
وبسم الله الرحمن الرحيم

یادواره دکتر کاظمی آشتیانی

وبینار میوم و ناباروری

چالشهای میوم در ناباروری

دکتر پریسا مصطفائی

جراح و متخصص زنان و زایمان، فلوشیپ ناباروری

عضو پژوهشگاه رویان

Challenges in myoma & Assisted Reproduction

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Challenges in ART and myoma

- **when should fibroids be removed to improve in vitro fertilization success?**
- **Does intramyometrial fibroids affect on IVF outcome?**
- **Does size of IM fibroids affect fertility?**
- **Does number of IM fibroids affect fertility?**
- **whether or not intramural fibroids in women with RIF should be removed**
- **whether or not intramural fibroids in women with RPL should be removed**

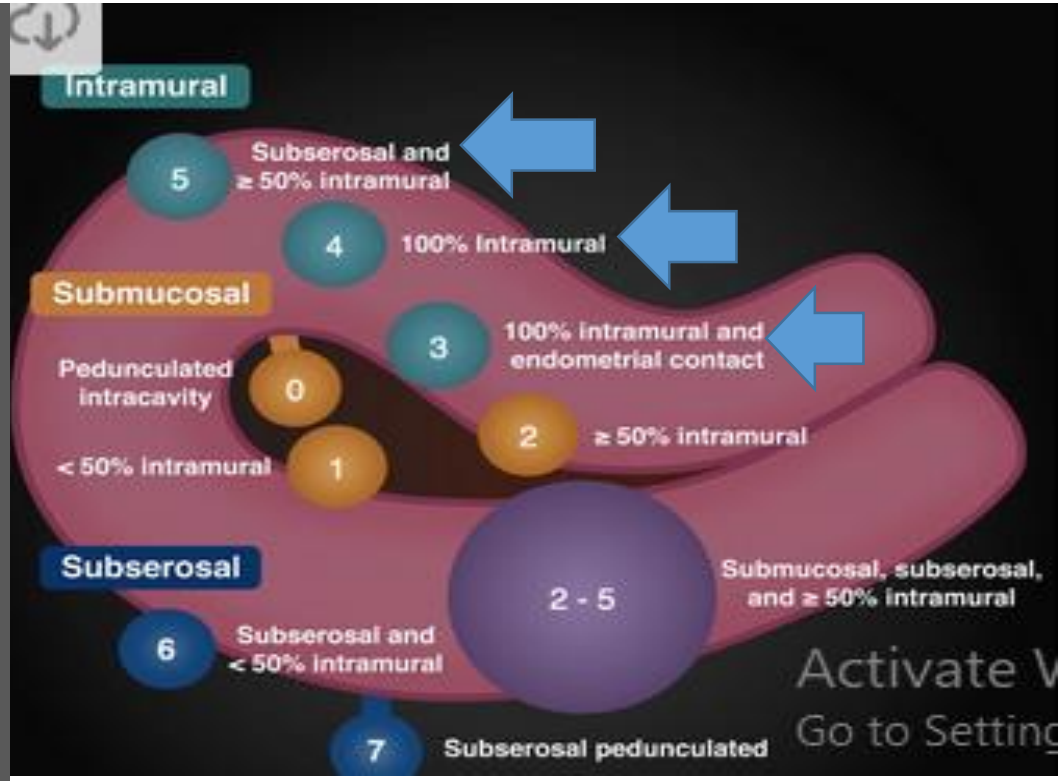
when should they be removed to improve in vitro fertilization success?

- A continued challenge is determining when fibroids are problematic and involved in the etiology of infertility, rather than an incidental finding.

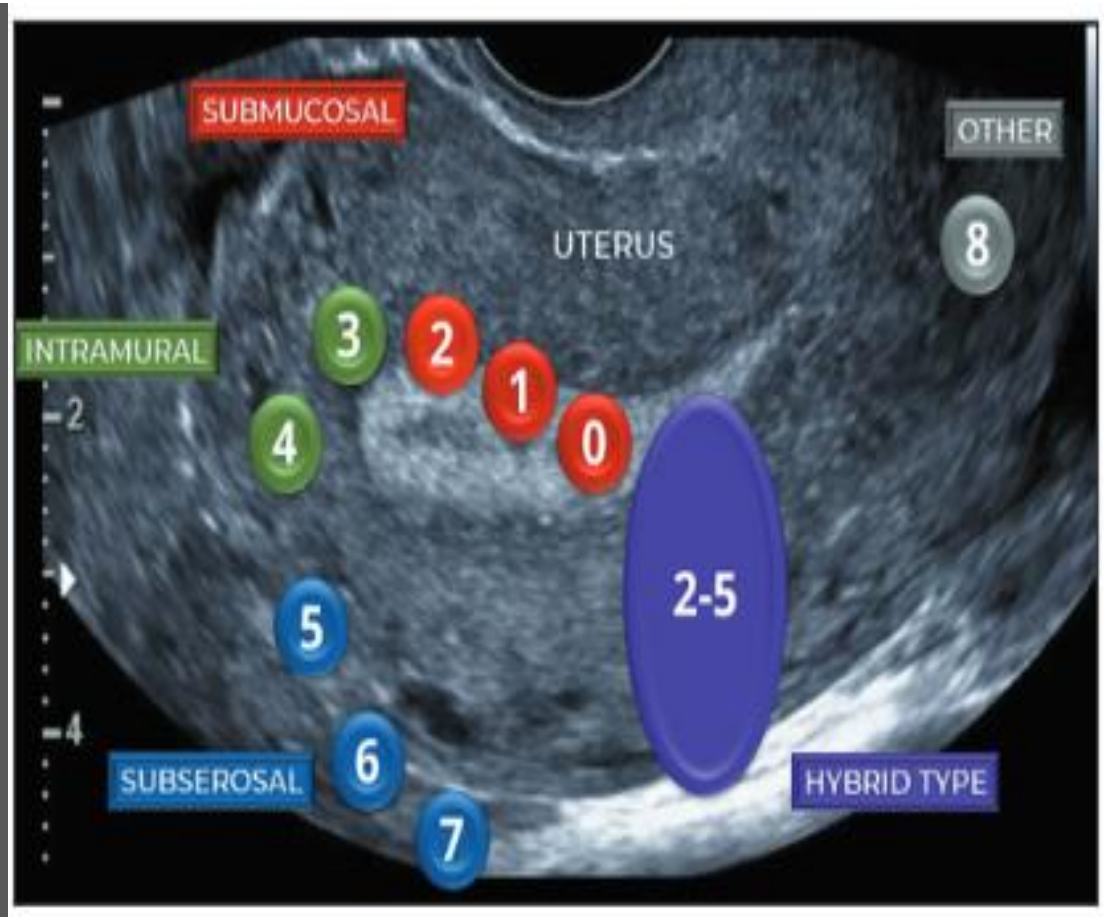
Fibroids are classified based on their size and location within the uterus .
Fibroids that are intracavitary or that project into the cavity and significantly distort its shape have been clearly associated with infertility.
The standard of care is to remove such fibroids as they are often associated not only with infertility, but also with bleeding and increased risk of spontaneous abortion.

Subserosal fibroids, remote from the uterine cavity, do not affect fertility and are typically not removed prior to in vitro fertilization (IVF). Subserosal (SS) fibroids do not appear to affect IVF outcomes .

The impact of intramural (IM) fibroids on the outcome of IVF-ICSI treatment remains incompletely understood , with studies yielding conflicting results ,Accordingto the fibroid classification system of (FIGO), IM fibroids include types 3, 4, and 5 .



- Type 3 is an IM fibroid and it is distinguished from type 2 by doing a hysteroscope with the lowest possible intrauterine pressure necessary to allow visualization. There should not be any bulge into the endometrial cavity. Type 4 is the classical IM fibroid. Type 5 even though >50% is IM is often classified as SS



- The average thickness of the myometrium at the body of the uterus ranges from 1.5 to 3 cm .Even though a fibroid can expand the thickness of the myometrium and remain type 3 and 4, there is a high chance that a fibroid >3 cm may have SM or SS component.

- Oliveira FG, ,Fertil Steril 2004
- . Khalaf Y, Hum Reprod 2006

Challenge 1:Effect of type 3 fibroids on IVF success

Type 3 lesions are totally extracavitary but abut the endometrium

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

Physiopathology of fibroids

Direct effect on endometrium

- Fibroids distort the endometrial cavity
- They may thin the endometrium immediately above the fibroid
- distort blood flow to the endometrium

Effect on adjacent tissue

The adverse effects of fibroids are also due to their **innate ability to biochemically signal** their surrounding environment. Fibroids produce abundant extracellular matrix as well as numerous cytokines and growth factors that have a profound impact on **adjacent tissues.**

A **remote effect of fibroids on endometrium**: -
Directed endometrial biopsies were obtained at the time of the hysteroscopy from well-defined regions within the uterine cavity, including areas overlying fibroids as well as areas that appeared unaffected by fibroids. Surprisingly, areas far removed from any fibroid had similar defects in endometrial receptivity as did areas directly over a fibroid.

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.

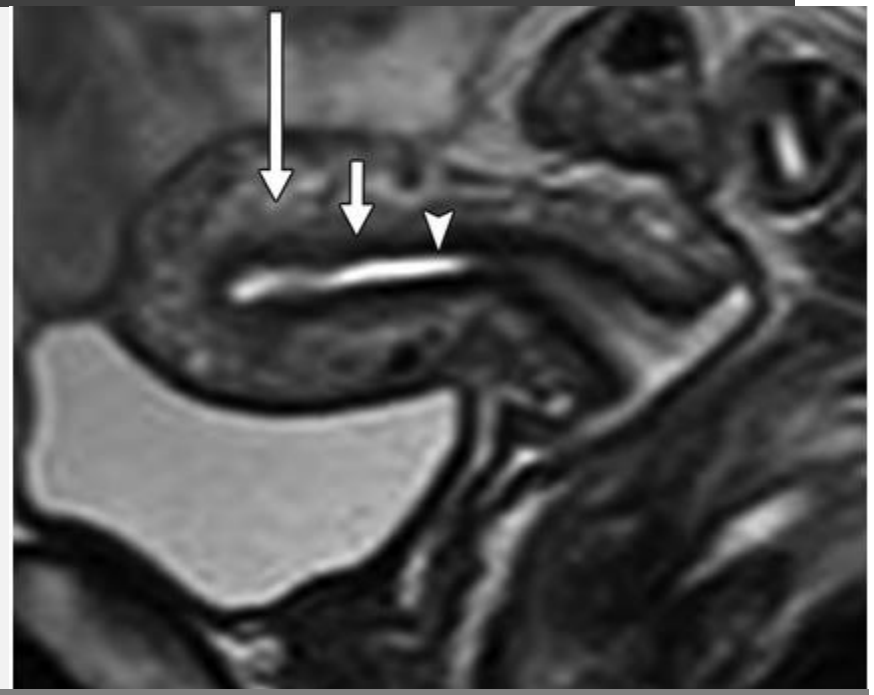
These data implicate a signaling molecule produced by the fibroids that reaches the entire endometrial cavity, regulating the adverse effects of fibroids on endometrial receptivity with obvious implications for IVF success.

