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وبینار میوم و ناباروری

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دکتر سمانه کاشی

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In The Name of GOD

Hypothetical Mechanisms
Of The Effect Of Fibroids
On Female Infertility

Introduction

- ▶ Fibroids are benign tumours of the myometrium and are the most common gynaecologic abnormality.
- ▶ Although most fibroids are asymptomatic, they can cause symptoms like heavy menstrual bleeding, pelvic pain, sexual dysfunction, pressure complaints, and infertility.
- ▶ The association between fibroids and infertility has been debated for decades.
- ▶ 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.

Hypothesis

- ▶ (1) Sexual dysfunction
- ▶ (2) Mechanical compression
- ▶ (3) Disturb peristalsis of the junctional zone
- ▶ Fibroids could induce a detrimental environment for implantation
 - ▶ (4) Changing the vagino-uterine microbiome
 - ▶ (5) Disturbing the levels of inflammation and autophagy
 - ▶ (6) Inducing molecular changes in the endometrium
 - ▶ (7) Inducing aberrant angiogenesis and altering the endometrial blood supply

Sexual dysfunction

Hypothesis 1: pelvic pain and dyspareunia interfering with sexual intercourse

- ▶ Sexual dysfunction in premenopausal women is a relatively common disorder with a prevalence of 30-50%.
 - ▶ Fibroids may be associated with **sexual dysfunction**.
 - ▶ Fibroids can cause **pelvic pain** and/or **dysmenorrhea** resulting in **dyspareunia**.
 - ▶ Fibroids can cause **heavy and/or prolonged menstrual bleeding**.
 - ▶ these problems could interfere sexual arousal ... negatively **influence the frequency of intercourse**, resulting in a reduced probability of pregnancy.

Sexual dysfunction

Hypothesis 1: pelvic pain and dyspareunia interfering with sexual intercourse

- ▶ No association was found between fibroid size and pelvic floor problems. But **fundal fibroids** were more associated with **dyspareunia**.
 - ▶ Treatment of fibroids, like **myomectomy**, may relieve pelvic pain during intercourse, thereby improving sexual function in these women.
 - ▶ Ferrero et al. (2006) did not find an association of fibroids with impaired sexual function, neither did they find an association between fibroid location and dyspareunia.
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- ▶ In conclusion, **sexual dysfunction in an infertile couple is a complex issue** and, along with possible treatment of fibroids, it might be necessary to also address **other medical or psychosocial problems**.

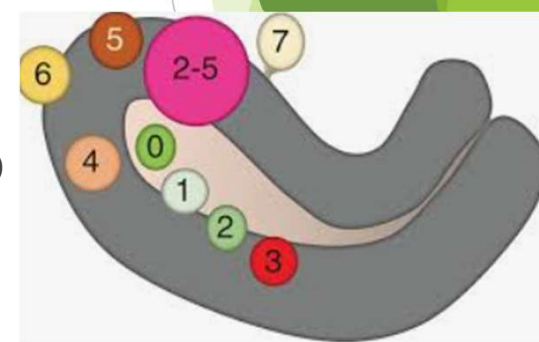
Disturbed oocyte and sperm transport

Hypothesis 2: physical compression of the interstitial part of the fallopian tubes or deformation of uterine cavity

- ▶ Fibroids can
 - ▶ obstruct sperm cells from reaching the oocyte
 - ▶ obstruct an embryo from reaching the uterine cavity
 - ▶ hinder implantation, by compressing the endometrium through mechanical distortion of the endometrial cavity, the interstitial part of the fallopian tubes or the cervix.
- ▶ Extrinsic compression by large subserosal or intramural fibroids can cause gross anatomical distortion of the interstitial part of the fallopian tubes, resulting in tubal factor infertility, as this could hinder sperm or oocyte penetration.

Disturbed oocyte and sperm transport Hypothesis 2: physical compression of the interstitial part of the fallopian tubes or deformation of uterine cavity

- ▶ It is essential to differentiate between fibroids that distort the uterine cavity:
 - ▶ submucosal fibroids FIGO type 0,1 and 2
 - ▶ intramural fibroids FIGO type 2-5
- ▶ fibroid types that do not distort the uterine cavity: intramural fibroids FIGO type 3,4,5
- ▶ subserosal fibroids: FIGO type 6,7
- ▶ Women with **cavity distorting fibroids** are demonstrated to have significant **lower implantation, CPR and LBR**, and significantly **higher miscarriage rates**.



