



UTERINE FIBROIDS-A COMPREHENSIVE REVIEW

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Received: 15-01-2023; Accepted: 02-02-2023; Published: 28-02-2023

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ABSTRACT

Uterine fibroid is a non-cancerous growth in the female uterus of a reproductive woman, ranging from age 40s and above. Even though according to research, females of age 20s and 30s also have few chances of this growth in their uterus, as long as they have reach a child bearing age (reproductive age); in this stage it is encouraged that such individual is treated with immediate effect to avoid the continuous multiplication of this growth. "Uterine fibroid embolism" can be a good choice for treatment, which is a minimally invasive technique. In other cases, where the fibroid case has multiplied so much, "myomectomy", "hysterectomy" or "laparoscopy" can be considered to remove the fibroid growth and/or remove the uterus entirely if the woman is no more interested to bear child or in the case that removal of the uterus, could terminate the fibroid permanently. According to research, it has been discovered that uterine fibroids affect Black women more (about 80%) than white women (about 70-75%). Various risk factors that causes fibroids includes; family history, smoking, vitamin D deficiency etc. Avoiding junk foods, avoiding foods rich in fats, avoid high caffeine and High sugary food is also a very good health lifestyle to avoid or maintain proper healthy lifestyle against UFs. Mifepristone, Asoprisnil (ASP), telapristone are good pharmaceutical formulation for maintenance of UFs. UFs tends to decrease its multiplication in the therapy of gonadotropin releasing hormone agonist (GnRH). Some of the classifications of uterine fibroids includes; Intramural fibroid, Submucosal fibroid, Sub-serosal fibroid, Cervical fibroids etc.

Keywords: Estrogen, Fibroid, Myomectomy, Hysterectomy.

1. INTRODUCTION

Uterine fibroids is a genealogical disorder; non-cancerous growth that develops in a woman's uterus. This usually can happen during the child-bearing age of a woman; meanwhile the main cause of fibroids is not clearly known, but some risk factors could be as a result of obesity, or vitamin D deficiency, family history, or early puberty.

Fibroid symptoms could include pelvic pain, heavy menstrual bleeding, constipation, leg pain, difficulty/frequent urination, irregular or prolong menstrual period.

Different surgical treatment has been carried out to ensure the treatment and removal of fibroid growth such as; "hysterectomy [1, 2]" (this is known as the removal of the uterus surgically; this can also lead to the removal of ovaries, fallopian tube, cervix, etc.), "myomectomy [1]" (this is a surgical method used for removal of uterine fibroids), "Laparoscopy" (this also

include "Mini-laparotomy techniques"/"mini-laparotomy-assisted vaginal surgery"; this method helps to prevent the problems caused during the surgical removal of large fibroids. This method is very good as it allows the surgeon to remove the fibroid from the uterus just by making a small incision/cut on the stomach of the patient. This procedure can also be referred as Keyhole Surgery).

2. ETIOLOGY AND PREVALENCE

The real cause of fibroids is not actually known, but according to scientific research, it is said that this fibroid which affect 70% of white women and also 80 percent of African women [3, 4] throughout their entire life time "could" be caused as a result of abnormal muscles present in the uterus and when these muscles are exposed to excess estrogen hormone, they form the non-cancerous tumors known as "fibroids".

This effect can be very dangerous as this affects the uterus (womb) of the woman and makes her incapable of child-bearing, hence reproduction [5] is stopped and continuity of humans is posed under danger as women's

womb are the major contributor to the human existence.

In essence, reduced production of estrogen could lower this tumor growth in the uterus.

