A 35 y/o lady just married come for check up she has 6cm intramural myoma class 3 without symptom what do you do ?
If it was class 2 would your decision change?

If she is 38 y/o does it change your decision ?

The same lady has a 15mm class 1 submucosal myoma without symptom. what do you do ?
If she is 38 y/o does it change your decision ?
If her AMH be 0.9ng/ml does it change your decision ?

A 35 y/o lady with unexplained infertility come for seeking fertility ? she has 6cm intramural myoma class 3 without symptom what do you do

If it was class 2 would it change your decision ?

The same lady has a 15mm class 1 submucosal myoma without symptom . what do you do ?
If she is 38 y/o does it change your decision ?
If her AMH is o.9 ng/ml does it change your decision ?

A 35 y/o lady is candid of icsi- embryo transfer due to sever male factor when doing tvs she has a 8 cm subserosal myoma what do you do ?
In which situation do you suggest myomectomy?

The same lady has a 4 cm intramural myoma class 4 whitout symptom does she need myomectomy ?

The same lady has a 1 cm submucosal myoma class 1 whitout symptom does she need myomectomy prior to embryo transfer? Or you wait and watch the outcome of first embryo transfer?

A 35 y/o lady candid of embryo transfer come for TVS she show her HSG which is suspicous to small filling defect in endometrial cavity what do you do ?


IN THE NAME OF GOD

Myoma and its impact on reproductive outcome

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2. PREVALENCE

General Population before age of 40 y	60%	*Baird et al, 2003*
Associated with infertility 33-40y	8%	*Borgfeld &Andolf, 2000*
The sole cause of infertility	2-3%	*ASRM, 2008*
ICS/IVF	25%	*Serdar & Bulun, 2013*

- Increasing number of infertile patients seeking ART and having myomas
  1. The recent trends of women to delay childbirth to their 30th and 40th
  2. Recent changes in the life style of women

(Petraglia et al, 2013)

Myoma and its impact on reproductive outcome

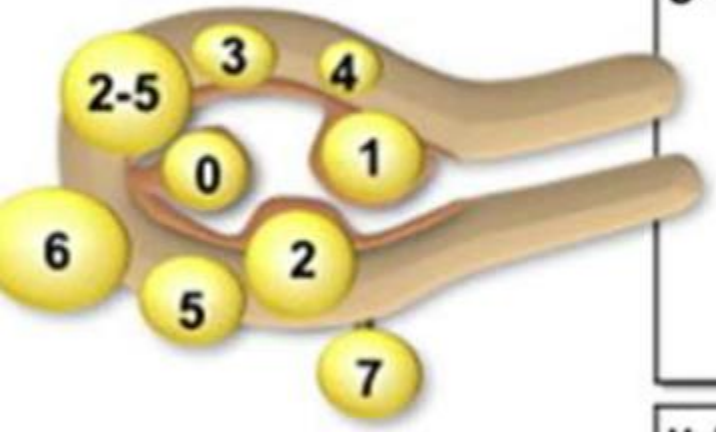
Six systematic reviews or meta-analyses published between 2001 and 2010 , assessed whether fibroids have an impact on fertility. On the whole, it appears that women with fibroids have decreased fertility. The presence of fibroids, regardless of location, significantly decreases both implantation and clinical pregnancy rates.

The impact of fibroid number and size on fertility has not been clearly elucidated. Reproductive success does, however, seem to be related to fibroid location.

1. CLASSIFICATION

FIGO, 2011: 10 subtypes

Leiomyoma subclassification system



SM - Submucosal	0	Pedunculated intracavitary
	1	<50% intramural
	2	≥50% intramural
O - Other	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserosal ≥50% intramural
	6	Subserosal <50% intramural
	7	Subserosal pedunculated
	8	Other (specify e.g. cervical, parasitic)

Hybrid leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.

