.,[a,b] Grigoris Grimbizis, M.D., Ph.D.,[c] and Rudi Campo, M.D.[a,b]

Potentially important parameters to be included in a classification system.

Parameter	Description
Affected area	Inner myometrium or outer myometrium
Localization	Anterior or posterior or fundus
Pattern	Diffuse or focal
Type	Muscular or cystic
Volume or size	Expressed as <1/3, <2/3, >2/3 or in cm

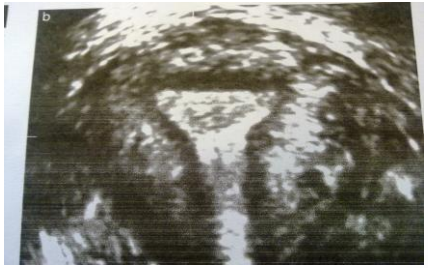
Gordts. Clinical aspects uterine adenomyosis. Fertil Steril 2018.

DIAGNOSIS

Trans-Vaginal 2D – 3 D Ultrasound

Exacoustos Ultrasound Obstet Gynecol 2011; 37: 471-479

	2D TVS	3D TVS
Accuracy:	83%	89%
Sensitivity:	75%	91%



Diagnostic accuracy of MRI for adenomyosis

Study	Design / Patients	Sensitivity	Specificity	PPV	NPV	AUC
Stamatopoulos et al / 2012	Prospective (N=135)	46.15	99.08	92.31	88.52	0.726 (0.643 – 0.799)
Moghadam et al / 2006	Retrospective (N=153)	38.71	90.98	52.17	85.38	0.648 (0.567 – 0.724)
Dueholm et al / 2001	Prospective (N=106)	63.64	88.10	58.33	90.24	0.759 (0.666 – 0.836)
Bazot et al / 2001	Prospective (N=120)	77.50	92.50	83.78	89.16	0.850 (0.773 – 0.909)
Reinhold et al / 1996	Prospective (N=119)	85.71	85.71	64.86	95.12	0.857 (0.781 – 0.914)
Ascher et al / 1994	Prospective (N=20)	88.24	66.67	93.75	50.00	0.775 (0.535 – 0.927)

- ***High Overall Diagnostic performance of MRI: Area Under the Curve (AUC) >0.75***
- ***High specificity (& high PPV): the possibility of adenomyosis found in MRI to be correctly diagnosed is very high (>90%)***

Stamatopoulos et al, JMIG, 19:620-626 , 2012

Hysteroscopy
Sub endometrial exploration - HISTOLOGY

Use of utero-spirotome under ultrasound guidance: (**A**) ultrasound guided insertion of spirotome; (**B**) spirotome with 1 cm corkscrew; and (**C**) representative biopsy obtained after use of the spirotome.

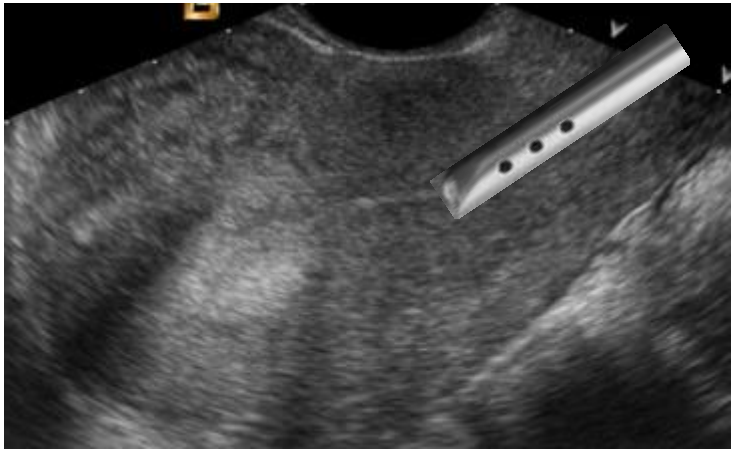
Gordts. Clinical aspects uterine adenomyosis. Fertil Steril 2018.