- Rackow B, Taylor HS. Submucosal uterine leiomyomas have a global effect on molecular determinates of endometrial receptivity. Fertil Steril 2010;93

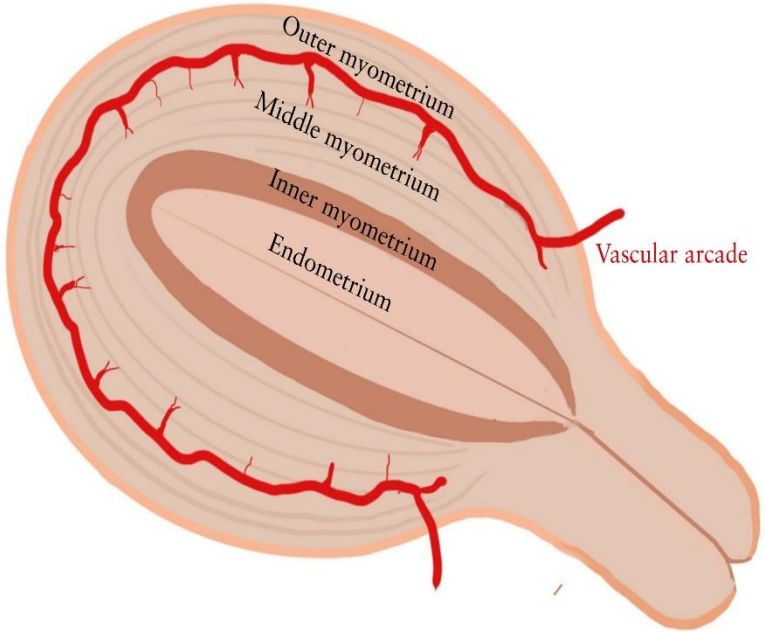
Pathophysiology specific to type3&4

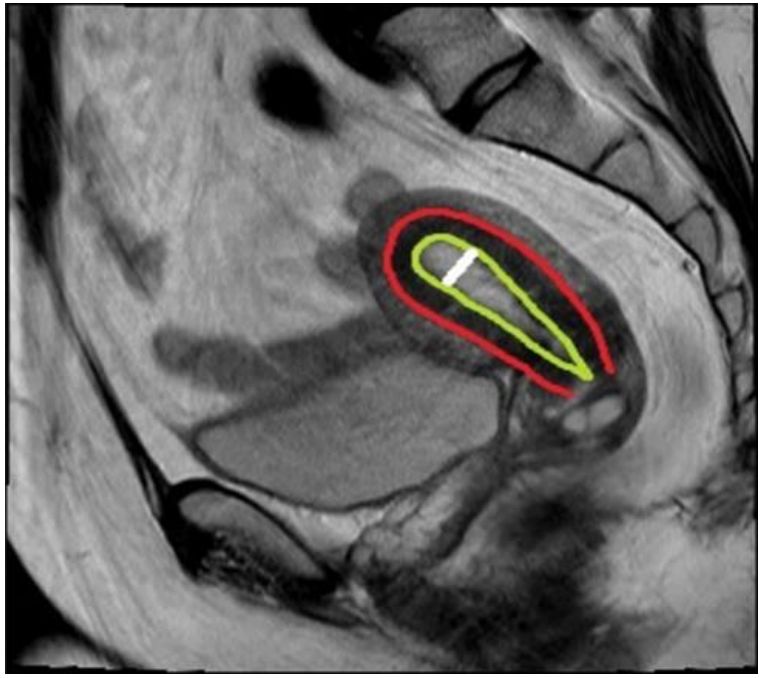
- In women of reproductive age, magnetic resonance imagining (MRI) has shown three distinct layers in the myometrium.
- The innermost layer that immediately abuts the endometrium is labelled the JZ .This zone may affect fertility by two different mechanisms.
- Firstly, the origin of myometrial peristalsis in the JZ .Disruption of this zone by fibroids may lead to increased peristalsis .
- Secondly, IM fibroids may cause thickening or disruption of the JZ leading to poor reproductive outcome .

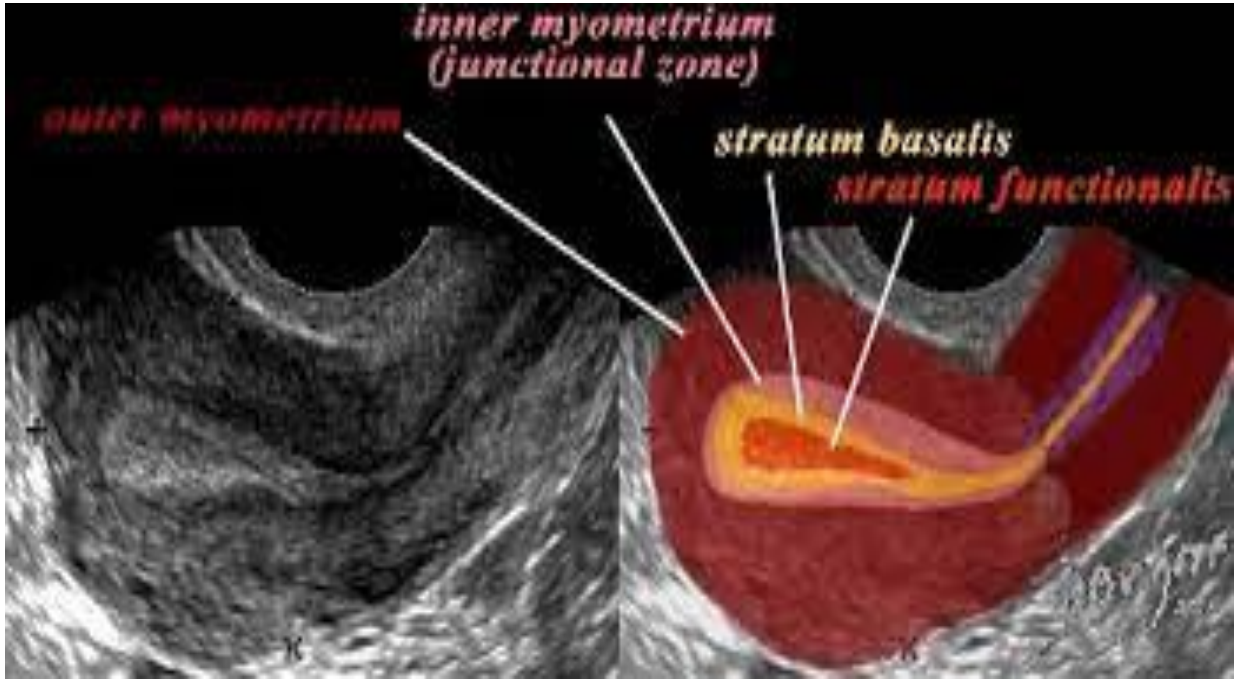
- Hricak H, AJR Am J Roentgenol 1983
- Jakimiuk AJ, Fertil Steril 2004
- Ishikawa H, J Clin Endocrinol Metab 2009

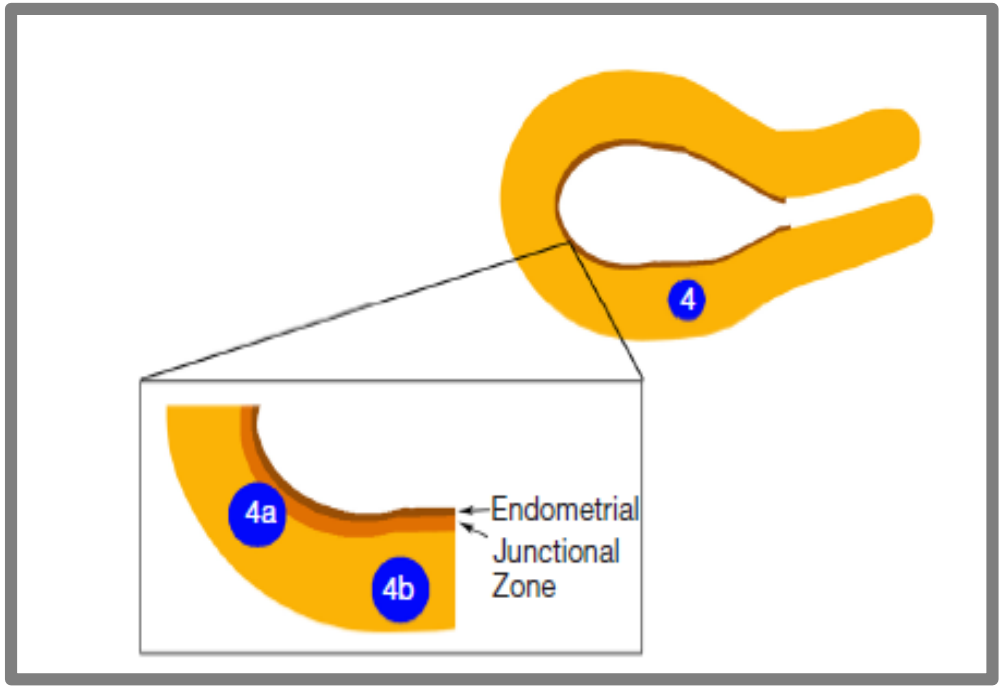


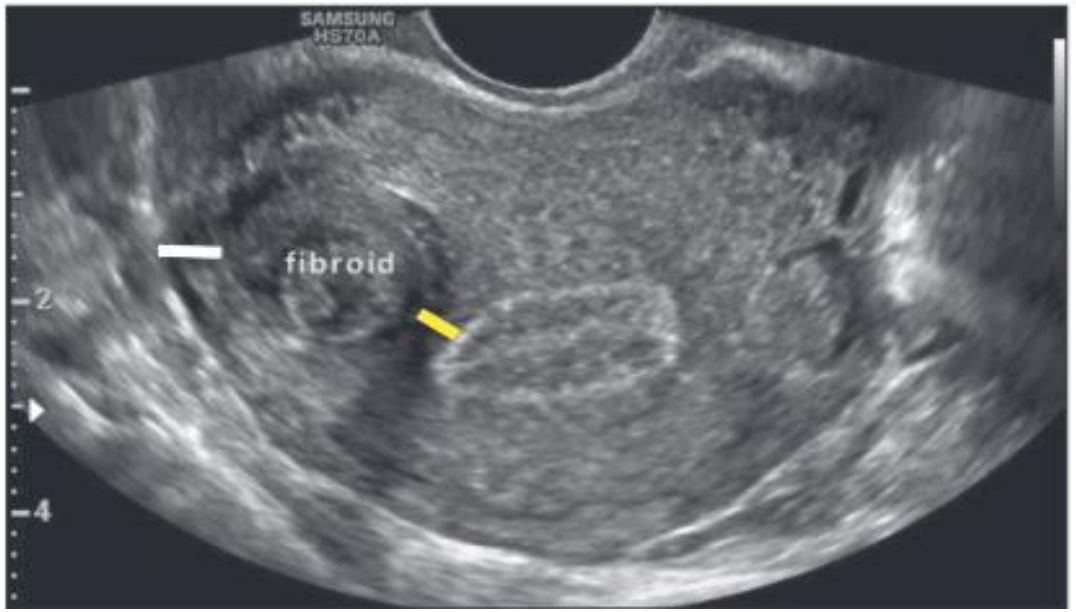
Sagittal T2-weighted image of 35-year-old woman in first part of her menstrual cycle shows zonal anatomy with endometrium (*arrowhead*), which is hyperintense; junctional zone (*short arrow*) as hypointense band; and outer myometrium (*long arrow*) with intermediate signal.