3. MECHANISMS OF ACTION

1. Changes of Anatomy:
    1. Distortion of the endometrial cavity
    2. Obstruction of the fallopian tubes.
2. Changes of Histologically
    1. Elongation and distortion of the glands
    2. Cystic glandular hyperplasia
    3. Polyposis and endometrial venule ectasia

    (Somigliana et al, 2007).

3. Changes of physiology

1. Increased uterine contractility
2. Impairment of the endometrial blood supply
3. Chronic endometrial inflammation.
4. Glandular atrophy and ulceration

(Somigliana et al, 2007).

5. Endocrine changes
   - supported by the theory of an abnormal local hormonal milieu

   (Galliano et al, 2015)
6. Paracrine changes on the adjacent endometrium
   - secretion of
     - vasoactive amines
     - local inflammatory substances

   (Mukhopadhaya et al, 2007).

- More than one of these mechanisms:
  - may be present at the same time
- The most important:
  - location of fibroids

  (Cook et al, 2010)

- Any of the above, may lead to impaired
  - Gamete transport : impaired fertilization
  - Implantation

  (Cook et al, 2010)

1. Impairment of fertilization

   Interference with sperm or ovum transport.

   a. *Enlargement& deformity of uterine cavity*
   b. *Uterine contractility*
   c. *Distortion of the cervix*
   d. *Distortion or obstruction of tubal ostia.*

2. Impairment of implantation

Implantation failure or gestation discontinuation

(Buttram & Reiter, 1981)

a. *Alteration of the endometrial contour*

b. *Persistence of intrauterine blood or clots*

c. *Focal endometrial vascular disturbance*

d. *Endometrial inflammation*

e. *Secretion of vasoactive substances*

f. *Enhanced endometrial androgen environment*

None of these putative mechanisms has been confirmed to be the etiologic factor.

Effect	Mediator	Reference
Tubal obstruction	Mechanical or space occupying	Deligdish and Lowenthal, 1970[36]
Compression of endometrium and distortion of cellular morphology	Mechanical or space occupying	
Dysfunctional uterine contractility and peristalsis	Mechanical or space occupying	Hunt and Wallach, 1974[38]; Buttram and Reiter, 1981[20]; Vollenhoven et al, 1990[39]; Nakai et al, 2001[40]
Disturbance of junctional myometrial zone	Mechanical or space occupying	Brosens et al, 2003[50]
[illegible]	[illegible]	[illegible]

- Depend upon
  1. Site.
  2. Size
  3. Number
  4. Proximity to the endometrium

Myoma and its impact on reproductive outcome

Published reports of the effect of fibroids on reproductive outcome and fertility may be
confusing or even contradictory. The contradictory findings can be explained in part by the lack of appropriate control groups, inconsistent evaluation of the uterine cavity, the imaging method used to diagnose fibroids or insufficient number of subjects (small sample size).

Myoma and its impact on reproductive outcome

For fibroids that distort the cavity there is consensus of a negative impact on both the clinical pregnancy rate and delivery rate .
In addition, studies have also reported an increased risk of spontaneous miscarriage with submucosal fibroids. Furthermore, with the presence of submucosal fibroids, there is good evidence that myomectomy can improve the fertility in general, and IVF outcome in particular .

Myoma and its impact on reproductive outcome

The evidence regarding the possible effects of subserosal fibroids on reproductive outcome is consistent. Neither the original studies [62,63,69,71] nor the meta-analyses [9-14] detected any detrimental effects on ART outcome associated with subserosal fibroids.
Furthermore no beneficial effect on fertility was noted when myomectomy was performed for subserosal fibroids [72].

