



Uterine fibroids: should we operate?

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*ESHRE Campus
Dubrovnik, 24-25 September 2010*



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LEARNING OBJECTIVES

- Distinguish between the different kinds of myoma
- To judge the benefit or necessity of performing a myomectomy
- To debate the necessity of a more accurate classification



EPIDEMIOLOGY

- 20-40% of women in reproductive age are affected by leiomyomas
- Myomas directly or indirectly associated with 5-10% of cases of infertility

Size

Location

Number

Type



20 – 50% with symptoms

Menorrhagia

Dysmenorrhoea

Infertility

American Fertility Society. Guidelines for practice: myomas and reproductive dysfunction. 1992



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Uterine Leiomyoma

Clinical Manifestations

- Bleeding
- Pain and pressure
- Urinary symptoms
- Pregnancy
 - Infertility
 - Recurrent spontaneous abortion
 - Obstetrical complications
- Asymptomatic



• Infertility and myoma controversial because

- difficult to prove causal relation
- reviews of previous (70-80) studies indicates a pregnancy rate of 50 % after myomectomy in infertile patients
- no well controlled randomized studies
- no clear description of size, numbers and location
- no standardization of diagnostic methods
- different outcome parameters
- results varying between 10- 70 % (Donnez et al.)



Infertility and myoma

More common in IVF patients

because of the delay of childbearing when fibroids
are more common

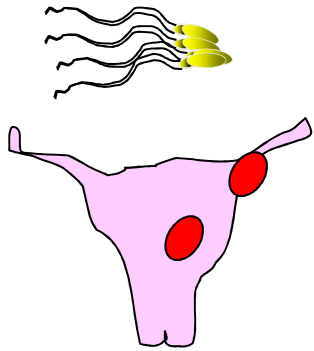
but also age decreases fertility



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Impact of Uterine Myomas on Fertility



Greater distance for sperm travel

Encroachment on tubal ostium. occlusion

Distortion of uterine cavity

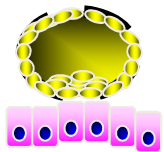
Vascular changes

Interfere normal rhythmic uterine contractions

Impaired implantation

Abnormal endometrial maturation

Alteration on oxytocinase activity



Hunt J. 1974 Clin.Obstet.Gynecol.

Iosif C. 1983 Acta Obstet.Gynecol.Scand

Vercellini, P. 1992 Fertil Steril

Verkauf B fertil Steril 1992

Wallach, E.E. 1995 Obstet.Gynecol.Clin.N.Am.

Mechanism of impaired fertility in case of intramural-submucosal myoma

Richards et al.(Hum Reprod Upd;1998,4)

- the numbers of caveolae in host myometrium and fibromyomata are conceivably decreased compared to normal myometra.
- This specific structural abnormality may affect calcium metabolism by causing a decrease in defect calcium extrusion and thus raising the intracellular calcium .
- Increased intracellular calcium produces myometrial irritability and hyperactivity.
- Resulting in disruption of the rhythmical contraction process of the JZ.



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Mechanism of impaired fertility in case of intramural-submucosal myoma

Szamatowicz et al 1997:

Reduced contractile pressure in the presence of fibromyomata which increases following myomectomy.



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Mechanism of impaired fertility in case of intramural-submucosal myoma

Subendometrial tumours

- causing endometrial erosion with subsequent inflammation altering the nature of the intrauterine fluid, resulting in an hostile environment.
- disrupt the endometrial blood supply, affecting nidation and sustenance of early embryo

Fahri et al 1995



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Uterine Leiomyoma

Classification

Based on the concept that fibroids are primarily interstitial and gradually forced outwards or inwards:

