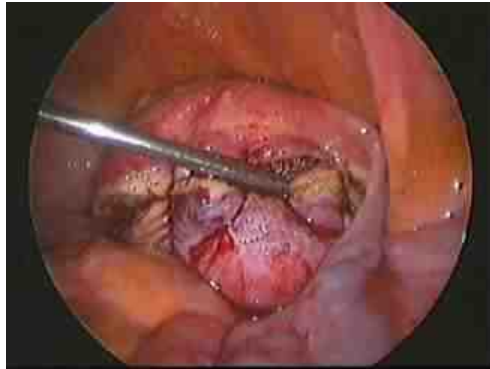


Laparoscopic Myomectomy Pros and Cons in Infertile Patients



Prof. Cihat UNLU, M. D.,
Istanbul Acibadem University Bakırkoy Hospital
Department of Obstetrics and Gynecology



Incidence

- Approximately 5% to 10% of women presenting with infertility are found to have one or multiple fibroids.

Donnez J, Jadoul P.

Hum Reprod 2002;17:1424-30

- However, when all other causes of infertility are excluded, fibroids are found in only 1% to 2% of the remaining women.

Cook H, Ezzati M, Segars JH, McCarthy K.

Minerva Ginecol 2010;62:225-36

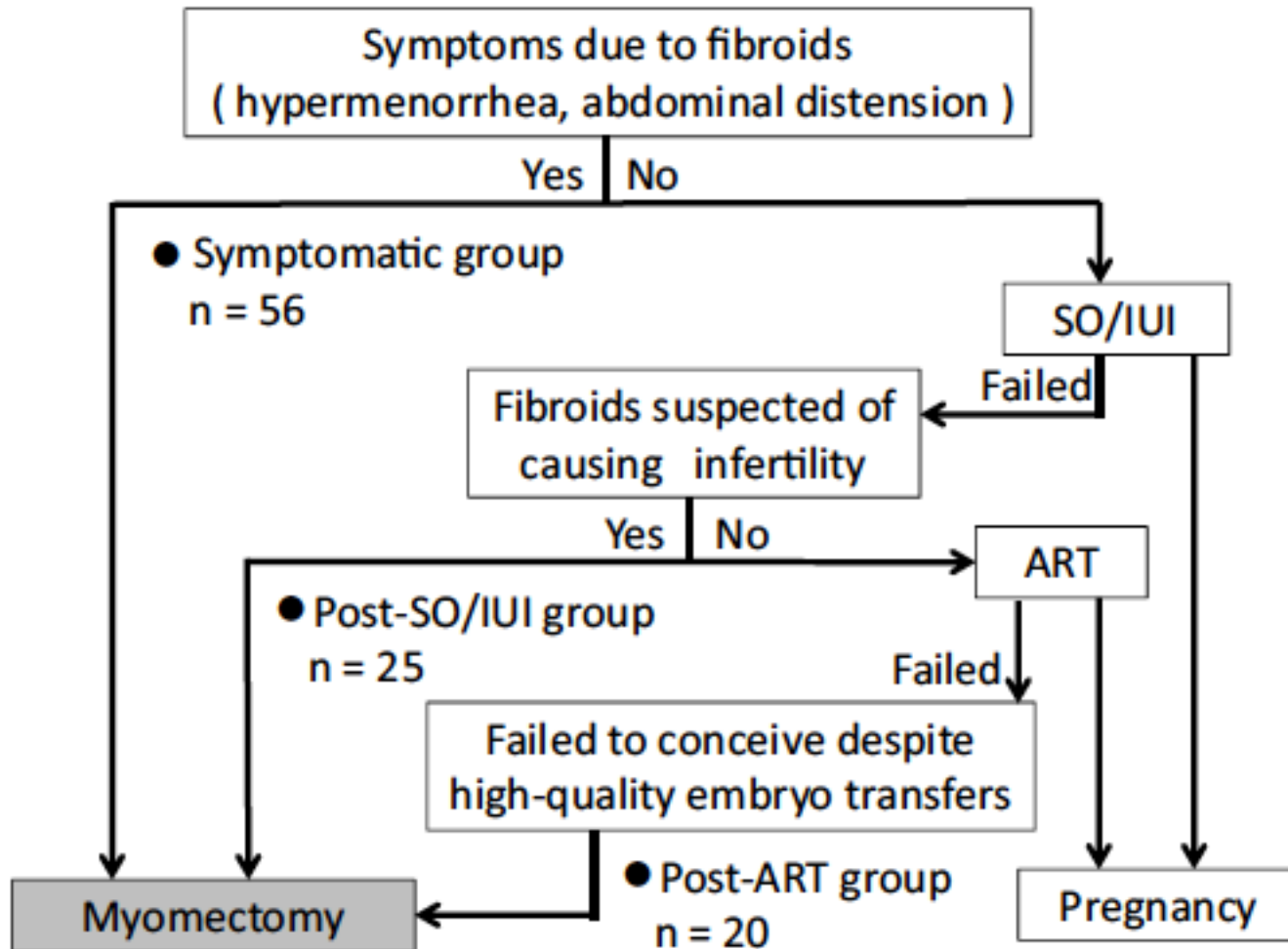
- There have been no appropriately designed studies to demonstrate a direct causal relationship between the presence of fibroids and infertility.