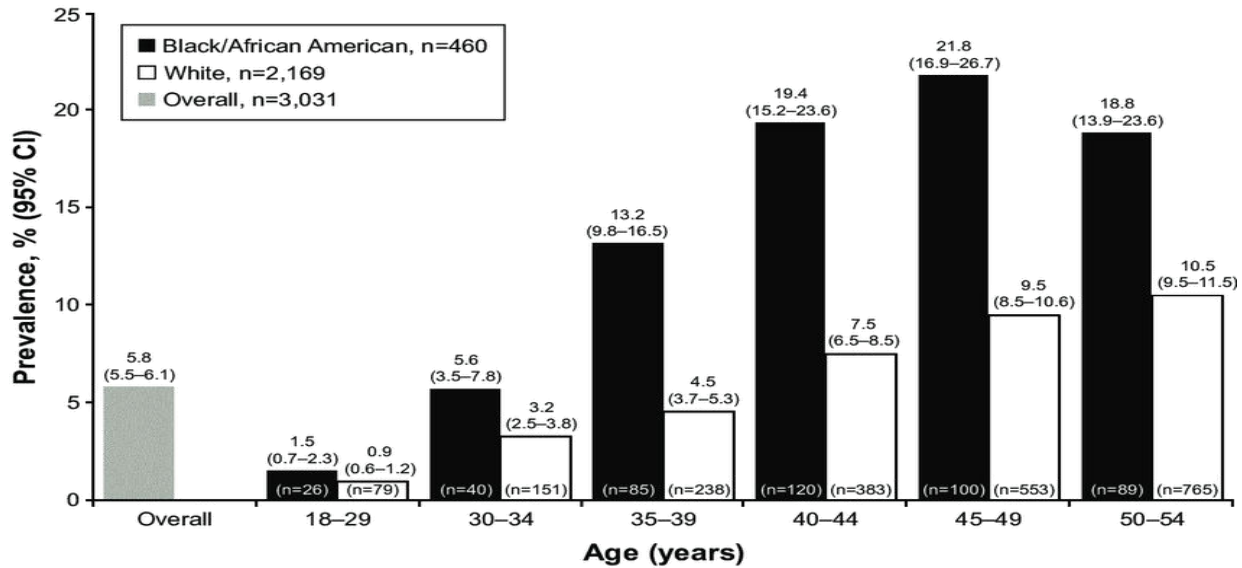


Fig. 1: Prevalence of UFs

2.1. Risk factors of fibroids

2.1.1. Age

According to research in the UK ultrasound record, it was discovered that women aged above 40 years old are more prone and more exposed to the risk of uterine fibroids.

2.1.2. Family background/history

A family with a history of uterine fibroid in the past, their women “could” stand a chance of having fibroid than those whose family never had such case in their lineage. This research was confirmed in Thailand women.

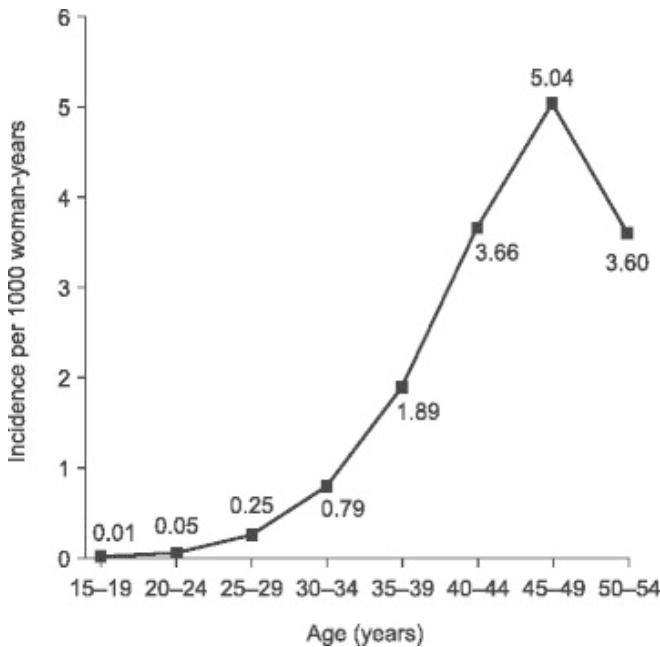


Fig. 2: Exposure to uterine cancer based on age

2.1.3. Smoking [6]

It is confirmed according to research that women who smoke, having low Body Mass Index (BMI less than 22.2 kg/m²) are prone to the risk of uterine fibroids. This is not applicable to Black Woman.

2.1.4. Reproduction status [7]

Both in black and white women; it is found that women of reproductive age who last gave birth for over a long period of time (like in the last five years or more) are more likely to have UFs when compared to women who just gave birth; this could be as a result of the excess of estrogen secretion, as the women is of child-bearing age.

2.1.5. Diseases/Health Condition

Disease/ill-Health conditions like diabetes, PCOD, cervical neoplasia, etc; could lead to the chances of UFs. Other risk factors include physical abuse, pollution, sexual abuse etc.