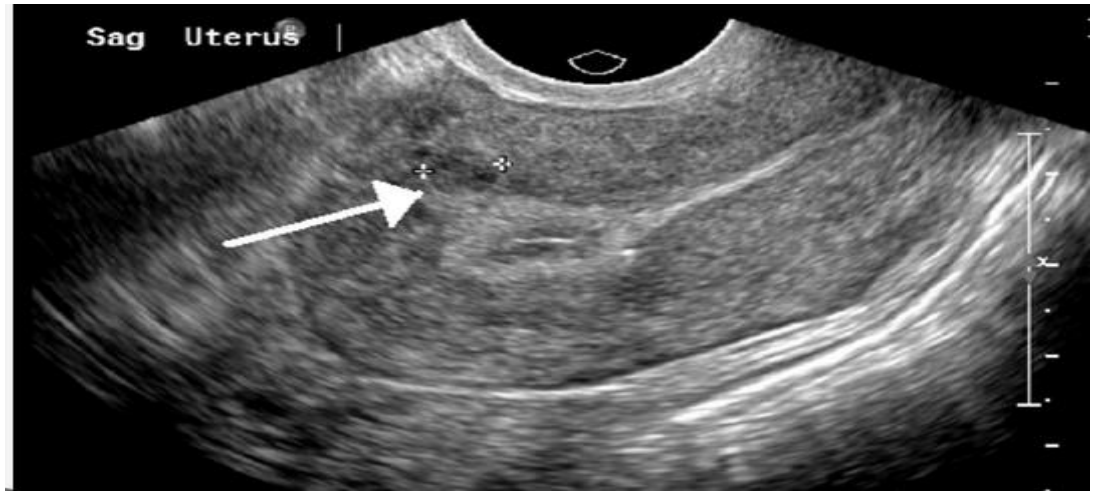

Outer myometrium
Middle myometrium
Inner myometrium
Endometrium
Vascular arcade




inner myometrium
(junctional zone)
outer myometrium
stratum basalis
stratum functionalis







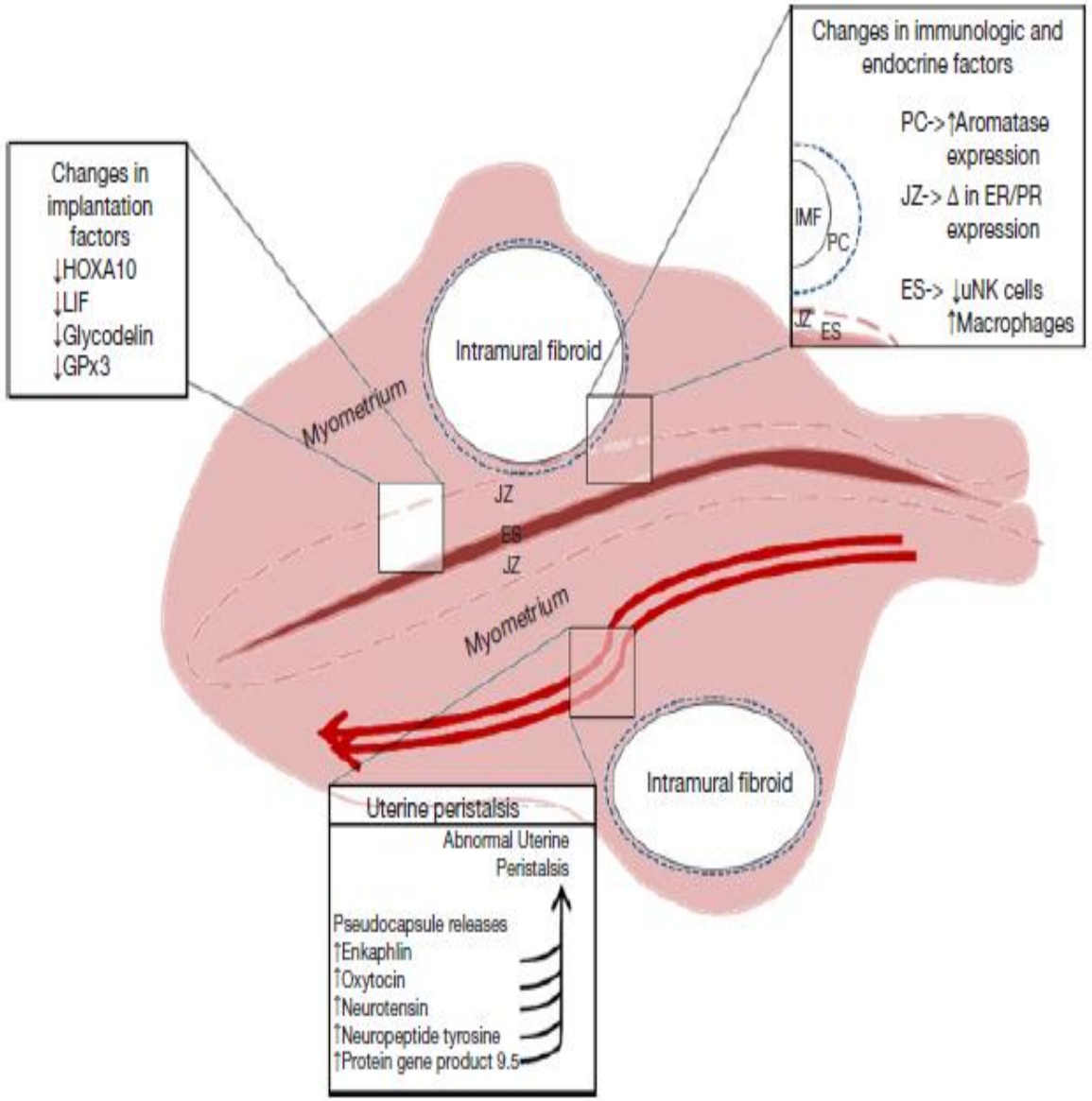
Based on FIGO classification, type 4 fibroid is a classical intramural fibroid. We postulate type 4 fibroid into type 4a and type 4b. Type 4a is fibroid which disrupts the junctional zone but has not reach the endometrium lining while type 4b is fibroid which does not disrupt the junctional zone.

Uterine myometrial peristalsis

There are 2 types of uterine contractions. The first is **focal and sporadic bulging** of the myometrium first described by Togashi *et al.* 1993

The second is the **rhythmic and subtle stripping movement in the subendometrial myometrium** known as uterine peristalsis (UP) captured by cine mode magnetic resonance imaging (cMRI). Fujiwara T, 2004

From menstruation to the mid-ovulatory phase of the menstrual cycle, the uterus contracts from the cervix to the fundus with increasing frequency. Post-ovulation, the contraction frequency decreases to relatively quiet during implantation. In the luteal phase, the direction of peristalsis is reversed (Lyons EA 2005). Based on the studies, UP is increased in patients with IM and SM fibroids during the mid-luteal phase and decreased during the peri-ovulatory phase compared to the healthy controls . Kido A, Clin Radiol 2014; Orisaka M, Eur J Obstet Gynecol Reprod Biol 2007



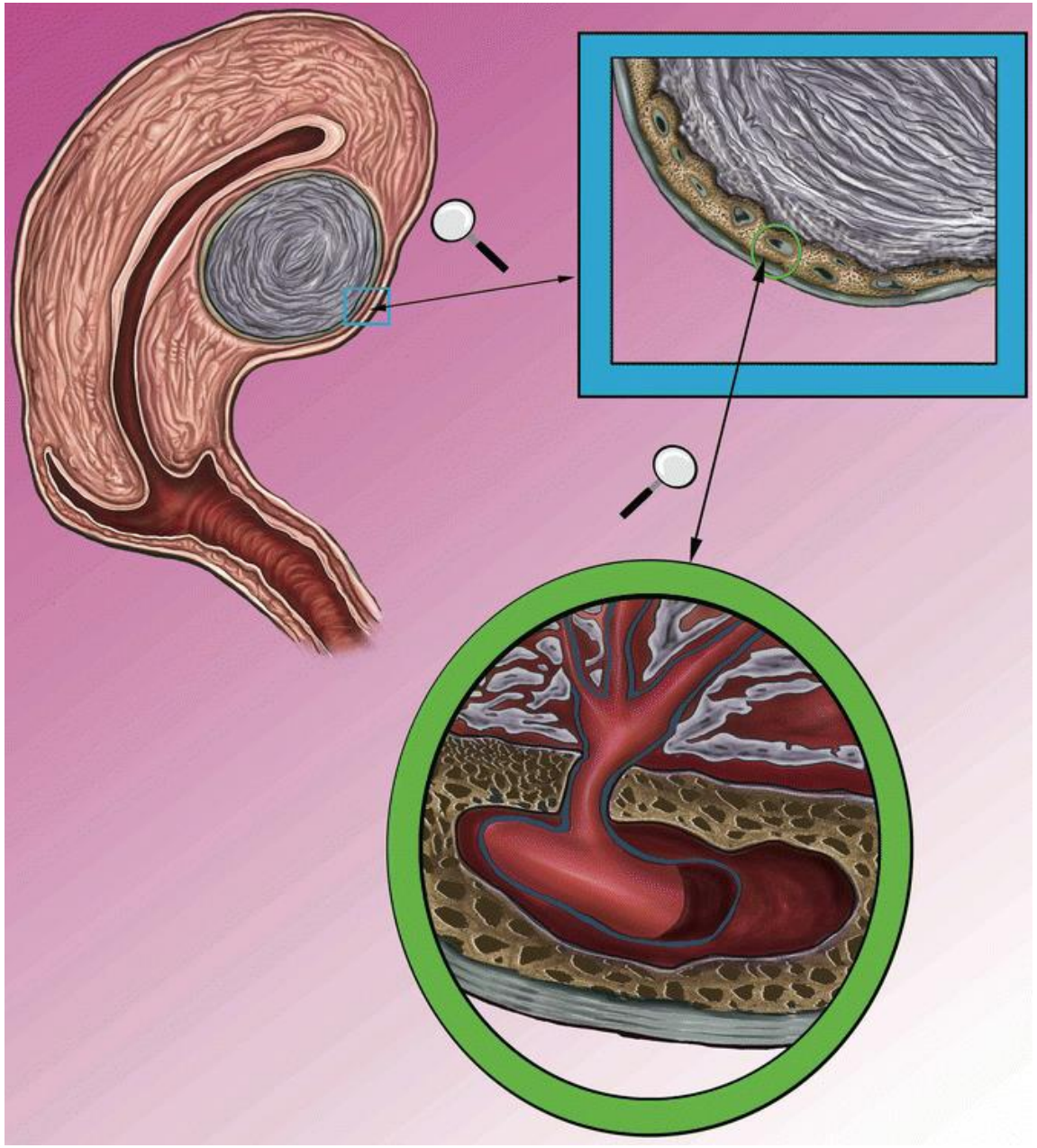
- The relationship between infertility and abnormal UP among patients with IM fibroids was explored by Yoshino *et al.* Yoshino O, Hori M, Osuga Y, et al. Decreased pregnancy rate is linked to abnormal uterine peristalsis caused by intramural fibroids. Hum Reprod 2010
- Ninety-five infertile patients with only IM fibroids underwent cMRI during the implantation period (luteal phase days 5–9) and were further categorized into two groups (low and high uterine peristaltic frequency). Low uterine peristaltic frequency was categorized as having <2 peristalsis in 3 mins while high frequency was categorized as having ≥2 movements within 3 mins.
- Results showed 34% of pregnancy rate in the low-frequency group while 0% in the high-frequency group within 2 years post-treatment. This demonstrates that abnormal UP is a likely cause of infertility. However, why some IM and even SM fibroids cause high frequency peristalsis while other doesn't is not known.