Fibroids and Infertility

Mechanisms of Action

- Mechanisms involving alteration of local anatomy, which is associated with the anatomic distortion of the endometrial cavity or the obstruction of the fallopian tubes.
- Mechanisms involving functional changes, for example, increased uterine contractility, impairment of the endometrial blood supply, and chronic endometrial inflammation. One of the most frequently observed histological changes attributed to fibroids is glandular atrophy and ulceration, affecting the proximal and even the distal part of the endometrium.
- Endocrine mechanisms supported by the theory of an abnormal local hormonal milieu
- Finally, fibroids may induce paracrine molecular effects on the adjacent endometrium, for example, secretion of vasoactive amines and local inflammatory substances to the extent that they are capable of impairing fertility

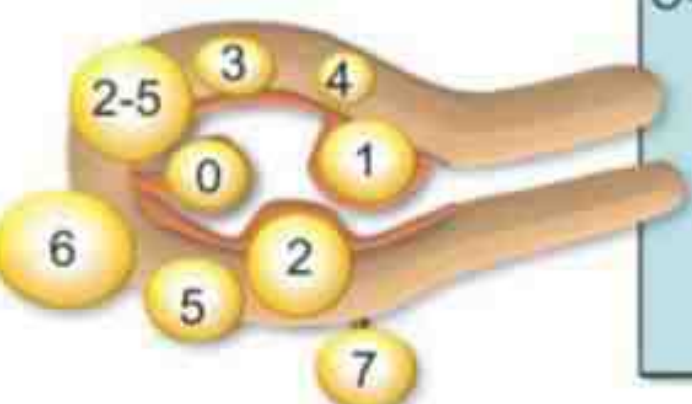
Identifying patients who can improve



Identifying patients who can improve fertility with myomectomy

- In this study, they report three important findings.
 - **First**, postmyomectomy pregnancy rates were higher in women who did not have additional infertility factors in comparison with women with infertility factors.
 - **Second**, the location of fibroids did not correlate with the post-myomectomy pregnancy rate.
 - **Third**, patients in the post-ART group, where enucleation penetrated the endometrial cavity, showed a significantly higher pregnancy rate than patients whose endometrial cavity had not been penetrated.

Pictorial leiomyoma classification system



S M-Submucous	0	Pedunculated Intracavitary
	1	<50% Intramural
	2	≥ 50% Intramural
O- Other	3	Contacts endometrium; 100% Intramural
	4	Intramural
	5	Subserous ≥50% Intramural
	6	Subserous < 50% Intramural
	7	Subserous Pedunculated
	8	Other (specify eg. cervical, parasitic)

Effect of fibroids on fertility: *all locations.*

Outcome	Number of studies/substudies	Relative risk	95% confidence interval	Significance
Clinical pregnancy rate	18	0.849	0.734–0.983	$P = .029$
Implantation rate	14	0.821	0.722–0.932	$P = .002$
Ongoing pregnancy/live birth rate	17	0.697	0.589–0.826	$P < .001$
Spontaneous abortion rate	18	1.678	1.373–2.051	$P < .001$
Preterm delivery rate	3	1.357	0.607–3.036	Not significant

Pritts. Fibroids and infertility. *Fertil Steril* 2009.

