

Università degli Studi di Padova Dipartimento di Salute della Donna e del Bambino - SDB U.O.C. Clinica Ginecologica e Ostetrica Direttore Prof. Giovanni B. Nardelli

#### Efficacia della miomectomia isteroscopica nel miglioramento del pregnancy outcome nelle pazienti infertili

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Scuola di Specializzazione in Ginecologia e Ostetricia Anno Accademico 2015-2016



#### Vi è un consenso generale nel ritenere che i miomi influenzino negativamente la capacità fertile nella donna

#### Anche se la maggior parte delle pazienti con fibromi sono fertili, le evidenze suggeriscono che la loro presenza possa interferire con la fertilità

(Pritts, 2001; Donnez and Jadoul, 2002; Benecke et al., 2005; Somigliana et al., 2007).



### **INFERTILITA'**

#### Componente critica della salute riproduttiva con una rilevanza sociale molto importante.

72,4 milioni di coppie infertili



40,5 milioni di trattamenti per la fertilita'

(Boivin et al. 2007)



Organizzazione Mondiale della Sanità (O.M.S.) American Fertility Society (A.F.S.)

- INFERTILITA': La coppia non è in grado di concepire e di avere un bambino dopo un anno o più di rapporti sessuali;
- STERILITA': uno o entrambi i coniugi sono affetti da una condizione fisica permanente che non rende possibile avere dei bambini.



### MECCANISMO D'AZIONE

•Alterazione dell'anatomia uterina con distorsione della cavità o ostruzione degli osti. Istologicamente si evidenziano allungamento e modificazione del decorso delle ghiandole, iperplasia ghiandolare cistica, poliposi, ectasia delle venule endometriali

•Alterazioni funzionali: aumento della contrattilità, alterazione dell'apporto di sangue, e infiammazione cronica endometriale. Istologicamente si evidenzia atrofia e ulcerazione ghiandole.

•Alterazioni endocrine per secrezione ormonale locale anomala

•Alterazioni molecolari paracrine: secrezioni di amine vasoattive e sostanze infiammatorie locali



# FIBROMI

- Tumori benigni più frequenti nelle donne.
- Dipendono dalla produzione ormonale ovarica
- Origine non è ancora perfettamente nota.
- Ipotesi di origine monoclonale. Si sviluppano dalla mutazione di una singola cellula staminale miometriale sotto influenza ormonale dopo multipli cicli di crescita incontrollata successiva degenerazione

(bulun serdar uterine fibroids NEJM 2013)



# EPIDEMIOLOGIA

- Colpiscono 7-8/10 donne
- Riscontro casuale in corso di esame istologico post isterectomia prevalenza del 75%

(Cook H. Ezzati the impact of uterine leyomioma on reproductive outcome).

- La prevalenza è più alta nelle pazienti con storia di infertilità.
- Tra le pazienti candidate a IVF o ICSI, 1/4 presenta fibromi
- Escluse tutte le altre cause di infertilità, i fibromi possono avere un ruolo rilevante solo nel <u>2-3%</u> dei casi



# CLASSIFICAZIONE

#### PALM-COEIN subclassification system for leiomyomas



From: Munro MG. Abnormal Uterine Bleeding. Cambridge: Cambridge University Press, 2010. Copyright © 2010 M. Munro. Reprinted with the permission of Cambridge University Press.



### CLASSIFICAZIONE

Fibroid classifications systems.

	Fibroid Classification	
Classical		FIGO (2011)
Submucosal – type 0	100% intracavity	0
Submucosal – type I	>50% intracavity	1
Submucosal – type II	<50% intracavity	2
Intramural	In contact with endometrium	3
Intramural	100% intramural	4
Intramural	Intramural but <50% subserosal	5
Subserosal	Subserosal but <50% intramural	6
Subserosal	Pedunculated	7



#### CLASSIFICAZIONE





# LASMAR'S CLASSIFICATION

Classificazione per la valutazione pre-operatoria è quella proposta da Lasmar et al. che considera non solo il grado di invasione miometriale ma anche altri parametri come l'estensione della base del fibroma in relazione alla parete uterina, la dimensione, e la posizione.