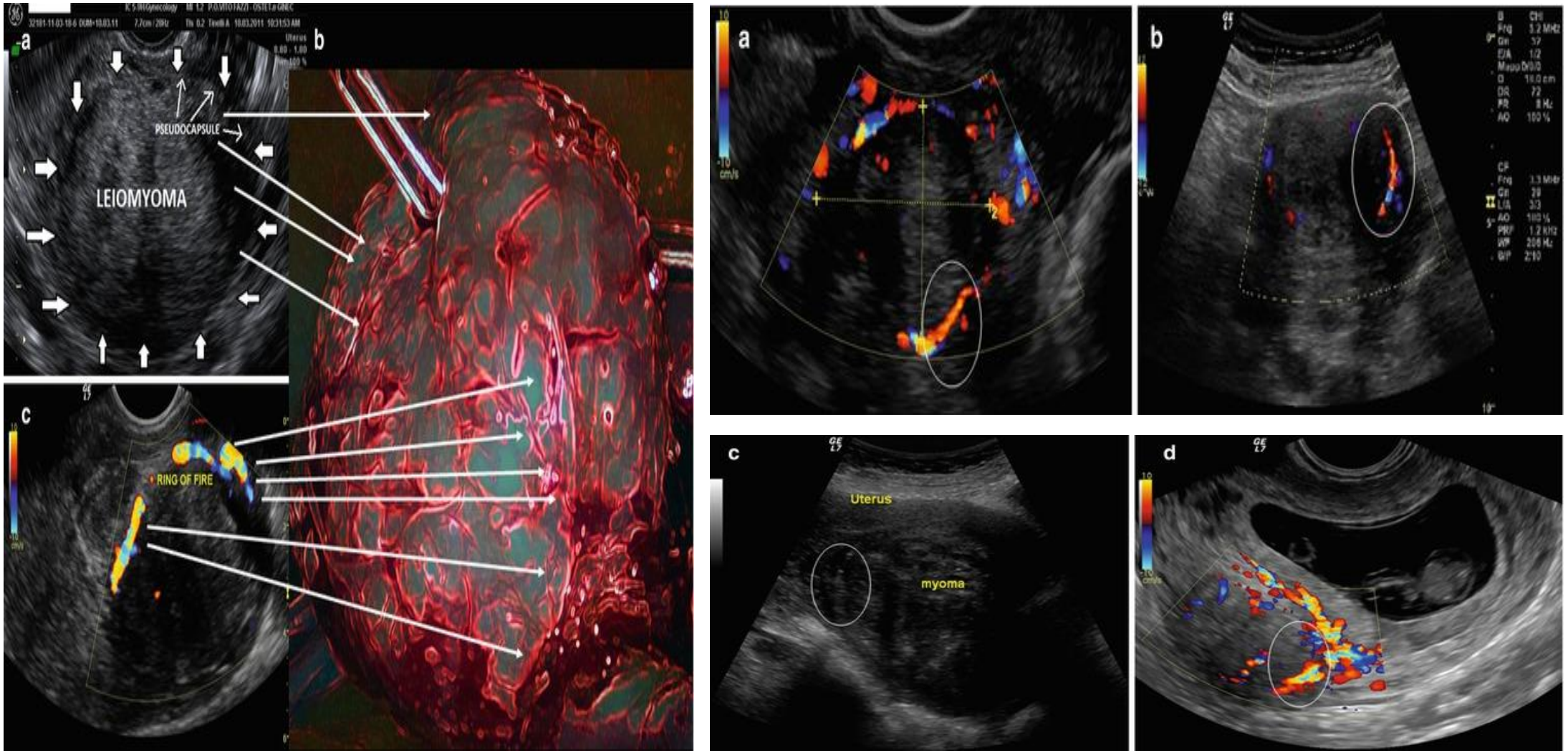
Since UP is at the JZ, disruption of this zone by fibroid may further increase UP (Brosens I, Hum Reprod 2010).
So, one can postulate that type 3 and type 4a fibroids may have more UP than type 4b fibroids leading to more subfertility.

- This needs to be further evaluated by clinical studies. There are several methods of measuring UP namely intrauterine pressure measurement, transvaginal ultrasound and cMRI. Each method has its own advantages and disadvantages . Measuring UP accurately and inexpensively will assist in determining which patients with IM fibroid will benefit from treatment.
- Kuijsters NP, Methorst WG Kortenhorst MSQ, et al. Uterine peristalsis and fertility: current knowledge and future perspectives: a review and meta-analysis. Reprod Biomed Online 2017;

Fibroid pseudocapsule

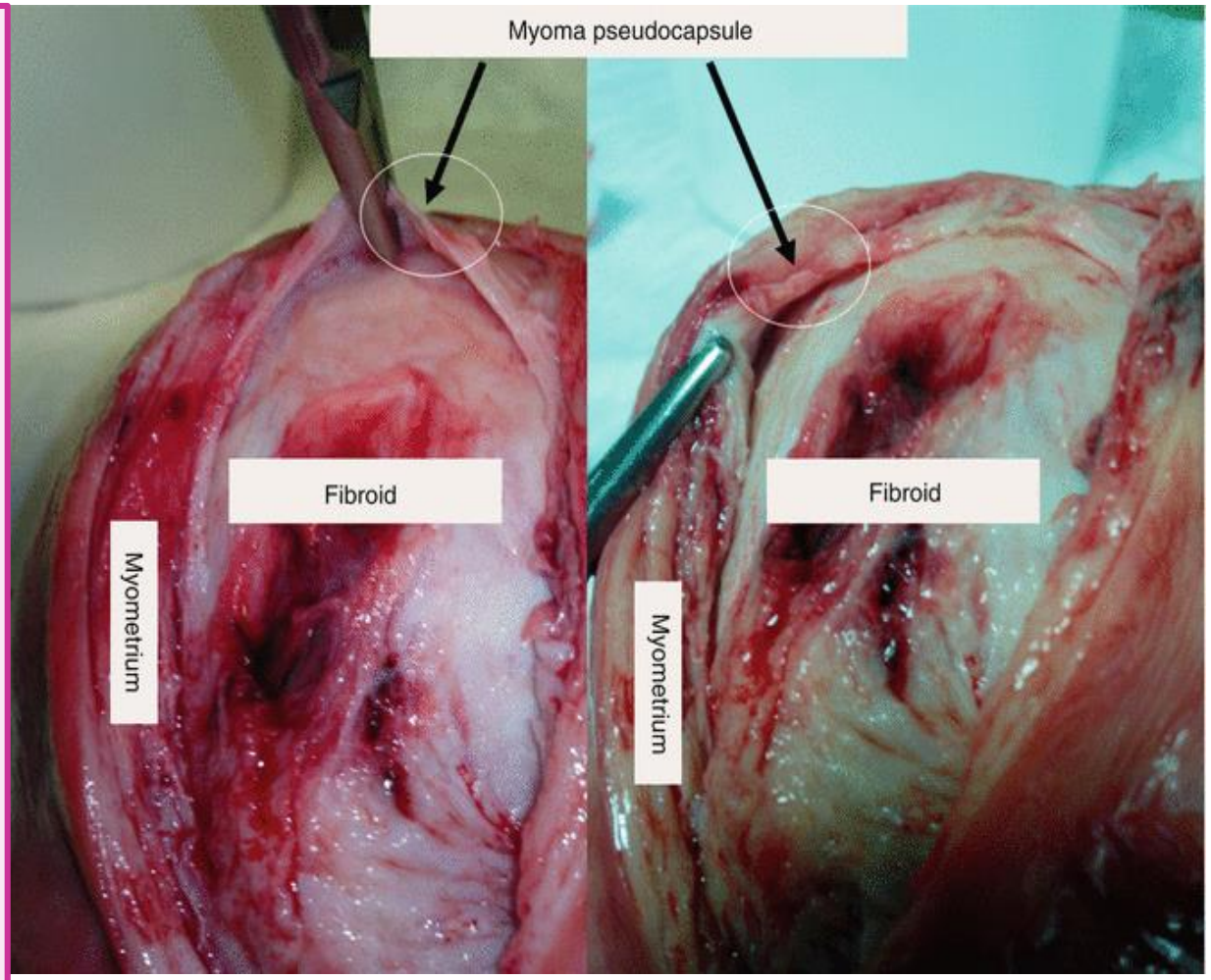
Leiomyoma is covered by a thin layer which can be identified easily during myomectomy, known as fibroid pseudocapsule (PC). This layer contains **bundle of smooth muscle cells** and **neurotransmitters.**
Besides, it is highly vascular to supply blood to the myoma and allows neovascularization to occur (Malvasi A, 2012). This statement is proven in studies showing an **upregulation of endogolin and CD34** (marker of neovascularization) in the PC compared to the fibroid and surrounding myometrium (De Falco M, Eur J Obstet Gynecol Reprod Biol 2009; Di Tommaso S, Mol Hum Reprod 2013).





. Myoma pseudocapsule is a neurovascular bundle or fibrovascular network attached to the fibroids, which separates the fibroids from the normal myometrium. At ultrasonographic exam, myoma pseudocapsule appears as a **white ring around fibroid**, and at echo **Doppler check**, it appears as a "**ring of fire",** even in pregnancy

Thickness of the PC varies with the type and location of the fibroid which may alter the expression of modulators. It is significantly **thicker** in **SM** than IM fibroids while significantly thicker in IM than SS fibroids. The thickness also increases as the fibroid approaches to the cervix resulting an increase in the expression of enkephalin and oxytocin which will alter the UP and affect fertility .Tinelli A, et al. A combined ultrasound and histologic approach for analysis of uterine fibroid pseudocapsule thickness. Reprod Sci 2014



The presence of PC and the associated cytokines, growth factors and hormones may be responsible for the abnormal UP which may result in pregnancy complications like premature uterine contraction resulting in preterm delivery in women with large IM fibroids . Shavell VI,, et al. Fertil Steril 2012;

- it is mandatory to perform intracapsular myomectomy without excising the PC to reduce intraoperative blood loss, enhance better uterine healing and correct musculature anatomical restoring to preserve the uterine functionality for reproductive purpose .

- .

- Tinelli A, Malvasi A, Hurst BS, et al. Surgical management of neurovascular bundle in uterine fibroid pseudocapsule. Journal of the Society of Laparoendoscopic Surgeons 2012
- Tinelli A. Uterine fibroid pseudocapsule: an update of its importance in fibroid management and female reproduction. International Journal of Gynecological, Obstetrical and Reproductive Medicine Research 2014

It is generally acknowledged that the closer the fibroid is to the uterine cavity and the endometrium lining, the more unfavourable effect it might have on fertility, reducing the odds for successful implantation and gestation.