- the relative risks of
 - clinical pregnancy,
 - implantation,
 - ongoing pregnancy/live birth were all significantly lower in women with myomas than in control subjects.
- the spontaneous abortion rate was significantly greater in women with fibroids.
- No significant difference in preterm delivery rates was observed

Fibroids and infertility: an updated systematic review of the evidence

Elizabeth A. Pritts, M.D.,^a William H. Parker, M.D.,^b and David L. Olive, M.D.^c

Two questions?

- 1. Do uterine fibroids, of specific size or location, decrease fertility?**
2. Does removal of the fibroid(s) enhance fertility?

Subserosal fibroids

- Subserosal fibroids do not appear to have an impact on fertility; all systematic reviews and meta-analyses agreed on this point.

Pritts EA, Parker WH, Olive DL.
Fertil Steril 2009;91:1215

Submucosal fibroids

- Submucosal fibroids (fibroids with endometrial impingement), however, have been shown uniformly to have a **negative impact** on rates of
 - implantation,
 - clinical pregnancy,
 - miscarriage, and
 - live birth/ongoing pregnancy

Pritts EA, Parker WH, Olive DL.

Fertil Steril 2009;91:1215

Intramural fibroids

- The greatest debate remains on the impact and treatment of intramural fibroids.
- Considering only the most recent good quality meta-analysis, intramural fibroids do seem to have an impact on both IR and CPR (RR 0.684; 95% CI 0.587 to 0.796, $P < 0.001$ and RR 0.810; 0.696 to 0.941, $P = 0.006$, respectively) but less than that of submucosal fibroids.

Pritts EA, Parker WH, Olive DL.

Fertil Steril 2009;91:1215

Effect of fibroids on fertility: *intramural fibroids*.

Outcome	Number of studies/ substudies	Relative risk	95% confidence interval	Significance
A. All studies				
Clinical pregnancy rate	12	0.810	0.696–0.941	$P = .006$
Implantation rate	7	0.684	0.587–0.796	$P < .001$
Ongoing pregnancy/live birth rate	8	0.703	0.583–0.848	$P < .001$
Spontaneous abortion rate	8	1.747	1.226–2.489	$P = .002$
Preterm delivery rate	1	6.000	0.309–116.606	Not significant
B. Prospective studies				
Clinical pregnancy rate	3	0.708	0.437–1.146	Not significant
Implantation rate	2	0.552	0.391–0.781	$P = .001$
Ongoing pregnancy/live birth rate	2	0.465	0.291–0.744	$P = .019$
Spontaneous abortion rate	2	2.384	1.110–5.122	$P = .002$
Preterm delivery rate	0	—	—	—
C. Studies using hysteroscopy in all subjects				
Clinical pregnancy rate	2	0.845	0.666–1.071	Not significant
Implantation rate	1	0.714	0.547–0.931	$P = 0.013$
Ongoing pregnancy/live birth rate	2	0.733	0.383–1.405	Not significant
Spontaneous abortion rate	2	1.215	0.391–3.774	Not significant
Preterm delivery rate	1	6.000	0.309–116.606	Not significant

Pritts. *Fibroids and infertility*. *Fertil Steril* 2009.

Fibroids and infertility: an updated systematic review of the evidence

Elizabeth A. Pritts, M.D.,^a William H. Parker, M.D.,^b and David L. Olive, M.D.^a



Uterine fibroids and subfertility: an update on the role of myomectomy

Paula C. Brady^{a,b}, Aleksandar K. Stanic^{a,b,c}, and Aaron K. Styer^{a,b,c}

- The effect of intramural fibroids on fertility remains unclear, and the literature has produced conflicting results.
- If all women with intramural fibroids underwent myomectomy, many would undergo unnecessary surgical intervention.
- To this end, additional prospective studies of greater numbers, more consistent study design, study populations, and endpoints will be required to assess the utility of myomectomy for intramural fibroids

- If intramural fibroids do have an impact on fertility, it appears to be small and to be even less significant when the endometrium is not involved. (II-3)
- In the matter of the surgical removal of intramural fibroids to improve fertility, data fail to show a clear benefit of myomectomy over myomas left in situ.

Carranza-Mamane, B., Havelock, J., Hemmings, R., Cheung, A., Sierra, S., Case, A., ... & Vause, T.. The management of uterine fibroids in women with otherwise unexplained infertility. *Journal of Obstetrics and Gynaecology Canada* (2015), 37(3), 277-285.

- In women with infertility, an effort should be made to adequately evaluate and classify fibroids, particularly those impinging on the endometrial cavity, using transvaginal ultrasound, hysteroscopy, hysterosonography, or magnetic resonance imaging. (III-A)

Intramural fibroids: Size

Surgery to whom?