Un punteggio da 0-2 viene dato ad ogni parametro, e le pazienti vengono divise in 3 gruppi.

Gli autori hanno riscontrato un'importante correlazione tra questo sistema e il grado di difficoltà della miomectomia, il tempo e il deficit del bilancio idrico.



### LASMAR'S CLASSIFICATION

#### Submucous myomas: A new presurgical classification to evaluate the viability of hysteroscopic surgical treatment—Preliminary report

#### Ricardo Bassil Lasmar, MD, Paulo Roberto Mussel Barrozo, MD, Rogério Dias, MD, PhD, and Marco Aurélio Pinho de Oliveira, MD, PhD

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#### **KEYWORDS:**

Submucous myomas; Hysteroscopy; Classification; Hysteroscopic myomectomy

#### Abstract

**STUDY OBJECTIVE:** To develop a new preoperative classification of submucous myomas for evaluating the viability and the degree of difficulty of hysteroscopic myomectomy.

DESIGN: Retrospective study (Canadian Task Force classification II-3)

SETTING: University teaching hospitals.

PATIENTS: Fifty-five patients who underwent hysteroscopic resection of submucous myomas.

**INTERVENTION:** The possibility of total resection of the myoma, the operating time, the fluid deficit, and the frequency of any complications were considered. The myomas were classified according to the Classification of the European Society for Gynaecological Endoscopy (ESGE) and by our group's new classification (NC), which considers not only the degree of penetration of the myoma into the myometrium, but also adds in such parameters as the distance of the base of the myoma from the uterine wall, the size of the nodule (cm), and the topography of the uterine cavity. The Fisher's exact test, the Student's *t* test, and the analysis of variance test were used in the statistical analysis. A p value less than .05 in the two-tailed test was considered significant.

**MEASUREMENTS AND MAIN RESULTS:** In 57 myomas, hysteroscopic surgery was considered complete. There was no significant difference among the three ESGE levels (0, 1, and 2). Using the NC, the difference between the numbers of complete surgeries was significant (p < .001) for the two levels (groups I and II). The difference between the operating times was significant for the two classifications. With respect to the fluid deficit, only the NC showed significant differences between the levels (p = .02).

**CONCLUSIONS:** We believe that the NC gives more clues as to the difficulties of a hysteroscopic myomectomy than the standard ESGE classification. It should be stressed that the number of hysteroscopic myomectomies used in this analysis was low, and it would be interesting to evaluate the performance of the classification in a larger number of patients. © 2005 AAGL. All rights reserved.



# LASMAR'S CLASSIFICATION

Table I:	Lasmar	's pre-surgical	classification	of submuce	ous myomas
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Points	Penetration	Size, cm	Base <sup>a</sup>	Third	Lateral wall (+1)
0 1	$0 \leq 50\%$	$\leq 2 \\ > 2 - 5$	$\leq 1/3$ >1/3 to 2/3	Lower Middle	
2 Score	>50% +	>5 +	>2/3 +	Upper +	=

<sup>a</sup>It refers to the extension of the base of the nodule with respect to the uterine wall on which the myoma is located. Score 0-4 (Group I): low complexity hysteroscopic myomectomy. Score 5-6 (Group II): complex hysteroscopic myomectomy, consider preparing with GnRH analogue and/or two stage surgery. Score 7-9 (Group III): recommend an alternative non-hysteroscopic technique.







#### Pregnancy outcome after hysteroscopic myomectomy

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#### Abstract

The objective of this longitudinal retrospective study was to evaluate the influence of submucosal myomas on pregnancy outcome in infertile patients after resectoscopic myomectomy. One-hundred and four women with at least a 1-year-long history of infertility and the presence of submucosal myomas as the only cause of infertility were selected after surgical treatment. Pregnancy, delivery and abortion rates were investigated. Patients were divided into three groups according to the myoma classification (G0, G1 and G2). Gestational outcomes were analyzed in the three groups correlated by size, location and number of fibroids. The total pregnancy rate was 85.8% and no difference was shown regarding myoma classification (G0 82.05% versus G1 87.09% versus G2 88.2%; p = ns). Pregnancy and delivery rates were not significantly related to the number, localization or diameter of the fibroids. The abortion rate was not statistically influenced by myoma type, but it was significantly interelated with myomas situated in the anterior uterine wall (p = 0.03). Pre-term delivery was significantly influenced by myomas localized in the fundic wall (p = 0.02). Caesarean section rates were not affected by the characteristics of the myomas. Our results support the idea that resectoscopic myomectomy should be offered to infertile women who wish to become pregnant independently of their localization and number.