- Emma E. Don et al, Infertility in patients with uterine fibroids: a debateabout the hypothetical mechanisms, Human Reproduction, 2023

- The effect of **NCD IM fibroids** such as type 3 and 4 fibroids on fertility remains controversial with studies yielding conflicting results.

- **Review on 10 retrospective studies and 5 prospective studies which show the impact of NCD IM fibroids on fertility outcomes**:
- The participants of these studies consisted of women who were undergoing ART (IVF and ICSI) as they were believed to be more sensitive to study on the implantation process .The outcomes were determined based on the pregnancy rate (PR), clinical pregnancy rate (cPR), live birth rate (LBR), delivery rate.

- Yarali H, Bukulmez O. The effect of intramural and subserosal uterine fibroids on implantation rate and clinical pregnancy rate in patients having ICSI. Arch Gynecol Obstet 2002;266:30-3.
- . Ng EH, Chan CC, Tang OS, et al. Endometrial and subendometrial blood flow measured by 3D power Doppler USS in patients with small intramural fibroids during IVF. Hum Reprod 2005

Intramural fibroids reduce fertility outcomes :

- **Yan *et al.* Fertil Steril 2018 *(***significant reduction of cPR, biochemical pregnancy rate (bPR) and LBR among women with **Type 3 fibroid** compared to healthy controls (cPR =27.8% *vs.* 43.9%; bPR =29.1% *vs.* 51.4**%; LBR =21.2% *vs.* 34.4%)** .
- **Khalaf *et al.'* Hum Reprod 2006:**the group with **small IM fibroids** demonstrated a significant reduction of cPR, ongoing PR (oPR) and LBR than the control group (cPR =23.6% *vs.* 32.9%; oPR =18.8% *vs.* 28.5**%; LBR =14.8% *vs.* 24%** respectively)
- . **Eldar-Geva *et al.* Fertil Steril 1998:** PR in the SM (10%) and IM fibroids (16.4%) compared to SS fibroids (34.1%) and control (30.1%)
- **Yan *et al.* Fertil Steril 2018** reported a significant reduction of **IR** in **type 3 fibroids** compared to the control group, 22.7% *vs.* 34.4% .
- **Guven *et al.* Reprod Biol Endocrinol 2013** stated single NCD IM fibroid with diameter <7 cm caused significantly **lower IR** and non-significantly higher MR .
- **. Surrey *et al.*, Fertil Steril 2001** the IR was significantly reduced among women <40 years old with fibroids compared to the age-matched control group, 21.4% *vs.* 33.3% respectively .

- Eldar-Geva *et al.* Fertil Steril 1998 and Hart *et al.* Hum Reprod 2001 also demonstrated significant reduction of **IR** among women with fibroids compared to the control group .
- A few studies reported insignificant increment of MR and reduction of the **IR** among women with fibroid compared to the control group.

- Bozdag G, et al. Single intramural leiomyoma with normal hysteroscopic findings does not affect ICSI-embryo transfer outcome. Reprod Biomed Online 2009
- Check JH, Choe JK, Lee G, et al. The effect on IVF outcome of small intramural fibroids not compressing the uterine cavity as determined by a prospective matched control study. Hum Reprod 2002

Similar fertility outcome between study and control groups

- several studies NCD fibroids does not adversely affect the pregnancy outcomes
- Vimercati *et al.* A,RBM online 2007 reported **no significant differences in cPR, IM and MR** between cavity distorting *vs.* NCD fibroids .
- Klatsky *et al.* also reported **no statistical difference in cPR, IR and MR** between patient with and without fibroids (cPR =47% *vs.* 54%, IR =36% *vs.* 38% and MR =15% *vs.* 9%) .
- Despite insignificantly lower PR in the IM and SS fibroid groups, Yarali *et al.* reported **similar** readings of **cPR, IR, MR** and multiple PR between groups of IM, SS and without fibroid .
- Oliveira *et al.* Bozdag *et al.* reported **comparable results of the bPR, cPR and IR** between women with single IM fibroid and without fibroids (bPR =43% *vs.* 42%; cPR =36% *vs.* 38%; IR =20% *vs.* 19% respectively) .
- Oliveira FG, FerSterility 2004; Yarali H, Arch Gynecol Obstet 2002; Vimercati A,RBM online 2007; Bozdag G, A,RBM online2009; Aboulghar MM, Fertility Society Journal 2004

- **No significant difference** was found in the **cPR, bPR, DR and MR** when comparing women with fibroids with diameter <6 cm and women without fibroid .
- By comparing fibroids with diameter <4cm *vs.* control group, the cPR and IR were **similar**.Oliveira FG, Fertil Steril 2004
- Two prospective studies reported **non-significant difference** in the **pregnancy outcomes between IM fibroids <5 cm** with the control group except lower trend of LBR and DR, higher trend of MR in the fibroid groups .
- Aboulghar *et al.* reported **non-significant differences of cPR** between women with fibroids, with previous myomectomy and without fibroids .They also found that the PR in fibroids <5 mm away from the endometrial lining was lower but not significant when compared to fibroids >5 mm away from the endometrium lining.
- Aboulghar MM, Al-Inany HG, Aboulghar MA, et al. The effect of IM fibroids on the outcome of IVF. Middle East Fertility Society Journal 2004

Does removal of intramural fibroids (myomectomy) improve pregnancy rates?

- ***Myomectomy improves pregnancy ?***
- They concluded that surgical removal of large and multiple fibroids resulted in better outcomes but there were also positive results for women with smaller fibroids. These improvements were resulted from the removal of the plausible cause of impaired fertility such as **altered UP** and **blood supply.**

ELSEVIER

THE JOURNAL OF MINIMALLY INVASIVE GYNECOLOGY

Original Article

Myomectomy Decreases Abnormal Uterine Peristalsis and Increases Pregnancy Rate

Osamu Yoshino, MD, PhD*, Osamu Nishii, MD, PhD, Yutaka Osuga, MD, PhD,
Hisanori Asada, MD, PhD, Shigeo Okuda, MD, PhD, Makoto Orisaka, MD, PhD,
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- Yoshino *et al.* identified patients with **IM fibroid who have increased frequency of UP by cMRI** .They then performed myomectomy on all these patients. MRI was done post-myomectomy to determine the reduction of UP and PR was evaluated following 8 months of ART. As a result, 14 of 15 patients had normalized UP, 6 of them achieved pregnancy. The authors also suggested that cMRI might play a role in selecting patient who is required for surgery.

- Yoshino O, Nishii O, Osuga Y, et al. Myomectomy decreases abnormal uterine peristalsis and increase pregnancy rate. J Minim Invasive Gynecol 2012;19:63-7.

- There appears to be sufficient evidence that intramural fibroid affects fertility but the evidence that myomectomy in such patients will improve pregnancy outcome is not strong.
- Alternatives to myomectomy in these patients are to shrink the fibroid or decrease the uterine peristalsis using medication.
- Methods to shrink these intramural fibroids include **ulipristal acetate**, gonadotrophin releasing hormone (**GnRH) agonist**, **uterine artery embolization** (UAE) and **high intensity focused ultrasound (HIFU)**. **Atosiban** can be used to suppress uterine peristalsis. These methods are discussed.

- We recommend that future research should be directed at development of an effective and cheap method of measuring uterine peristalsis**. Until measurement of uterine peristalsis is easily available, it is difficult to recommend routine myomectomy** in subfertile patients with small intramural fibroid and non-invasive methods such as HIFU appears to be a more attractive method to shrink these fibroids to improve fertility, but this need to be assessed in clinical studies.

- In patients with increased UP, atosiban may be given but this option has not been explored in clinical studies as well. UAE may not be a good option for small IM fibroids because of the complications discussed above. HIFU is an attractive option to shrink these small IM fibroids because it is a non-invasive technique with very few side effects. Its use in small fibroids has not been explored in clinical studies.

ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Effect of type 3 intramural fibroids on in vitro fertilization–intracytoplasmic sperm injection outcomes: a retrospective cohort study

Fertility and Sterility- 2018

Lei Yan, M.D., Ph.D., Qian Yu, M.D., Ya-nan Zhang, M.D., Zizhen Guo, M.D., Zhongyuan Li, M.D., Jinlei Niu, M.D., and Jinlong Ma, M.D., Ph.D.

Center for Reproductive Medicine, Reproductive Hospital Affiliated to Shandong University; National Research Center for Assisted Reproductive Technology and Reproductive Genetics; Key Laboratory for Reproductive Endocrinology of Ministry of Education; and Shandong Provincial Key Laboratory of Reproductive Medicine, Jinan, People's Republic of China

We included 151 patients with type 3 intramural fibroids and 453 matched control subjects who underwent IVF-ICSI. The rate of ‘‘other protocol’’ used in COH was significantly higher in women with type 3 fibroids than in the control subjects ($P<.001$).

The experimental group had a significantly lower implantation rate. **Type 3 fibroids also resulted in a lower frequency of live births and clinical pregnancy**.

There was no significant difference between the groups in the rate of clinical miscarriage.

Compared with the corresponding control subjects, patients

with type 3 fibroids with a **single fibroid diameter** (SD) or **total reported fibroid diameter (**TD) **>2.0 cm** also had significantly lower rates of live birth, clinical pregnancy, and implantation.

Type 3 fibroids with SD or TD <=2.0 cm had no significant difference in IVF-ICSI outcomes compared with corresponding control subjects.

From this study we can safely conclude that
large, intramural fibroids in close proximity to the endometrial cavity do affect IVF success rates by impacting endometrial receptivity and embryo im plantation. ¦
We should consider removing intramural fibroids when in close proximity to the endometrial cavity. Further clinical trials are needed to determine of myomectomy truly restores optimal endometrial receptivity.

Large fibroids produce more TGF-b3 and those closest to the uterine cavity allow more TGF to reach endometrial cells.
One would predict that the size of the fibroid would determine TGF-beta production and that the amount of TGF-b reaching the cavity would vary by the square of the distance from the cavity ($1/X^2$, where X is the distance from the fibroid to the endometrium).

As the effect would be ex pected to vary with the square - of the distance, even relatively **small differences in proximity** to **the endometrial cavity** would result in **profound differences** in the ability of fibroids to affect the adjacent endometrium. Those close to the endo metrial cavity would have a severe effect while those even slightly removed from the cavity are predicted to have a much smaller effect.

. We can likely ignore fibroids that are a significant distance from the endometrial cavity.

International Journal of GYNECOLOGY & OBSTETRICS

REVIEW ARTICLE

Impact of FIGO type 3 uterine fibroids on in vitro fertilization outcomes: A systematic review and meta-analysis

Alessandro Favilli, Andrea Etrusco ✉, Vito Chiantera, Antonio Simone Laganà, Ettore Cicinelli, Sandro Gerli, Amerigo Vitagliano

First published: 15 May 2023 | https://doi.org/10.1002/ijgo.14838 | Citations: 4

In total, 1020 patients were included: 324 with FIGO type 3 myomas and 696 controls (without myomas). A pooled data analysis showed a **significantly lower live birth rate** (OR 2.16, 95% CI 1.55–3.01, $I^2 = 0\%$, $P < 0.00001$), **clinical pregnancy rate** (OR 2.06, 95% CI 1.52–2.81, $I^2 = 0\%$, $P < 0.00001$), and **implantation rate** (OR 1.77, 95% CI 1.35–2.32, $I^2 = 0\%$, $P < 0.00001$) in women with untreated myomas compared with controls. The number and size of fibroids correlated with a worsening of IVF outcomes.