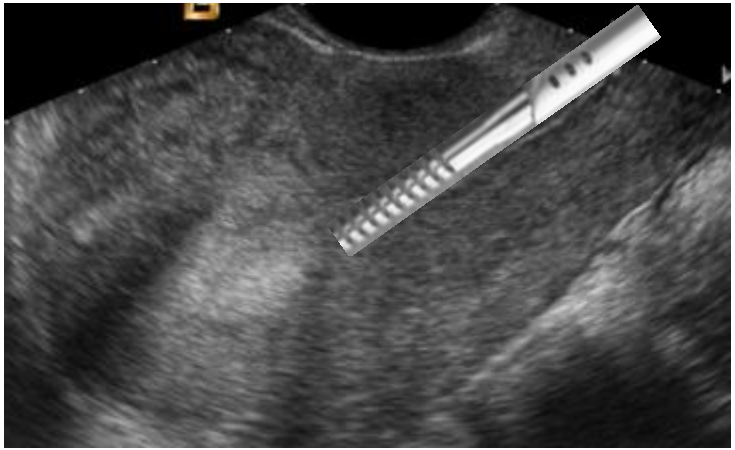
New Tools for Myometrial Exploration

Spirotome

A device made to harvest high quality samples from soft tissues.

It is built on the pioneering concept of a cutting helix on a cutting canula well identified by Ultrasound.