2.2. Pathology of uterine fibroid

UFs occur as a result of excessive growth of the smooth muscles and the connective tissues in the uterus. It has been clinically proven that progesterone and estrogen receptors are present in the fibrous growth. An increase in the estrogen level in the uterus, causes an increase in the fibroid growth. This fibroid growth damages the fallopian tube (which is responsible for fertilization of oocytes and reproduction & conception). UFs rarely cause nor lead to cancerous cells (about only 0.1 to 0.8% chance that fibroid growth can be cancerous). It is good to note that estrogen and progesterone are

important regulators of UFs. According to clinical research, it is observed that fibroid growth is extremely high in the presence of increased level of estrogen secretion; especially during the reproductive age, and tend to decrease during menopausal age, as there will be reduced secretion of estrogen and progesterone level in the uterus. UFs tend to decrease its multiplication in the therapy of gonadotropin releasing hormone agonist (GnRH). Combination of the Gonadotropin Releasing Hormone (GnRH) and the progesterone therapy does not show any effect in reducing the volume or multiplication of the UFs.

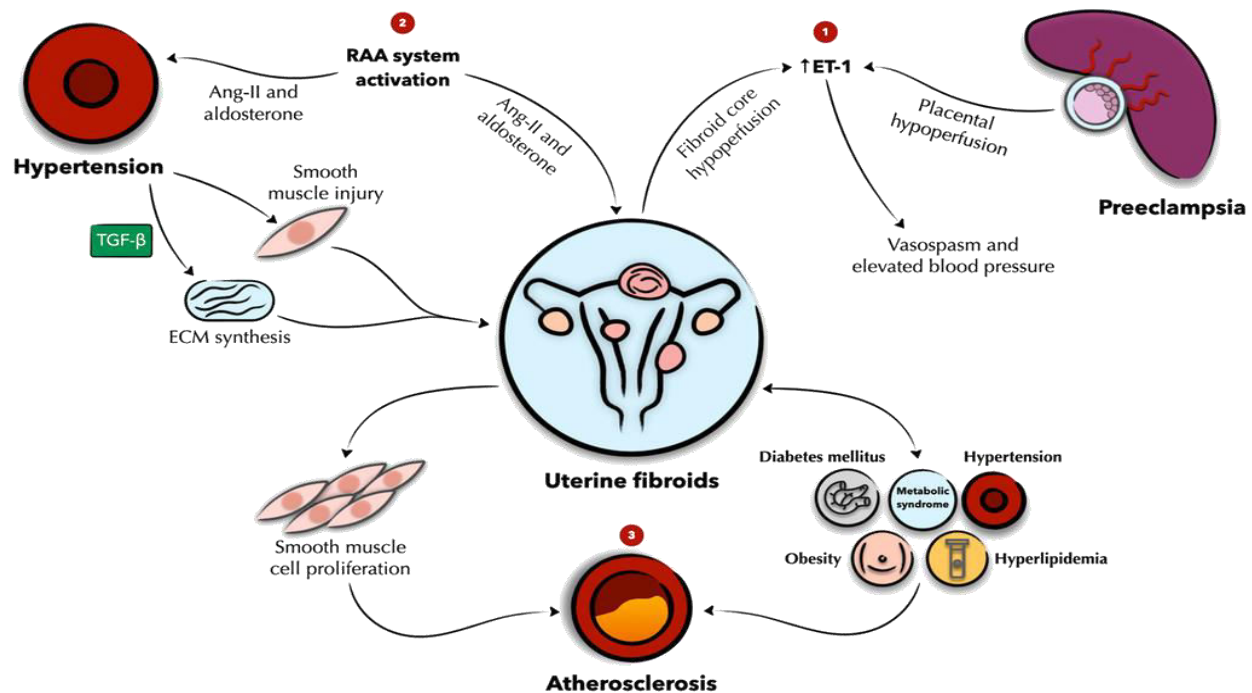


Fig. 3: Pathogenesis of UFs

3. CLASSIFICATION/TYPES OF FIBROID

3.1. Intra-mural fibroids

This is the type of fibroid that grows within the muscular wall of the uterine. This type of fibroid can be treated by non-surgical method (uterine fibroid embolism) [11].

3.2. Sub-mucosal fibroids

This type of fibroids could cause Abdominal Uterine Bleeding. This type of fibroids grows within the inner lining of the uterine.

3.3. Sub-serosal fibroids

This is a type of fibroid that grows outside of the uterus. It is non-cancerous;

3.4. Cervical fibroids

These are smooth non-cancerous tumors in the cervix. Cervical fibroids could bleed, cause pain during sexual intercourse, or interfere with urination. This can be observed during pelvic examination.

