European Society of Human Reproduction and Embryology

COURSE 9

"Reproduction and uterine fibroids: importance of the inner myometrium"

Special Interest Group
Reproductive Surgery

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PRE-CONGRESS COURSE 9

Special Interest Group Reproductive Surgery
"Reproduction and uterine fibroids: importance of the inner myometrium"

CONTENTS

PRE-CONGRESS COURSE 9 - PROGRAM

Room "Gratte Ciel 3"

Special Interest Group Reproductive Surgery

Reproduction and uterine fibroids: importance of the inner myometrium?

Course co-ordinators: S. Gordts (B) , A. Strandel (S), M. Gergolet

Course description: The course intends to elucidate on the role of the presence of uterine fibroids related to their position in the inner and/or outer myometrium and their influence on reproduction. Is there a link between fibroids and fertility? Is myomectomy a fertility enhancing procedure and if so when should it be performed and how? Does new treatment modalities have a place in the treatment of patients trying to conceive? Many questions to which we hopefully will be able to give an accurate answer at the end of the day.

Target audience: reproductive surgeons and all those involved with reproduction and counselling of patients.

Program

Disease burden and manifestations

09.00 - 09.15 Epidemiology and developmental factors - ***M. Gergolet***
09.15 - 09.35 Fibroid growth : vascular and molecular characteristics - ***(TBA)***
09.35 - 09.45 Discussion
09.45 - 10.15 Fibroids and fertility: what is the link? - ***G. Kunz (D)***
10.15 - 10.30 Discussion

10-30 - 11.00 Coffee break

Advances in diagnosis and treatment

11.00 - 11.30 Imaging and possibilities of ultrasound - ***(TBA)***
11.30 - 12.00 MRI: an added value or a gimic ? - ***M. Bazot***
12.00 - 12.30 Discussion

12.30 - 13.30 Lunch

Advances in diagnosis and treatment

13.30 - 14.00 Diagnostic and operative hysteroscopy - ***S. Gordts (B)***
14.00 - 14.15 Discussion
14.15 - 14.45 Innovations in fibroid treatment: place in reproduction? - ***T. Tulandi (CND)***
14.45 - 15.00 Discussion

15.00 - 15.30 Coffee break

Advances in management

15.30 - 16.30 Surgical treatment to enhance fertility?
Contra: ***A. Strandell (S)***
Pro: ***T. Tulandi (CND)***

16.30 - 17.00 Round table: objectivation of selection criteria

Epidemiology and developmental factors

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Epidemiology

Uterine fibroids are the most common benign tumors in the female pelvis. They are cause of 200.000 to 300.000 hysterectomies every year and the first cause for hysterectomy in the United States (Schwartz 2000, Faerstein et al 2001, Wise et al. 2004).
Due to the fact, that are most of times asymptomatic or are cause of mild clinical signs, the real incidence could be undervalued. From 1989 to 1993, almost 95,000 premenopausal nurses were studied. The incidence rate of fibroids was 8,9 among white women and 30,6 among black women (Marshall et al. 1997). The incidence of fibroids among infertile women without any obvious cause of infertility is estimated to be 1-2.4 per cent but appropriate prospective study has not been done yet (Vercellini et al. 1999, Donnez et al.2002)
The prevalence varies between 20 up to 50 %, found in autopsies of women older than 40 and is two to three folds higher in black women (Wise et al. 2004, Faerstein et al. 2001).
Data on real incidence and prevalence of fibroids in female population are difficult to assess. At first, most of fibroids develop by the fifth decade of life and are asymptomatic, second, only a small part of fibroids lead to hysterectomy (Schwartz 2001).

Symptomatology

Among 25 % of women with fibroids present clinical symptoms like prolonged menstrual bleeding, pelvic pressure or pain, resulting in pressure upon adjacent organs, excessive uterine bleeding and in some case dyspareunia (Schwartz 2001, Flake et al. 2003, Ferrero et al. 2006). In an epidemiologic study done on an extended population in Washington State based on discharge records of 2065 women who delivered in years 1987-1993 complications in pregnancy, labor and delivery were analyzed. Fibroids were cause of increased odds ratio for abruptio placentae (3,87), placenta praevia and olygohydramnios. There are cause of dysfunctional labor (OR:1,90), breech presentation (OR:3,98) and caesarean delivery (OR: 6,39)(Coronado et al.2000).
In a randomly selected population women with fibroids were asked about the intensity of menstrual bleeding. Even small fibroids were associated with heavy bleeding, and the intensity increased with their size. Surprisingly heavy bleeding did not differ in intramural fibroids in comparison to submucosal (Wegienka et al. 2003).
Fibroids cause different reproductive dysfunctions in 20 up to 50 percent of cases. Surgical therapy usually improves spontaneous conception in couples when fibroid is the exclusive etiology of infertility suggesting, that myomectomy is useful in treatment of patients with fibroids and otherwise unexplained infertility. (Vercellini 1999, Donnez et al. 2002, Marchionni 2004).

Risk or protective factors influencing develop and growth

The initiators of fibroids are unknown. Various factors may influence the incidence of fibroids in female population like ethnicity, constitutional factors as obesity, reproductive history, voluptuous habits and some grade of heritability.

Age
Almost 50 percent of fibroids develop by the fifth decade of life. The increased prevalence of fibroids in older women could be also due to the 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 and to have gynaecological surgery (Flake et al. 2003).
Menopause signs a precipitous decline of fibroids and their symptoms (Schwartz 2001, Boynton-Jarret et al. 2004).

Ethnicity
Black women present a two to three folds higher incidence higher than Caucasian women (Marshall et al 1997). Meilahn studied a randomly selected population on the fifth decade of life. 27,3 percent of women have had a hysterectomy due to fibroids. For black women the rate of hysterectomy was three times higher than for withes, they were significantly younger at surgery and less educated (Meilahn et al 1989).
Faerestein found even stronger correlation between fibroids and Black ethnicity. He found an odds ratio of 9,4 and was even stronger when adjusted for health behaviour (Faerstein et al. 2001). Similar data report Marshall, who found a higher incidence of known risk factors for fibroids in black premenopausal ethnic group. Even after adjustment for factors predisposing to fibroids he still found a unexplained higher incidence of this pathology in black women (Marshall et al. 1997). Sadan studied the concentration of oestrogen and progesterone receptors in fibroids and normal myometrium of white and black women. Histologically the fibroids were similar between the two ethnic groups. The oestrogen and progesterone receptors in fibroids did not differ between the two ethnic groups, but the receptor concentration in normal myometrium was higher in Caucasian population. He suggests two different biochemical pathways of its pathogenesis starting from a genetic predisposition as initiating factor: the amount of oestrogen receptors in the black population and an alteration of the steroid metabolism in the white ethnic group (Sadan et al. 1988). Amant did not found differences in oestrogen or progesterone receptors in myometrium of patients with fibroids between different ethnic origin. The study did not found differences on transcriptional or on protein level between ethnic groups (Amant et al 2003).
Wei studied 22 gene products among black, Asian, Hispanic and white women. Among black women he found significant up regulation of progesterone receptor A and a down regulation of retinoid acid receptor alpha in fibroids compared to myometrium (Wei et al. 2006).
Al–Hendy investigated gene polymorphism in the oestrogen receptor alpha. The PP genotype was significantly associated with an increased risk of uterine fibroids in white and black women but not in Hispanic ethnicity. PP genotype women had a RR of 6.42. Fibroids in those women was significantly larger. The ostrogen receptor alpha PP genotype was significantly higher in black women than white or Hispanic (Al-Hendy et al. 2006).

Familiarity
The incidence of fibroids is higher in women who have a first degree relative with fibroids. The relative risk varies between 2,3 to 4 (Ligon and Morton 2001) In a Finnish twin cohort study was observed only a slight genetic predisposition to develop fibroids in women whose sisters had a fibroid either in monozygotic or in dizygotic twins. The Authors suggest that in the development of fibroids reproductive and anthropometric factors such body mass index could play a more important role, rather then genetic factors. (Luoto et al. 2000).

Social economic factors
In a case control study in the Baltimore area women with fibroids had a lower education and were older. In the fibroid group, there was a lower percent of married women (Faerstein et al. 2001).

Obesity
Almost all papers found a positive correlation between uterine fibroids and obesity. The relative risk increase with the increase of BMI (Rongières 1999). In the Baltimore case control study mentioned above the odds ratio between the women in the lowest quartile and those in the highest

quartile was 2,3. Starting from the hypothesis that fibroid growth is hormone dependent authors did not find higher oestrogen levels in premenopausal obese women. They suggest an increase of bio availability due to a decrease of sex hormone binding protein. Hyperinsulinemia in obese women plays an important role as cofactor in these women (Ferstein et al 2001).

Menstrual pattern and obstetric history

Early menarche is associated with an increased risk for fibroids (Parazzini et al 1996, Samadi et al. 1996). Women who were < 10 years of age at menarche have a RR of 1,24 while those who have had menarche at 16 years or more have a relative risk of 0,68.

Parity plays a protective role while infertility seems to be a risk factor. The risk reduces with the number of deliveries. The relative long time in witch during pregnancy women are not exposed to unopposed estrogens explain this hypothesis. (Parazzini et al. 1996, Marshall et al 1998). Data are susceptible of potential bias: women with children are more willing to get hysterectomy than those who still want children. More, fibroids could be a cause of infertility and not a consequence, but the relative risk remain higher among nulliparous women even after exclusion of infertile ones (Baird 2004, Marshall 1998).

Atherogenic risk factors

Hypertension and diabetes, two atherogenic factors suspected to represent risk factors for fibroids, could be considered only an occasional finding in obese women. Cross matching analyses of data suggest that hypertension and diabetes could be independent factors promoting growth of fibroids. Several theories suggest that the pathogenesis of fibroids and of atheromatous plaque may be similar, starting from the postulate that fibroids may arise either from myometrium, connective tissue or arteries. In fact, one of the key steps in atherogenic plaque formation is smooth cell proliferation (Boynton-Jarret et al. 2003).

Authors found a 1,7 to 2,1 fold adjusted risk for fibroids in patients with hypertension, but not a significant higher risk in patients with diabetes (Faerstein et al.2001). A slight, non significant, increase of relative risk was found in patients with diabetes mellitus. Authors however suggest a fascinating biological role of hyperinsulinemia in the pathogenesis of fibroids. Insulin can promote mitosis, promote vascular smooth cell proliferation and the growth of fibroids. Insulin could also have a gonadotropic function (Faerstein 2001).