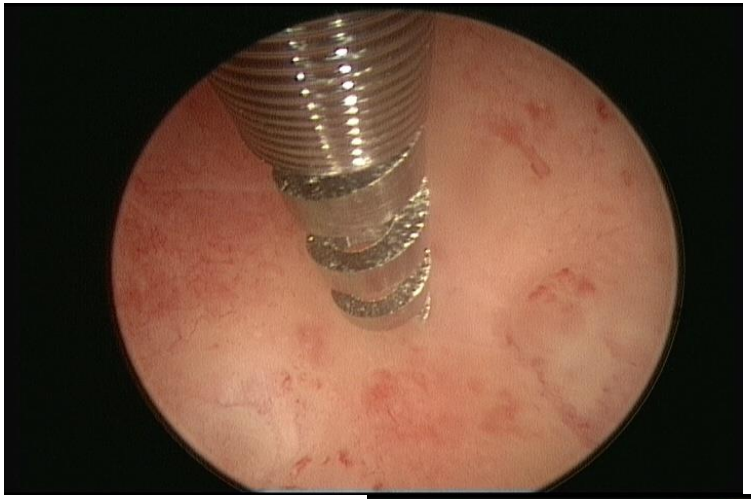


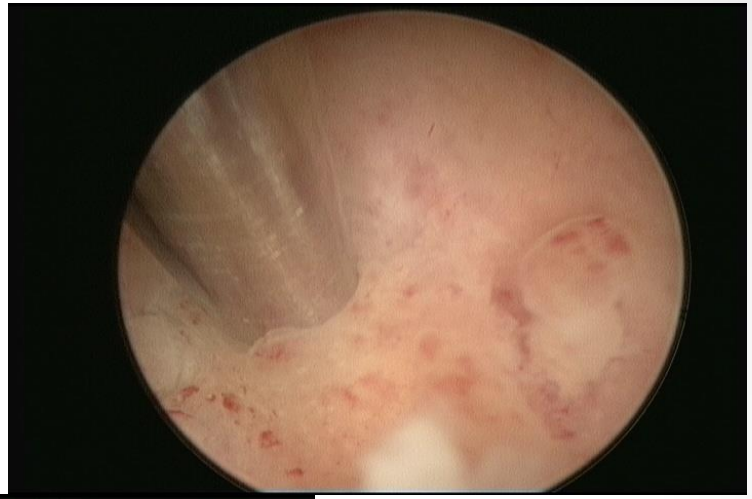


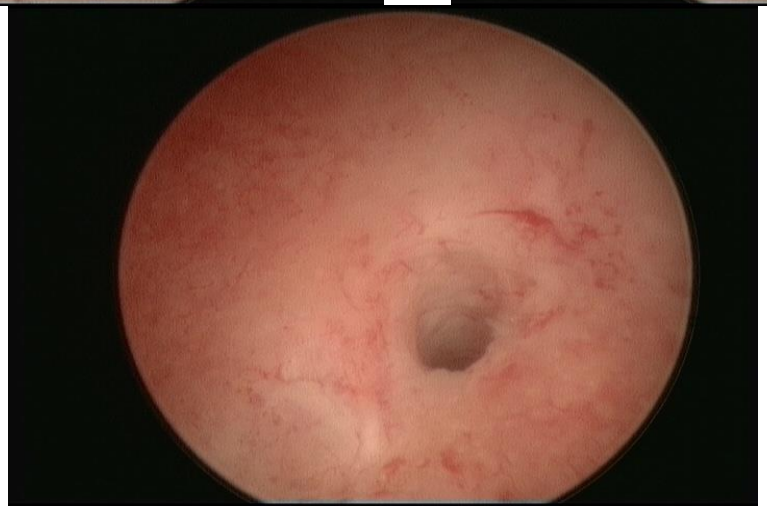
The Throphy hysteroscope can be

removed leaving the outer sheet in place.

application of Utero-Spirotome° for myometrial biopsy can be done or serves as a guide to intramural lesions







Trophy Scope – Spirotome - Ultrasound

CLINIC / REPRODUCTION

Adenomyosis: Clinic

± 30% asymptomatic

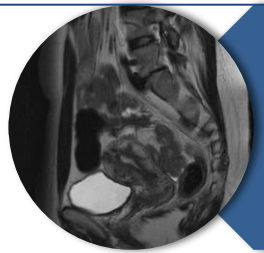
ABNORMAL UTERINE BLEEDING

PAIN

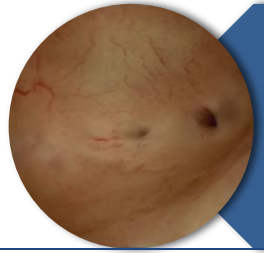
CPP, dysmenorhea, dyspareunia)

REPRODUCTIV E FAILURE

Adenomyosis and reproduction



DYSREGULATION MYOMETRIAL ARCHITECTURE



ALTERED ENDOMETRIAL FUNCTION

Campo S et al. Obst Gynecol International 2012

Dysregulation myometrial architecture

Different protein expression in adenomyotic tissue compared to normal myometrium

different smooth muscle cells

abnormal calcium cycling

loss normal contractions

Adenomyosis: loss of nerve fibers at the endometrial-myometrial interface

Ectopic endometrial glands: triggering inflammatory reaction (cytokines, prostaglandines)

H. Liu, J. Lang, X. Wang, and S. Wu, Fertil Steril, 89, 6, pp. 1625–1631, 2008.

M. K. Mehasseb, S. C. Bell, J. H. Pringle, and M. A. Habiba, Fertil Steril, 93, 7, pp. 2130–2136, 2010.

M. Quinn, J Obstet Gynaecol, vol. 27, no. 3, pp. 287–291, 2007

Altered endometrial function

1. Abnormal high level of free radical concentrations
2. Aberrant endometrial development in proliferative phase
3. Abnormal intra-myometrial metabolism
4. Lack expression implantation markers
5. Altered function of HOX A10 gen

Essentiel embryonic development and normal endometrial growth
Significantly lower in mid-secetory phase in women with adenomyosis

H. S. Taylor *Hum Reprod Up*,2000 vol. 6
C. P. Fischer et al.*Fertil Steril 2011*, vol. 95

Adenomyosis does not affect implantation, but is associated with miscarriage in patients undergoing oocyte donation

To evaluate the effect of adenomyosis on endometrial gene expression and its correlation with oocyte donation outcome.