#### Keywords

Abortion rate, delivery rate, hysteroscopic myomectomy, pregnancy rate, submucous myomas

#### History

Received 10 May 2013 Revised 22 October 2013 Accepted 5 November 2013 Published online 5 December 2013



Sono state esaminate 104 donne inviate presso il servizio di Ginecologia della Clinica Ginecologica e Ostetrica di Padova

#### Criteri di inclusione

- presenza di 1 o > miomi sottomucosi
- desiderio di gravidanza
- almeno 1 anno di storia di infertilità inspiegata
- età compresa tra 18 e 42 anni



# MATERIALS AND METHODS

Valutazione pre-operatoria:

- eco TV: margine libero miometriale (limite di sicurezza >4 mm)
- isteroscopia diagnostica: numero, dimensione e sede dei miomi.
- Successivamente era stata eseguita la miomectomia con resettoscopio monopolare da 26 F, ottica a 12°.
- Miomi G1-G2 : "enucleation in toto"
- G0: slicing



# MATERIALS AND METHODS

	Myomas and surgical characteristic			
	G0	G1	G2	Tot
Patients n.	39 (37.5)	31 (29.8)	34(32.7)	104
Age mean	$37 \pm 4.4$	$36 \pm 4.4$	$35 \pm 4.5$	$35.7 \pm 4.4$
Single myomectomy	37 (40.6)	27 (29.7)	27 (29.7)	91 (87.5)
Multiple myomectomy	2 (15.4)	4 (30.7)	7 (53.9)	13 (12.5)
Diameter mean mm	$26.79 \pm 8.24$	$30.48 \pm 8.31$	$27.20 \pm 8.74$	$28.02 \pm 8.8$
Diameter $\geq$ 30 mm	16 (30.2)	20 (37.7)	17 (32.1)	53(50.9)
Diameter <30 mm	23 (45.1)	11 (21.6)	17 (33.3)	51(49.1)
Mean operative time (min)	$16.02 \pm 11.1$	$21.58 \pm 11.7$	$21.67 \pm 10.8$	$19.54 \pm 11.0$
Two steps	1 (0.96)	1(0.96)	3 (2.88)	5 (4.8)
Location				
Anterior	11	11	7	29
Posterior	17	8	16	41
Lateral	6	7	1	14
Fundus	1	2	8	11
Cornual	2	2	_	4
Istmus	2	1	2	5
GnRh analogs	-	5 (25.0)	15(75.0)	20(19.2)



# RISULTATI

- Pregnancy rate totale 85,8%
- Numero di gravidanze ottenute simile in tutti i gruppi
- Il numero e la dimensione dei fibromi non influiscono sul PR
- La localizzazione del mioma sembra essere l'unico fattore in grado di interferire col il successo di una gravidanza (miomi situati sulla parete anteriore si associano ad un rischio più elevato di aborto)
- Non correlazione tra delivery rate con numero, dimensioni o localizzazione del mioma
- 42 (61.8%) parti a termine di gravidanza
- 26 (38,2 %) parti tra la 33+0 e 37+6 sg.
- No very low preterm birth
- Correlazione tra la posizione del mioma e l'età gestazionale al parto (associazione tra miomi fundici e parto pretermine)
- 39 (57,4%) parti spontanei
- 29 (42,6 %) TC per motivi esclusivamente ostetrici



### RISULTATI

Table 2. Pregnancy rate and obstetrical outcome according to fibroids features. Data are expressed by mean  $\pm$  SD, or number and percentage.

