ESHRE Campus symposium: How can surgery increase the success rate in ART

The role of intramural myomas on ART outcome

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MONFALCONE
ITALY

EPIDEMIOLOGY

- Most common benign tumors in the female pelvis
- Incidence:
  - 8,9 % among white women
  - 30,6 % among black women

(Marshall et al. 1997)

Uterine leiomyomas

- ✓ Most common benign tumors of the uterus
- ✓ Occur in 25 - 50% in women over the age of 30
- ✓ Frequency increases with age and more common in some ethnic groups especially in Afro Caribbean
- ✓ Affect 25% of women in reproductive age

(Elahi SM & Odejinmi F J ObstGyn 2008)

- ✓ Pathogenesis is unknown
- ✓ Related to Estrogens – occur only after puberty and degenerate after menopause
- ✓ 50% remain asymptomatic

(West PC Repr Med Review 2009)

EPIDEMIOLOGY

- Data on real incidence and prevalence is difficult to assess due to a high proportion of asymptomatic women
  (Schwartz 2001).

SYMPTOMATOLOGY

- Only 25 percent of women with fibroids present with clinical symptoms
  - prolonged or excessive menstrual bleeding
  - pelvic pressure or pain
  - dyspareunia
    (Schwartz 2001, Flake et al. 2003, Ferrero et al. 2006)

SYMPTOMATOLOGY

- Complications in pregnancy and delivery

Complication	RR
abruptio placentae	3,87
placenta praevia	1,76
olygohydramnios	1,80
polyhydramnios	2,44
dysfunctional labor	1,90
breech presentation	3,98
caesarean delivery	6,39

(Coronado et al.2000)

RISK AND PROTECTIVE FACTORS

- Age
- Ethnicity
- Familiarity
- Social economic factors
- Obesity
- Menstrual pattern – obstetric history
- Atherogenic factors
- Diet
- Uterine irritation
- Enviromental estrogens

RISK AND PROTECTIVE FACTORS
AGE

- 50 percent of fibroids develop in the fifth decade of life
  - growth and the subsequent appearance of clinical signs of fibroids already existing
  - women in late fourth and fifth decade are more willing to get regular gynaecological examination

(Flake et al. 2003)

RISK AND PROTECTIVE FACTORS
ETHNICITY

Hysterectomies for noncancerous conditions in Maryland

	Black women N= 409	White women N= 836	P
Presence of fibroids	89%	59%	
Age of diagnosis	37,5	41,6	<0,001
Age of hysterectomy	41,7	44,6	<0,001
Uterine burden	420,8 g	319,1 g	<0,001
≥ 7 fibroids	57%	36 %	<0,001
Anemia (<35 %)	56 %	38 %	<0,001
Pelvic pain	59 %	41 %	<0,001

(Kjerulff et al. 1996)

RISK AND PROTECTIVE FACTORS
ETHNICITY

- Different pathogenesis in the two ethnic groups
  - higher amount of ER in uterine tissue and
  - higher incidence of known risk factors for fibroids in black ethnic group.

    (Sadan et al. 1988 Marshall et al 1997)
  - in Caucasian women is supposed to be an alteration of the steroid metabolism

    (Sadan et al. 1988)

RISK AND PROTECTIVE FACTORS
ETHNICITY: ER alpha PP genotype

- Incidence of PP genotype:
  - black ethnicity 35%
  - white 13%
  - hispanic 16%
- RR= 6.42
- Larger tumor burden >400g
- Mechanism: enhanced proliferative response to estrogens

  (Al-Hendy et al 2006)

RISK AND PROTECTIVE FACTORS
FAMILIARITY

- Controversial findings
  - 2,3 to 4 fold higher risk if first degree relatives presents fibroids

    (Ligon and Morton 2001)
  - Finnish twin cohort study: slight genetic predispositon either in monozygotic or dizygotic twins (reproductive and anthropometric factors play more important role)

    (Luoto et al. 2000)

RISK AND PROTECTIVE FACTORS

SOCIAL AND ECONOMIC F.