Boynton-Jarret studied relation between diastolic blood pressure and fibroids in more than 100,000 premenopausal US nurses. At every 10 mmHg increase of diastolic blood pressure, the risk increased significantly either in women taking anti hypertensive drugs or in those without therapy. The risk for fibroids rose with the duration of hypertension and was independent from other factors like body mass index contraceptive use and obstetric history.

Cigarette smoking seems to have a protective role in fibroids development. Although smoking is a well known pro-atherogenic factor, it can be that his antiestrogenic function outweigh this effect. The reduction of risk is dose dependent. Ross observed an 18% decreased risk for women who smoked approximately 10 cigarettes per day up to 33 % in those who smoked 20 cigarettes per day (Ross et al. 1986). Smokers present also a reduced risk of endometrial cancer and an earlier menopause (Flake et al. 2003). Other studies found only a slight reduction of RR, in particular in women smoking 20 years or more (Farestein et al. 2001, Wise et al. 2004). The protective effect of smoking must be attributed to an antiestrogenic effect. Components present in burned tobacco may inhibit aromatase, decreasing oestrogen availability.

Diet

Several studies associate beef and red meat as an increased risk factors of fibroids while high fiber and low fat diets seem to play a protective role. Data are not homogeneous and are controversial (Flake et al. 2003).

Alcohol consumption, particularly beer, increases the risk for fibroids. No association between risk for fibroids and coffee or caffeine consumption have been found (Wise et al. 2004).
Phitoestrogens are present almost in 300 plants. The most dietary source of phitoestrogens is soy. These substances have a weak estrogenic effect but in particular concentration may have an antiestrogenic function (Flake et al. 2003).

Uterine Irritation
A group of 318 women have been studied with the aim to correlate fibroids and uterine irritation. Women with a history of pelvic inflammatory disease (PID) have a relative risk of 1,8. In particular chlamidial infection is associated with a 3.2 fold increased risk for fibroids. The risk increase with the number of PID episodes. IUD use seems not to be an independent risk factor for fibroids, but in correlation with infections or fever the OR increased to 5.3. With the use of talc in the genital area the risk increases two times (Faerstein 2001).

Environmental estrogens
Xenoestrogens have been associated with negative effects on male and female reproductive activity. The pesticide DDT (dichlorodiphenyltrichloroethane) and other organochlorine pesticides have an estrogenic activity. Although they have being banned for several decades, DDT is still detectable in fat tissue. Higher levels of DDT have been found in fibroid tissue rather than in normal myometrium. Higher blood levels of DDT have been found in women with fibroid than in those without them. In some conditions like lactation and fasting the DDT mobilize from the fat tissue. The exposure levels are several folds higher than those encountered in the environment (Flake et al. 2004). Exposures to xenoestrogens in low doses but in particular sensitive period like neonatal age could have deleterious effect on the reproductive system and may contribute to fibroid development (Walker 2002). Early exposure to diethylstilbestrol (DES) causes uterine fibroids in animal models. Baird found fibroids in the 100 percent of black women exposed to DES and in the 76 % of white women. Exposed women had larger fibroids (Baird et al. 2005). In rats carrying a defect of the Tsc2 tumor suppressor gene predisposed to fibroids, the early exposure to DES cause an increased tumor suppressor gene penetrance from 65 to more than 90 %. Authors suppose that early exposure to environmental factors during development can reprogram normal tissue responses in genetically predisposed individuals (Cook et al. 2005).

Conclusions

Fibroids development is clearly under influence of hormonal milieu. There are few doubts that fibroid growth is oestrogen dependent. In fact they develop during fertile age and regress in menopause or after therapy with Gn RH analogues.
Obesity and infertility are clearly risk factors. It is still not known how much the black ethnicity influence the prevalence of fibroids *per se* or is biased with a higher prevalence of risk factors in this population. Multiple parity and smoking undoubtedly play a protective role, other factors play a less significant effect and data are contrasting and unclear.
Either risk or protective factors mentioned above carry out their effect through an oestrogen like activity, with increasing or reducing the hormone bioavailability or by acting on oestrogen receptors. Tsibris designed a pathway to fibroids that include three inducers: oestrogen stimulation unopposed by progesterone, higher all trans retinoic acid levels (atRA) and higher peroxisome proliferators activated receptor γ (PPAR γ) and retinoid X receptor α (RXRα).
Further studies will elucidated the genetic and molecular changes responsible for fibroid development. Therapy with SERM (selective estrogen receptor modulator) like Raloxifene, combined with PPAR γ antagonist or RXT α antagonist and agonist could be advantageous in the conservative therapy of fibroids (Tsibris et al.1999). Recently gene therapy is becoming a clinical reality. Al Hendy experimented adenovirus-expressing dominant-negative ER to arrest leiomyoma

growth. The same author hase has described the utility of the herpes simplex virus-thymidine kinase (HSV-TK) plus ganciclovir (GCV) suicide gene-therapy system to effectively eradicate leiomyoma cells (Al-Hendy et al 2006). The final goal of clinical practice is to reduce surgery, especially patients desiring to preserve their fertility potential, to develop tools for new medical therapy and to reduce the burden of these tumors.

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Importance of the inner myometrium. Fibroids and fertility: what is the link?
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Objectives:

- The concept of the archimetra as the organ of human reproduction
- Adenomyosis and endometriosis as diseases of the inner myometrium
- Fibroids as related to the different layers of the myometrium
- The link between fibroids and sterility

Summary

The archimyometrium or `junctional zone` or `inner myometrium` as the innermost of three myometrial layers surrounds the whole endometrium and is characterised by a predominantly circular arrangement of the muscular fibres (Werth and Grusdew, 1898, Wetzstein, 1965, Noe et al., 1999, Kunz et al., 2000). Unlike the two outer layers of the myometrium that develop late during ontogeny and therefore termed neomyometrium (Werth and Grusdew, 1898), the anlage of the archimyometrium can already be identified during the first trimester of gestation (hence its denomination). The ontogenetically early formation of the archimyometrium is pertinent to its function that results from the fusion of the two paramesonephric ducts and their mesenchymal elements to form the primordial uterus (Werth and Grusdew, 1898, Noe et al., 1999). The bipartition of the circular subendometrial myometrium in the upper part of the uterine corpus and its separate continuation through the cornua into the respective tubes is the morphological basis of directed transport capacities of the uterus during the menstrual cycle. (Kunz et al., 1996, Kunz et al., 1998b, Noe et al., 1999). The archimetra itself, consisting of the endometrium and the adjacent archimyometrium or junctional zone, is the organ responsible for basic reproductive procedures in human such as directed sperm and embryo transport and implantation of the blastocyst (Kunz et al., 1996, 1998, 2006, 2007). Thus directed transport of sperm and preimplantation embryos into the tube or fundo-cornual region ipsilateral to the site of the dominant ovarian structure constitutes a genuine uterine function and results from both, the specific structure of the archimyometrium with its fundo-cornual bipartition of the circular fibers (Werth and Grusdew, 1898, Noe et al., 1999) and the effects of the utero-ovarian counter-current system providing an ipsilaterally increased input of hormones from the dominant ovarian structure into the uterine cornual region (Kunz et al., 1998b).

There is growing evidence that diseases of the inner myometrium such as adenomyosis represent an important factor in infertility. This has been shown in infertile women with endometriosis and in baboons with life-long infertility (Barrier et al., 2004, Kunz et al., 2005). Endometriosis and sterility are linked to the existence of adenomyosis and vice versa (Leyendecker et al., 1996, Kunz et al., 2000, 2005) and a number of studies have demonstrated an impairment of ovarian functions such as follicular development and oocyte quality and fertilization rates in women with diseases of the junctional zone (Toya et al., 2000, Garrido et al., 2002, Navarro et al., 2003). As a consequence of these data regarding the association between fibroids and sterility it appears reasonable to assume that not only the

different sizes of fibroids but the sites of their localization as related to the different layers of the myometrium might play an important role if the establishment of an early pregnancy and its further development is compromised.

Although the use of MR imaging with respect to the definition of size, number and localization of fibroids is still discussed controversially (Hricak et al., 1983; Brosens et al., 1995; Reinhold et al., 1998; Brosens et al., 1998, Tamai et al., 2006, Vercellini et al., 2006), everybody agreed that this imaging technique represents the best method to visualize the different compartments and their alterations of the non pregnant uterus non-invasively. However, by means of endovaginal sonography (EVS) fibroids can be documented highly reliable as well.

The physician dealing with reproductive disorders often encounters women suffering from infertility in association with fibroids. Besides problems including menorrhagia and pain fibroids are associated with infertility and pregnancy complications. Hence prior to the use of ART it has to be decided whether fibroids might hinder successful treatment and thus have to be removed. Before all fibroids are classified according to their topographical location into submucous, intramural and subseroid fibroids.

There is growing evidence that fibroids of the inner myometrium, i.e. submucous fibroids, have the most negative effects on successful human reproduction. In a meta-analysis Donnez and Jadoul (2002) have shown that the pregancy rate of women with fibroids bulging into the uterine cavity was significantly lower with 9% as compared to the pregancy rate of 33% in women with myomas of different locations within the myometrium. In view of these and other data there is evidence that the removal of submucous fibroids resulted in the highest pregnancy rates.

The apparently negative effects of submucous fibroids on the pregancy rate can be related to a distortion of the uterine cavity and to a disruption of the anatomical and functional continuity of the archimetra as the organ of menstrual cyclicity. It appears reasonable to assume that a subsequent dysfunction of the uterine organ archimetra by inner myometrium fibroids can be attributed to a dysfunction of a number of basal reproductive pathways. Fibroids of the inner myometrium negatively affect myometrial contractility during the menstrual cycle resulting in impaired directed sperm transport and embryo implantation. It has been shown by MR cinematography in women with submucous fibroids that the uterine peristaltic contractions were partly disrupted; however this could not be observed if the fibroids were located in other sites of the uterine wall. Either as a consequence due to an increased migration or to a delayed implantation and early growth retardation data from IVF cycles have provided evidence that fibroids of the inner myometrium or junctional zone have significantly decreased embryo implantation rates. It can be suggested that the decidual process is also linked to the archimetra with the junctional zone. It appears conceivable that disruptions of the inner myometrium by fibroids predisposes for impaired placentation and probably subsequent obstetrical complications.