After identifying the 25 window of implantation genes strongly related with endometrial receptiveness and the implantation process

Martinez-Conejero et al Fertil Steril. 2011 Oct

RESULT(S):

- Similar endometrial gene expression pattern in both the adenomyosis group and controls
- 34 dysregulated genes in adenomyosis patients were identified but none belonged to the group of window of implantation genes.

Junctional zone - Adenomyosis

Given the fact that the presence of adenomyosis involves

alterations of the myometrium,

alterations of the JZ

it seems reasonable to hypothesise the existence of a relationship with subfertility/reproduction

IVF/ET outcomes in relation to myometrial thickness

Hyun Sik Youm et al

J Assit Reprod Genet. 2011 Sept 24

Three groups according to maximum myometrial thickness:

- group A (<2.00 cm): 302 patients, 397 cycles
- group B (2.00–2.49 cm): 63 patients, 81 cycles
- group C (≥2.50 cm): 48 patients, 73 cycles

Hyun Sik Youm et al J Assit Reprod Genet. 2011

Table 2 Response to ovarian stimulation and clinical outcomes

	Group A (397 cycles)	Group B (81 cycles)	Group C (73 cycles)	*P*-value
E_2 level, hCG day (pg/mL)[a]	1930.2±1319.1	1725.3±1314.0	2017.0±1306.7	NS
Endometrial thickness, hCG day (cm)[a]	1.1±0.2	1.1±0.2	0.9±0.2[b]	0.001
No. of oocytes retrieved[a]	11.4±7.2	11.8±8.2	10.2±5.0	NS
No. of fertilized oocytes[a]	8.2±5.6	8.3±6.4	7.5±3.9	NS
Fertilization rate per retrieved oocyte (%)[a]	82.2±18.7	81.7±17.0	82.1±19.6	NS
No. of embryos transferred[a]	3.1±0.8	3.2±0.8	3.1±0.8	NS
Implantation rate (%)	264/1158 (22.8)	55/251 (21.9)	28/228 (12.3)[b]	0.002
2000–2004 (290 cycles)	133/627 (21.2)	25/123 (20.3)	11/102 (10.8)[b]	0.04
2005–2009 (261 cycles)	131/531 (24.7)	30/128 (23.4)	17/126 (13.5)[b]	0.03
Clinical pregnancy/cycle (%)	224/397 (56.4)	43/81 (53.1)	23/73 (31.5)[b]	0.02
2000–2004 (290 cycles)	122/219 (55.7)	24/43 (55.8)	8/28 (28.6)[b]	0.02
2005–2009 (261 cycles)	102/178 (57.3)	19/38 (50.0)	15/45 (33.3)[b]	0.02
Abortion/clinical pregnancy (%)	29/224 (12.9)	9/43 (20.9)	12/23 (52.2)[b]	<0.001
2000–2004 (290 cycles)	16/122 (13.1)	5/24 (20.8)	5/10 (50.0)[b]	0.009
2005–2009 (261 cycles)	13/102 (12.7)	4/19 (21.1)	7/13 (53.8)[b]	0.001
Ectopic pregnancy/clinical pregnancy (%)	9/224 (4.0)	1/43 (2.3)	0/23 (0.0)	NS
2000–2004 (290 cycles)	5/122 (4.1)	1/24 (4.2)	0/10 (0.0)	NS
2005–2009 (261 cycles)	4/102 (3.9)	0/19 (0.0)	0/13 (0.0)	NS
Live birth/cycle (%)	186/397 (46.9)	33/81 (40.7)	11/73 (15.1)[b]	<0.001
–2004 (290 cycles)	101/219 (46.1)	18/43 (41.9)	5/28 (17.9)[b]	0.017
–2009 (261 cycles)	85/178 (47.8)	15/38 (39.5)	6/45 (13.3)[b]	<0.001