3.5. Symptoms of uterine fibroids [12]

Fibroid seems to be quite common among women of child bearing age; up to 40 and above women, meanwhile, there are various symptoms of UFs e.g. Heavy bleeding/painful bleeding, abdominal discomfort, painful urination, painful defecation, painful sexual intercourse/ discomfort during sex, backache, leg pain, pelvic pain, menstrual period lasting for a longer period of time, frequent urination, infertility,

pica (the craving to eat clay) and bowel and bladder pressure.

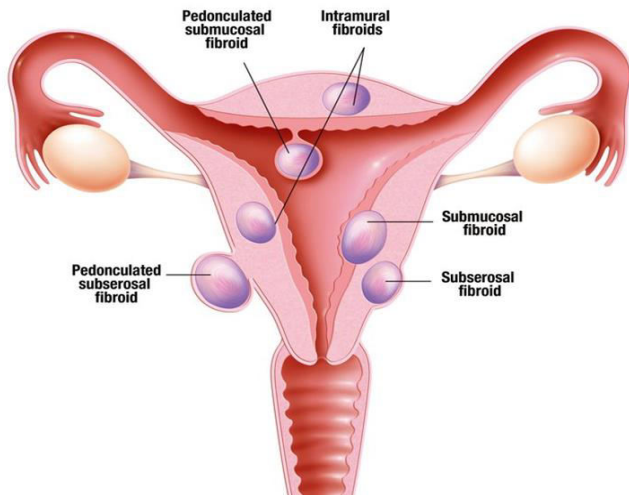


Fig. 4: Classification & location of uterine fibroids

Uterine Fibroids, not only occur in age 40s women but can also occur in women of age 20s and 30s. It can grow quite big. Every women needs to keep in check and be informed on the signs and symptoms of uterine fibroids and for early treatment to prevent further effect as this seems to pose danger to reproduction and fertility; which hence threaten continuity of human life.

Coming to think of it, if 30%-45% or even 50% of women (irrespective of Race), this would me making a lot of women infertile which is very bad image to the society and the society at large. This effect also keeps women unhappy, seeing their inability to conceive and have their own child and contribute to the continuity of human life to the earth and having their children make impact in the society.

According to clinical research, when these cases (UFs) are detected at early stage or in younger females; Uterine Fibroid Embolism be used to block blood supply to the fibroid tumor, hence causing them to shrink. Its benefit is that it helps the younger patient to stay fibroid free for a very long period of time, other than going through “Hysterectomy”.

4. TREATMENT OF UTERINE FIBROIDS

As UFs has pose serious threat to the fertility of female gender; let’s look at some possible means of putting to and end of this uterine fibroids, and hence make women free from such disease, and enhance their confidence and happiness, with a good and sound health for a living; hence ensure that reproduction continue and fertilization of the ova easier and faster.

These measures could be followed to terminate the growth of uterine fibroids can be classified into:

4.1. Surgical methods

These methods are used to permanently terminate the growth of fibroids in the uterine walls.

4.1.1. Myomectomy[13]

This is a surgical technique used for the removal of uterine fibroids. This technique does not guarantee that it’s occurrence won’t happen again. It just used to remove the fibroid in the uterus at present.

4.1.1.1. Procedure for myomectomy

The area to for an incision to be made is anesthetized. A small cut is made at the lower abdomen. The doctor uses a wire-loop Resectoscope or Hysteroscopic Morcellator to cut and remove the fibroid tumor with a blade. Stitches are made on the uterus and the lower abdomen and allowed for proper healing.