- ▶ Myomectomy of submucosal fibroids appears to restore reproductive potential.
- ▶ There is still debate about whether myomectomy of intramural and subserosal fibroids can improve reproductive outcomes.
- ▶ When patients simultaneously suffer from fibroid-related symptoms, myomectomy of submucosal, intramural, or subserosal fibroids would not delay the time to live birth despite the required recovery time after surgery and the risk of intrauterine adhesions (Don et al., 2022).
- ▶ If a fibroid is located close to the interstitial part of the fallopian tube, it may be challenging to restore its anatomy after myomectomy without disturbing the transport functions.
- ▶ Futures studies are needed to elucidate the benefit of myomectomy in these specific cases.

Disturbed oocyte and sperm transport, and detrimental environment for implantation

Hypothesis 3: disturbed peristalsis of the junctional zone in the myometrium

- ▶ Fibroids possibly disturb
 - Frequency
 - Direction
 - Amplitude
 - coordination of junctional zone peristalsis
- ▶ resulting in inadequate oocyte and sperm transport.

- ▶ The **contractility** of the **subendometrial layer** or **inner myometrium** in a non-pregnant uterus moves in specific patterns and directions **depending on the phase of the menstrual cycle**.(Harmsen et al., 2022).

Disturbed oocyte and sperm transport, and detrimental environment for implantation

Hypothesis 3: disturbed peristalsis of the junctional zone in the myometrium

- ▶ By junctional zone peristalsis, the journey of sperm through the genital tract to the fallopian tubes is enhanced during the late follicular phase until ovulation.
- ▶ After ovulation, junctional zone peristalsis decreases dramatically to support implantation
- ▶ Altered junctional zone peristalsis is considered to cause IVF failure, because alterations to the direction and/or frequency of the contractions could induce the evacuation of an embryo out of the uterine cavity.
 - ▶ Additionally, the contraction amplitude is of influence. Frequent contractions of low amplitude can favour implantation.


- ▶ Fibroids negatively influence the frequency, direction, and coordination of junctional zone peristalsis, although their **influence on the amplitude of contractions has not been explored**.
- ▶ **only submucosal fibroids**, not intramural or subserosal fibroids, cause **loss of uterine peristalsis**.
- ▶ in women with **symptomatic fibroids**, the presence and frequency of **peristalsis and the cervix-to-fundus direction** of contractions were significantly **decreased**, without relationship to the fibroid location or other fibroid characteristics (Kido et al., 2014).
- ▶ Furthermore, **submucosal fibroids** have a significantly **thicker pseudocapsule**, like a neurovascular bundle surrounding the fibroid, compared to both intramural and subserosal fibroids (Tinelli et al., 2018).
- ▶ Hypothetically, this pseudocapsule could play a role in infertility, since it has a recently discovered **neuroendocrine function**, possibly influencing junctional zone **peristalsis** (Tinelli et al., 2018).


- ▶ **treatment of fibroids**, such as uterine artery embolization, high-intensity focused ultrasound (HIFU) or myomectomy, **can restore** the presence, direction, frequency, and coordination of junctional zone **peristalsis**.
- ▶ Moreover, Yoshino et al. (2012) found that not only the frequency of junctional zone peristalsis was normalized after myomectomy, but the pregnancy rate also was increased (n ¼ 15, pregnancy rate: 40%) (Yoshino et al., 2012).
- ▶ studies about obstetric outcomes after **myomectomy of submucosal fibroids** generally report a **positive effect** of the procedure.
- ▶ we still need to elucidate whether this effect is in part because of the normalization of junctional zone peristalsis

Detrimental environment for implantation

Hypothesis 4: changes in the vagino-uterine microbiome

- ▶ Today it is known that **human fetal development is far from a sterile event.**
- ▶ Fibroids may induce **inflammation** and **changes in local nutrients**, as well as heavy and **prolonged menstrual bleeding**, all of which influence the vagino-uterine microbiome.
- ▶ A **microbiome** was found not only in the vagina and endocervical canal, but also in the uterine cavity and fallopian tubes, and even the intrafollicular environment can have its own active microbiome
- ▶ The cervicovaginal microbiota is dominated by **Lactobacilli** species and changes in this dominance may influence the reproductive potential

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- ▶ In women with **non-Lactobacillus-dominated microbiota** in the endometrial fluid, a significant **decrease in implantation**, pregnancy, ongoing pregnancy, and live birth rates was found compared to women with a Lactobacillus-dominated microbiota.
 - ▶ Gynaecological diseases, like **endometriosis**, **ovarian or endometrial cancer** and **polycystic ovary syndrome** and uterine **myoma** have been shown to influence the microbiome in the female reproductive tract.
 - ▶ It is important to note that the **microbiome** comprises more than a simple accumulation of bacteria and in many cases it is formed by complex 3-dimensional lattices, also described as the **biofilm**.