	Group B (81 cycles)		*P*-value	Group C (73 cycles)		*P*-value
	B-1 (52 cycles)	B-2 (29 cycles)		C-1 (21 cycles)	C-2 (52 cycles)	
Implantation rate (%)	44/162 (27.2)	11/89 (12.4)[a]	0.007	9/64 (14.0)	19/164 (11.6)	NS
Clinical pregnancy/cycle (%)	33/52 (63.5)	10/29 (34.5)[a]	0.012	9/21 (42.9)	14/52 (26.9)	NS
Abortion/clinical pregnancy (%)	4/33 (12.1)	5/10 (50.0)[a]	0.01	4/9 (44.4)	8/14 (57.1)	NS
Live birth/cycle (%)	28/52 (53.8)	5/29 (17.2)[a]	0.001	5/21 (23.8)	6/52 (11.5)	NS

B-1: Group B without myometrial striation, heterogeneous myometrium, myometrial cysts, or poor definition of the endometrial–myometrial junction

B-2: Group B with myometrial striation, heterogeneous myometrium, myometrial cysts, or poor definition of the endometrial–myometrial junction

C-1: Group C without myometrial striation, heterogeneous myometrium, myometrial cysts, or poor definition of the endometrial–myometrial junction

C-2: Group C with myometrial striation, heterogeneous myometrium, myometrial cysts, or poor definition of the endometrial–myometrial junction