	Pregnancy	Term delivery	Preterm delivery	Miscarriage	р
Multiple myomectomy	10 (90.9)	4 (36.3)	3 (27.3)	3 (27.3)	ns
GO	32 (82.0)	14 (35.9)	7 (17.9)	11 (28.2)	ns
G1	27 (87.0)	12 (38.7)	10 (32.2)	5 (16.1)	ns
G2	30 (88.2)	16 (47.0)	9 (26.5)	5 (14.7)	ns
Diameter $\geq$ 30 mm	44 (83.0)	19 (35.8)	14 (26.4)	11 (20.8)	ns
Diameter <30 mm	45 (88.2)	23 (45.1)	12 (23.5)	10 (19.6)	ns
Location					
Anterior	26 (89.3)	8 (27.6)	8 (27.6)	10 (34.5)†	0.03
Posterior	32 (78.0)	20 (40.8)	6 (14.6)	6 (14.6)	ns
Lateral	9 (64.2)	4 (28.6)	4 (28.6)	1 (7.1)	ns
Fundus	12 (100)	4 (36.3)	6 (54.5)‡	2 (18.2)	0.02
Cornual	5 (100)	3 (75.0)	1 (25.0)	1 (25.0)	ns
Istmus	5 (100)	3 (60.0)	1 (20.0)	1 (20.0)	ns

<sup>†</sup>Miscarriage rate is statistically significant in anterior location of fibroids.

‡Preterm delivery rate is statistically significant in fundus location of fibroids.



CONCLUSIONI

Dai dati raccolti si può affermare che tutti i tipi di miomi, indipendentemente dal numero, sito e dimensione dovrebbero essere rimossi .

La miomectomia isteroscopica dovrebbe essere raccomandata per Pazienti che presentano come unica causa di infertilità miomi sottomucosi.



# RACCOMANDAZIONI

Current recommended practice for the treatment of myomas.

Туре	Indication for surgical t	Current recommendations		
	Impact on reproductive potential	Effectiveness of surgical intervention	Additional indications	
Submucosal	Significant impairment	Significant improvement	Abnormal Uterine Bleeding	Excision: Hysteroscopic
Intramural >4cm	Significant impairment	Improvement (need further evidence)	Potential pregnancy complications Symptoms	Excision: Preferably laparoscopic
Intramural <4cm Subserosal	Unclear Nonsignificant	Unclear Nonsignificant	Unclear Potential complications	Expectant management <sup>a</sup> Expectant management <sup>b</sup>

<sup>a</sup> Surgery indicated only in cases of multiple IVF failures or poor obstetrical outcome.

<sup>b</sup> Surgery indicated only in the presence of associated symptoms or poor obstetrical outcome.



#### MARGINE MIOMETRIALE LIBERO

#### Should the myometrial free margin still be considered a limiting factor for hysteroscopic resection of submucous fibroids? A possible answer to an old question

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**Objective:** To evaluate the feasibility of the hysteroscopic resection of type II submucous fibroids regardless of the myometrial free margin separating them from the serosa and to report the dynamic changes the margin undergoes after the various phases of resection.

Design: A prospective observational study.

Setting: A tertiary-level university hospital.

Patient(s): Thirteen women with single type II submucous fibroids of  $\leq 5$  cm in diameter regardless of the myometrial free margin.

Intervention(s): Hysteroscopic myomectomy and ultrasound evaluation of myometrial free margin before and after each phase of the procedure.

Main Outcome Measure(s): The possibility of a complete one-step resection, the incidence of intraoperative or postoperative complications, and the analysis of the dynamic changes occurring in myometrial free margin.

**Result(s):** Complete resection was performed successfully in all patients. No complications were registered. The myometrial free margin decreased on the distension of the uterine cavity and then increased progressively and significantly after the various phases of resection.

**Conclusion(s):** In selected cases and in experienced hands, hysteroscopic myomectomy of type II submucous fibroids may be performed successfully and safely regardless of the myometrial free margin. Myometrial free margin increases progressively with each step of the procedure probably leading to an increasing margin of safety. (Fertil Steril<sup>®</sup> 2011;95:1764–8. ©2011 by American Society for Reproductive Medicine.)