Based on immunohistochemical findings it has to be assumed that fibroids of the inner myometrium differ from outer myometrial fibroids not only from their location and effect on reproductive physiology but from their aetiology. Recent studies and own data have shown that the steroid receptor expression in submucous fibroids is higher as compared to fibroids with different location. This correlates very well with data that a number of diseases of the inner myometrium such as adenomyosis, endometriosis and adenomyomas are closely related to a hyperestrogenism of the archimetra. Furthermore with respect to the incidence rates of all

these diseases of the inner myometrium an evident correlation has been described. It has to be assumed that fibroids of the inner myometrium derive from distinct progenitor cells as compared to the fibroids of the outer myometrium. From yet unpublished data we have found evidence that fibroids of the inner myometrium exhibit a cyclically dependant steroid hormone receptor expression as the normal archimyometrium but not intramural or subserosal fibroids that may derive from the onto- and phylogenetically more recent neomyometrium. The different origin of inner myometrium fibroids is confirmed by the notion that these fibroids have fewer chromosomal abnormalities than outer myometrial fibroids.

Lecture summary

The modern view of the uterine muscular architecture differentiates between the inner myometrium or archimyometrium and the outer myometrium. While the outer myometrial layers represent the organ of pregnancy and delivery does the inner myometrium as a part of the onto- and phylogenetically older archimetra provide basic reproductive functions such as directed sperm and embryo transport, decidualization, implantation and placentation. Fibroids of the inner myometrium which differ in many aspects from those of the outer myometrium disrupt the continuity of the inner myometrium and thus compromise the physiology of early reproductive processes either during natural or during artificial cycles. While in fibroids of the outer myometrium without a disruption of the architecture of the inner myometrium number and size matter should inner myometrial or submucous fibroids be considered to be removed surgically prior to the use of ART almost independent from the diameter as measured by imaging means.

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Werth R, Grusdew W 1898 Untersuchungen über die Entwicklung und Morphologie der menschlichen Uterusmuskulatur. *Archiv der Gynäkologie* **55**, 325-409.

Reproduction and uterine fibroids

Importance of the inner myometrium

MRI: an added value or a gimmick?

Marc Bazot

ESHRE 2007, Lyon, France

Introduction

«30%» «5-10%» «1-3%»

Fertility, gestation, delivery

Indeterminate ultrasonography

Second-line technique examination

Treatment

Childbearing function

How, when and why performing MRI examination?

Detection

Characterization

Diagnosis of a latero-uterine mass

Treatment evaluation

Symptomatic leiomyomas

Gestation and delivery

Uterine peristalsis

MRI protocol

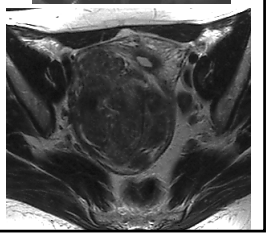
⇨ Recommendations:

Fast, antiperistaltic drugs, abdominal belt

⇨ MRI technique:

TSE-T2: Sagittal-Axial-*Coronal*

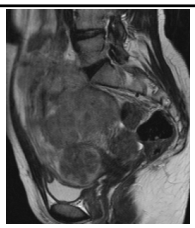
At least one T1 (-/+ fat-suppression)



Dynamic-contrast-enhanced MRI

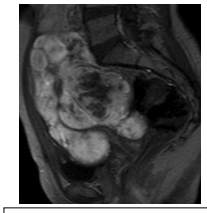
Delayed contrast-enhanced MRI

MRI mapping



Optimal technique:

- Detection
- Count number
- Location
- Characterization



MRI > US if:

> 5 myomas

Large size

Degenerative changes

Sub-serous

Treatment modalities

Uterine myomas in the infertile patient: preoperative localization with MRI versus US and hysterosalpingography. Dudiak *et al*. Radiology 1988; 167-627-30

Location

Size

Morphology

	Sensitivity	Specificity	Précision	P value
MRI (n=11)	85%	100%	94%	0.015
versus US (n=9)	69%	97%	87%	0.043
MRI (n=11)	91%	-	96%	0.005
versus Sonohyst (n=10)	18%	98%	72%	0.005

US compared with MRI for the diagnosis of adenomyosis: correlation with histopathology. Bazot *et al*. *Human Reprod 2001*; 16: 2427-33

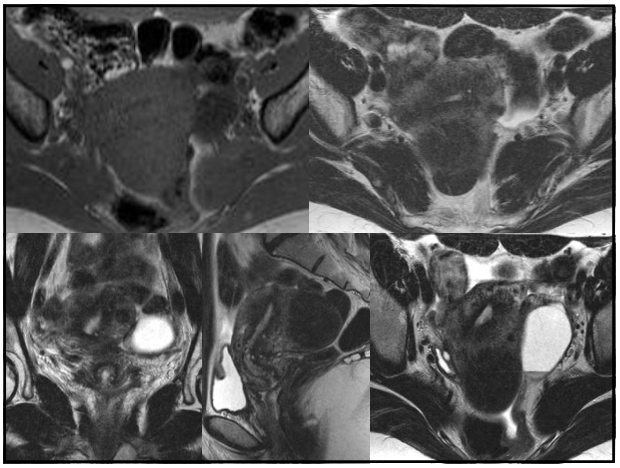
120 consecutive patients (hysterectomy)

Adenomyosis (33%) / Leiomyoma (47.5%)

	Sensitivity	Specificity	PPV	NPV
TVUS	65%	98%	93%	89%
MRI	78%	93%	84%	89%

TVUS = MRI for adenomyosis in women without myoma

MRI recommended for women with associated myoma



Does pelvic magnetic resonance imaging differentiate among the histologic subtypes of uterine leiomyomata? Schwartz *et al*. Fertil Steril 1998;70: 780-7

Prospective study

54 patients

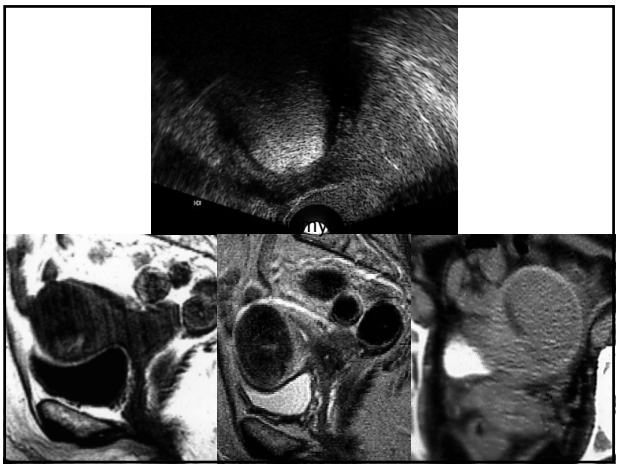
MRI analysis:

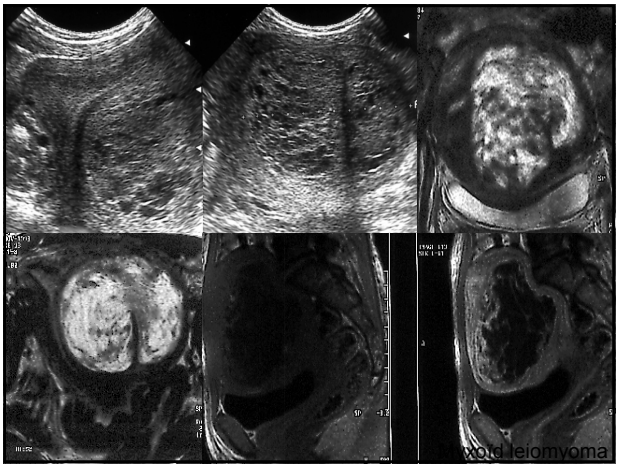
Signal

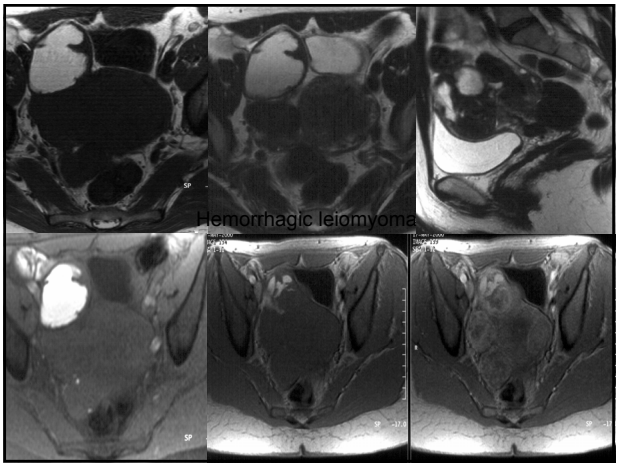
Contours

Benign *vs* malignant

Type	Accuracy	Sensitivity	Specificity
All	69%	-	-
Non degenerative	-	95%	72%
Cellular	-	10%	100%
Cystic	-	80%	98%
Hemorraghic	-	100%	86%




oid leiomyoma


Hemorrhagic leiomyoma

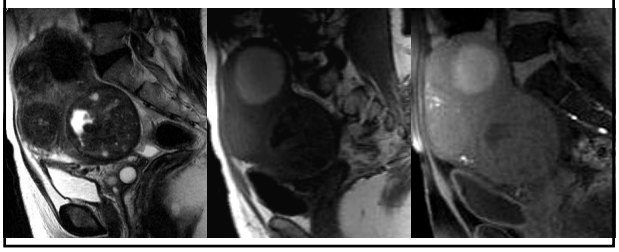
Red degeneration of uterine leiomyoma: MR appearance
Kawakami *et al*. JCAT 1994;18:925-8