- Submucosal
- Intramural
- Subserosal



Proposal of Classification

■ Submucosal (JZ) fibroid

- type 0, I, II (ESH-criteria, 1994)
- type III : abutting the endometrium

■ “Outer myometrium” fibroid

- type IV: intramural
- type V, VI: subserosal, pedunculated

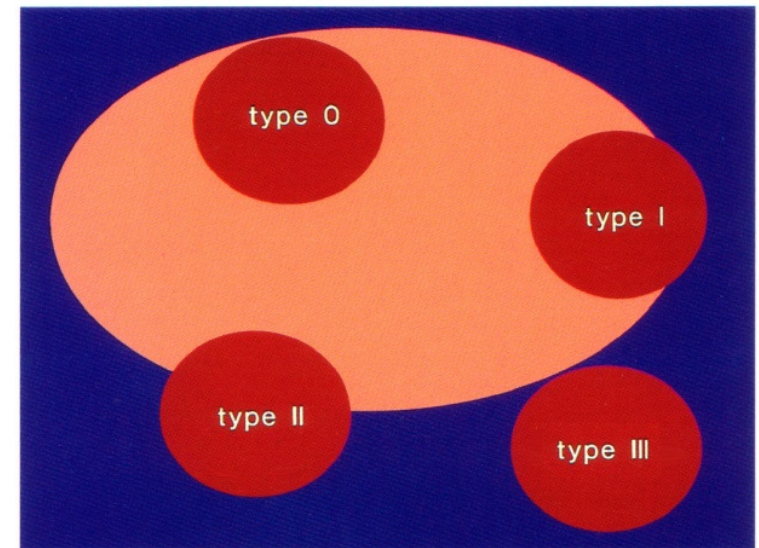
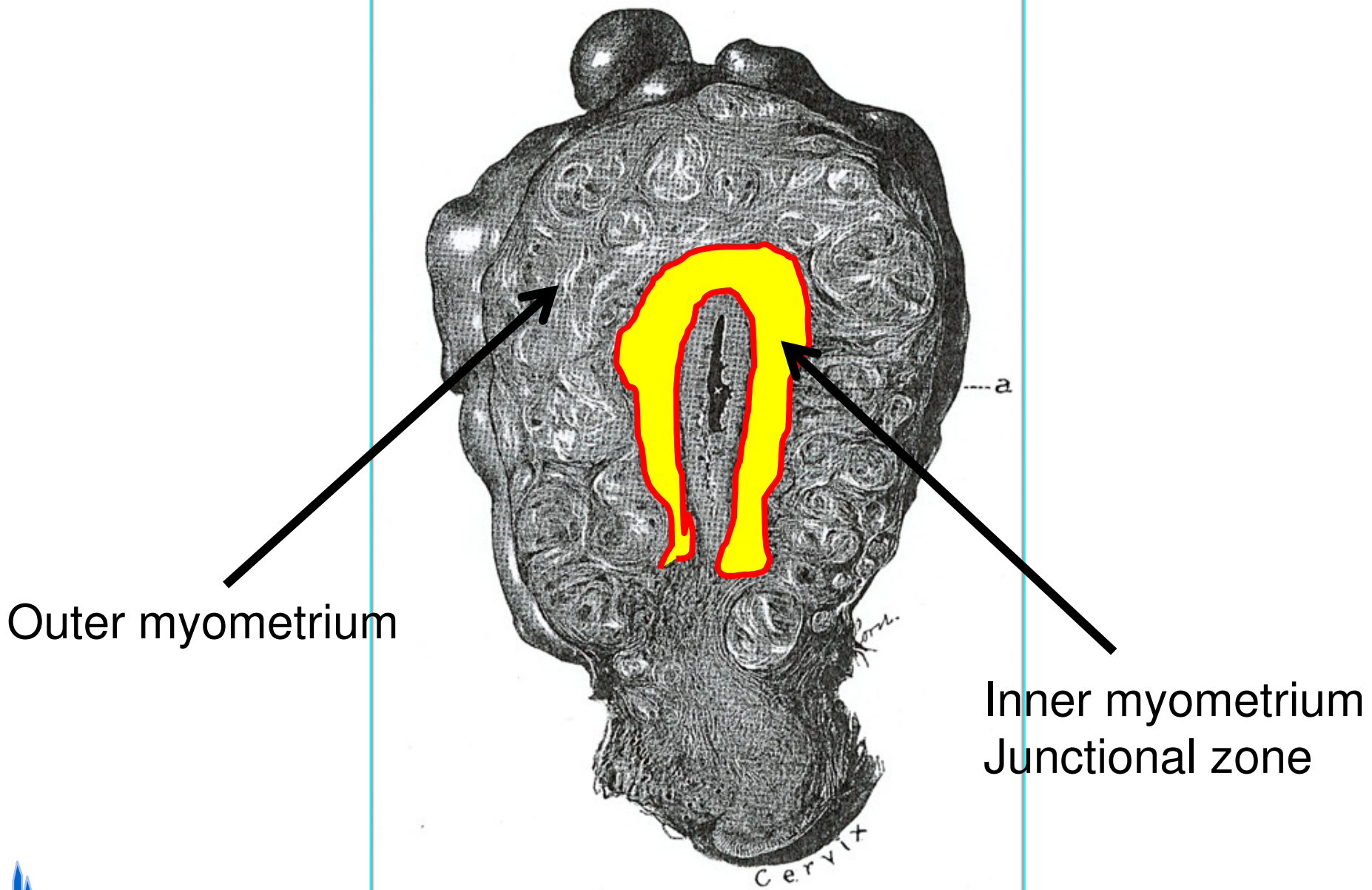