	Cases n=318		Controls n= 394	
	No	%	No	%
Mean age (years)	42,3 (6,4)		39,9 (6,0)	
Marital status				
Married	193	60,7	276	70,1
Separated, divorced or widowed	75	23,6	77	19,5
Never married	50	15,7	41	10,4
Education				
College degree or more	146	45,9	232	58,9
More than high school, less than college	92	28,9	87	22,1
High school or less	80	25,2	75	19.0

Faerstein et al. 2001, Case control study among premenopausal women in the Baltimore area

RISK AND PROTECTIVE FACTORS

OBESITY

- RR increases with the increase of BMI
- Not linked to oestrogen levels
- There is an increase in bio availability due to a decrease of SHBP.

(Faerstein et al 2001 Baltimore case control study)

RISK AND PROTECTIVE FACTORS

MESNTRUAL PATTERN AND OBSTETRIC HYSTORY

- Early menarche presents increased risk for fibroids
- Parity plays a protective role
- Infertility seems to be a risk factor and not a consequence

(Parazzini et al 1996, Samadi et al. 1996 Baird 2004, Marshall 1998)

RISK AND PROTECTIVE FACTORS
ATHEROGENIC RISK FACTORS

- Pathogenesis of fibroids and of atheromatous plaque may be similar.
  - hypertension and diabetes are independent factors promoting growth of fibroids

    (Boynton-Jarret et al. 2003)
  - 1,7 to 2,1 fold adjusted risk for fibroids in patients with hypertension.

    (Faerstein et al.2001)

RISK AND PROTECTIVE FACTORS
ATHEROGENIC RISK FACTORS

- A slight not significant higher risk in patients with diabetes
- Hyperinsulinemia: insulin can promote mitosis, promote vascular smooth cell proliferation and the growth of fibroids. Insulin could also have a gonadotropic function

  (Faerstein 2001)

RISK AND PROTECTIVE FACTORS
ATHEROGENIC RISK FACTORS: SMOKING

- Seems to have a protective role and is dose dependent
- The protective effect of smoking must be attributed to an antiestrogenic effect.
  - components present in burned tobacco may inhibit aromatase, decreasing oestrogen availability.

    (Farestein et al. 2001, Wise et al. 2004)

RISK AND PROTECTIVE FACTORS
DIET

Risk Factors	Protective factors
Beef and red meat	High fiber and low fat diets
Alcohol (beer)	
Phitoestrogens (soy)	
Caffeine ???	

(Flake et al. 2003), (Wise et al. 2004)

RISK AND PROTECTIVE FACTORS
UTERINE IRRITATION

- A group of 318 women studied with the aim to correlate fibroids and uterine irritation.

Risk factor	RR
history of PID	1,8
Chlamidial infection	3,2
IUD with infections or fever	5,3
talc in the genital area	2,0

(Faerstein 2001)

RISK AND PROTECTIVE FACTORS
ENVIRONMENTAL ESTROGENS

- DDT and other organochlorine pesticides have estrogenic activity.
- In women with fibroids DDT levels was significantly higher than in those without fibroids.
- DDT is stored in fat tissue, during lactation and fasting the DDT mobilize into the blood stream. Exposure levels are several folds higher than those in the environment

(Flake et al. 2004)

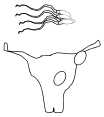
RISK AND PROTECTIVE FACTORS
ENVIRONMENTAL ESTROGENS

- Eearly exposures to xenoestrogens and other environmental factors in neonatal age could have deleterious effect on the reproductive system.
  - normal tissue responses can be reprogrammed in genetically predisposed individuals leading to fibroid development.

(Walker 2002, Cook et al. 2005)

- Obesity and infertility are clearly risk factors.
- Is black ethnicity a risk factor *per se* or is it biased by other known risk factors is still not determined.
- Multiple parity and smoking play a protective role.
- Other factors have less significant effect, data are controversial and not definitive.