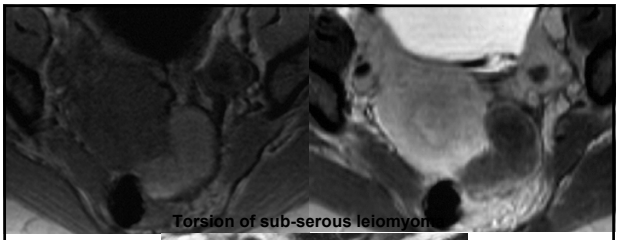
⇨ Acute abdominal pain

Hyperintense ring on T1

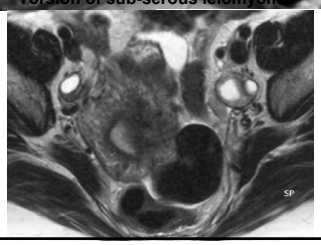
Hypointense ring on T2

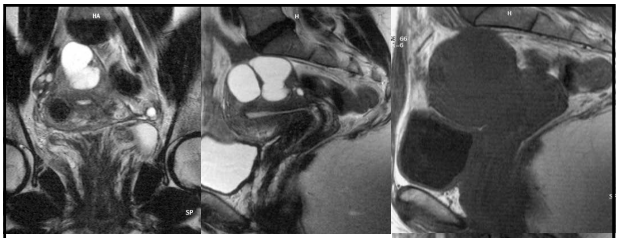
Peripheral dilated vessels





Torsion of sub-serous leiomyoma





Differential diagnosis

Myoma with cystic degenerative changes

Myometrial vestigial cyst

Cystic adenomyoma

The value of MRI in distinguishing leiomyomas from other solid pelvic masses when sonography is indeterminate. Weinreb *et al*. AJR 1990; 154: 295-9

19 indeterminate pelvic masses

Subserous leiomyoma

- Close to uterus
- Hyposignal T2, iso-hyposignal T1

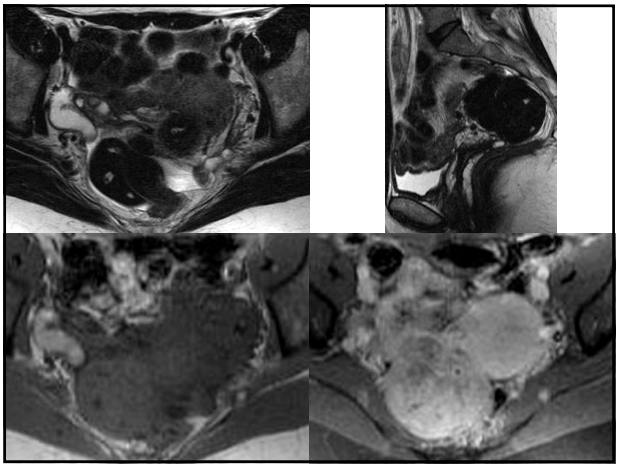
11/13 VP

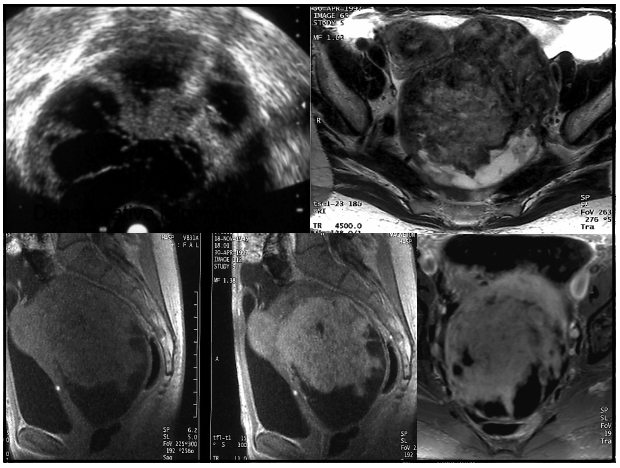
Other tumors:

Degenerative leiomyomas

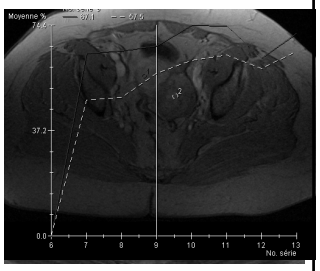
Ovarian fibroma

Ovarian cancer





Value of DCE-MRI for the differentiation between ovarian fibroma and subserous uterine leiomyoma. Thomassin-Naggara *et al*. JCAT 2007; 31: 236-42



Smooth muscle tumors of uncertain malignant potential and leiomyosarcomas of the uterus: MR findings. Tanaka *et al*. JMRI 2004; 20: 998-1007

Tumor Size, Location, Hormonal Status, and Signal Intensity Pattern of the Patients

	Benign (%)	Nonbenign (%)
Tumor size		
<10 cm	5 (41.7)	4 (33.3)
>10 cm	7 (58.3)	8 (66.7)
Tumor location		
Submucosal	0 (0)	2 (22.2)
Intramural	8 (66.7)	7 (44.4)
Subserosal	4 (33.3)	3 (33.3)
Hormonal status of the patients		
Reproductive	2 (16.7)	5 (44.4)
Perimenopausal	2 (16.7)	0 (0)
Postmenopausal	8 (66.7)	7 (55.6)
Signal intensity pattern		
LL	4 (33.3)	1 (8.3)
LH	5 (41.7)	2 (16.7)
HL	1 (8.3)	0 (0)
HH	2 (16.7)	9 (75)
Well-demarcated Unenhanced area[a]		
+	3 (25)	9 (81.8)
–	9 (75)	2 (18.2)

Surgical and radiological management of uterine fibroids in the UK
Chapman *et al*. Curr Opin Obstet Gynecol 2006; 14: 394-401

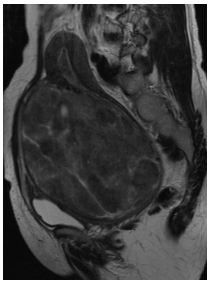
Minimally invasive gynecologic procedures

(Hysteroscopic myomectomy)

Vaginal myomectomy

Uterine artery embolization

MRI-guided percutaneous laser ablation



Hyperintense uterine leiomyoma at T2-weighted MRI: Differentiation with DCE-MRI and clinical applications. Yamashita *et al*. Radiology 1993;189: 721-5

74 ordinary leiomyomas versus 34 hyperintense myomas on T2-w

⇨Echo de spin T2

Hyperintense *homogenous*: Cellular leiomyomas (n=21)

Hyperintense *heterogeneous*: Degenerative leiomyomas (n=13)

overlap

⇨DCE-MRI

Early intense homogeneous uptake: Cellular leiomyomas

Weak delayed heterogeneous peripheral uptake: Degenerative leiomyomas

⇨Treatment by GnRH analogues

Uterine fibroleiomyoma: MR imaging appearances before and after embolization of uterine arteries. Burn *et al*. Radiology 2000; 214:729-34

18 patients

MRI before and after embolization (M2 - M6)

Signal and volume of myomas

⇨ Volume reduction: 43% - 59%

Initial hypersignal T1: pejorative

Initial hypersignal T2: contributive

Predictive value of MRI signal and contrast-enhancement characteristics on post-embolization volume reduction of uterine fibroids. Harman *et al*. Acta Radiol 2006; 47: 427-35

20 patients – 28 fibroids

MRI before and after embolization (M0 - M6)

Signal and volume of myomas

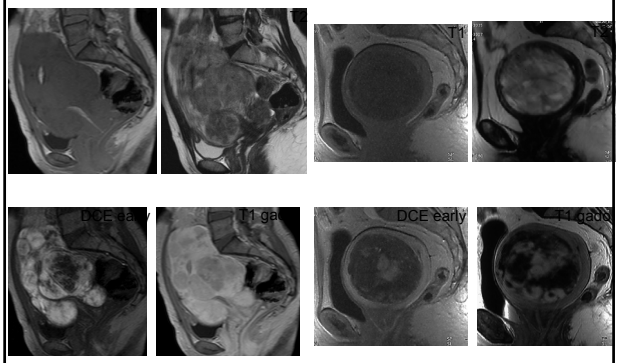
⇨ Decrease rate: 44.6%

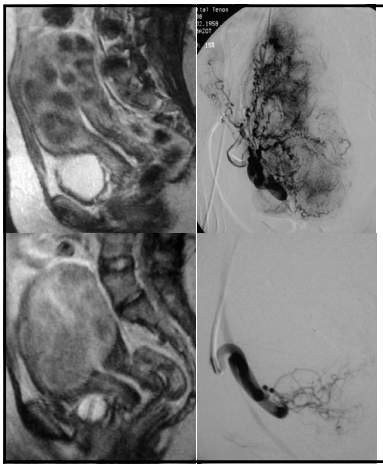
☺ Initial hypersignal T2

☺ Initial marked contrast enhancement

☹ Initial hypersignal T1

Cellular leiomyoma versus Degenerative leiomyoma





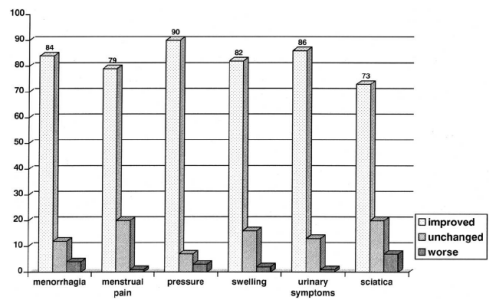
MRI before embolization

Initial arteriography

MRI after embolization

Final arteriography

Uterine artery embolisation for symptomatic fibroids: clinical results in 400 women with imaging follow up
Waller and Pelage. BJOG 2002;11:1262-72



⇨ Thirteen pregnancies

12/24 active and 3 unexpected

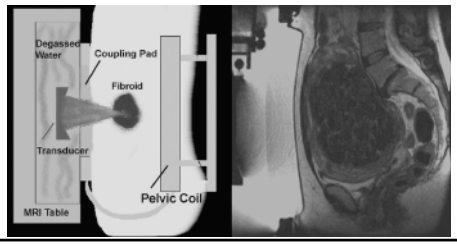
A review of MR imaging-guided focused ultrasound surgery of uterine fibroids
Fennessy *et al*. Top Magn reson Imaging 2006;17: 173-9

MRgFUS equipment for fibroid treatment

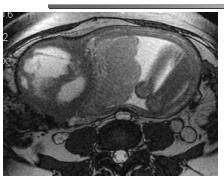
Patient selection

Pretreatment image analysis

Sonifications



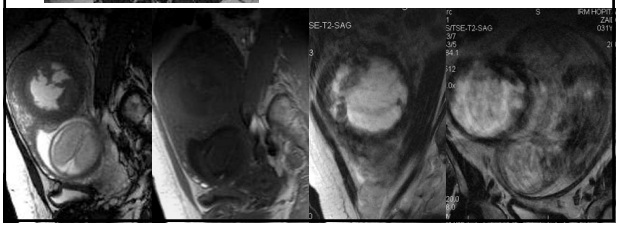
Prenatal MR imaging assisting in differentiating between large degenerating intramural leiomyoma and complex adnexal mass during pregnancy
Sherer *et al*. J Matern fetal Med 2000; 9:186-9



Pain

Pelvic mass ?