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- ▶ Research needs to be done in patients with fibroids specifically to clarify what these conditions do to the **vagino-uterine microbiome** and whether treatment like myomectomy can restore a healthy and receptive vagino-uterine microbiome.

Hypothesis 5: disturbed levels of inflammation and autophagy

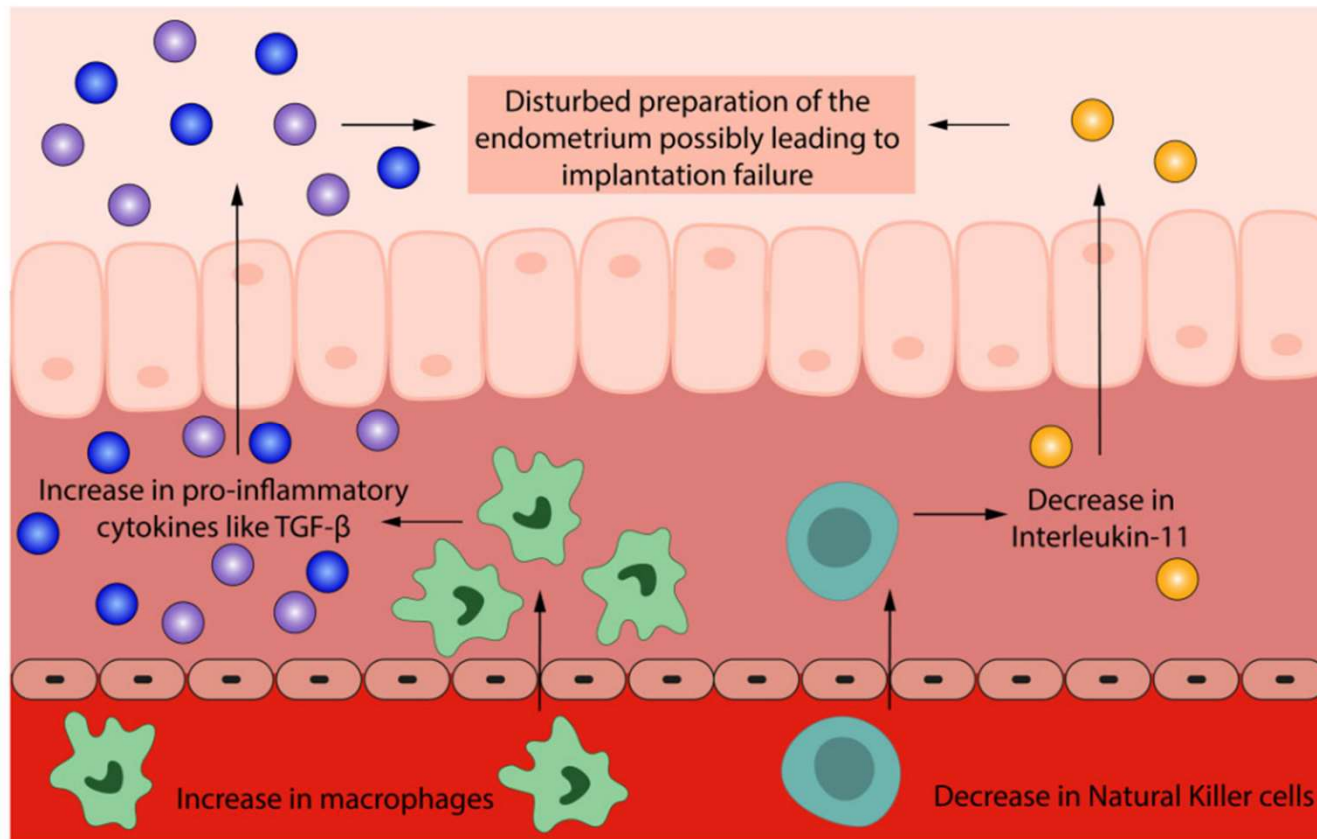
- ▶ female reproductive tract has a **symbiotic relationship with its microbiome**, by **detection of these microbes by the immune system** is followed by a complex responses.
- ▶ **The uterine immune system is very unique**
 - Adaptation to hormonal stimuli during the menstrual cycle
 - toleration of the semi-allogeneic fetus
 - Different response of immune cells in
 - ✓ Phases of the menstrual cycle
 - ✓ Implantation
 - ✓ Pregnancy