- Somigliana: **>5cm**

Somigliana E et al . Hum Reprod 2011;26:834e9.

- Oliveira: **>4 cm**

Oliveira FG et al. Fertil Steril 2004;81: 582e7.

- Yan: **>2.85cm**

Yan L, et al. Fertil Steril 2014;101:716

Medical Therapy

- Because current medical therapy for fibroids is associated with
 - suppression of ovulation,
 - reduction of estrogen production, or
 - disruption of target action of estrogen or progesterone at the receptor level, and
 - it has the potential to interfere in endometrial development and implantation,

there is no role for medical therapy as stand-alone treatment for fibroids in the infertile population. (III)

Carranza-Mamane, B., Havelock, J., Hemmings, R., Cheung, A., Sierra, S., Case, A., ... & Vause, T.. The management of uterine fibroids in women with otherwise unexplained infertility. *Journal of Obstetrics and Gynaecology Canada* (2015), 37(3), 277-285.

Two questions?

1. Do uterine fibroids, of specific size or location, decrease fertility?
2. **Does removal of the fibroid(s) enhance fertility?**

SURGICAL MANAGEMENT

- Well-designed surgical intervention trials for myomectomy and infertility are sparse, with a single RCT published to date.
- This study demonstrated **an improvement** in spontaneous conception rates after the surgical removal of **submucosal fibroids**, but pregnancy rates following the removal of intramural or subserosal fibroids were **no more improved** than in the expectant management group of women with **intramural-subserosal fibroids** in situ.

Bozdag G, Esinler I, Boynukalin K, Aksu T, Gunalp S, Gurgan T.

Reproductive Biomedicine Online 2009;19:276-80

Effect of myomectomy on fertility: *submucosal fibroids.*

Outcome	Number of studies/ substudies	Relative risk	95% confidence interval	Significance
A. Controls: fibroids in situ (no myomectomy)				
Clinical pregnancy rate	2	2.034	1.081–3.826	<i>P</i> = .028
Implantation rate	0	—	—	—
Ongoing pregnancy/live birth rate	1	2.654	0.920–7.658	Not significant
Spontaneous abortion rate	1	0.771	0.359–1.658	Not significant
Preterm delivery rate	0	—	—	—
B. Controls: infertile women with no fibroids				
Clinical pregnancy rate	2	1.545	0.998–2.391	Not significant
Implantation rate	2	1.116	0.906–1.373	Not significant
Ongoing pregnancy/live birth rate	3	1.128	0.959–1.326	Not significant
Spontaneous abortion rate	2	1.241	0.475–3.242	Not significant
Preterm delivery rate	0	—	—	—

Pritts. Fibroids and infertility. *Fertil Steril* 2009.

Fibroids and infertility: an updated systematic review of the evidence

Elizabeth A. Pritts, M.D.^a, William H. Parker, M.D.^b and David L. Olive, M.D.^a

Effect of myomectomy on fertility: *intramural fibroids (fibroids in situ controls).*

Outcome	Number of studies/ substudies	Relative risk	95% confidence interval	Significance
Clinical pregnancy rate	2	3.765	0.470–30.136	Not significant
Implantation rate	0	—	—	—
Ongoing pregnancy/live birth rate	1	1.671	0.750–3.723	Not significant
Spontaneous abortion rate	1	0.758	0.296–1.943	Not significant
Preterm delivery rate	0	—	—	—

Pritts. Fibroids and infertility. Fertil Steril 2009.

Fibroids and infertility: an updated systematic review of the evidence

Elizabeth A. Pritts, M.D.,^a William H. Parker, M.D.,^b and David L. Olive, M.D.^a

No difference in implantation or pregnancy rates unless
the uterine cavity itself was distorted by the myomas

Fibroid (n)	PR/ET %
Distorted cavity (65)	9
Not distorted cavity (487)	34
Control (1636)	40

• *Donnez & Jadoul (2002).*

- In women with otherwise unexplained infertility, **submucosal fibroids** should be removed in order to improve conception and pregnancy rates. (II-2)
- Removal of **subserosal fibroids** is not recommended. (III-D)
- There is fair evidence to recommend against myomectomy in women with **intramural fibroids** (hysteroscopically confirmed intact endometrium) and otherwise unexplained infertility, regardless of the size of the fibroids. (II-2D)
- If the patient has no other options, the benefits of myomectomy should be weighed against the risks, and management of intramural fibroids should be individualized. (III-C)

Carranza-Mamane, B., Havelock, J., Hemmings, R., Cheung, A., Sierra, S., Case, A., ... & Vause, T.. The management of uterine fibroids in women with otherwise unexplained infertility. *Journal of Obstetrics and Gynaecology Canada* (2015), 37(3), 277-285.