Indeterminate US



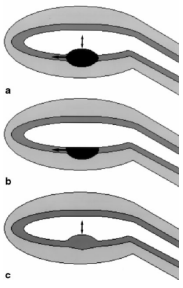
Uterine peristalsis shown on cine MRI using ultrafast sequence
Nakai *et al*. *JMRI* 2003; 18: 726-33

1.5-T magnet, phased-array coil

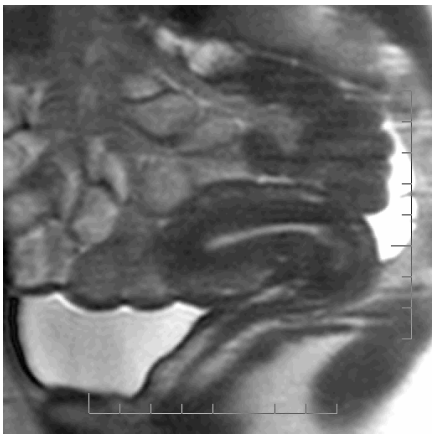
1. Wave conduction in JZ
2. Endometrial stripping movements

Three patterns of peristalsis

Major role in sperm transport, nidation



Leyendecker et al. *Human Reprod 1996*; 11; 1542-51



Uterine contractions evaluated on cine MR imaging in patients with uterine leiomyomas. Nishino *et al*. *Eur J Rad* 2005; 53: 142-6

26 patients:

- *16 submucosal leiomyomas*
- *10 intramural or subserosal leiomyomas*

Peristaltic movements (EMI):

- *12/16 patients with submucosal lesions*
- *10/10 with other leiomyomas*

Focal myometrial movements:

- *9/16 patients with submucosal myomas*

Dysfunctional contractility

Pregnancy loss

A comparison of uterine peristalsis in women with normal uteri and uterine leiomyoma by cine MRI. Orisaka *et al*. Eur J Obstet Gynecol Reprod Biol 2007

21 patients:

- *3 normal ovulatory volunteers*
- *19 premenopausal women with leiomyomas*

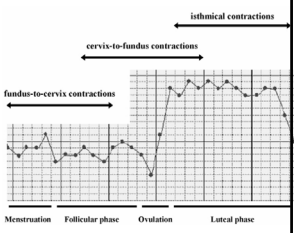
Peristaltic movements (EMI):

- *Always detected*

Abnormal peristaltic patterns

- menstruation (n=3/5)
- mid-luteal phase (n=3/5)

Hypermenorrhea and infertility?



Conclusion

⇨ Second-line technique examination

Morphologic and vascular features

Uterine peristalsis

Treatment options

⇨ Useful added value

DIAGNOSTIC AND OPERATIVE HYSTEROSCOPY

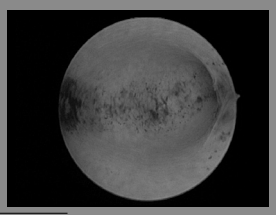
S.GORDTS

ESHRE
PRE-CONGRES COURSE

LYON 2007

LIFE
Leuven Institute for Fertility & Embryology

Diagnostic hysteroscopy



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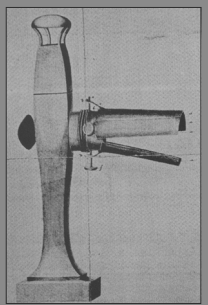

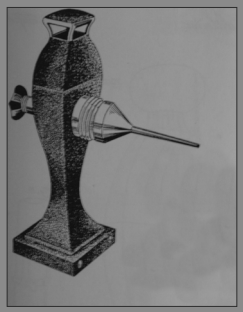

Philipp Bozzini
1773-1809

"lichtleiter" (1806)
War archives, Vienna

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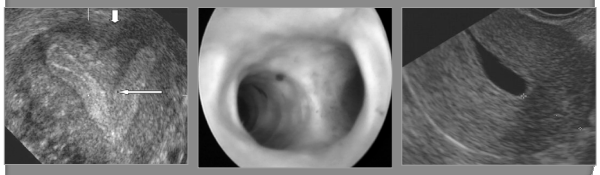
First line diagnostic procedures

Trans vaginal Ultrasound

Fluid Mini Hysteroscopy

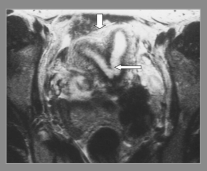
Kontrast Sonography



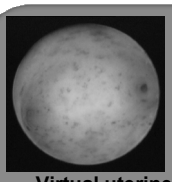
HSG

To invasive

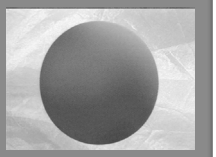
To expensive



MRI



HYSTEROSCOPY
SPECIFIC PROBLEMS

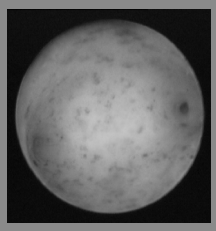


- Virtual uterine cavity
- Endometrium is very fragile
- Distension medium resorting - loss
- Instrument diameter and optical quality
- Documentation
- Slow learning curve
- Cost benefit for the surgeon is generally poor

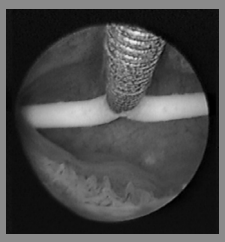
Minihysteroscopy: Findings

- Congenital pathologies
- Acquired pathologies:
  - Large lesions:
    - Myoma, polyp, adhesions
  - Subtle lesions:
    - Mucosal elevation, hypervascularisation, strawberry pattern, diffuse polyposis, exofitic or necrotic lesions,

Minihysteroscopy in the infertile patient Subtle changes can impair fertility?

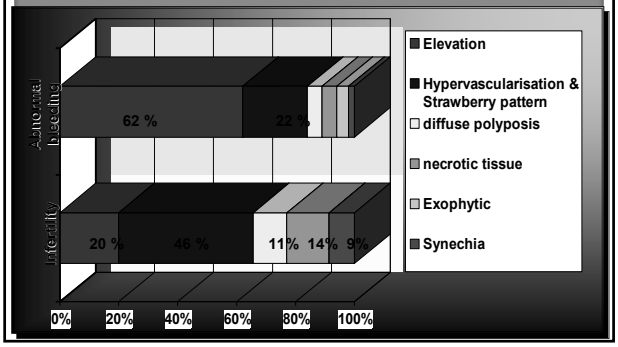


Fertile environment ?



Infertile environment ?

Subtle lesions



Hysteroscopic findings in patients with repeated IVF failure

Nb patients with 2 IVF failures and nl. HSG n=55

SUBMUCOUS LEYOMYOMA	2
POLYPS	10
ADHESIONS	6
ENDOMETRITIS	7

Oliveira et al. Fertil Steril, 80, 2004

Hysteroscopic findings in subfertile patients

	No	%
Total	530	100
Normal	370	69.8
No diagnosis	9	1.7
Abnormal	151	28,5

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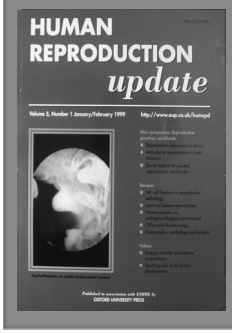
Specific characteristics for minimal invasive approach

- Ambulatory endoscopic unit
- Watery distension medium
- Small diameter instrumentation with high optical quality
- Atraumatic technique

Ambulatory Endoscopic Unit For minimal invasive approach

- No conventional OR
- No general anaesthesia

Watery distension medium For minimal invasive approach



Hydro floatation shows subtle lesions,

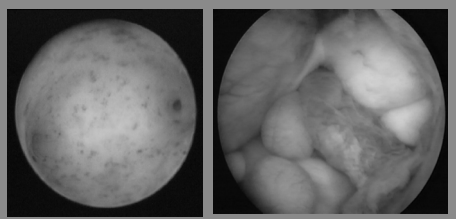
Rinsing effect in case of bleeding

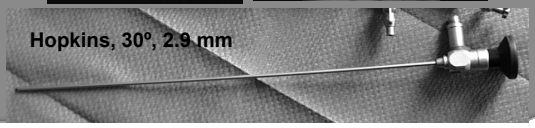
Less discomfort than CO2 gas.

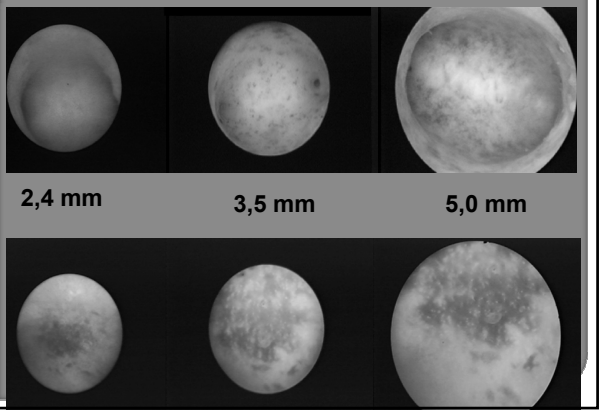
Scientific evidence that ringer lactate Is to be preferred

Only for unipolar surgery Purisole is indicated

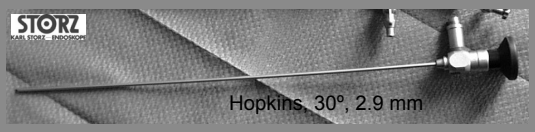
mini endoscopes For minimal invasive approach

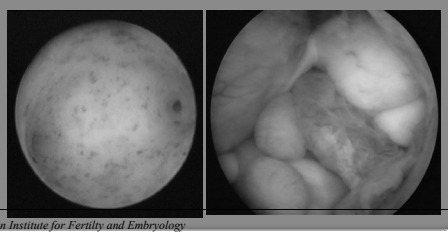






TVE
Mini-instruments





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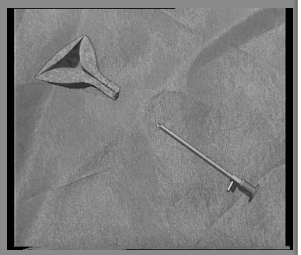
Minihysteroscopy
Atraumatic technique

- No speculum
- No tenaculum
- No cervical dilatation
- No anaesthesia, no analgesia
- Atraumatic and sight controlled insertion of the hysteroscope.