Figure 16.21: The ESH classification of the submucous myomas.



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Junctional Zone Myometrium

Functional important entity in reproduction

- Ontogenetically related to endometrium
- Cyclic changes in SSH receptors
- Role in gamete transport and implantation



Junctional Zone Myometrium

Important role in Reproduction

Functional important entity in reproduction

- Early changes from time of implantation
- Decidualisation and trophoblast invasion
- Defective transformation of JZ spiral arteries in spectrum of pregnancy complications



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THE OUTER MYOMETRIUM

Less important role in reproduction



Muscle contractions
during delivery



Impact of myoma on fertility: Review

Donnez et al ,2004

	Distorting cavity		No distortion		Control	
	PR %	N	PR %	N	PR %	N
Elder Geva 1998	10	1/10	16.4	9/55	30	38/318
Stoval 1998	37	34/91	53	48/91		
Farhi 1997	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	46/141	41.6	169/406	40.4	661/1636



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Fibroids affecting IVF results : review

Pritts EA 2001 Obstet Gynecol Surv 56: 483-491

Review of 11 studies: 3 prospective controlled

8 retrospective controlled

No randomization

Women with otherwise unexplained infertility

Location of fibroids related to pregnancy, implantation
and deliveries



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Submucosal myoma and Infertility in IVF (Pritts EA 2001)

	<u>n Studies</u>	<u>Cycles</u>	<u>RR*</u>	<u>95% C.I.</u>
Pregnancy	2	510	0.321	0.130 - 0.697
Implantation	1	541	0.277	0.096 - 0.720
 <u>AFTER RESECTION</u>				
	<u>n Studies</u>	<u>Cycles</u>	<u>RR*</u>	<u>95% C.I.</u>
Pregnancy	2	157	1.719	1.134 - 2.582
Implantation	1	55	0.980	0.453 - 2.409

* Referent is infertile control without LM



Myoma and Infertility: Review

(Pritts EA 2009 Fertil Steril 91, 4:1215-1223)

Conclusions

Subserosal fibroids do not affect fertility or spontaneous abortion rates

Submucosal fibroids lowers fertility rates and myomectomy enhances rates of conception and live births

Intramural myoma with or without distortion of the uterine cavity may cause a detrimental effect on conception and reaching viability with pregnancy. Effect of myomectomy is unclear.