Hypothesis 5: disturbed levels of inflammation and autophagy

- ▶ In women without fibroids:
 - ▶ **NK cells** are the most abundant lymphocytes found in the decidua during implantation and in first trimester pregnancy.
- ▶ In patients with fibroids:
 - ▶ **CD68+ macrophages** exist in abundance at the myometrial site of the fibroid. These macrophages produce various growth factors, including transforming growth factor b (**TGF-b**), which attracts even more macrophages.
 - ▶ **Low levels of interleukin (IL)-11** are associated with **decreased numbers of NK cells**, and IL-11 is decreased during the window of implantation in patients with fibroids. This reduction in IL-11 may therefore result in implantation failure in these women.

Hypothesis 5: disturbed levels of inflammation and autophagy



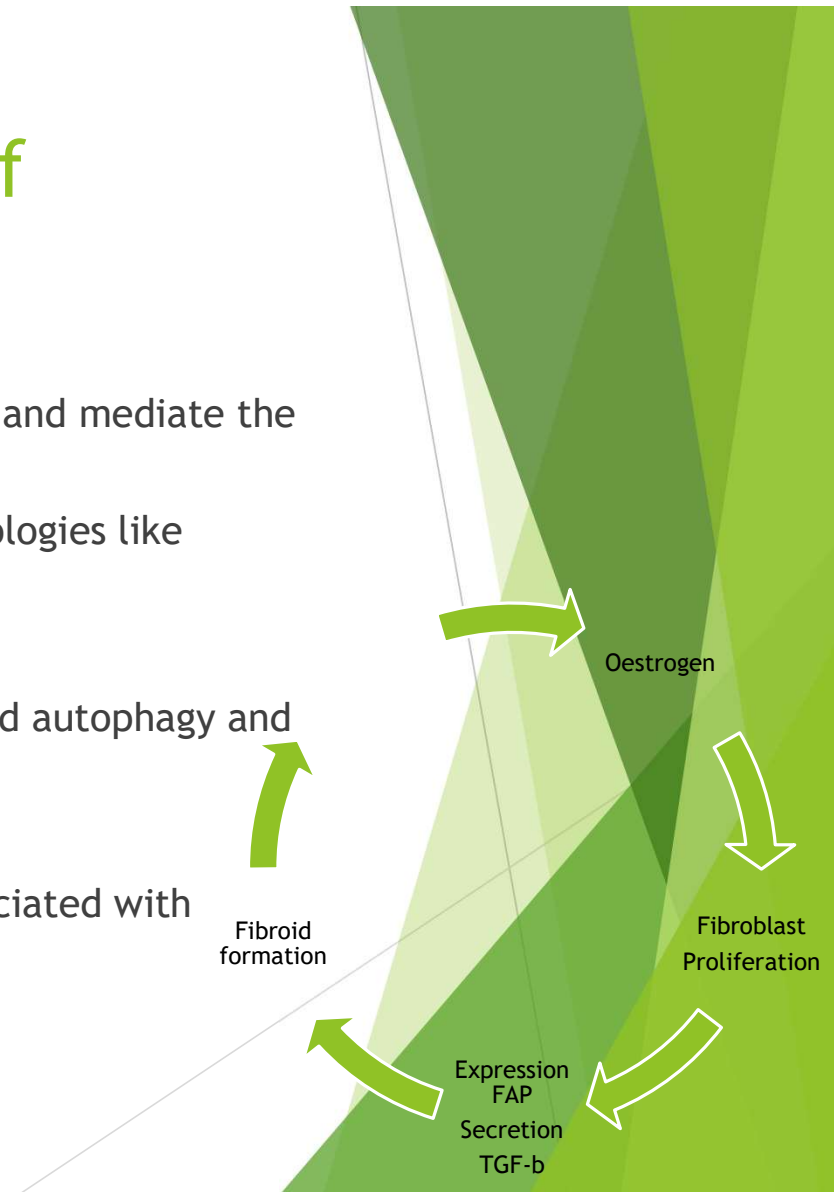
- ▼ Two possible inflammatory routes how fibroids could negatively influence implantation and cause infertility.