Key Words: Submucous fibroids, hysteroscopy, myomectomy, ultrasound, myometrial free margin







### TECNICHE RESETTOSCOPICHE



Coold loop technique (sec Mazzon)

Slicing mediante ansa angolare della parte intracavitaria del mioma.

Una volta raggiunta la base rottura meccanica dei tralci fibrosi mediante anse a freddo (anse sec. Mazzon)



### TECNICHE RESETTOSCOPICHE



Enucleation in toto' (Litta's technique):incisione ellittica sulla mucosa che riveste il mioma con 908 Collins electrode. Al livello della sua riflessione sulla parete uterina finchè non si individua il piano di clivaggio. Vengono resecati tralci fibrosi che circondano I miociti.

Il mioma protrude in cavità facilitando la rimozione mediante slicing



### MORCELLAMENT





#### **Review Article**

#### Hysteroscopic Morcellation Versus Resection for the Treatment of Uterine Cavitary Lesions: A Systematic Review and Meta-analysis

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From the Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, Minnesota (Drs. Shazly, Laughlin-Tommaso, Breitkopf, Hopkins, Burnett, Green, and Famuyide), Department of Obstetrics and Gynecology, Assiut University, Assiut, Egypt (Dr. Shazly), Mayo Clinic Library, Mayo Clinic, Rochester, Minnesota (Dr. Farrell), and Evidence-based Practice Center, Center for Science of Healthcare Delivery, Mayo Clinic, Rochester, Minnesota (Dr. Murad).

**ABSTRACT** This systematic review and meta-analysis compares hysteroscopic morcellation with electrosurgical resection to treat uterine cavitary lesions. A search of Ovid MEDLINE, Ovid Embase, Scopus, and Web of Science was conducted through August 18, 2015, for randomized controlled trials (RCTs) and prospective and retrospective studies, regardless of surgical indication and study language or sample size. Seven studies were eventually included (4 RCTs and 3 retrospective observational studies), enrolling 650 women. The meta-analysis showed that the total procedure time was significantly shorter for morcellation than for resection (weighted mean difference = 9.36 minutes; 95% confidence interval [CI], -15.08 to -3.64). When reviewing RCTs only, intrauterine morcellation was associated with a smaller fluid deficit and lower odds of incomplete lesion removal. This difference was not statistically significant in observational studies. There was no significant difference in the odds of surgical complications (odds ratio = 0.72; 95% CI, 0.20–2.57) or the number of insertions (weighted mean difference = -3.04; 95% CI, -7.86-1.78). In conclusion, compared with hysteroscopic resection, hysteroscopic morcellation is associated with a shorter operative time and possibly lower odds of incomplete lesion removal. The certainty in evidence was limited by heterogeneity and the small sample size. Journal of Minimally Invasive Gynecology (2016) **I**, **I** – **I** © 2016 AAGL. All rights reserved.



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# MORCELLAMENT





#### L'isteroscopia diagnostica sistematica è indicata in pazienti senza sospetto di anomalie uterine con storia di infertilità o poliabortività





#### Efficacy of hysteroscopy in improving reproductive outcomes of infertile couples: a systematic review and meta-analysis

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**BACKGROUND:** The scientific community has been re-evaluating the clinical relevance of hysteroscopy in the diagnosis and treatment of uterine factors and its role in the infertility work-up, thanks to its potential capability to improve reproductive outcomes and reduce time to pregnancy.

**OBJECTIVE AND RATIONALE:** The objective of this systematic review and meta-analysis was to assess the efficacy of diagnostic and operative hysteroscopy in improving the live birth rate (LBR) of infertile women, with and without intrauterine abnormalities, at any stage of the infertility work-up.