- **Conclusions**
- **FIGO type 3 myomas are significantly associated with a lower implantation rate, cumulative pregnancy rate, and live birth rate**. Furthermore, **their deleterious effect on the outcome of IVF increases further with increasing size and number**.
- Nevertheless, no firm conclusions could be drawn about the potential benefits of surgery for FIGO type 3 uterine fibroids on IVF outcomes.

Middle East Fertility Society Journal
Volume 16, Issue 1, March 2011, Pages 38-39

Debate

Myomectomy before IVF: Which fibroids need to be removed?

Abdel-Maguid I. Ramzy

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https://doi.org/10.1016/j.mefs.2010.12.011 Get rights and content

- The real threat that myomas impose on the outcome of IVF cycles lies in one of two fields:
- **the myometrial contractility** and
- **the endometrial receptivity**.
- As for the first, it causes discordant contractility of the myo-fibrils due to the mere effect of the myoma .This will affect the stage immediately following embryo transfer. It is only prudent to believe that the size and the number of the corporeal intramural myomas will be the main controversial issue in this respect.
- The latter factorthe endometrial receptivity may be, the key element here.

- Endometrial receptivity is a sum of multiple factors:
- mechanical,
- chemical,
- vascular, etc.
- Uterine myomas may have a direct or indirect effect on all or each of these factors. this effect is rather localized depending as well on the site and number of the myomas even that they appear, on transvaginal sonography (TVS), innocent and away from the cavity.These factors cannot be predicted by ultrasound alone.

- We have to deploy proper judgment in each **individual case** based on the age as well as the number and size of the intramural myomas.
- A single myoma of 4cm size or less that is not encroaching on the cavity in a woman in her late thirties may deserve a single trial to get pregnant through IVF without Myomectomy. If that fails or ends in a miscarriage, she may be counseled for surgery before the second trial.
- However larger and multiple myomas, especially in a younger patient may deserve surgery before enrolling her in her first IVF cycle.
- Single sub-serous myomas of sizes less than 5cm may well be ignored and the patient is allowed to go through IVF. However if larger or associated with intramural myomata, surgery may be considered prior to enrolling her in an IVF cycle.

conclusion

- **NCD IM fibroid** with infertility poses a difficult clinical challenge. There appears to be enough evidence that NCD IM fibroid affects fertility. Type 3 fibroids may have a higher risk of poor pregnancy outcome compared to type 4 fibroids .
- Since disruption of the JZ appears to be an important cause of subfertility, type 4a fibroids may have a poorer outcome than type 4b fibroids. This will be difficult to prove in clinical studies because it is difficult to visualize the JZ and the changes in its thickness during the menstrual cycle on transvaginal ultrasound.

- There are many possible causes why IM fibroids affect fertility. The only measurable cause appears to be increased **UP.** Unfortunately, not all patients with IM fibroids have increased UP. Currently there is no good and inexpensive method of measuring UP. cMRI seems to be an accurate method but it is expensive .
- Transvaginal ultrasound method is a cheaper modality but it is still very user dependent. A better method needs to be devised to measure UP easily and effectively.

- With vitrification, pregnancy after frozen embryo transfer is improving It has been suggested that myomectomy should not be the first line treatment in patients with small IM fibroids. In patients with many frozen embryos, the strategy could be to consider surgical or non-surgical intervention only in patients who have a failed embryo transfer.

- Some authors recommend surgery only for cases like **repeated IVF treatment failure**, **fibroid related obstetrical complications** and **recurrent miscarriage** .

- Nejad EST, Moini A, Amirchaghmaghi E, et al. Effect of IM uterine myoma on the outcome of ART cycles. Iranian Journal of Reproductive Medicine 2007
- Somigliana E, De Benedictis S, Vercellini P, et al. Fibroids not encroaching the endometrial cavity and IVF success rate: a prospective study. Hum Reprod 2011

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Volume 37, Issue Supplement_1

JOURNAL ARTICLE

O-229 To remove or not to remove – debate continues FREE

K.D Nayar

Human Reproduction, Volume 37, Issue Supplement_1, July 2022, deac106.007,
https://doi.org/10.1093/humrep/deac106.007
Published: 30 June 2022

Surgery in patients with intramural fibroids presenting

with infertility, should be considered to be a risky procedure, not only because of the limited evidence of the efficacy of myomectomy on -

reproductive outcomes but also because of the potential for several surgery-related com plications.

We need to investigate other modalities such as uterine artery em-

bolization and magnetic resonance-guided focused ultrasound.

- The studies favoring myomectomy indicate that It is better to perform myomectomy prior to ART cycle women with reduced ovarian reserve, advanced maternal age, recurrent pregnancy loss or previous failed IVF cycles.

The pros and cons of myomectomy should be carefully explained in each case.

Couples should be aware of the **possible complications** of myomectomy including:

- the likelihood of blood transfusion
- a small risk (1%) of hysterectomy,
- a relatively high risk of adhesion formation over the uterine scar
- a small but serious risk of scar rupture during the ensuing pregnancy.

the couples should also understand that intramural **fibroids may cause** :

- implantation failure
- number of other problems including miscarriage (in both first and second trimesters),
- red degeneration,
- preterm delivery,
- placental abruption,
- fetal growth restriction,
- malpresentation,
- difficulty with delivery,
- intrapartum and postpartum hemorrhage

The final decision must be individualized, and the involvement of a reproductive surgeon in the decision-making process is recommended.

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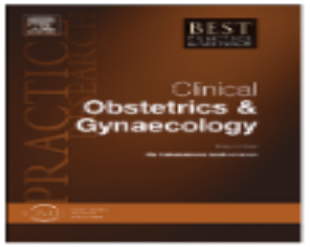

6

What to do when good-quality embryos repeatedly fail to implant

C. Coughlan [a, b, *]

Intramural fibroid: Although women with RIF should have submucous fibroids removed, the possible contribution of intramural fibroids, which are not distorting the uterine cavity, to RIF is far from being clear.

There is no consensus on whether or not intramural fibroids in women with RIF should be removed .Many clinicians would recommend removal of intramural fibroids if they are more than 4 cm in diameter.

There is a lower threshold to remove an intramural fibroid if it is situated in **the anterior lower uterine segment**, as it may pose problems in delivery of the fetus, especially if cesarean section is required.

IMPLANTATION

- The pregnancy rate by IVF and embryo transfer can be improved by removing SM fibroids with hysteroscopic surgery.
  Implantation rates are low even in patients with intramuscular fibroids, but unfortunately, surgical removal of intramuscular fibroids generally do not improve results.
  Subserosal fibroids have not been shown to interfere with implantation.
  for intramuscular fibroids and subserosal fibroids, little is known about how factors such as the number, size, and location of fibroids may affect pregnancy. (Pritts EA, et al. Fertility And Sterility 2009, Vol 91, p1215–1523.)
  With fibroids, it is important not to jump to conclusions and to plan carefully, as surgery can also impact future pregnancies.

Uterine factors in recurrent pregnancy losses

Fertility and Sterility® Vol. 115, No. 3, March 2022

Marie Carbonnel, M.D., Paul Pirtea, M.D., Dominique de Ziegler, M.D., and Jean Marc Ayoubi, M.D., Ph.D.
Department of Obstetrics and Gynecology and Reproductive Medicine, Hopital Foch, Faculté de Médecine Paris Ouest, Suresnes, France

Intramural leiomyomas have a questionable impact on fertility and early pregnancy development, which may due to differences related to their size. Indeed, the size of intramural myomas can augment the risk of RPL, especially when myomas are>4 cm, a point of view that remains controversial according with certain researchers .

Pritts EA,. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 2009

The presence of multiple fibroids is a significant predictor of miscarriage and RPL .Benson CB, Outcome ofpregnancies in women with uterine leiomyomas identified by sonographyin the first trimester. J Clin Ultrasound 2001

- Myomectomy improves
- the chances of pregnancies in case of **submucosal myomas**, but the data are insufficient to support a true decrease of preg-nancy losses and even less for the possible cure of RPL .
- No clear benefit of surgery has been demonstrated for **intra mural myomas** with no impact on the uterine cavity .
- Pritts EA,. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 2009
- The risk-benefit ratio has to be takeninto account, and all options have to be discussed with the patient before surgery. Surgeons should adopt a routine adhe sion reduction strategy and good surgical techniques.
- De Wilde RL, Prevention of adhesions in gynaecological surgery: the 2012 European
- field guideline. Gynecol Surg 2012

- Surgical removal of intramural fibroids is not recommended by international guidelines.
- There are no studies on the effect of treatment of fibroids on the miscarriage rate in women with RPL.
- The AAGL practice guidelines concluded that at least in selected patients, submucous myomectomy may reduce the risk of spontaneous abortion .(AAGL practice report: practice guidelinesfor the diagnosis and management of submucous leiomyomas, Jaslow, 2014)

- ESHRE Guideline Group on RPL, Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, et al. ESHRE guideline: recurrent pregnancy loss. Hum Re prodOpen 2018;&2023

Recurrent Pregnancy Loss

Guideline of European Society of Human Reproduction and Embryology

ESHRE Recurrent Pregnancy Loss Guideline Development Group

- Surgical removal of intramural fibroids is not recommended in women with RPL. There is insufficient evidence to recommend removing fibroids that distort the uterine cavity.
- ESHRE Guideline Group on RPL:2023


THANKS FOR
YOUR
ATTENTION

CASE 1

- A 36-year-old nullipara presented for treatment with an 8-year history of secondary infertility and a previous myomectomy.
- Her BMI was 24.7 kg/m^2, and she was counseled and selected for IVF-ET treatment following the confirmation of bilateral tubal blockage. She underwent controlled ovarian hyperstimulation protocol.
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- On stimulation day 5, a TVS revealed tiny follicles in the left ovary, but the right was not visualized. On stimulation day 8, a TVS revealed a poorly defined left ovary with very tiny follicles, whereas the right ovary was not visualized. Her stimulation day 5 estradiol level of 413 pg/mL and endometrial thickness of 7.8 mm were suggestive of apparent follicular development (i.e., a good response). This necessitated a further search using a transabdominal scan, which showed four follicles in the right ovary and two follicles in the left ovary, with the largest measuring 15.5 mm. On stimulation day 11, the six follicles were still visualized on a transabdominal scan, with the largest measuring 20.1 mm, and the endometrial thickness was 10.5 mm. She underwent an intramuscular injection of 10,000 IU of hCG on the same day and OCR was carried out 34 hours after the hCG injection.