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Submucosal myoma

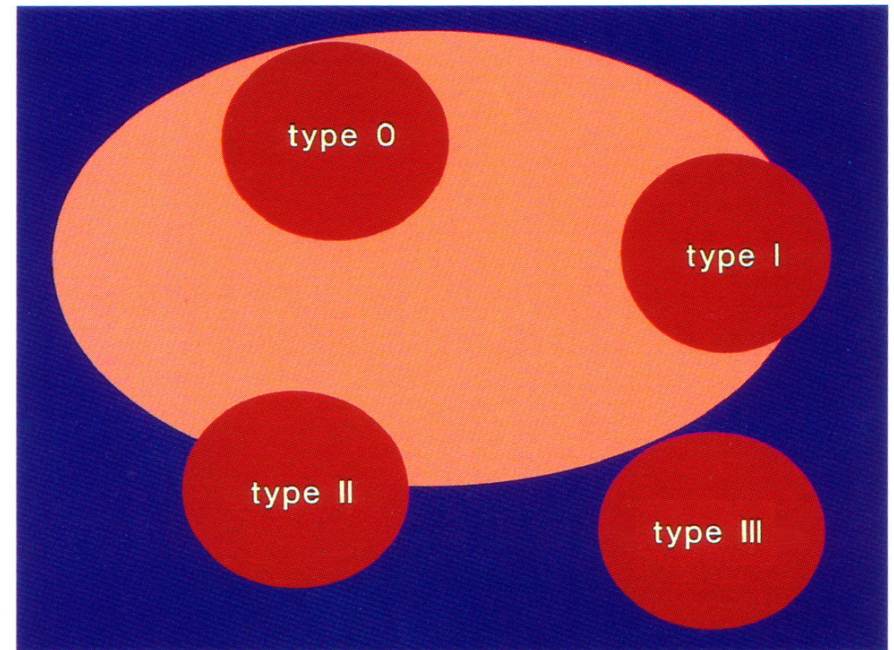
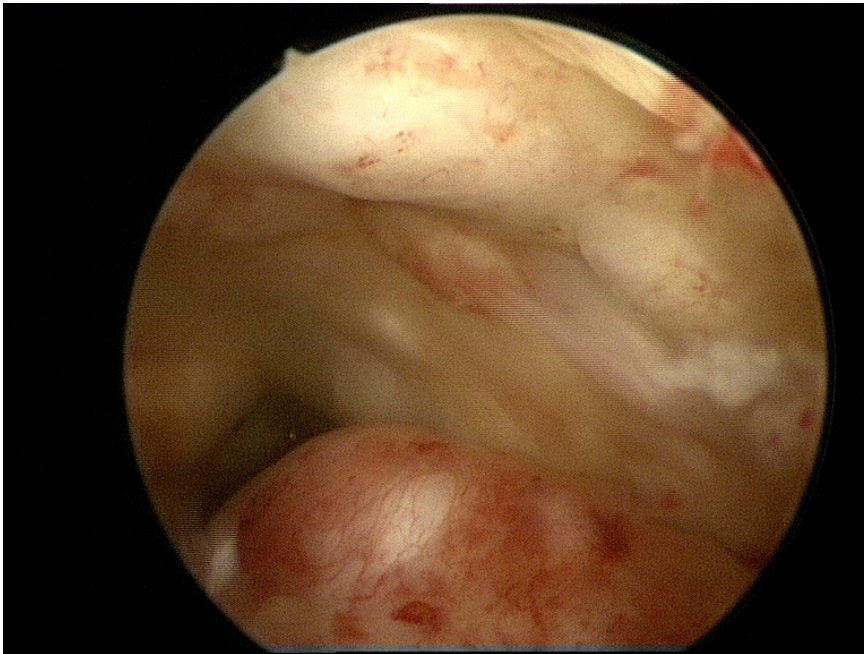


Figure 16.21: The ESH classification of the submucous myomas.



Submucosal myoma

Fibroids and reproductive outcome (Klatsky et al Am J Obst Gynecol 2008)

	Implantation rate	Clinical pregn. rate	Spontaneous abortion rate
Submucous	3%	14 %	46.7 %
Control	11.5 %	30.4 %	21.9 %

Summary of the data of the IVF model shows that patients with fibroid distorting the endometrial cavity have impaired implantation and pregnancy rates

(Somigliana E. et al Hum reprod Update2007,13)

Rackow, B, Taylor H (Fertil Steril,2008) found that submucous leiomyoma have a global decrease in endometrial Hox gene expression , a molecular marker of endometrial receptivity.