Myoma and its impact on reproductive outcome

The greatest debate remains on the impact and treatment of intramural fibroids. Part of the disagreement between studies may result from inappropriate evaluation of the endometrial cavity causing the erroneous inclusion of submucosal fibroids in the group of intramural fibroids

Myoma and its impact on reproductive outcome

The effect of intramural fibroids (those not distorting the uterine cavity) on reproductive
outcome was unclear until recently.
Farhi et al in 1995 [60] did not find a detrimental effect for fibroids that did not affect the uterine cavity. However in 1998, two separate groups,
Eldar-Geva et al [61] and Stovall et al [62] reported reduced pregnancy rate

Myoma and its impact on reproductive outcome

In 2007, Somigliana et al [12] reported a meta-analysis of the literature on the effects of
fibroids on fertility and ART outcome. Data for intramural fibroids were pooled from 7 different studies and meta-analysis demonstrated a statistically significant detrimental effect on both the clinical pregnancy rate and the delivery rate .

In 2008 Pritts et al [14] published an updated systematic review of the existing controlled studies on the effects of fibroids on fertility. The authors evaluated 347 studies of which 23 met the inclusion criteria. They were able to confirm the previously suggested negative impact of intramural fibroids on ART outcome on clinical pregnancy rate and live birth rate.

Pritts et al [14] also found that intramural fibroids were associated with an increased risk of spontaneous miscarriage .

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human reproduction

META-ANALYSIS *Infertility*

The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis

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BACKGROUND: The influence of fibroids on fertility is poorly understood. Submucosal and intramural fibroids that distort the endometrial cavity have been associated with decreased pregnancy rates (PRs) following IVF treatment. However, there is uncertainty about the effect of intramural fibroids that do not distort the endometrial cavity on IVF outcomes.

METHODS: We conducted a systematic review and meta-analysis of studies to evaluate the association between non-cavity-distorting intramural fibroids and IVF outcome. Searches were conducted on MEDLINE, EMBASE, Cochrane Library and Web of Science. Study selection and data extraction were conducted independently by two reviewers. The Newcastle-Ottawa Quality Assessment Scales were used for quality assessment. Meta-analysis was performed if appropriate.

RESULTS: We identified 19 observational studies comprising 6087 IVF cycles. Meta-analysis of these studies showed a significant decrease in the live birth (RR = 0.79, 95% CI: 0.70–0.88, $P < 0.0001$) and clinical PRs (RR = 0.85, 95% CI: 0.77–0.94, $P = 0.002$) in women with non-cavity-distorting intramural fibroids compared with those without fibroids, following IVF treatment.

CONCLUSION: The presence of non-cavity-distorting intramural fibroids is associated with adverse pregnancy outcomes in women undergoing IVF treatment.

1. Distorting cavity

(Donnez & Jadoul, 2002).

- Not distorting:

  No difference in implantation or CPR

- Ddistorting

  adverse pregnancy outcomes

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

- Not distorting cavity:
  - significantly lower LBR
    (RR=0.78; 95% CI: 0.69-0.88) and
  - higher miscarriage rates

(RR=1.89; 95% CI:1.47-2.43)

(Pritts et al 2009, meta-analysis. 18 studies)

  - significantly lower CPR

(RR=0.85; 95% CI: 0.77-0.94) and

  - lower LBR

(RR=0.79; 95% CI: 0.70-0.88)

(Sunkara et al 2010, meta-analysis19 trials)

2. Not distorting cavity but Size

- Adverse pregnancy outcomes in women undergoing IVF

≥3 cm

(Rice et al, 1988, Rosati et al, 1989, Yan et al 2014; Christoponles et al., 2016)

≥ *4 cm*

(Oliveira et al, 2004 ; Khalaf et al, 2006; Vimercati et al 2007)

≥ 5 cm

(Li et al, 1999; Somigliana et al, 2011.)

≥ *7 cm*

(Ramzy et al, 1998; Jun et al, 2001; Olivera et al, 2003)

3. Not distorting cavity but Number of fibroids (3cm):

≥3

(Feliciani et al, 2003)

≥2

(Christoponles et al., 2016)

Number of fibroids	PR (%)
<3	37
>3	28
Control	41

Myoma and its impact on reproductive outcome

More controversial are the type 3 fibroids that are in close proximity to the endometrium yet are 100% intramural.

These fibroids typically do not distort the cavity when viewed hysteroscopically and yet, their close proximity to the uterine cavity suggests that they may have an impact.