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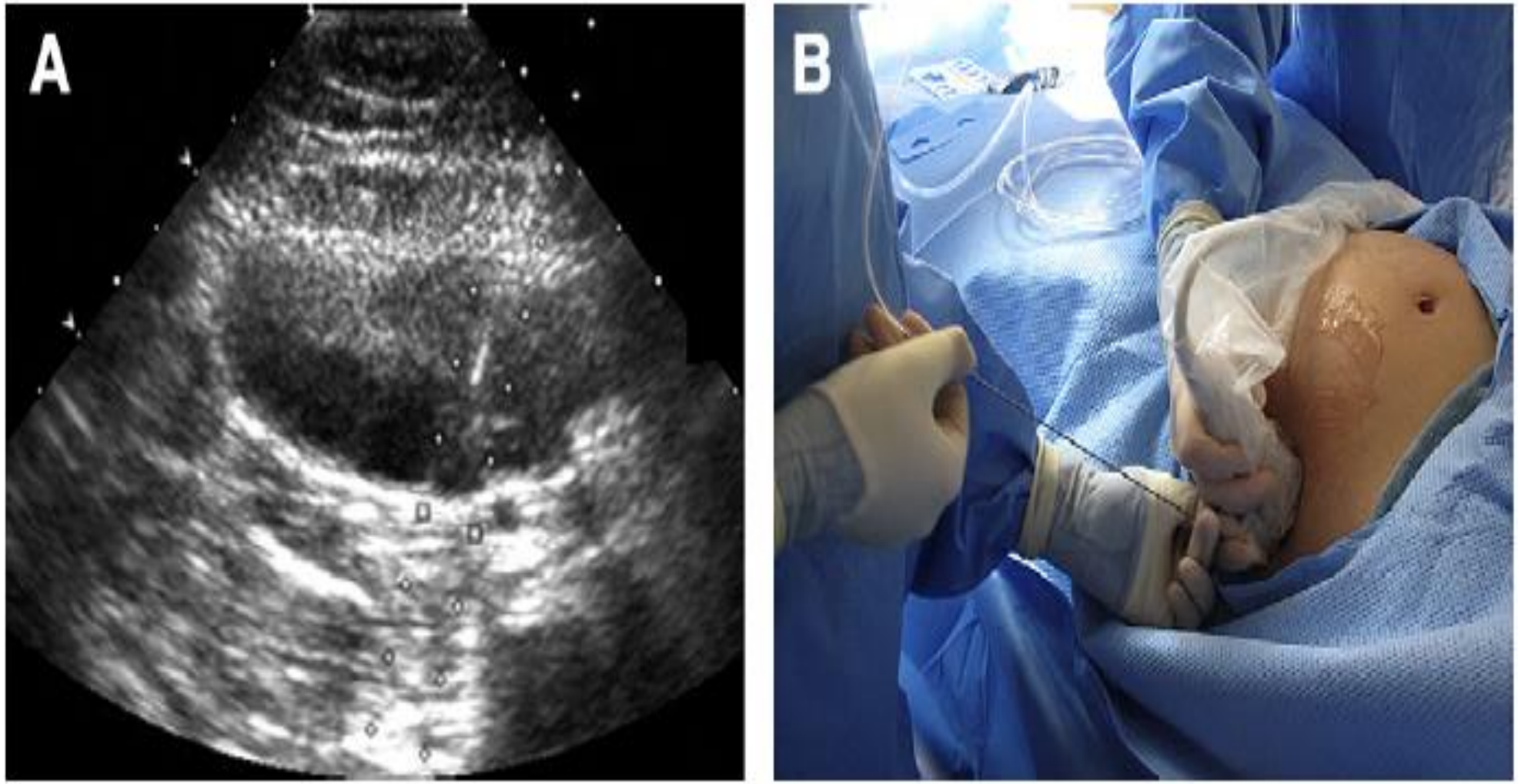
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Case Report ISSN 2639-9342

Gynecology & Reproductive Health

Fibroids and Infertility: Transabdominal Ultrasound Guided Oocyte Retrieval in Patient with Massive Multiple Leiomyomas - Case Report

Culej Diana, MD[1*], Bursac Danijel, MD, PhD[1], Pavan Jukic Doroteja MD, PhD[1,2], Planinic Rados Gordana MD[1], Valetic Josip MD[1] and Duic Zeljko MD, PhD[1,2]

[1]*Department of Obstetrics and Gynecology, University Hospital Merkur, Zagreb, Croatia.*

[2]*School of Medicine, University of Zagreb, Croatia.*

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Culej Diana, MD, Department of Obstetrics and Gynecology, University Hospital Merkur Zajčeva 19, 10 000 Zagreb, Tel: +385981931909, Croatia.

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32-year-old patient G2, P0 who came to our Department for secondary sterility treatment.

There was no known teratogen exposure, consanguinity, or family history of hereditarydiseases or malformations. From the family history we can find that patient's mother had hysterectomy due to uterine fibroids.

Patient had one ectopic pregnancy in 2007. A laparoscopic (LSC) salpingectomy was performed. Since 2007, she has been monitored for uterine fibroids.

Due to the increase in fibroids, **ulipristal acetate therapy** (Esmya) was introduced for 3 months.
As part of infertility assessment, a **diagnostic hysteroscopy** (HSCP) was performed in 2016, which did not reveal any pathological findings in the uterine cavity.

Sonography (US) exam revealed uterus with multiple fibroids. The largest fibroid was described like subserous anterior and right with diameter of 41x37mm (type 6), isthmic anterior and posterior fibroids 22 mm in diameter (type 4),
in the fundus subserous (type 6) and two intramural fibroids (type3) measuring 17 mm, partly showing a neat cavum.
The right ovary could not been shown (most likely was hidden behind the fibroid).
The left ovary was normal.

After detailed exam she underwent controlled ovarian hyperstimulation with short antagonistic GnRH protocol.
Due to the fact that the ovaries could not been reached in usual transvaginal path, we performed transabdominal ultrasound-guided retrieval and collected 3 oocytes. Frozen embryo transfer was performed on day 5.

The patient had a pregnancy until the 27th week of pregnancy when she reported to the emergency maternity ward due to lower abdominal pain. She was hospitalized due to abdominal pain and elevated inflammatory parameters attributed to degenerative myoma changes.

Antibiotic therapy for 5 days was ordinated with analgesics and spasmolytics for symptomatic therapy. During the stay she was afebrile, and inflammatory parameters decline.
During US exam low lying placenta was found (22 mm) and an increase in myoma-conglomerate of fibroids on the right back side of uterus sizing 130x30 mm, and also on the back side of uterus retrocervically 70x80 mm.
Shewas released after 9 days.

She was hospitalized second time, with 30 + 4/7 gestations, for uterine contractions.
Therapy for fetal lung maturation with Dexamethasone was performed according to the scheme. Total steroid doze of 24 mg was administered in divided dose 24 hours apart with tocolysis for 2 days.

At the age of 31 weeks of gestation,
she bled profusely from the uterus with deep variable decelerations in the CTG record, and due to the threatening asphyxia of the fetus, labor was completed surgically.
Cesarean section was performed by corporal incision with lower median laparotomy. Intraoperatively, a fibroid-altered uterus and fetal head fixed between 2 posterior wall myomas were described

Live premature male child was born. 1720 grams and 42 cm long,
Apgar score was 4/6. The early postpartum course went smoothly.
The neonatal care period was successfully completed and the child and the mother were released after 13 days after Cesarean section.

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- November 2021**Indian Obstetrics & Gynaecology**

A 39-years-old patient presented at Hospital and Research Institute, for undergoing an IVF treatment preceded by a previous failed IVF treatment carried out before.

An USG was done on the patient and she was diagnosed with a bulky uterus with **multiple submucosal**, **intramural** and **subserosal** uterine fibroids. She had a surgical history for an appendectomy that was performed 7 years ago.

Patient was admitted and asked to get an MRI. The

patient was counselled for a myomectomy.

A MRI done onthe pelvis showed an enlarged uterus with a volume of 137 ccwith several lesions in the submucosal region in the lateral

wall, in the endometrial cavity, as well as in the right lateral wall

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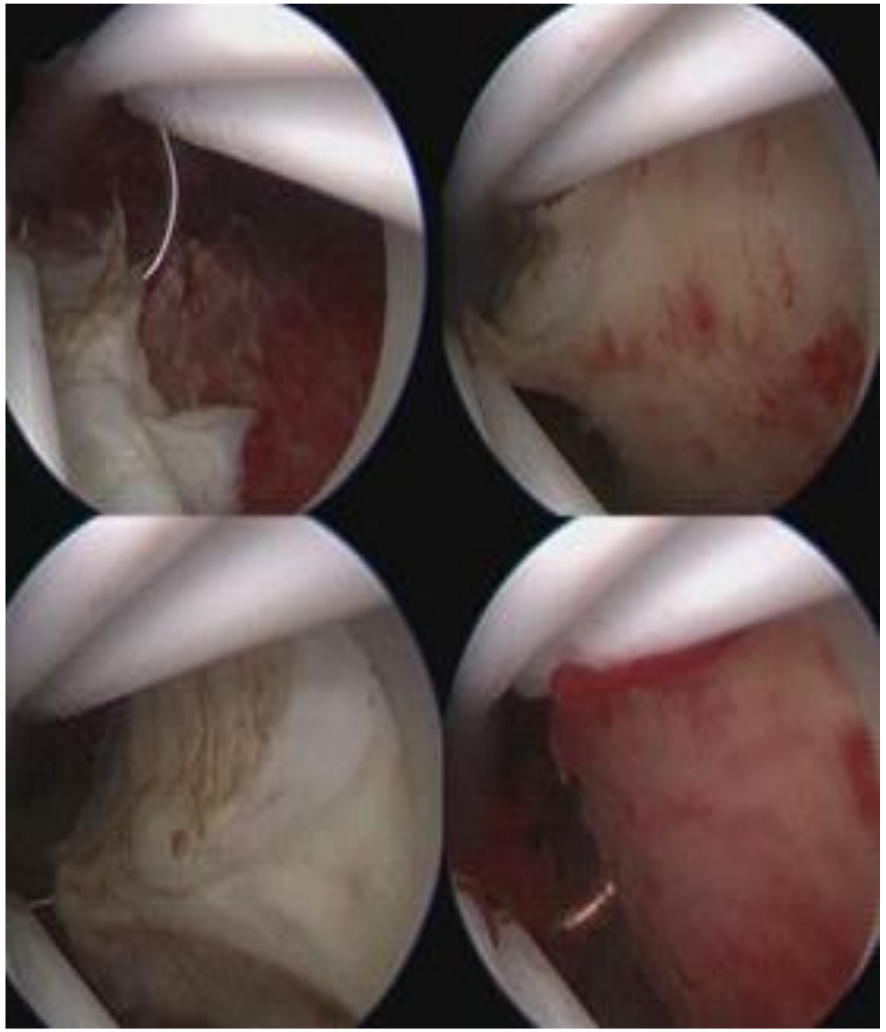

A laparoscopic myomectomy was also done wherein

12 subserosal and 13 intramural fibroids were removed.

- The patient was discharged after three days..

Simultaneously egg retrieval was done from a donor.

IVF cycle was planned using donor eggs and Husband's Semen

Considering advanced maternal age and male factor, oocyte

actvation was done to improve fertilization rate. Nine

- embryos were formed. Embryo freezing of three embryos Day 3 and six embryos Day 5 was done.