LIFE

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Office hysteroscopy

prospective, multicentre,
randomised controlled trial

To score objectively
- Pain score
- Visualisation quality

Stratified for Total instrument diameter
Vaginal delivery (0 versus >=1)

LIFE
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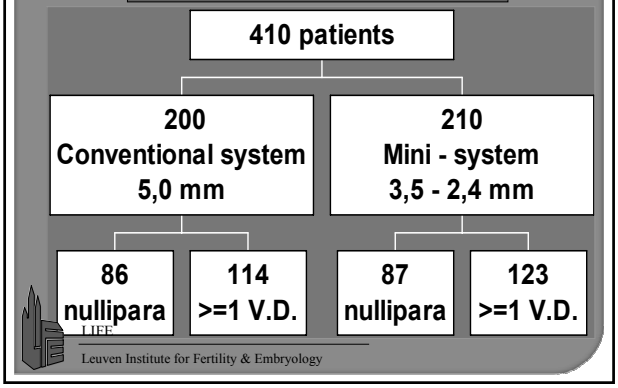
Office hysteroscopy



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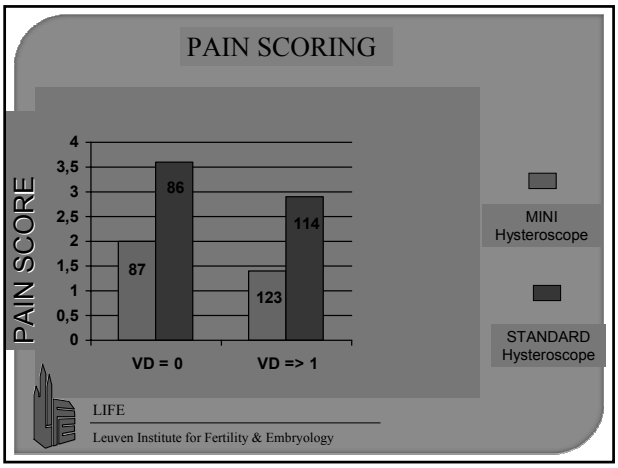
PAIN SCORE

☺ 😐 ☹

QUALITY OF VISUALISATION

Excellent
Sufficient
Insufficient
No visualization

LIFE
Leuven Institute for Fertility & Embryology


PAIN SCORING
PAIN SCORE
4
3,5
3
2,5
2
1,5
1
0,5
0
87
86
123
114
VD = 0
VD => 1
MINI Hysteroscope
STANDARD Hysteroscope
LIFE
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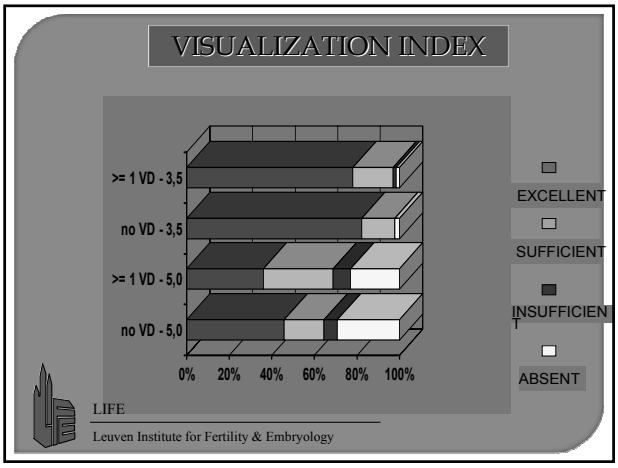
VISUALIZATION INDEX
>= 1 VD - 3,5
no VD - 3,5
>= 1 VD - 5,0
no VD - 5,0
0%
20%
40%
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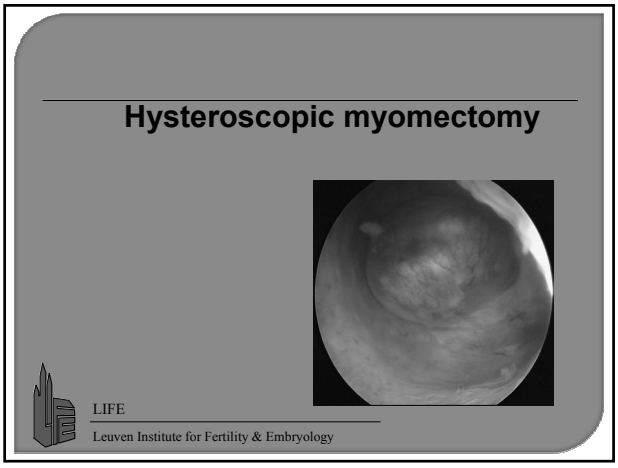
ABSENT
LIFE
Leuven Institute for Fertility & Embryology

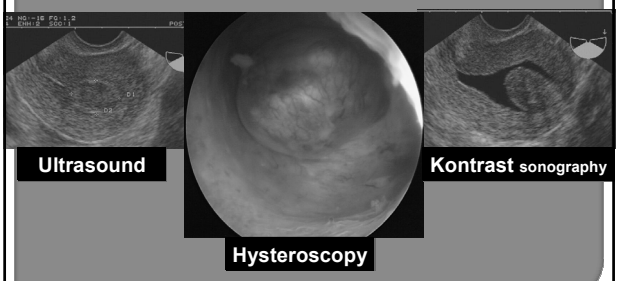

Hysteroscopic myomectomy
LIFE
Leuven Institute for Fertility & Embryology

Proper diagnosis of fibroids ?

What do we have to know

1. Cavity involvement
2. Number of myomata
3. Endometrial vascularisation
4. Size and location

Proper diagnosis of fibroids ?



Ultrasound

Hysteroscopy

Kontrast sonography

Supplemantary exams necessary ?

When ?

dd adenomyoma – myoma

Multiple myoma

Diffuse enlargement of uterine wall

How ?

MRI imaging

Ultrasound guided Hysteroscopic exploration

Hysteroscopic myomectomy

Indications for treatment

- ABNORMAL BLEEDING
- INFERTILITY
- PAIN ?
- ASYMPTOMATIC?

Submucosal myoma and Infertility in IVF (Pritts EA 2001)

	n Studies	Cycles	RR*	95% C.I.
Pregnancy	2	510	0.321	0.130 - 0.697
Implantation	1	541	0.277	0.096 - 0.720

AFTER RESECTION

	n Studies	Cycles	RR*	95% C.I.
Pregnancy	2	157	1.719	1.134 - 2.582
Implantation	1	55	0.980	0.453 - 2.409

* Referent is infertile control without LM

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%

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%

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%)*

L.Gianaroli, et al.

*X^2=6.76 p<0.01

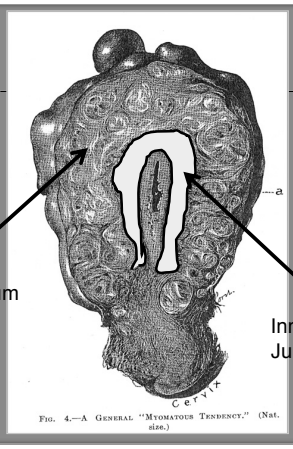


FIG. 4.—A GENERAL "MYOMATOUS TENDENCY." (Nat. size.)

Outer myometrium

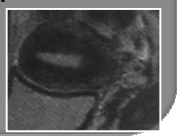
Inner myometrium
Junctional zone

Brosens et al.

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**



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 sustenancy of early embryo

Fahri et al 1995

Uterine Myoma and Pregnancy

Washington State Birth Records

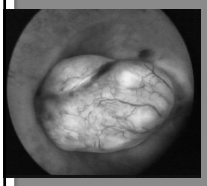
- Abruptio placentae	**OR: 3.87**	**95% CI: 1.63, 9.17**
- First trim. Bleeding	**OR: 1.82**	**95% CI: 1.05, 3.20**
- Dysfunctional labor	**OR: 1.85**	**95% CI: 1.26, 2.27**
- Breech presentation	**OR: 3.98**	**95% CI: 3.07, 5.16**
- Caesarean delivery	**OR: 6.39**	**95% CI:5.46, 7.50**

Coronado et al. 2000

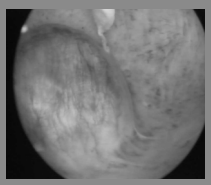
Hysteroscopic Treatment Uterine Myomata?

1. Hysteroscopic resection in conventional OR
2. See and treat in ambulatory environment

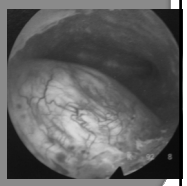
The ESGE* classification of submucous myomas



TYPE 0



TYPE 1



TYPE 2

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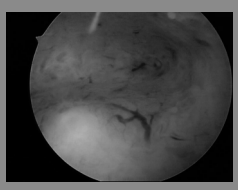
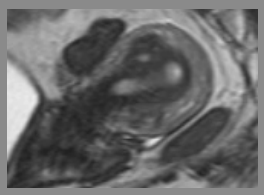
Myoma Typ 2 - Adenomyoma



MYOMA



Adenomyoma

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Hysteroscopic Myomectomy

Operative risks are related to

- Location (% intramural part)
- Numbers of myomas
- Surgical technique
- Distension fluid
- Size
- Endometrial vascularisation

Hysteroscopic Myomectomy

Surgical technique

- Surgery only under clear vision
- Coagulation of major vessels
- Concomitant ultrasound or laparoscopy available
- Intramural resection
  without destroying the surrounding myometrium
  minimal myometrial safety margin of 5 mm

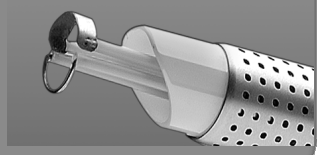
Hysteroscopic Myomectomy

Distension fluid

- Monopolar surgery using non-ionic solutions s.a. manitol, sorbitol or glycine has higher risk of side effects due to fluid overload.
- Bipolar surgery using ionic solutions (saline) is safer

Hysteroscopic Myomectomy

- Bipolar resectoscope is recommended but
  - Smaller loop
  - Different surgical manoeuvres
  - More bubbles
  - Modern generator



Hysteroscopic Myomectomy

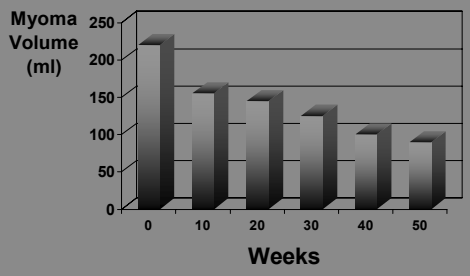
- Pressure and flow controlled pump system with continuous control of fluid balance to work at minimal necessary pressure

Reducing operative risk by GnRH-a therapy ?