Impact of Intramural Myomas on Fertility



Greater distance for sperm travel
Encroachment on tubal ostium. Occlusion
Distortion of uterine cavity
Vascular changes
Interfere normal rhythmic uterine contractions

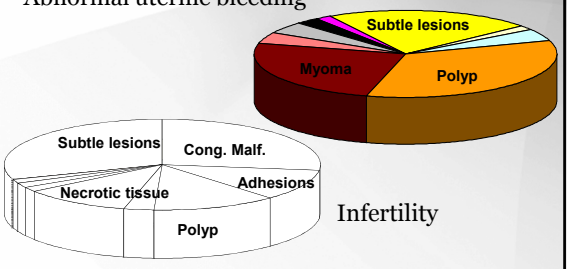
Impaired implantation
Abnormal endometrial maturation
Alteration on oxytocinase activity

1526 consecutive diagnostic hysteroscopies

HYSTORY	NEG	Previous miscarriage	Previous abortion	Pprovious delivery	Total
	(group A)	(group B)	(group C)	(group D)	
Number	952	354	97	123	1526
Normal cavity	592 (62%)	196 (55%)	57 (59%)	88 (72%)	933 (61%)
Sub-septum > 1 cm	108 (11%)	49 (14%)	6 (6%)	5 (4%)	168 (11%)
Endometrial polyp	129 (14%)	26 (7%)	6 (6%)	8 (6.5%)	169 (11%)
Adhesions	81 (8.5%)	60 (17%)	24 (25%)	20 (16%)	185 (12%)
Myomas	13 (1.5%)	2 (0.5%	2 (2%)	0	17 (1.5%)
Malformations	5 (0.5%)	2 (0.5%)	0	0	7 (0.5%9
Combination of more anomalies	24 (2.5%)	19 (5%)	2 (2%)	2 (1.5%)	47 (3%)

Abnormal findings

Abnormal uterine bleeding



Infertility

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Submucosal and intramural fibroids without distorting the endometrial cavity: Is treatment necessary?

- Sunkara SK in 2009 reviewed & meta-analysis of 19 observational studies, Overall of 6087 IVF cycles and compared LBs & PRs in women with intramural or subserous fibroids without endometrial cavity distortion to women with normal uterus and no fibroids
- Results demonstrated Significant Decrease in
  - Live births (RR 0.97, 95%, CI: 0.70 – 0.88, P<0.0001)
  - Clinical PR (RR 0.85, 95%, CI: 0.77 – 0.94, P<0.02)
- Conclusion: The presence of non–cavity distorting intramural fibroid is associated with adverse pregnancy outcomes in women undergoing IVF treatment

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)
  - 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)

Medical Treatment Options

- Letrozol (non steroidal aromatase inhibitor) 5mg/d,orally for 3mths (reduced myoma volume and no effect on MBI), (Gurates B et al 2008)
- GnRHa / LHRHa – for 1 until 3 months
  reduced myoma volume, less intraoperative bleeding, for pts with low Hg
- Mifepristone / Asoprisnil for cervical priming
  used orally or sublingual or vaginally no difference equal results
- Nomegestrol acetate (very potent progestogen) day 1-14, 5mg daily, for rapid thinning of the endometrium, and easier operative field
  (Levy BS Acta ObstGyn Scand 2008)

Disadvantages of Hormonal therapy

- High cost
- Side effects menopausal symptoms
- Increased recurrence rate may render small fibroids less visible (Fedelle 1990)
- Increased risk of uterine perforation due to reduced myometrial thickness (Bradley 2002)
- Increased risk of the 'sinking' phenomenon due to decreased elasticity of the myometrium / E2 deficiency (Lin et al 2000)
- No advantage for short or long term outcomes (Campo et al 2005)

Impact of Intramural Myomas on Fertility

Myomectomy efficacy allows pregnancy in 60% of the patients with unexplained infertility in the first year following surgery

Vercellini P.1998 Hum.Reprod.

Impact of Intramural Myomas on Fertility

The decision to proceed with myomectomy in an asymptomatic patient with unexplained infertility remains controversial. Current data suggest surgical treatment for patients who have uterine cavity distortion.

Sachev and Seifer. Infert. and Reprod. Clin, North Am. 2002

When is it necessary to treat?

Meanwhile there are almost no doubts of the benefits of treating submucous leiomyomas, there is no homogeneous opinion on the treatment of intramural leiomyomas between 1,5 and 5 cm.