- The patient was then started on 3.75 mg of decapeptyl
- injection once every month for three months. The patient was
- also prescribed to start tablet ethinylestradiol and desogestrel
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- The patient returned after seven months. A re-look
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- and right anterior wall of the uterus. The endometrium and
- endometrial cavity were normal hence embryonic transfer was
- decided to be carried out in the subsequent month.

A month after the patient arrived transfer was planned and two embryos of Day 5 were transferred successfully in the patient's uterus with the endometrial thickness being 9 mm.

The patient was prescribed injection atosiban 6.75 mg which was administered 30 minutes before embryo transfer. Luteal phase support was given.. The patient was tested positive for β-hCG 14 days post embryo transfer. The patient was then prescribed tablets estradiol valerate, dydrogesterone, aspirin, progesterone injection, and L-arginine sachets.

The patient had a single live intrauterine pregnancy which was known 30 days post embryo transfer.

Points†	Size (cm)	Topography	Extension of the base	Penetration	Lateral wall
0	≤2	Low	≤1/3	0%	+1 point
1	>2–5	Middle	>1/3–2/3	<50%	
2	>5	Upper	>2/3	>50%	

† Sum of points reflects complexity and therapeutic options: 0–4 (group I): low complexity hysteroscopic myomectomy; 5–6 (Group II): high complexity hysteroscopic myomectomy, consider preoperative GnRH analog and/or two-step resection; 7–9 (Group III): consider alternative to hysteroscopic technique.

- Myomectomy may appear to be a big procedure to perform in patients with small IM fibroid/s. Non-surgical modalities may be another option.
- While UPA seems encouraging, this may be an option to reduce the size of fibroids especially the type 3 and 4a fibroids. The shrinkage may move the fibroid away from the endometrial lining and the JZ thus improving IR. However, this needs to be balanced with the risk of liver complications. GnRHa may have similar effect as UPA although this has not been researched in clinical studies.
- Ulipristal, a selective progesterone-receptor modulator, in particular has shown promise. Recent studies by Donnez *et al.* have shown a reduction in bleeding and fibroid size with ulipristal versus placebo, as well as non-inferiority compared with leuprolide .Additionally, ulipristal was shown to be less likely to cause hot flashes in study subjects than leuprolide acetate. Donnez J, Tomaszewski J, Vazquez F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N. Engl. J. Med.* 366, 421–432 (2012).

Does size of IM fibroids affect fertility?

- **The results showed a significant reduction of cPR, LBR, bPR and IR in fibroid diameter >2 cm compared to the control group**.
- One study showed NCD **fibroids >2.85 cm** had significant negative impact on the LBR and DR but insignificantly higher MR compared to the control group .Yan L,. Fertil Steril 2014
- Christopoulas *et al.* BJOG 2017 reported **multiple fibroids** or **NCD fibroids >3 cm** lowered the cPR and LBR significantly .
- Vimercati *et al.* Reprod Biomed Online 2007 reported **fibroids >4 cm** have adverse impact in the pregnancy outcomes since they require more ART cycles .
- This statement was supported by another study conducted by Oliveira et al where IM fibroids >4 cm lowered the cPR and IR more than the IM <4 cm, SS fibroids and the control groups .

- ***Correlation between the number and location of fibroids with the fertility outcomes***

- Yan *et al.* reported absence of significant differences of cPR and DR on the number of fibroids as compared to the control group .They also found that single and multiple fibroids have the similar outcomes**.**
- **No correlation was found between the number and location of the IM fibroids on the IVF-ICSI outcomes** .
- Few studies reported **absence of correlation** between the size of the fibroids with cPR .
- Furthermore, Surrey *et al.* demonstrated **no correlation** between the total mean fibroid diameter or volume and the implantation among women with fibroids regardless of their age .
- Oliveira FG, FerSterility 2004; Yarali H, Arch Gynecol Obstet 2002; Vimercati A,RBM online 2007; Bozdag G, A,RBM online2009; Aboulghar MM, Fertility Society Journal 2004
-

In a retrospective cohort study, Christopoulos et al. identified that women with multiple fibroids or with fibroids R30 mm in diameter exhibited significantly lower
clinical pregnancyand live birth rates although the uterine cavity was not distorted (7). In a retrospective study, Yan et al. concluded that non–cavity-distorting
fibroids >2.85 cm in diameterhad a significant negative impact on the live birth rate
after IVF treatment: Patients with type 3 fibroids had lower live birth rates and higher
clinical miscarriagerates, but the differences did not reach statistical significance.
In addition, the small sample size of type 3 fibroids should be considered, because only 19 patients were identified at that time.

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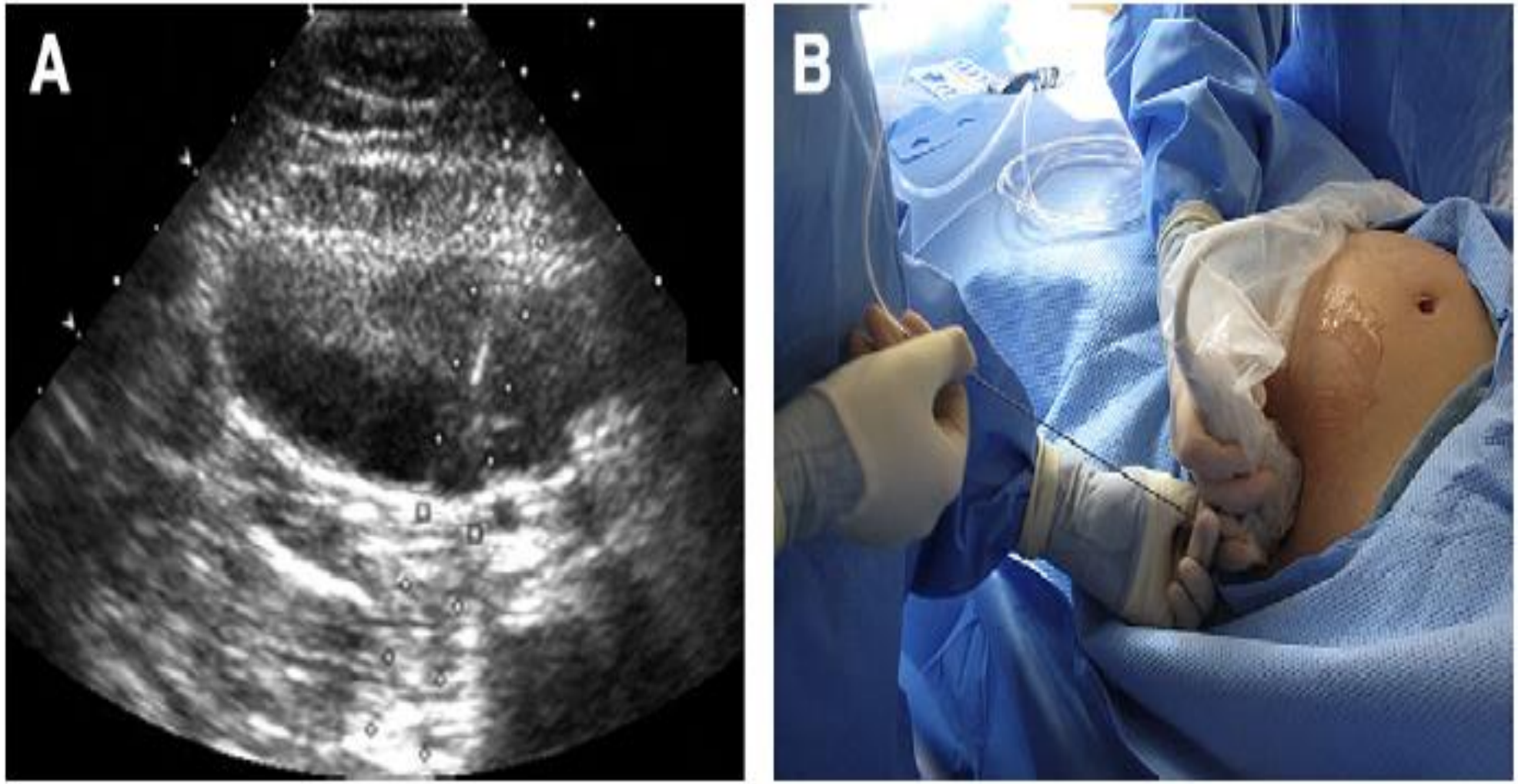
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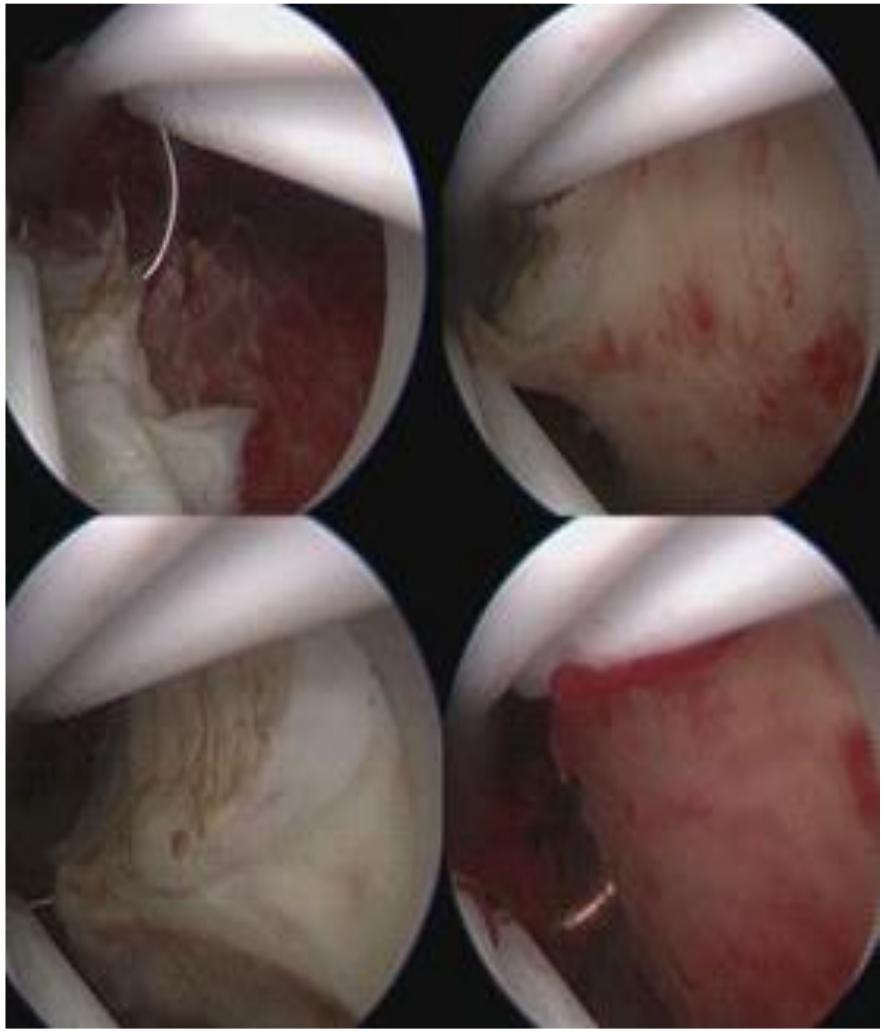

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