Hyun Sik Youm et al

J Assit Reprod Genet. 2011 Sept 24

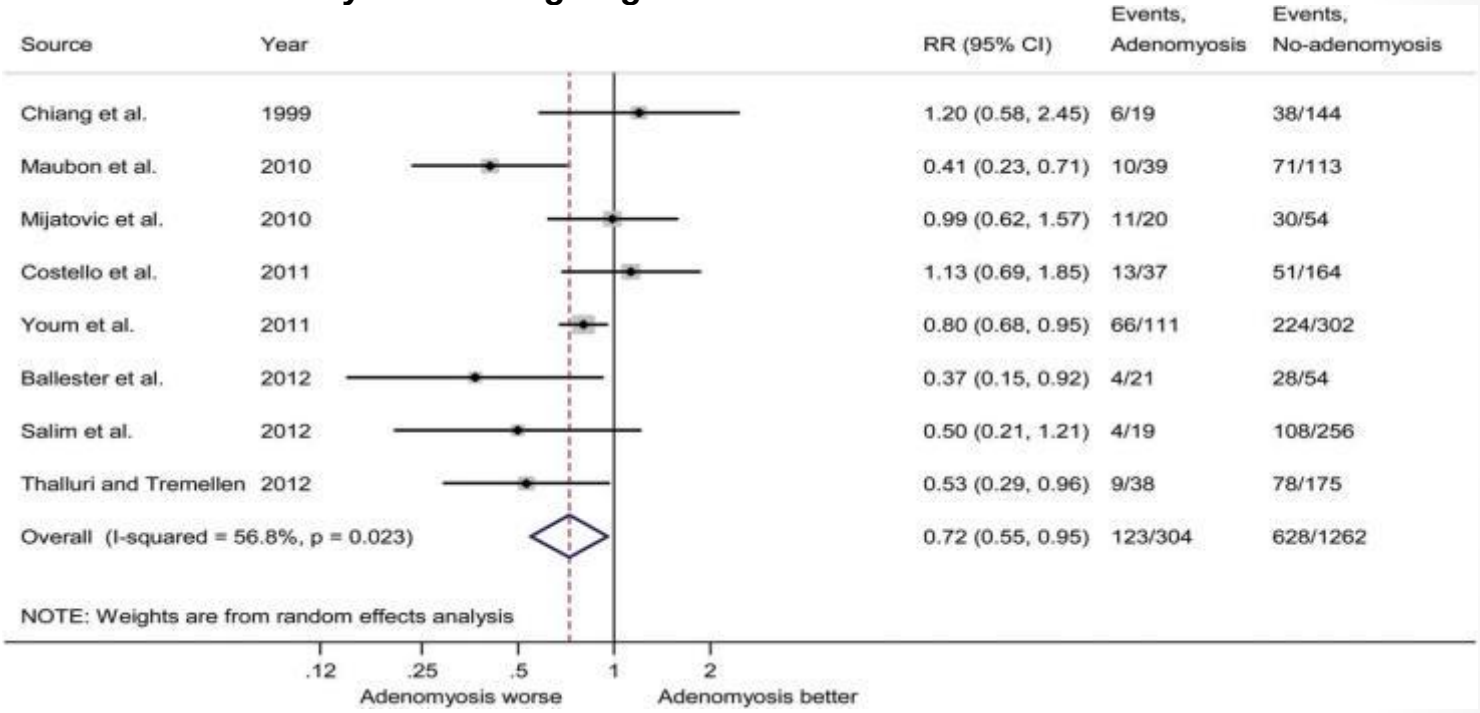
Conclusions

- Myometrial thickening of more than 2.50 cm exerts overall adverse effects on IVF-ET outcomes.
- Even with mild thickening (2.00–2.49 cm), the presence of sonographic findings suggestive of adenomyosis is associated with adverse outcomes of IVF-ET.

Hyun Sik Youm et al

J Assit Reprod Genet. 2011 Sept 24

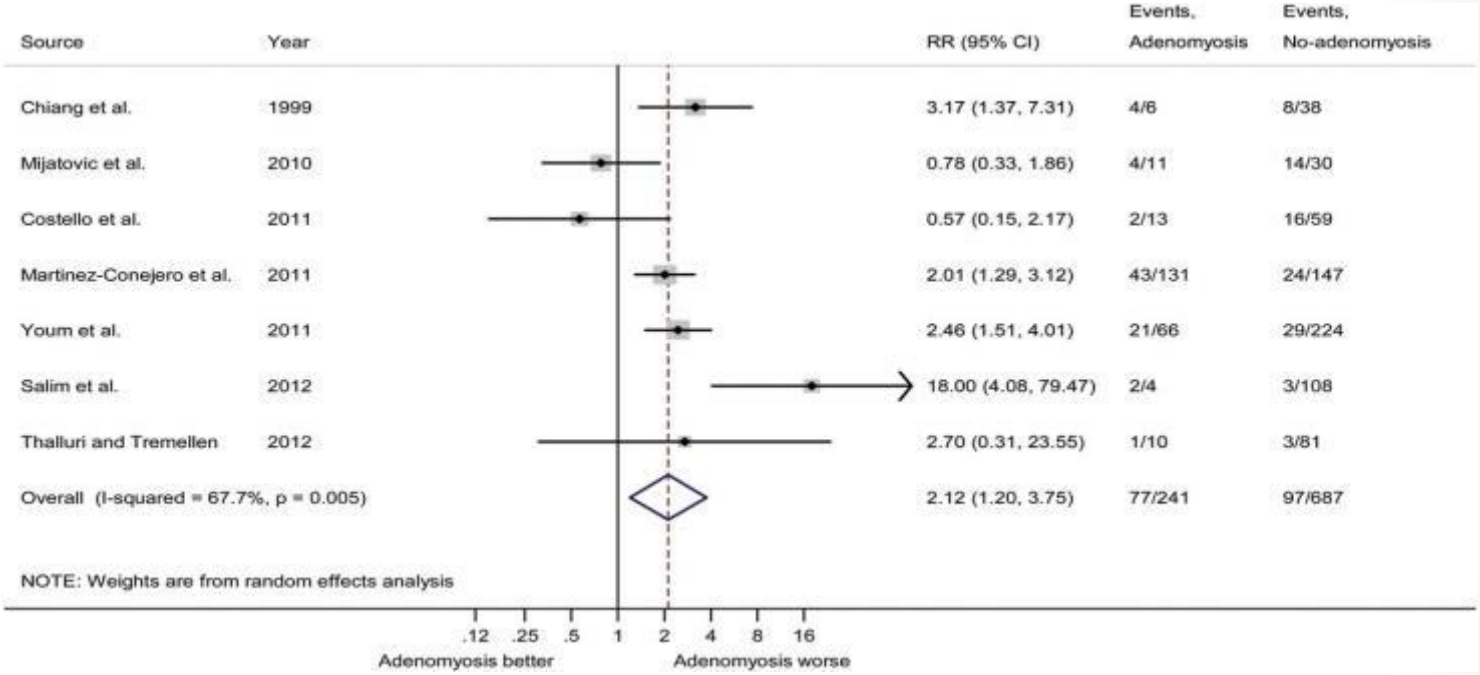
Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of clinical pregnancy in infertile women with or without adenomyosis undergoing IVF/ICSI.