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Effect of intramural myoma

A plausible mechanism for intramural fibroids not distorting the cavity has been seen in a possible disruption of the junctional zone within the myometrial layer at the initial stages of embryo invasion and placentation.

(Horne AW, Critchley HO, Semin reprod Med, 2007,25: 483)

Intramural fibroids negatively affects IVF results

Hart R et al 2001 Hum reprod 11: 2411-2417

Khalaf Y et al 2006 Hum Reprod 10: 2640-2644

Intramural fibroids do not affect IVF results

Ng EH, Ha PC, 2002, Hum Reprod 3: 765-770

Oliveira Fg et al. 2004 Fertil Steril 81: 582-587

Klatsky Pc et al. 2007, Hum Reprod 2: 521-526



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Effect of large intramural fibroids (>5 cm) Hart R et al Hum Reprod 2001 16(11): 2411

Results of IVF where all significantly reduced:

Implantation rate	dropped from	20.2 to 11.9 % (p=0.018)
Pregnancy rate	dropped from	34.1 % to 23.3 % (p=0.016)
Ongoing pregnancy rate	dropped from	28.3 to 15.1 % (p=0.003)

Large intramural myoma negatively affects pregnancy outcome after IVF

Large intramural myomas should be removed before IVF



Large intramural myoma >5cm

If myomectomy is beneficial in patients before IVF it do not necessarily mean that myomectomy should be performed systematically in women trying to conceive not needing an IVF treatment because risks of adhesion formation after myomectomy.



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Intramural fibroids smaller than 5 cm

Should they be disregarded?

Should we operate before IVF?

Should we operate after IVF failure?

and so yes after how many failures?

Should we operate before any infertility treatment?

Should the decision be influenced according to the cost of IVF in different countries?



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Intramural fibroids smaller than 5 cm

Check et al. (Hum reprod, 2002) no difference in implantation rates and pregnancy rates, but they find a lower delivery rate and higher rate of miscarriage; conclusion: study needed

Oliveira et al. (Fertil Steril 2004) no effect on pregnancy rates and no higher incidence of miscarriages, but only one cycle



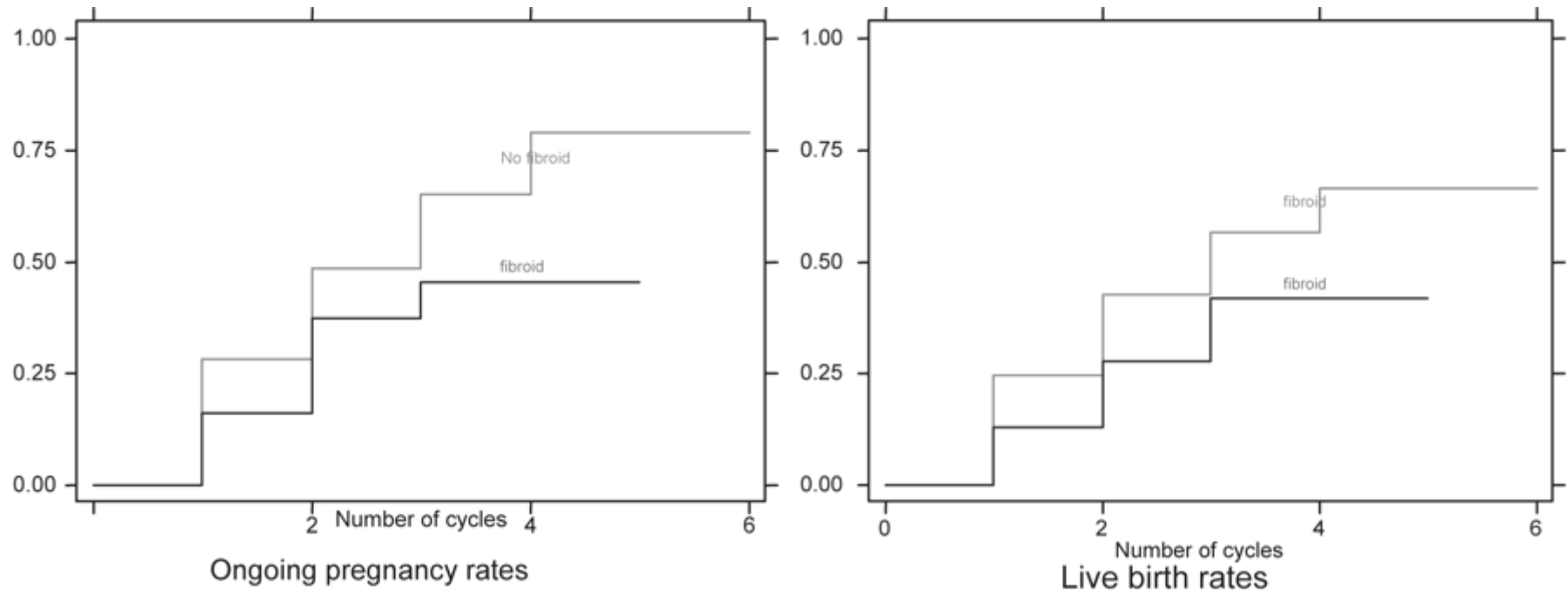
Influence of small intramural fibroids: cumulative outcome
(Khalaf et al Hum Reprod 2002)