Hypothesis 5: disturbed levels of inflammation and autophagy

- ▶ In patients with fibroids Local endometrial **inflammatory changes** may contribute to the observed **structural changes** like
 - ▶ **glandular atrophy**
 - ▶ **Ulceration**
 - ▶ **elongated glands**
- ▶ resulting in
 - ▶ implantation failure
 - ▶ early pregnancy loss
 - ▶ infertility
- ▶ Myomectomy whether or not could re-establish the normal endometrial inflammatory state?
- ▶ More research is needed to verify whether fibroids alter autophagy in the endometrium and whether this contributes to fibroid related infertility.

Hypothesis 5: disturbed levels of inflammation and autophagy

- ▶ Autophagy is essential to maintain endometrial homeostasis and mediate the menstrual cycle and implantation.
- ▶ Disturbed levels of autophagy can lead to endometrial pathologies like fibroids.
- ▶ Decreased expression of ATG4D is shown to promote impaired autophagy and then fibroid growth.
- ▶ High expression of fibroblast activation protein (FAP) is associated with fibroids.



Hypothesis 6: molecular changes in the endometrium

HOXA10
HOXA11

E-cadherin

Normal
Implantation

Low expression
HOXA10
HOXA11

Low expression
E-cadherin

Fibroid

- ▶ In women with **submucosal fibroids**, HOXA10 and HOXA11 are significantly decreased in the endometrium.

- ▶ Also, in infertile women with **intramural fibroids (without cavity distortion)**, a lower expression of both HOXA10 and the cell adhesion molecule E-cadherin was found during the window of implantation compared to that in fertile women without fibroids

E-cadherin is supposed to be essential for embryonal development and blastocystic implantation.

Hypothesis 6: molecular changes in the endometrium



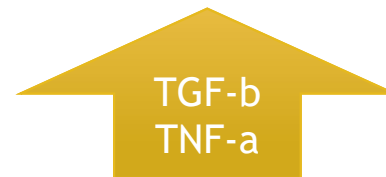
Bone morphogenetic protein type II:
increases endometrial receptivity



Impaired decidualization and implantation

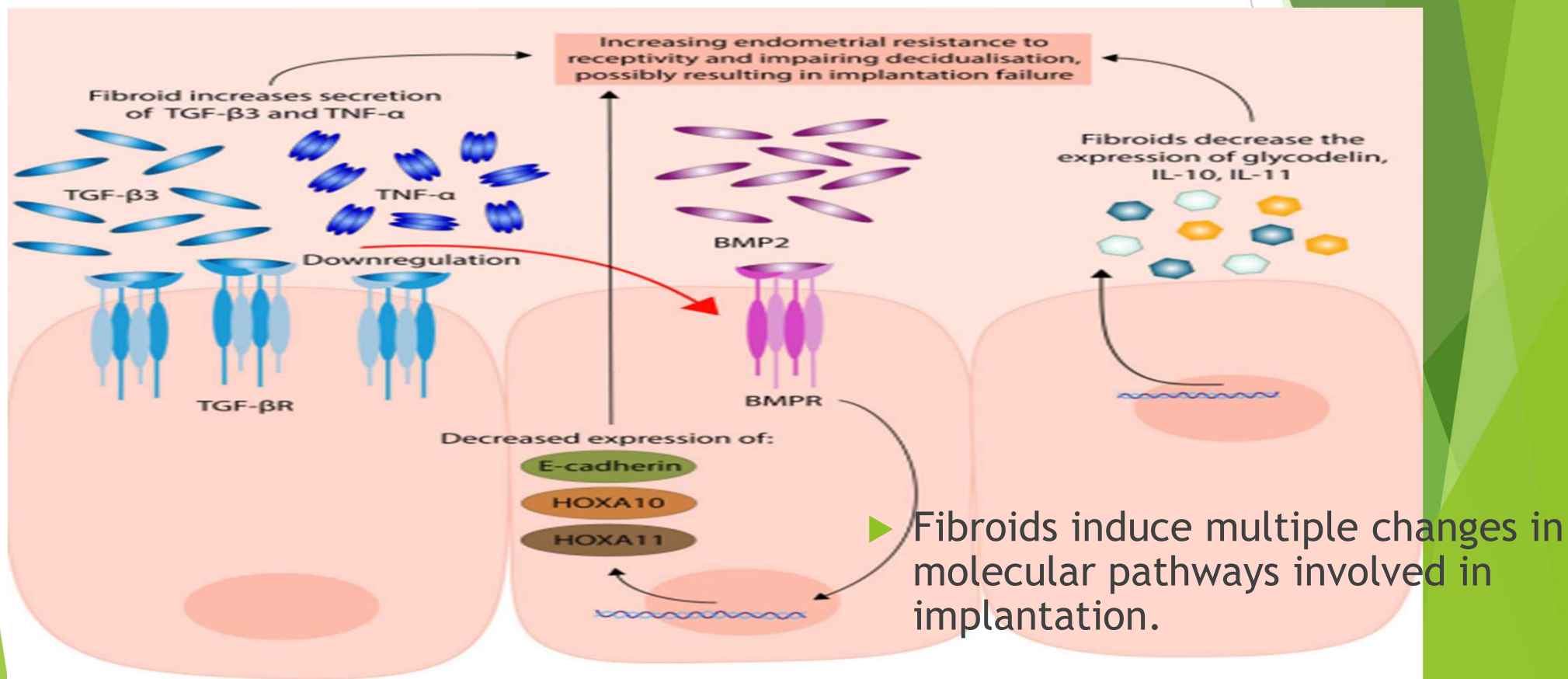
Hypothesis 6: molecular changes in the endometrium