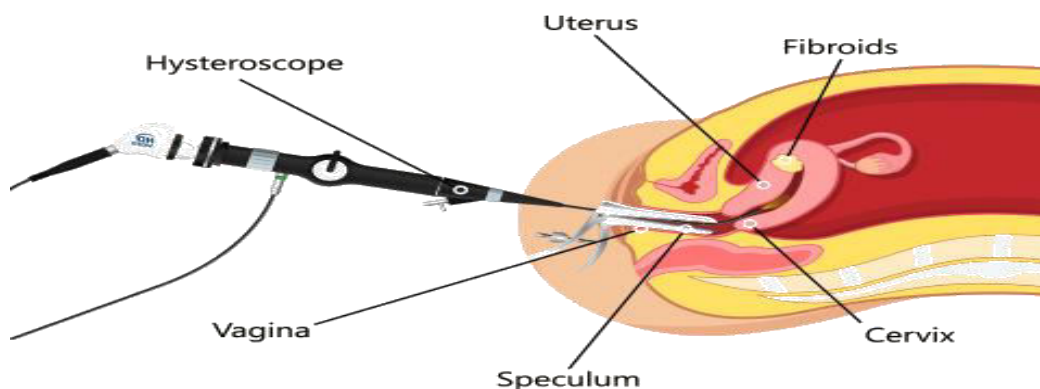


Fig. 5: Surgical procedure for myomectomy

4.1.2. Hysterectomy[14, 15]

This is known as the surgical removal of uterus, as a result of the fibroids. It uses High Frequency Electrical Energy to cut the uterine tissue, while being anesthetized in order to reduce pain.

4.1.3. Laparoscopy

This is an invasive surgical procedure used to remove uterine fibroid. It has faster recovery rate as it involves only a little hole-like opening in the abdomen, in which the surgical instruments, insufflator, trocars, video

monitors endoscopes and cameras are used to perform a successful laparoscopy surgery. This technique helps to reduce the after effect which normal surgery usually cause.

4.1.4. Uterine Fibroid Embolism

This technique is a minimally invasive [14] alternative to myomectomy and hysterectomy. This method is used to cause the stoppage of supply of blood to the fibroid tumor, and hence causing the shrinkage of the fibroids, and stoppage in its growth.



Fig. 6: Laparoscopy equipments



Fig. 7: Laparoscopic surgery equipment

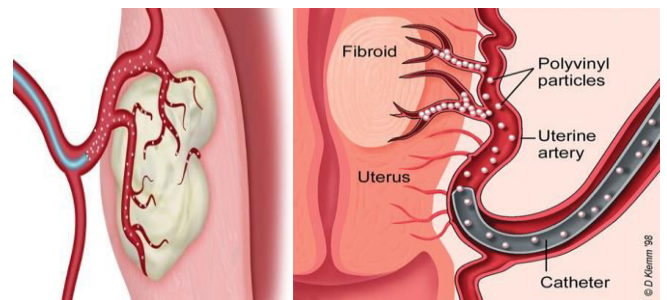


Fig. 8: Uterine fibroid embolism

4.1.5. Radiofrequency Ablation

This is also a minimally invasive method, used to cause shrinkage of the tumor size.

4.1.6. Endometrial Ablation

In this method, the lining of the uterus is removed in order to control heavy bleeding. Equipment used includes; wire loops, electric current, laser, etc.

4.2. Non-surgical method

The non-surgical method does not terminate the fibroids, but can cause some shrinkage in the size of the uterine fibroids size and management of the fibroid pain and size.

4.2.1. Administration of GnRH analogs

There are actually two types of GnRH used; (a) Super-agonists (b) Antagonists.

4.2.1.1. Super-agonist analogs

They cause desensitization and lead to the suppression of the Gonadotropin Hormone secretion. According to the publication Filicori et al in 1983, the uterine fibroid case conducted and the administration of these analog (GnRHA) quickly lead to the stoppage and reduced the size of the uterine tumor

4.2.1.2. The Antagonist

It inhibits GnRH induced signal-transduction, & gonadotropin secretion.

4.2.2. Gonadotropin-releasing hormone receptor blockers[16]

This helps to block the GnRH by following two different route; (a) by the synthesis of non-peptide substance, which directly block GnRH Receptor (b) The second path involves the synthesis of Gonadotropin-releasing hormone receptor Agonist (GnRHA) along with antagonist and super agonist.

4.2.3. Oral contraceptives[17]

Oral contraceptives are made-up of estrogen and progestin. Research was conducted in 1995, and it was reported that the prolong use of this oral contraceptives causes a significant shrinkage in the Uterine Fibroids.

4.2.4. Mifepristone[18]

This is an anti-progestin that has been clinically proven to shrink the size of fibroid after it's intensive usage for complete three months and also help in the menstrual flow.

4.2.5. Danazol

This is a steroidal androgen hormone; it does not shrink the size of fibroids, but are administered in women with fibroid to cause stoppage in bleeding and hence seize menstrual flow.

4.2.6. Administration of synthetic progestin

According to Goldzieher et al in 1966, first attempted the use of synthetic progestin in the treatment and management of uterine fibroids with the aim of observing "Red Degeneration [19, 20]" which usually occur during pregnancy. In few weeks, histological modification was observed almost at the end of the pregnancy; but it's quite unfortunate as this research is not validated yet.