	Pregnancy rate	Ongoing PR	Live birth rate
Intramural < 5 cm	23.6 %	18.8 %	14.8 %
Control	32.9 %	28.5 %	24 %

(p < 0.05)



Intramural fibroids and cumulative outcome assisted conception



40 % reduction of success rate in each cycle



Results(I)

	Group 1 (N=75 patients with myomas)	Group 2 (N=127 patients without myomas)
N.of embryos/ET (M ± SD)	2.02 ± 0.4	2.14 ± 0.6
N.of clinical pregnancies (%)	45 (34.9%)	53 (41.1%)
Implantation rate %	48/267 (18%) *	63/238 (26.5%) *
N.of abortions (%)	18 (40%)*	10 (18.9%)*

***X²=4.34 p<0.05**

Gianaroli et al.



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Results(II)

	<3 Myomas	≥3 Myomas	Control
Tot. N.of transfers	94	35	129
Age (M ± SD)	37.26 ± 5.4	38.53 ± 5.34	37.5 ± 4.6
N.of myomas (M ± SD)	2.16 ± 0.7	3.57 ± 2.3	/
N.of embryos/ET (M ± SD)	1.3 ± 0.9	1.7 ± 0.9	1.3 ± 0.6
N.of clinical pregnancies (%)	35 (37.2%)	10 (28.6%)	53 (41.1%)
N.of abortions %	12 (34.3%)	6 (60%)*	10 (18.9%)*

Gianaroli et al.



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Intramural Leiomyoma

Pregnancy Rate after IVF

	Subjects	PR	Controls	PR
Hart	106	23%*	322	34%
Stovall (cycles)	91	37%*	91	53%
Eldar-Garcia	46	16%*	249	30%
Khalaf Y	122	24%*	322	33%



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Intramural Leiomyoma

Pregnancy Rate after IVF

	Subjects	PR	Controls	PR
Surrey	73	51%	316	60%
Check	61	34%	61	48%
Ramzy	39	38%	367	34%
Oliviera	130	48%	245	45%
Klatsky	94	47%	275	54%



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Intramural Leiomyoma

Miscarriage Rate After IVF

	Subjects	MR	Controls	MR
Eldar-Garcia	46	33%	249	30%
Check	61	34%	61	20%
Ramzy	39	20%	367	15%
Oliveira	130	27%	245	29%
Gianaroli	129	40%*	129	19%*

Is intramural fibroid a misnomer?