Fibroid



- ▶ TNF-a is involved in
 - ❖ Immunological pregnancy loss
 - ❖ Implantation failure
 - ❖ Infertility

A summary of possible molecular routes how fibroids could negatively influence implantation and cause infertility



Hypothesis 7: aberrant angiogenesis and impaired endometrial blood supply

- ▶ **Aberrant endometrial angiogenesis** and **disturbed vessel maturation** caused by fibroids may result in both abnormal uterine bleeding and infertility.
- ▶ Fibroids, especially those close to the uterine cavity, can restrict endometrial blood flow.
- ▶ One study found that in women with fibroids and a lower uterine artery PI and RI, conception rates were significantly lower.
- ▶ Future research could identify key targets for possible therapy or evaluate whether myomectomy can restore normal endometrial angiogenesis.

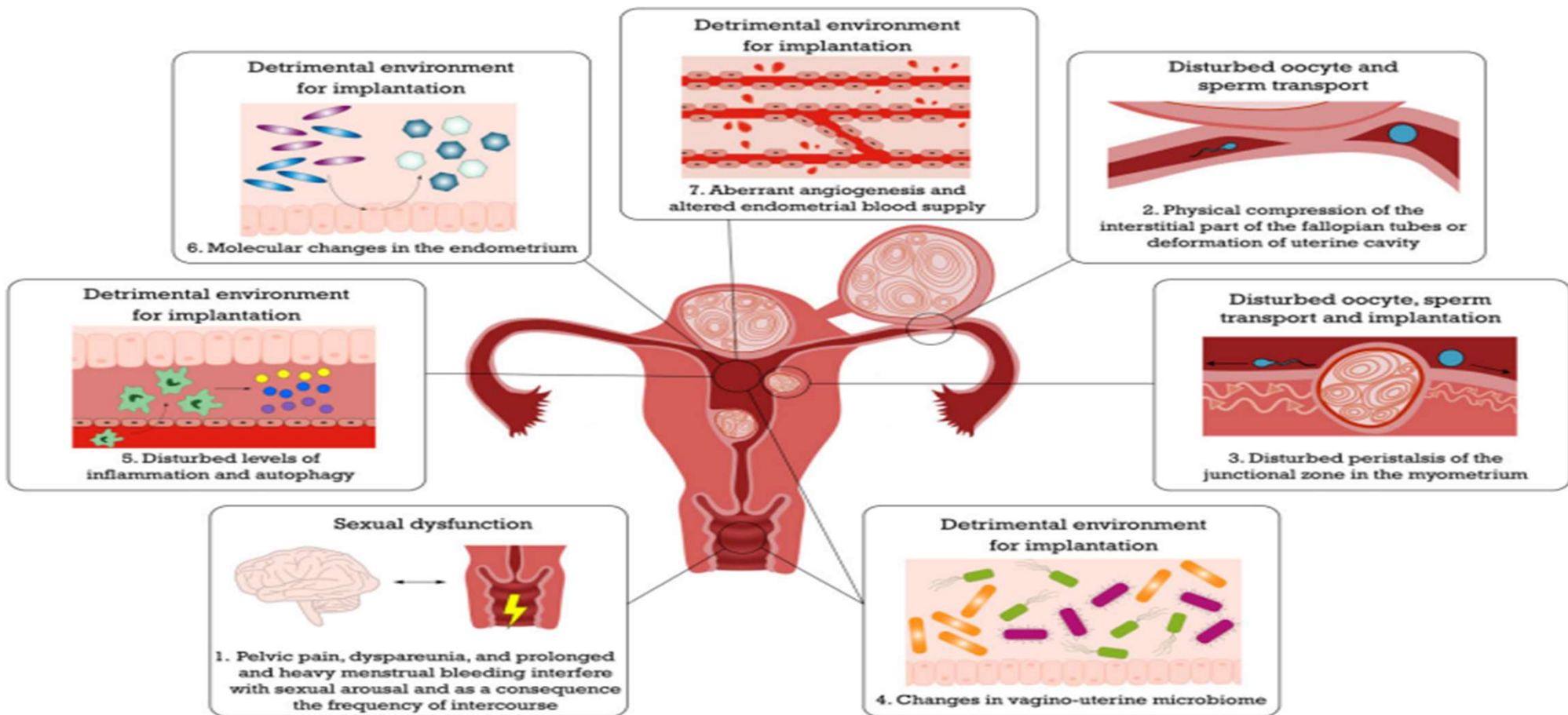
Increased risk of miscarriage

- ▶ patients with fibroids can also experience a number of problems during pregnancy, including miscarriage or early pregnancy loss.
- ▶ 2-fold increase in miscarriage rate in women with fibroids (Benson 2001)
- ▶ Miscarriage rate in women with multiple fibroids was significantly higher compared to women with a single fibroid (Gianaroli 2008)
- ▶ Fibroid location is not important but submucosal fibroids are more important.
- ▶ Submucosal fibroids seem to affect junctional zone peristalsis and molecular changes in the endometrium
- ▶ A recent meta-analysis of 1394 pregnant women with fibroids versus >20 000 pregnant women without fibroids, and excluding women with recurrent pregnancy loss or infertility care, found no association between fibroids and the risk of miscarriage.
 - ▶ current data are conflicting and do not answer the question of whether there is or is no association between fibroids and miscarriage.

Summary

- ▶ Infertility in patients with fibroids may have various causes.