Effect of hysteroscopic myomectomy on fertility: systematic review of the evidence

	No. of studies	RR	95% CI	P-value
Controls: fibroids in situ (no myomectomy)				
Clinical pregnancy rate	2	2.03	1.08-3.83	0.028
Spontaneus abortion rate	1	0.77	0.36-1.66	NS
Controls: infertile women with no fibroids				
Clinical pregnancy rate	2	1.54	1.00-2.39	NS
Spontaneus abortion rate	2	1.24	0.47-3.24	NS

Pritts EA et al, 2009

SIS MAR

Myomectomy vs. expectant management in subfertile patients with one submucous fibroid <4 cm: a prospective, randomized study

	Hysteroscopic myomectomy (n=52)	Expectant management (n=42)
Pregnancy (%)		
Yes	43.3	27.2
No	56.7	72.8

RR = 1.9 (95% CI 1.0 – 3.7)

Casini et al, 2005

SIS MAR

Effect of Uterine Fibroids on IVF Outcome

Subserosal

- Fahri	1995	normal
- Elder-Garcia	1998	normal
- Healy	2000	normal
- Oliveira	2004	normal

Submucosal

- Fahri	1995	decreased
- Elder-Garcia	1998	decreased
- Healy	2000	decreased

Conclusion: no effect unless the cavity is involved?

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Material and Methods

•Retrospective case control study

	Group 1 (N=75 patients with myomas)	Group 2 (N=127 patients without myomas)
N.of transferred cycles	129	129
Age (M ± SD)	35.8 ± 4.9	35.7 ± 4.8
Type of myomas	I.M. or I.M.-S.S.	/
N.of myomas (M ± SD)	2.46 ± 2.8	/
Size of myomas (M ± SD) (cm)	1.84 ± 1.4	/

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%)
N.of abortions (%)	18 (40%)*	10 (18.9%)*

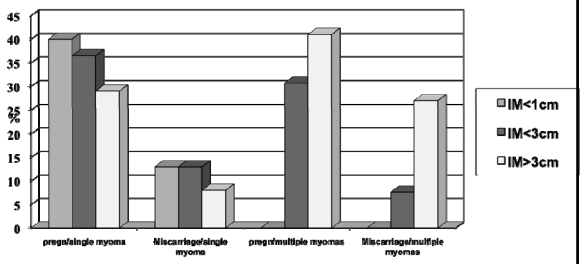
*X^2=4.34 p<0.05

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%)*

*X^2=6.76 p<0.01

Results(III)



Results(III)

Size of myomas	Before ART (N=129 cicli) Single	Multiple	Pregnancies(%) (N=45) Single	Multiple	Abortions(%) (N=18) Single	Multiple
IM≤ 1cm	15	3	6(40%)	0	2(13%)	0
IM< 3cm	52	13	19(36.5%)	4(30.7%)	7(13%)	1(7.6%)
IM≥ 3cm	24	22	7(29%)	9(41%)	2(8%)	6(27%)

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ART results pre and post myomectomy

- N. patients: 5
- Mean (± SD) age: 39 ± 5.1
- Causes of infertility: 2 tubal factors; 2 oocytes donation; 1 male factor
- Karyotype normal

	Pre myomectomy	Post myomectomy
N. of ET	5	7
N. of abortions	1	1
Full term pregnancies	0	4

Impact of Intramural Myomas on In Vitro Fertilization

Patients who undergo IVF cycles and presenting intramural myomas, could have an increased risk of miscarriage. This risk is more marked in patients with 3 or more myomas.

Impact of Intramural Myomas on In Vitro Fertilization

Some leiomyomas affect fertility but...

The evaluation of which leiomyoma has an impact on reproduction has to be criterious to avoid unnecessary surgery. There is not yet enough evidence to support prophylactic myomectomy for all patients with leiomyomas, specially for those with one o two tumors smaller than 3 cm.

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Impact of Intramural Myomas on In Vitro Fertilization

Is it rational to invest human and economic resources if there might be reduced possibilities of pregnancy and increased risk of spontaneous abortion without a previous myomectomy?

S.I.S.ME.R.:approach to the problem

	Before ART		After 1st ART		After 1st abortion	
	Single	Multiple	Single	Multiple	Single	Multiple
Submucous	M	M	-	-	-	-
Subserous	No	No	No	No	No	No
I.M.< 1	No	No	No	M?	M?	M
I.M.< 3cm	No	M	M?	M	M	M
I.M.> 3cm	M	M	M	M	M	M

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Thank you