Adhesions after myomectomy

- Postoperative formation of adhesions after myomectomy is extremely high: in one study it was
 - 94% with uterine incisions on the **posterior wall** and
 - 55% when the incision occurred on the **anterior wall**
- Obviously these adhesions may have a negative impact on fertility in women where this is already a concern.

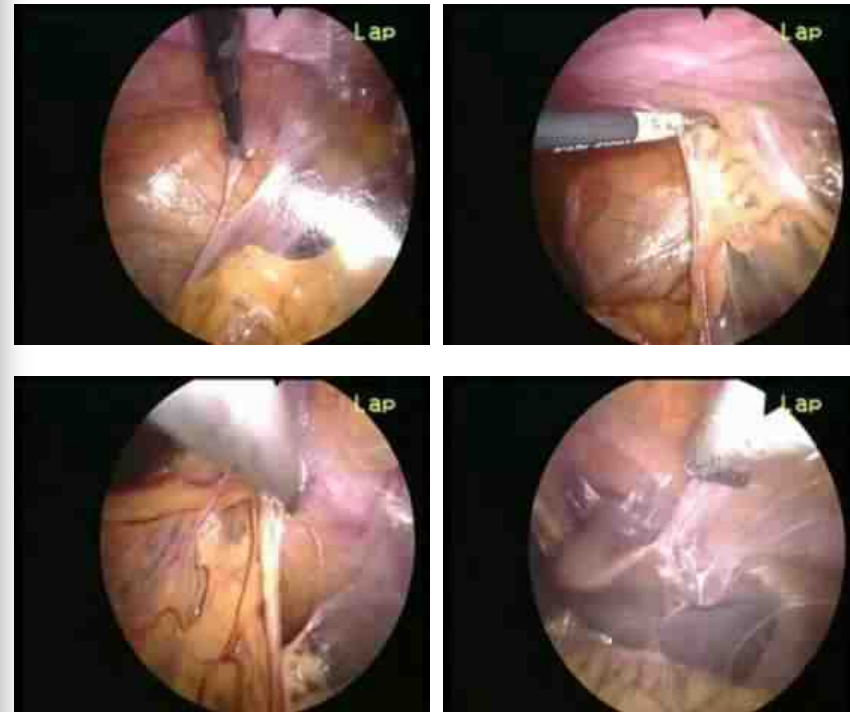
Postoperative adhesions

Adhesion

- laparotomy without barrier (**28.1%**)
laparoscopy without barrier (**22.6%**)
- laparotomy with barrier (**22.0%**)
laparoscopy with barrier (**15.9%**).

Tinelli A et al. Fertil Steril. 2011 Apr;95(5):
1780-5

Myomectomy is associated with a high risk of de-novo adhesion formation that may decrease fertility.



from archive of GY

Reproductive Outcomes

L/S vs L/T

- Pregnancy rates were similar following in the laparoscopy and laparotomy groups (53.6% vs. 55.9%).
- There was lower febrile morbidity in the laparoscopy group (26.2% vs. 12.1%), shorter hospital stay, and a lower postoperative drop in hemoglobin.

Seracchioli R, et al.

Hum Reprod 2000;15:2663

Reproductive Outcomes

L/S vs L/T

- 12 mo.s postoperatively, cumulative pregnancy rates were similar in the laparoscopy and laparotomy groups (52.9% vs. 38.2%).
- Miscarriage rates and preterm delivery rates were also similar between groups and similar to expected rates in the general population.
- Interestingly, in the subgroup of patients undergoing myomectomy for non-fertility indications the cumulative pregnancy rate was greater in the laparoscopy subgroup (73.7% vs. 50%).
- In this study, it appears myomectomy was not considered a contraindication to vaginal delivery, and 31% of all patients who delivered underwent a successful vaginal delivery.

Palomba S, et al.