- ▶ 7 hypotheses:
 - ❑ 1. Fibroids can cause **pelvic pain, dyspareunia, and prolonged and heavy menstrual bleeding**, which can disturb **sexual arousal** and frequency of intercourse, resulting in a reduced probability of conception.
 - ❑ 2 . Fibroids could negatively influence oocyte and sperm **transport** by **disturbing myometrial peristalsis** of the junctional zone, and/or by **mechanical compression** on the interstitial part of the fallopian tubes or **deformation of uterine cavity**.
 - ❑ Fibroids could cause a **detrimental environment for implantation** in five different ways:
 - ❑ 3. by disturbing **myometrial peristalsis** of the junctional zone
 - ❑ 4. by altering the **vagino-uterine microbiome**
 - ❑ 5. Affecting the levels of **inflammation and autophagy**
 - ❑ 6. Stimulating **molecular changes** in the endometrium
 - ❑ 7. Disturbing **angiogenesis** and the endometrial blood supply

7 postulated hypotheses responsible for the detrimental effect of fibroids on fertility.



Conclusion

- ▶ Fibroids are the most common benign tumors and not all patients with fibroids suffer from infertility while not all infertile patients have fibroids.
- ▶ Numbers of studies underline the **possible negative effect of fibroids on fertility and reproductive outcomes**.
- ▶ **Insight in the underlying mechanisms** provides options for the development of targeted therapy and to increase the effect of fibroid surgery due to improved **patient selection** of who will benefit from a fertility sparing myomectomy.
- ▶ Structural and routinely assessment of fibroids, **sizes**, **localization**, and **vascularization** in women who want to become pregnant and in women with infertility before possible surgery is needed to develop prediction models and to gain insight in the underlying mechanisms of fibroid related infertility.