**SEARCH METHODS:** PubMed, Embase, the Cochrane Library and the Clinical Trials Registry using Medical Subject Headings and free text terms were searched up to June 2014, without language or year restrictions. Randomized controlled trials (RCTs) enrolling infertile women with no suspected intrauterine cavity abnormalities and comparing hysteroscopy versus no hysteroscopy at any stage of the diagnostic work-up, but prior to the first attempt of standard IVF or ICSI or after (one or more) failed attempts of IVF/ICSI were included. RCTs enrolling infertile women with intrauterine abnormalities and comparing operative versus diagnostic hysteroscopy were also included. RCTs enrolling infertile women with intrauterine abnormalities and comparing operative versus diagnostic hysteroscopy were also included. Risk of bias was assessed using the criteria recommended by the Cochrane Collaboration and the overall quality of evidence was assessed using the GRADE approach. Results were pooled by meta-analysis using the random effect model.

**OUTCOMES:** The primary outcome evaluated was the LBR, while secondary outcomes were pregnancy rate, miscarriage rate and procedurerelated complications. Five hundred and eighty-eight records were retrieved after removing duplicates. Nine studies were included, with 2976 participants. Four studies included infertile women with one or more failed IVF/ICSI cycles. Two studies included infertile women who were candidates for their first IVF/ICSI. One study included candidates both for first IVF/ICSI and with one or more failed IVF/ICSI cycles. Two studies included infertile women affected by uterine fibroids and endometrial polyps, who had not received IVF/ICSI nor were candidates. Seven studies were included in the meta-analysis. Comparing hysteroscopy with no hysteroscopy prior to any (first or subsequent) IVF/ICSI attempt in infertile women without intrauterine abnormalities, there was very low-quality evidence that hysteroscopy increased LBR (relative risk (RR) 1.48, 95% confidence interval (CI) 1.20–1.81; three studies with 1088 participants) and moderate quality evidence that it increased pregnancy rate (RR 1.45, 95% CI 1.26–1.67; seven studies, 2545 participants). Results on pregnancy rate were confirmed in the subgroup analysis of five studies including only women with one or more implantation failures (RR 1.41, 95% CI 1.14–1.75) and three studies where hysteroscopy was performed before the first IVF/ICSI attempt (RR 1.55, 95% CI 1.26–1.91). Comparing operative hysteroscopy for intrauterine abnormalities in infertile women with already diagnosed polyps or fibroids, there was low-quality evidence that operative hysteroscopy increases pregnancy rate (RR 2.13, 95% CI 1.56–2.92). None of the studies comparing operative versus diagnostic hysteroscopy assessed LBR.

**WIDER IMPLICATIONS:** Robust and high-quality RCTs are still needed before hysteroscopy can be regarded as a first-line procedure in all infertile women, especially during the basal clinical assessment of the couple, when assisted reproductive treatment is not indicated yet.

Key words: hysteroscopy / infertility / live birth rate / meta-analysis / pregnancy rate / polyps / myomas / systematic review



# VANTAGGI

In alcuni studi è stato dimostrato che i benefici dell'isteroscopia vadano oltre il trattamento di anomalie uterine; i meccanismi implicati sembrano essere:

- l'irrigazione della cavità uterina potrebbe avere un effetto positivo sull'impianto e sul PR dato che rimuove molecole dannose come glico proteine anti adesive sulla superficie endometriale implicate nella recettività endometriale (cox-2, mucin I, integrin a Vb3) Takahashi et al 2000
- L'isteroscopia diagnostica potrebbe facilitare l'embryo transfer mediante la lisi di eventuali aderenze cervicali durante il passaggio dell'isteroscopio e permettendo di studiare la morfologia e il decorso del canale cervicale e
- La manipolazione meccanica dell'endometrio potrebbe amplificare la recettività modulando l'espressione di geni che codificano per fattori necessari per l'impianto Glycodelin A (Mirkin et al 2005), alpha 4 laminina, alpha 6 integrina e metalloproteinasi I di matrice (Almong et al 2010)





- Da un primo confronto sembra che l'isteroscopia diagnostica e il trattamento di anomalie uterine migliori il PR
- II PR sembra essere migliorato anche in caso di riscontro isteroscopico normale suggerendo che la semplice esecuzione della procedura conferisca un fattore prognostico positivo per instaurarsi di una gravidanza