Fertil Steril 2007;88:933-41

- In the infertile population, cumulative pregnancy rates by the laparoscopic and minilaparotomy approaches are similar, but the laparoscopic approach is associated with a
 - quicker recovery,
 - less postoperative pain, and
 - less febrile morbidity. (II-2)

Carranza-Mamane, B., Havelock, J., Hemmings, R., Cheung, A., Sierra, S., Case, A., ... & Vause, T.. The management of uterine fibroids in women with otherwise unexplained infertility. *Journal of Obstetrics and Gynaecology Canada* (2015), 37(3), 277-285.

- Widespread use of the laparoscopic approach to myomectomy may be limited by the technical difficulty of this procedure.
- Patient selection should be individualized based on the number, size, and location of uterine fibroids and the skill of the surgeon.
(III-A)

Pros

- The feasibility, safety and efficiency of laparoscopic and abdominal myomectomy are compared.

Adamian 1996,
Seineira 1997,
Dubuisson 2000,
Doridot 2001,
DiGregorio 2002,
Landi 2003,
Sinha 2003,
Malzoni 2006

Pros

- Five prospective RCTs ([Mais 1996](#), [Serrachioli 2000](#), [Rossetti 2001](#), [Alessandri 2006](#), [Holzer 2006](#)) and several case-control studies ([Stringer 1997](#), [Silva 2000](#)) have demonstrated numerous advantages of laparoscopic myomectomy over abdominal myomectomy in terms of short-term efficiency
 - shorter hospitalization,
 - faster recovery time,
 - less expense,
 - less pain).

Pros

- As far as long-term efficiency is concerned, the 2 different surgical approaches should be compared with respect to
 - fertility outcome,
 - pregnancy outcome and
 - recurrence rates.

Serrachioli 2000

The November 24, 2014, FDA statement

- Laparoscopic power morcellators are contraindicated in gynecologic surgery in which the tissue to be morcellated is known or suspected to contain malignancy .

AAGL Practice Report: Morcellation During Uterine Tissue

Extraction Journal of Minimally Invasive Gynecology, Vol 21, No 4, July/August 2014

Risk factors for uterine sarcoma	
Variable	Effect
Age	Mean age at diagnosis 60 years [71]
Black race	Two-fold higher incidence of LMS [72]
Tamoxifen therapy	Prolonged tamoxifen use defined as ≥ 5 years [73]
Pelvic irradiation	Association especially strong for carcinosarcoma [74]
HLRCC	Rare autosomal dominant syndrome. Uterine sarcomas associated with HLRCC are often found in younger women [75]
Survivors of childhood retinoblastoma	Higher risk of sarcomas in general, including uterine sarcomas [76]

HLRCC = hereditary leiomyomatous and renal cell carcinoma;
 LMS = leiomyosarcoma.

A Medical-Legal Review of Power Morcellation in the Face of the Recent FDA Warning and Litigation

Raquel Ton, BS, Gokhan S. Kilic, MD, and John Y. Phelps, MD, JD, LL.M.*

- The ACOG, AAGL, AUGS, SGO, and SGS still support power morcellation as an effective therapeutic option when used in properly selected and informed patients.
- To reduce liability exposure, gynecologists who elect to continue to use morcellation devices should inform the patient of the risk of disseminating cancerous cells in the event of uterine malignancy.
- In addition, they should document in the medical record that the patient has been informed of the risks associated with power morcellation devices.

Based on FDA Warnings: Only option is hysterectomy

- 100,000 women undergoing laparoscopic hysterectomy with 100,000 women undergoing open hysterectomy showed that the laparoscopic surgery group would experience,
 - 20 fewer perioperative deaths,
 - 150 fewer cases of pulmonary or venous embolus,
 - 4800 fewer wound infection
- Importantly, the open surgery group would have 8000 fewer quality-of-life years