Vercellini P et al. Hum. Reprod. 2014;29:964-977

human reproduction

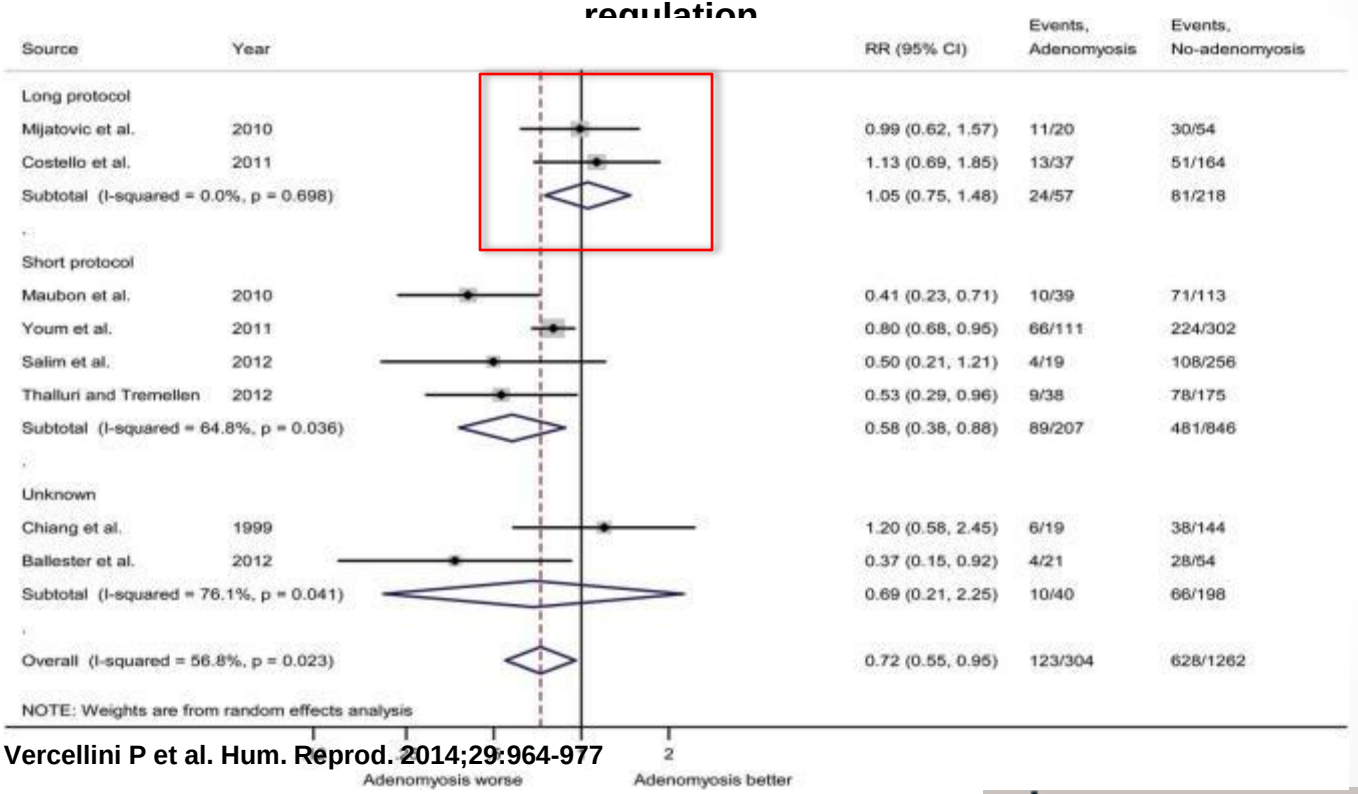
Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the risk of miscarriage in clinical pregnancies obtained at IVF/ICSI in women with or without adenomyosis.