The intramural fibroid should be classified as either outer myometrium or JZ fibroid.



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Uterine Myoma and Pregnancy

Washington State Birth Records

- Retrospective population-based study 1987-1983
- 2,065 singletons
- Comparison group selected randomly; matched by birth year
- No match by age, parity, or race/ethnicity

Coronado et al. 2000



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Uterine Myoma and Pregnancy

Washington State Birth Records

- Abruptio placentae	OR: 3.87	95% CI: 1.63, 9.17
- First trim. Bleeding	OR: 1.82	95% CI: 1.05, 3.20
- Dysfunctional labor	OR: 1.85	95% CI: 1.26, 2.27
- Breech presentation	OR: 3.98	95% CI: 3.07, 5.16
- Caesarean delivery	OR: 6.39	95% CI: 5.46, 7.50



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Coronado et al. 2000

Uterine Myoma and Pregnancy

Israeli Populations-based Study

- - Virtually all singleton deliveries of southern Israel occur at Soroka University Medical Center
- - Period 1988-1999 (n=105909) (0.65% myomas, n= 690)
- LM independently associated with:
 - Caesarean delivery OR: 6.7 95%CI:5.5,8.1
 - Placental abruptio OR: 2.6 95%CI:1.6,4.2
 - <36 weeks gestation OR: 1.34 95%CI:0.7,2.8



Leiomyomas and infertility

- It is rarely probably that they cause infertility but ...
It has been described:
 - A longer seeking of pregnancy (Hasan et al. 1990)
 - A reduction of the success of ART (Stovall et al. 1998; Khalaf et al. 2006)
 - Relation with spontaneous abortion (Muhieddine et al. 1992) (Matsunaga et al. 1980)
 - A same probability of pregnancy after myomectomy compared to patients with no uterine pathology (Buttram & Reiter 1981)