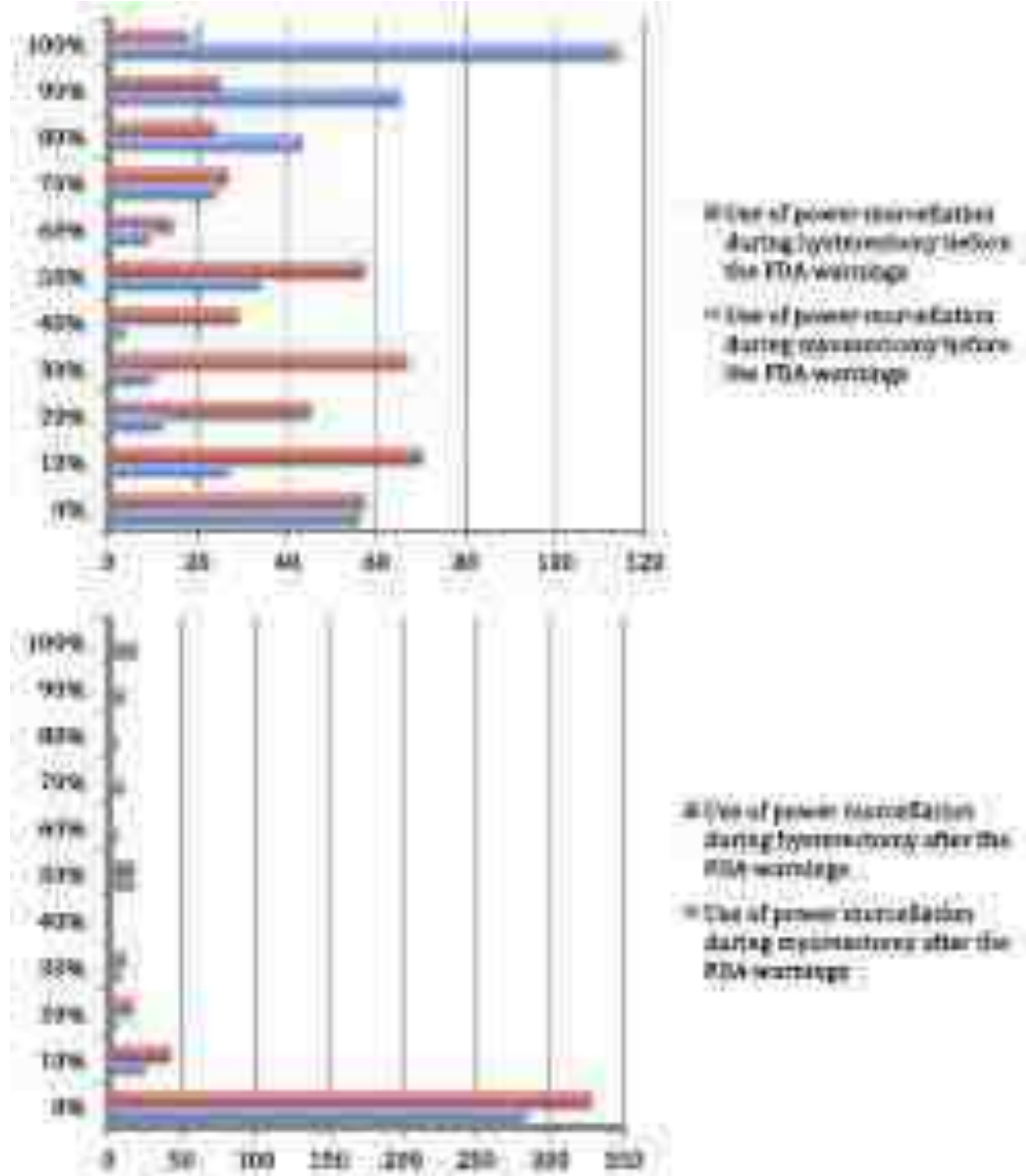
- A recently published study found that in the 8 months following the FDA safety communication,
 - the use of laparoscopic hysterectomy decreased by 4.1% ($p = .005$) and that of
 - both abdominal and vaginal hysterectomy increased (by 1.7% [$p = .112$] and 2.4% [$p = .012$], respectively).
 - The rate of major surgical complications (not including blood transfusions) increased significantly, from 2.2% to 2.8% ($p = .015$),
 - as did the rate of hospital readmission within 30 days, from 3.4% to 4.2% ($p = .025$).

Harris JA, Swenson CW, Uppal S, et al.
Practice patterns and postoperative complications before and after the Food and Drug
Administration safety communication on power morcellation.
Am J Obstet Gynecol.2015;214:98.e1–98.e13.