AIM

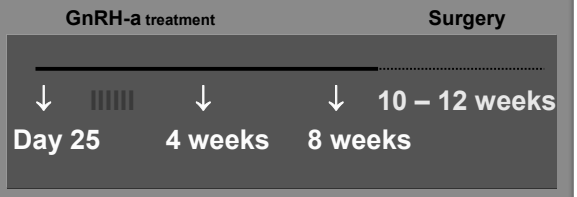
- Induction of amenorrhoea
  - control any concomitant menorrhagia
  - correction of pre-operative anaemia
- Reduction size of the fibroid(s)
- Reduction in total uterine volume

Reduction in volume of the fibroids?



Fibroids tend to return to their pretreatment size about 6 months after discontinuing treatment

Combined medical - surgical approach



GnRH-a treatment should be phase one of a two-phase treatment plan for uterine fibroids followed by surgery

A. Golan, Hum Reprod. 1996

Combined medical - surgical approach

Absolute Indications

- **Myoma larger than 2 cm**
- **Anaemia**

Relative Indications

- **More than one sub-mucous myoma**
- **Myoma localisation**
- **Endometrial vascularisation**

Hysteroscopic Myomectomy

videosequens

Hysteroscopic Myomectomy

1. **Hysteroscopic resection in conventional OR**
2. **See and threat in ambulatory environment**

Operative hysteroscopy in the conventional OR

Characteristics

Surgery is more difficult
- Myoma surgery, Ablation, Asherman

Dilatation of the cervix, concomitant laparoscopy

Instrumentation set up is more complex
- Resectoscope
- Fluid control pump system

Uni or bipolar surgery

Higher risk of complication
- TUR syndrome
- Bleeding
- perforation

Ambulatory operative Hysteroscopy

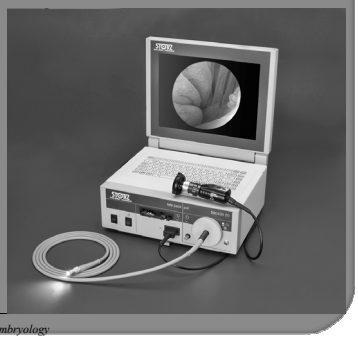
Indications

- **biopsy of suspected lesion**
- **removal IUD**
- **removal synaechiae**
- **polypectomy**
- **congenital malformation (septum, T uterus)**
- **small myoma**

Ambulatory Endoscopic Unit

TELE PACK

comprehensive, multifunctional and compact documentation terminal that can be used as a compact system in the doctor's office



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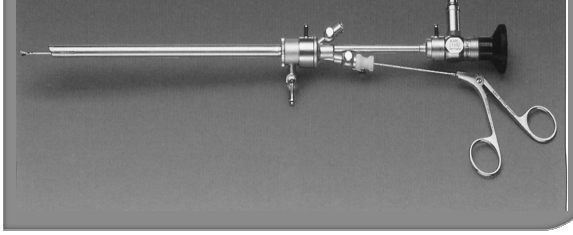
Ambulatory operative Hysteroscopy

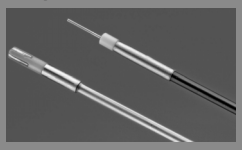
• 30° rod lens optic:	**2.0 mm 2.9 mm**
•Operative single flow sheath:	3.6 mm 4,3 mm
• Operative continuous flow sheath :	4,2 mm 5.0 mm



Ambulatory operative Hysteroscopy

5 French Mechanical and Bipolar probes

- **Grasping forceps, Biopsy forceps, Scissors**
- **Bicag (Storz)**
- **Bipolar needle (STORZ)**
- **Versapoint (GYNECARE)**



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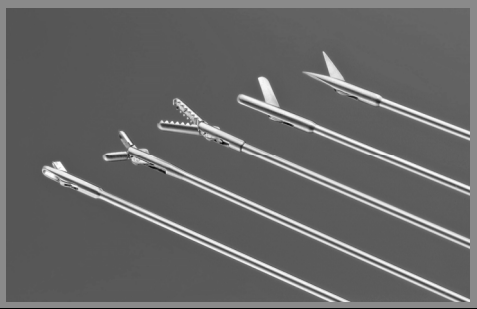
Ambulatory operative Hysteroscopy

5 French Mechanical probes



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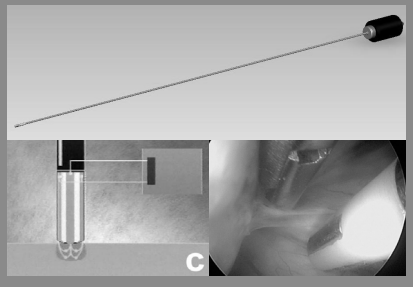
Bipolar coagulation probe (Storz)



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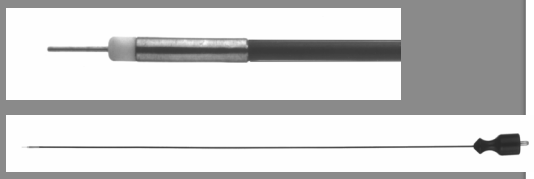
BIPOLAR NEEDLE (STORZ)



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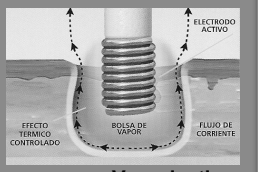
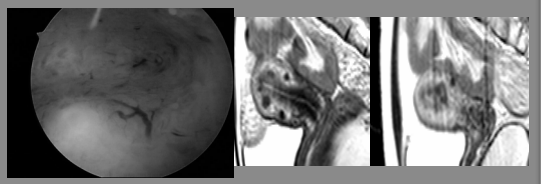
VERSAPOINT (GYNAECARE)



Vaporisation

Ambulatory surgical intervention

Exploration of intramyometrial laesion



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Hysteroscopic Myomectomy

Long-term results in patients with AUB

Results depend on

1. **Uterine size**
2. **Number of myomas**
3. **Type (% intra-mural part)**
4. **Size of myoma**

Conclusions 1

Submucous myoma with alteration of the uterine cavity should be treated both in the infertile as in patients with abnormal uterine bleeding.

Hysteroscopic myomectomy is an effective treatment for patients with symptomatic submucous myoma, particularly when the uterus is not grossly enlarged the amount of fibroid(s) are limited and the localization is mainly inside the uterine cavity.

With the improvement of bipolar instrumentation the indications for hysteroscopic approach are increasing .

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Conclusions 2

See and threat can be done in an ambulatory environment under conscious sedation.

Especially in the field of reproductive medicine the indications for minimal invasive hysteroscopic surgery are significant and increasing.

In our hands the dissection of uterine septa, correction of T shaped uterus, resection of myoma < 2 cm and treatment of Asherman syndrome is done in this set up. The value of this experience is not yet scientificaly validated.

Leuven Institute for Fertilty and Embryology

Leuven Institute for Fertility & Embryology

Stephan Gordts

Rudi Campo
Patrick Puttemans
Sylvie Gordts
Marion Valkenburg
Ivo Brosens

Innovations in fibroid treatment: place in reproduction?

Togas Tulandi MD, MHCM
Professor of Obstetrics and Gynecology
Milton Leong Chair in Reproductive Medicine
McGill University

Case presentation

- 35-45 yrs
- Severe menstrual bleeding leading to anemia
- Large fibroid
- Wants to preserve her fertility

OUTLINE

- Scope of the problem
- Relationship between reproductive function and myoma
- Different treatments
  - Abdominal myomectomy vs. Laparoscopic myomectomy
  - Uterine fibroid embolization
  - Focused ultrasound
- Effects on reproductive function
- Conclusions

Objectives

After completion of the course the participant will be able to:

- Describe the effects of myoma on reproductive function
- Outline management strategy for reproductive aged women
- Analyze, critically evaluate different techniques and properly select the best management

Causes of uterine bleeding

- Pregnancy complications
- Drug-related
- Intrauterine lesions: fibroid, polyp
- IUD related
- Anovulation

- *Coagulation disorder (5-24% adolescents)*

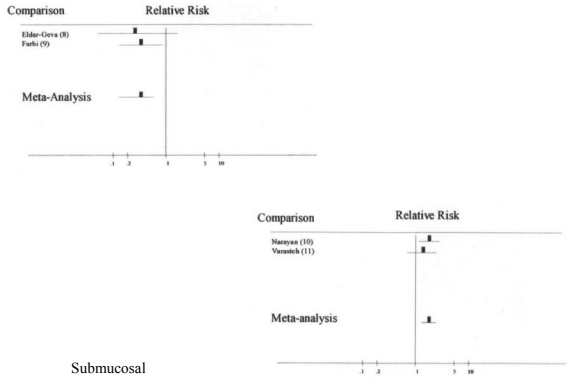
- *Endometrial hyperplasia, cancer*
- *Genital atrophy*

ABNORMAL UTERINE BLEEDING EVALUATION I

- History and Physical Examination
- Serum hCG
- CBC, Ferritin
- Bleeding Time, PT, PTT (von Willebrandt)
- TSH, Thyroid Function Tests
- Endometrial sampling

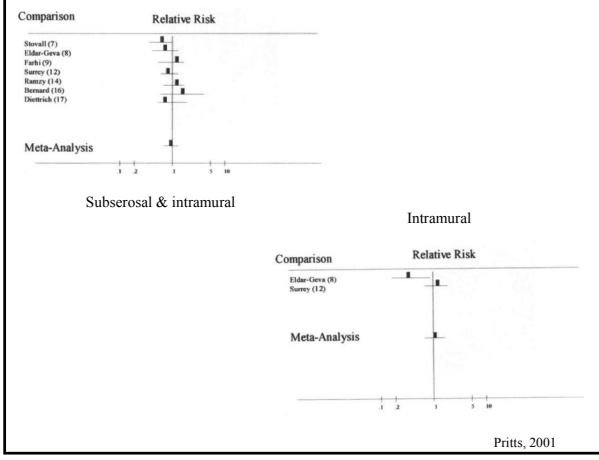
ABNORMAL UTERINE BLEEDING
EVALUATION II

- Transvaginal Ultrasound
- Sonohysterogram (SHG)
- Hysteroscopy



Submucosal

Pritts, 2001



Subserosal & intramural

Intramural

Pritts, 2001

A Randomized Study of Myomectomy by laparotomy vs. laparoscopy (1)

	Laparotomy (n: 65)	Laparoscopy (n: 66)
Febrile morbidity*	26.2%	12.1%
Hemoglobin drop (g/dl)	2.2	1.3
Blood transfusion	3 patients	None
Hospital stay*	5.9 days	3.1 days

Seracchioli et al, 2000

A Randomized Study of Myomectomy by laparotomy vs. laparoscopy (2)

	Laparotomy	Laparoscopy
Pregnancy Rate	55.9%	53.6%
Abortion rate	12.1%	20%
Premature labor	7.4%	5.0%
Uterine Rupture	0	0

Seracchioli et al, 2000

Advantages of Laparoscopic Myomectomy

- Small incisions
- Short hospital stay
- Less postoperative pain
- Rapid recovery
- Good assessment of other organs
- Lower morbidity
- Less adhesion formation (60%)

RTC: Mais et al, 96; Stringer et al, 97

Laparoscopic suturing

Disadvantages of Laparoscopic Myomectomy

- Technically demanding
- Needs expertise in laparoscopic suturing
- Time consuming
- Concerns of integrity of the uterine scar

Ovarian failure following embolization

- **Estimation 1%**
- **Cause: embolization of utero-ovarian vasculature.**
- **Particles in the ovarian vessels.**

Treatment of Uterine Fibroids — Is Surgery Obsolete?