The adverse effects of fibroids are also due to their innate ability to biochemically signal their surrounding environment

Myoma and its impact on reproductive outcome

Fibroids distort blood flow to the endometrium.

Fibroids produce abundant extracellular matrix as well as numerous cytokines and growth factors that have a profound impact on adjacent tissues.

fibroids making sufficient quantities of TGF- b and in close enough proximity to the endometrial cavity, allowing this signaling molecule to reach the endometrium, will impact fertility

Myoma and its impact on reproductive outcome

HOX genes, leukemia inhibitory factor as well as beta 3 integrin were all reduced throughout the entire endometrium, including areas that were visually unaffected by the fibroid.
Surprisingly, areas far removed from any fibroid had similar defects in endometrial receptivity as did areas directly over a fibroid

1. Medical management

- No role for medical therapy as stand-alone treatment for fibroids in the infertile population.

(III)

(SOGC CLINICAL PRACTICE GUIDELINE, 2015)

- Current medical therapy for fibroids:
  1. Suppression of ovulation
  2. Reduction of estrogen production, or
  3. Disruption of target action of estrogen or progesterone at the receptor level
     - interfere in endometrial development and implantation

2. Uterine artery embolization

- UAE Vs. myomectomy:
  - lower PR
  - Higher miscarriage rates
  - More adverse pregnancy outcomes (II-3)
  - loss of ovarian reserve, especially in older patients. (III)
- Women, fertile or infertile, seeking future pregnancy should not be offered UAE as a treatment option for uterine fibroids. (II-3E)

(SOGC CLINICAL PRACTICE GUIDELINE, 2015)

5. Strategy for management

(Serour and Serour. 2016).

- Myomectomy or ART can be an appropriate first line of treatment or complimentary to each other.
  - Choice of the strategy depends upon
    - size
    - site
    - number of myomas,
    - other associated causes of infertility,
    - ovarian reserve
    - age of the woman
    - duration of infertility
    - outcome of previous treatment if any.
  - Appropriate counseling is necessary for the choice of the most appropriate patient's centered strategy.

CONCLUSION
(Zepiridis et al, 2016)

Type	Indication for surgical treatment			Current recommendations
	Impact on reproductive potential	*Effectiveness of surgical intervention*	*Additional indications*	
Submucosal	Significant impairment	Significant improvement	Abnormal Uterine Bleeding	Excision - Hysteroscop
Intramural >4cm	Significant impairment	Improvement (need further evidence)	Potential pregnancy complications Symptoms	Excision - Preferably laparoscop
Intramural <4cm	Unclear	Unclear	Unclear	Expectant managemen
Subserosal	Non Significant	Non Significant	Potential complications	Expectant management

* surgery indicated only in cases of multiple IVF failures or poor obstetrical outcome
** surgery indicated only in the presence of associated symptoms or poor obstetrical outcome

Table 1 Indications for preconception myomectomy

	Infertile patients[10]	Patients with unexplained infertility[11]	Pre-IVF or pre-natural conception in infertile patients[12,13]
Submucous myomas	Suggested (myomectomy improves PR, but not OPR, LBR, MR)	Suggested	Suggested FIGO L0–L2 of any size
Intramural myomas	Controversial (not sufficient evidence to recommend myomectomy even if the presence of myomas reduces fertility)	Discussed (suggested in patients undergoing IVF or cases of unexplained infertility with no other options of treatment)	In some cases FIGO L3–L5 > 50 mm
Subserosal myomas	Not recommended	Not recommended	In some cases FIGO L6–L7 only for improving symptoms or to prevent pregnancy complications

FIGO, International Federation of Gynecology and Obstetrics; IVF, *in vitro* fertilization; LBR, live birth rate; MR, miscarriage rate; OPR, ongoing pregnancy rate; PR, pregnancy rate.

Myoma and its impact on reproductive outcome

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)

Myoma and its impact on reproductive outcome

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)