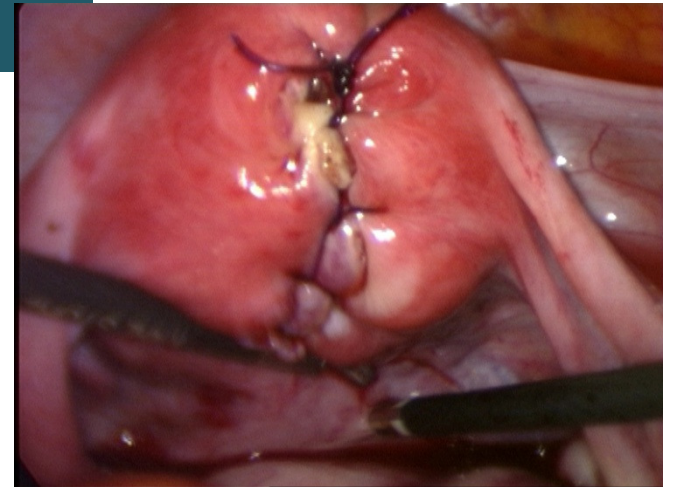


Risks of Myomectomy

Morbidity: infection, blood transfusion

Complications : laparotomy and /or laparoscopy

Postoperative adhesion formation



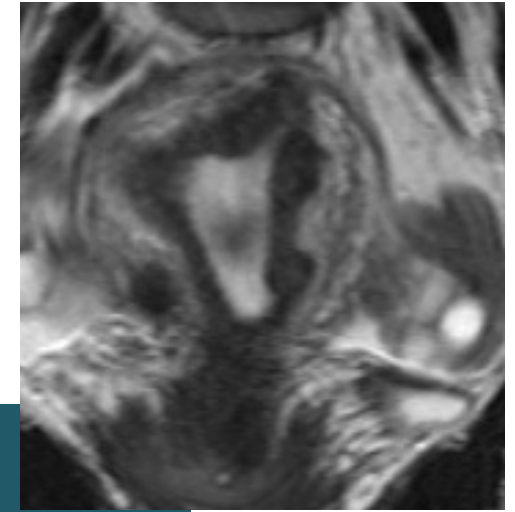
MYOMECTOMY AND INFERTILITY

AUTHOR	(n)	ADHESIONS	ADNEXAL ADHESIONS
Laparoscopy			
Hasson (92)	24	67 %	NR
Mais (95)	50	64 %	36%
Bulletti (96)	14	28.6 %	NR
Dubuisson (98)	45	35.6 %	24.4 %
Total	133	51.1 %	30.5 %
Laparotomy			
Starks (88)	20	100 %	NR
Tulandi (93)	26	100 %	76.9 %
Mamsg (95)	27	92.6 %	NR
Bulletti (96)	14	71.4 %	NR
Ugur (96)	48	83.3 %	64.6 %
Total	135	89.6 %	68.9 %

NR: no report

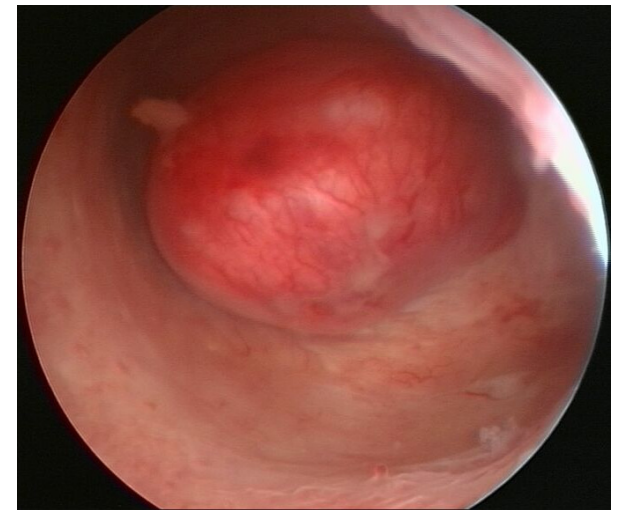
Dubuisson et al, Hum Reprod Update, 2000.

Conclusions I



Despite the lack of randomized studies the sharp decline in pregnancy rates in case of *submucous myoma* is quite convincing and myomectomy should be performed before ART

Decreased	clinical pregnancy rate
	implantation rate
	live birth rates
Increased	abortion rates



Conclusions II

Intramural myoma:

more controversial ; lack of homogeneous opinion

decreased fertility

increased pregnancy loss

effect of myomectomy ?

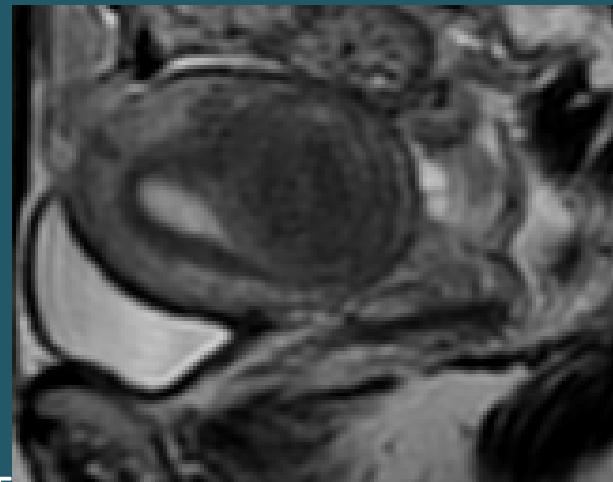
Consensus:

intramural myoma > 5cm

advice to operate before ART
(*mostly distorting cavity?*)

intramural < 5 cm?

reported outcome varies between no differences and
significant decreased cumulative pregnancy rates?



Conclusions III

Controversies in final conclusion are probably due to :

- differences in investigation between the different studies
- lack of properly performed investigation: need for standardization
- evaluation related to distance to and/or involvement of junctional zone?
- need for randomized studies



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Conclusions IV

Obstetric outcome:

retrospective population based cohorts

increased risk of

- abruptio placentae**
- Caesarian section**
- pre-term delivery**
- breech presentation**



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