Vercellini P et al. Hum. Reprod. 2014;29:964-977

human reproduction

Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of clinical pregnancy in infertile women with or without adenomyosis undergoing IVF/ICSI after a short or long protocol down-regulation



Vercellini P et al. Hum. Reprod. 2014;29:964-977

human reproduction

Longterm pituitary downregulation before frozen embryo transfer could improve pregnancy outcomes in women with adenomyosis
Niu Z et al. Gynecol Endocrin, 2013

339 patients with adenomyosis

	194 GnRha = HRT	145 HRT
Clin. Pregn%	51.35%	24.8%
Implantation %	32.56%	16.07%
Ongoing pr%	48.91%	21.38%

Junctional zone - Implantation

- Excessive inner myometrium contractions have been shown to reduce implantation rates in both spontaneous and stimulated cycles.

- There is an inverse correlation between the frequency of uterine peristalsis on the day of embryo transfer and pregnancy outcome. High-frequency endometrial waves on the day of embryo transfer appear to affect the IVF-ET outcome in a negative manner, possibly by expelling embryos from the uterine cavity.

Adenomyosis cause of failed implantation

Adenomyosis

- primarily a disease of the uterus (archimetra)
- constitute a single entity with variable phenotypes
- results from iatrogenic or auto-traumatization of the archimetra with dislocation of basal endometrium

Kunz et al.

Adenomyosis cause of failed implantation

Adenomyosis: identical pathologic effect??

Iatrogenic

↳ dislocation of basal endometrium

↳ uterine pathology

auto-traumatization

uterine pathology →

↳ dislocation of basal endometrium

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HYPOTHESIS ON THE EFFECT OF ADENOMYOSIS ON IMPLANTATION

Conclusion

- Adenomyosis has a detrimental effect on IVF outcome with a reduction of pregnancies and live birth rates and an increased rate of miscarriages
- It appears that diffuse adenomyosis fares worse than focal or localized adenomyosis
- Long term GnRha pretreatment might have a beneficial therapeutic effect on adenomyosis and improve IVF outcome

Hisao Osada Uterine adenomyosis and adenomyoma: the surgical approach
Fertil Steril 2018; 109: 3: 406-417

Conclusion:

Focal adenomyosis lesion treat laparoscopically.

Diffuse adenomyosis preferably be treated by laparotomy or preferably by laparoscopically-assisted laparotomy.

Open surgery is safer than laparoscopy in that it can thoroughly excise the lesions to prevent the recurrence and to properly reconstruct the defect created by the surgery in order to prevent uterine rupture in subsequent pregnancy

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CONCLUSIONS

- It is still too early to know how important the abnormal endo-myometrium is compared to the myriad of other possible factors, but it seems more and more evident that the presence of an abnormal *endometrium and junctional zone* plays an important role in many pathological conditions observed in the human reproductive tract.

- Research in this area must be encouraged, so that soon clinical applications may become possible.

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Place diagnostic explorative hysteroscopy ?

With increasing evidence of the importance of uterine integrity on reproduction,

- uterine exploration should not be restricted to the uterine cavity but should also include an exploration of the endometrium, inner and outer myometrium.

- A fusion of hysteroscopy and ultrasound with the possibility of sub-endometrial tissue prelevation can contribute to a better understanding of the pathology and the impact on reproduction.

Life Expert Centre
METHODOLOGY

Reproductive uterine diagnosis and treatment "Life Expert Centre Method"

THANK YOU

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STEPHAN GORDTS