Togas Tulandi, M.D., M.H.C.M.

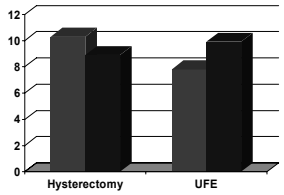
In the early 1990s, Jacques H. Ravina first applied the technique of embolization of uterine arteries to treat uterine fibroids in women at high risk for complications during surgery[1] in an effort to control uterine bleeding. Embolization was then expanded for the treatment of patients who were undergoing myomectomy in order to decrease intraoperative bleeding. In 1993, Ravina and colleagues started using uterine-artery embolization as a primary treatment for uterine fibroids.

Today, interventional radiologists worldwide perform uterine-artery embolization. Most of them embolize the uterine arteries bilaterally and not only the branch supplying blood to a particular fibroid (Fig. 1). In observational studies, embolization has been followed by a significant reduction in uterine volume, a decrease in excessive uterine bleeding, a low rate of subsequent hysterectomy, and a high rate of sustained symptom control (up to 80%) 5 years after the procedure.[2-4] However, comparisons of uterine-artery embolization with other treatments on the basis of observational data are limited by the inherent differences in women who are referred for one treatment instead of another.

In this issue of the *Journal*, Moss et al., writing for the Randomized Trial of Embolization versus Surgical Treatment for Fibroids (REST) Investigators,[5] report on the results of a randomized, multicenter trial comparing uterine-artery embolization with abdominal surgery in women with symptomatic uterine fibroids. The investigators randomly assigned 106 women to undergo embolization and 51 to undergo surgery (including 43 hysterectomies and 8 myomectomies). On the basis of results on the Medical Outcomes Study 36-Item Short-Form General Health Survey questionnaire, they found no significant differences in the quality-of-life scores between the two groups at 1 year, although symptom scores were better in the surgical group at that follow-up assessment. Complication rates were similar at 1 year in the two groups, although the study was not powered to detect differences in these rates or to detect rare complications. Of note, complications generally occurred earlier in the surgical group (typi-

Day 3 FSH value before and after UFE
(Healy, Busaglo, Seti & Tulandi, 2004)

- 68 pts UFE, 16 hysterectomy
- Day 3 FSH: not different



Not recommended

- **Laparoscopic Myolysis**
- **Laparoscopic Uterine artery ligation**

Temporary Uterine Artery Occlusion

Vilos et al, 2005

MRgFUS

From Fennessy & Tempany, 2006

Medical treatment

- Mefenamic acid
- Tranexamic acid (Cyklokapron acetate 1 gm 3-4 times daily)
- GnRHa *53% of women after medical treatment required hysterectomy before the 2nd year.*
- L-norgestrel-releasing intrauterine system

  42% eventually underwent hysterectomy

Case presentation

- 35-45 yrs
- severe menstrual bleeding leading to anemia
- Large fibroid
- Wants to preserve her fertility

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Surgical treatment to enhance fertility. Contra

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Learning objectives

1. To understand the basic concepts of evaluating studies on myomectomy for fertility.
2. To describe the potential risks and benefits of different methods of myomectomy.
3. To understand the importance of proper counseling before deciding for myomectomy.

Lecture summary

Background
Uterine fibroids are the most common type of tumor in the female reproductive system. The presence of fibroids can be associated with subfertility and miscarriage in women of reproductive age. For women wishing to maintain their fertility, myomectomy has been suggested in selected cases. There is however, a lack of high quality studies proving that myomectomy is effective in improving fertility. This lecture will present an up-to-date literature search on the possible risks and benefits of myomectomy focussing on intramural fibroids.

Fibroids association with reproductive failure
The link between fibroids and subfertility has several possible explanations, including impaired gamete transport and reduced implantation ability due to local factors affecting receptors and vascular supply. The association is not easily studied epidemiologically, but the IVF situation may serve as a model to study implantation in the presence of fibroids. These studies are not entirely in consensus and those with negative findings usually include a small sample size. In a study of 432 patients, the cumulative live birth rate after three cycles was compared in patients with fibroids < 5 cm to patients without fibroids (1). After adjusting for confounding variables, the presence of fibroids was found to significantly reduce the live birth rate at each cycle by 45% (HR=0.55, 95% CI=0.32-0.95, P=0.03) and the authors concluded that small intramural fibroids are associated with a significant reduction in the cumulative pregnancy, ongoing pregnancy and live birth rates after three IVF/ICSI cycles. Another prospective study demonstrated by logistic regression that the presence of intramural fibroids was one of the significant variables affecting the chance of an ongoing pregnancy, even after controlling for the number of embryos available for replacement and increasing age, particularly age > or =40 years, odds ratio 0.46 (CI 0.24-0.88; P = 0.019) (2). The conclusion stated that an intramural fibroid halves the chances of an ongoing pregnancy following assisted conception.

It is important to remember that these studies concern IVF-pregnancies and not pregnancies achieved after spontaneous conception. A systematic review could only demonstrate a negative impact if submucous or fibroids with an intracavitary component was present (3). Furthermore, even if there is an association between the presence of uterine fibroids and reduced chance of pregnancy, these studies do not answer whether surgery is beneficial or not.

Validity of studies on intervention
To properly evaluate the efficacy of myomectomy, we would need to have a randomized controlled trial (RCT) comparing surgery to expectancy with long enough time for follow-up to study spontaneous conception and no such study has been conducted.
RCT is considered to contribute with the highest level of evidence to evaluate the efficacy of an intervention, since the randomization will give an even distribution of known and unknown factors, affecting fertility. Usually systematic reviews of RCT's are considered to have the same high level of evidence. In the second level we find observational studies like cohort studies and case-control studies. In the third level, uncontrolled studies like case series have a rather poor validity for evaluation of treatment effects.

Evidence for beneficial effect of myomectomy?
What types of studies are available for evaluation of myomectomy to increase fertility? Unfortunately, the majority of studies are case-series comparing pregnancy results after surgery to the 100% of pregnancy failure before surgery. The problem is the lack of a proper control group, since few patients would like to join the expectancy group. Another problem is the difficulty in blinding the patient to whether or not she has had surgery.
Available studies demonstrate cumulative clinical pregnancy rates of 57-67% after one year (4). Factors associated with postoperative cumulative conception rate were typical subfertility factors like age, duration of infertility and additional infertility factors and not factors relating to the fibroids or the surgery.

A systematic review from the Cochrane library had the aim to determine the efficacy and safety of the removal of uterine fibroids in subfertile women by laparotomy, laparoscopy or hysteroscopy when compared with expectant management or each other (3). Only one randomized controlled study was included (131 women) and this was probably underpowered. There was no evidence of a difference in outcome in terms of clinical pregnancy rate and live birth rate when fibroids were removed via laparotomy or laparoscopy for infertility. There were no randomised controlled studies comparing hysteroscopic removal or no intervention with other surgical modalities. The authors concluded that there is limited evidence to suggest that there is no difference in fertility efficacy outcome if fibroids are removed via laparotomy when compared to laparoscopy. There is no good randomised controlled evidence to support hysteroscopic removal of fibroids compared to other surgical modalities for fertility efficacy.
An analysis of the 109 medical records of symptomatic patients who had myomectomy over a 5-year period revealed the following complication rates: 34 (31%) had an estimated blood loss of 500 ml and 23 of these patients needed blood transfusion (5). There were four cases of unscheduled hysterectomies due to uncontrollable bleeding. Pyrexia was the most common (38%) postoperative complication followed by superficial wound infection in 5%. In view of the risks and potential failure of treatment associated with myomectomy, the authors stress the fact that patients should be properly counselled before embarking on myomectomy and they strongly advocate local data to form the basis of the advice given during the consultation rather than what obtains in the literature.

In contrast, another observational study found the main determinants of pregnancy rate after surgery to be diameter and intramural localization of the myomas (compared to subserous) and type of surgery (laparoscopy superior to laparotomy) in addition to patient age (6).
A long-term complication, presented in several case-reports, is the occurrence of uterine rupture in a pregnancy subsequent to laparoscopic myomectomy.

The effect of GnRH analogue prior to fibroid surgery has been summarized in a systematic review from the Cochrane library (7). The use of GnRH analogue for three to four months prior to surgery reduces both uterine volume and fibroid size. They are beneficial in the correction of pre-operative iron deficiency anaemia, if present, and reduce intra-operative blood loss. If uterine size is such that a midline incision is planned, this can be avoided in many women with the use of GnRH analogue. For women undergoing hysterectomy, a vaginal procedure is more likely following the use of these agents. In a cost-effectiveness analysis, the benefits did not justify the costs.

Conclusions

The impact of fibroids on fertility is difficult to measure. IVF-studies indicate that the chance of a pregnancy after IVF treatment is impaired by the presence of fibroids. The efficacy of myomectomy in improving fertility as not been tested in a RCT. There is limited evidence to make any comparisons between laparotomy and laparoscopy concerning fertility efficacy.

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