Impact of the 2014 Food and Drug Administration Warnings Against Power Morcellation

Deirdre A. Lum, MD*, Eric R. Sokol, MD, Jonathan S. Berek, MD, MMS, Jay Schulkin, PhD, Ling Chen, MD, MPH, Cori-Ann McElwain, BA, and Jason D. Wright, MD

Journal of Minimally Invasive Gynecology (2016) -, ---





Perspective

An Open Letter to the Food and Drug Administration Regarding the Use of Morcellation Procedures in Women Having Surgery for Presumed Uterine Myomas

Elizabeth Pritts, MD

Robert Bristow, MD

David Olive, MD

William Parker, MD

Andrew M. Kaunitz, MD

Jonathan S. Berek, MD, MMS

David S. Guzick, MD, PhD

Linda Bradley, MD

- The FDA has estimated that for every 458 women undergoing surgery for myomas, 1 woman would be found to have an occult LMS.
- If atypical leiomyomas and non-peer reviewed data are excluded, the FDA identified 8 cases of LMS among 12,402 women undergoing surgery for presumed leiomyomas, a prevalence of 1 in 1550, or 0.064%.

- Pritts et al. recently published a more rigorous metaanalysis of 133 studies and reported a prevalence of LMS in women undergoing surgery for presumed myomas of 1 in 1960, or 0.051%.
- Bojahr et al [4] recently published a large population-based prospective registry study and reported 2 cases of occult LMS among 8720 women undergoing surgery for myomas, a prevalence of 0.023%.

Incidence of occult leiomyosarcoma in presumed morcellation cases: a database study

Ana M. Rodriguez^a, Mehmet R. Asoglu^a, Muhammet Erdal Sak^b, Alai Tan^{c,d},
Mostafa A. Borahay^a, Gokhan S. Kilic^{a,*}

- The overall risk of being diagnosed with occult leiomyosarcoma is 12.9 per 10,000 in laparoscopic-assisted supracervical hysterectomy and myomectomy for patients younger than 49.
- There is no evidence of occult leiomyosarcoma 1 year after operation for patients younger than 40 who underwent laparoscopic myomectomy.

Prognosis for Women With Morcellated LMS

- LMSs removed intact without morcellation have a poor prognosis.
- Based on SEER data, the 5-year survival in women with stage I or II LMS is only 61%.
- Whether morcellation influences the prognosis of women with LMS is not known, and the biology of this tumor has not been well studied.
- Distant metastasis, primarily through hematogenous dissemination, occurs early in the disease process.

- No difference in outcomes between 10 cases using power morcellation and 5 cases using scalpel morcellation followed for a median of 27 months (range, 2–93 months).

Oduyebo T, Rauh-Hain AJ, Meserve EE, et al.
The value of reexploration in patients with inadvertently morcellated uterine sarcoma.
Gynecol Oncol. 2014;132:360–365.

- Morcellation within containment bags was recently introduced in an attempt to avoid spread of tissue.
- These methods **have not yet been proven effective or safe**, and there is a concern that bags may make morcellation more cumbersome and less safe.

Conclusions

- Current evidence for the relationship between fibroids and infertility remains inconclusive.
- Myomas that distort the uterine cavity, irrespective whether they are submucous or intramural, adversely affect fertility both spontaneous and during IVF treatment.
- Laparoscopic procedures have higher probability to conceive, possibly thanks to a reduced occurrence of postoperative adhesions.

- Laparoscopy can be considered an appropriate, safe and effective tool to perform myomectomy under certain conditions. Relevant technical skills, correct material and assistance and accurate preoperative diagnosis of the number, size and location of myomas are nevertheless required.

L/S myomectomy

- Cost effective
- Associated with lower intensity of post operative pain
- Shorter hospital stay
- Less blood loss
- Less post operative complications
- Lower frequency of adhesions
- Longer operative time

TAKE HOME MESSAGE!

Current recommended practice for the treatment of myomas

Type	Indication for surgical treatment			Current recommendations
	<i>Impact on reproductive potential</i>	<i>Effectiveness of surgical intervention</i>	<i>Additional indications</i>	
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	Unclear	Unclear	Unclear	Expectant management ^a
Subserosal	Nonsignificant	Nonsignificant	Potential complications	Expectant management ^b

^a Surgery indicated only in cases of multiple IVF failures or poor obstetrical outcome.

^b Surgery indicated only in the presence of associated symptoms or poor obstetrical outcome.

L.I. Zepiridis et al.

Best Practice & Research Clinical Obstetrics and Gynaecology (2016) 1-8

XI. TÜRK ALMAN JİNEKOLOJİ KONGRESİ

11 - 15 Mayıs 2016
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Belek / ANTALYA



Thank you...