4.2.7. Raloxifene

This is used in post-menopausal women to reduce the size of fibroids and also used to treat or prevent osteoporosis. Administration of drugs which lower estrogens level are strongly advised in patients with fibroid and this may help in the shrinkage and temporary stoppage in the growth of fibroid tumors.

4.2.8. HIFU

This is known as High intensity focused ultrasound. This uses High intensity along with magnetic resonance imaging (MRI) for guiding and monitoring the treatment.

4.3. Natural products for treatment of fibroids

These include supplements that can be taken, and some healthy lifestyles that can be practiced to shrink and avoid fibroid growth respectively;

4.3.1. Natural products to help reduce excess secretion of estrogen

4.3.1.1. Flaxseed

This is a food that contains phytoestrogen (they help to replace the estrogens that are already damaged in the body). Flaxseed contains properties that help in the healing fibroids.

4.3.1.2. Cold Water Fish

Consuming cold water fish products such as "Mackerel, Sardines, tuna, salmon"; helps to improve healing of fibroid growth as they are anti-inflammatory.

4.3.1.3. Curcumin

This is found in turmeric; it contains anti-oxidant and anti-inflammatory properties which has been claimed (according to some research) to have the properties to destroy fibroid cells and also cause stoppage in the growth of uterine fibroids.

4.3.1.4. GreenTea

According to recent research carried out in Post-menopausal women; the extract from green tea and also vitamin D, caused a significant reduction and shrinkage on the size and growth of uterine fibroids.

4.3.1.5. Resveratrol

This is a natural anti-oxidant that suppresses the growth of uterine fibroid cells and the formation of extra-cellular matrix [21].

4.3.1.6. Consumption of food rich in Fibres

This helps to remove excess estrogen content in the body, and reduce the risk of increased formation of fibrin; as fibrin (as uterine fibroids happens as result of increased fibrin content in the uterus) fibrin is the major component of blood clotting after menstruation. Fibres like broccoli, apples, nuts, leafy vegetables or green vegetables etc.

4.3.1.7. Cruciferous vegetables

These vegetables help in metabolizing excess of estrogen present in the body. Examples of these vegetables include; Arugula, Cabbage, Brussels sprouts, Cauliflower, Bok Choy, broccoli and collard green etc.

4.3.1.8. Indole-C-carbinol

This is a phytochemical present in Cruciferous vegetables (example; cabbage). It helps in stopping the occurrence of hormone related problems.

4.3.1.9. DIM

This is a supplement, used to improve the body's ability to metabolise and remove excess estrogen levels naturally. "DIM" is formed from the breakdown of INDOLE-C-CARBINOL in the stomach.

5. LIFESTYLES TO PRACTICE

- Avoiding junk foods
- Avoiding foods rich in fats
- Avoid high caffeine and High sugary food
- The above mentioned interfere with the metabolism and detoxification of estrogen
- Practice clean and a health environment, as certain environmental toxins like Xenoe-strogens could contribute to the formation of uterine fibroids.
- Eating organic food more often could help reduce the risk of development of fibroids and also shrink fibroids.

- Avoid taking food containing high content of synthetic preservatives.
- Avoid exposure of self to toxic chemicals.

5.1. Available pharmaceutical formulation for fibroids [22]

There are currently no available pharmaceutical formulations practically available or discovered for the treatment of fibroids. Apart from surgical removal of uterine fibroids; fibroid growth and shrinkage are managed using certain drugs like NSAIDs (Non-Steroid Anti-Inflammatory Drugs) as they are very effective in relieving fibroid pain. Another well-known drug; Tranexamic Acid (Lysteda, Cyklokapron etc) help to relieve heavy menstruation. Gonadotropin-Releasing Hormone (GnRH) Agonists which include Lupron Depot, Eligard, Triptorelin (Trelstar, Triptodur Kit) and Goserelin (Zoladex). Mifepristone [32] is also another class of drug which is very good in the management of fibroids, as it has ability to shrink them. Asoprisnil (ASP); this drug contains partial antagonist and agonist of the class of PR ligands; it's activity being *in-vivo*. PROELLEX also known as (telapristone): Attardi et al in 2002, examined the *in-vitro* properties of a compound named proellex (or telapristone) that was synthesized by USNIH; this drug was found to bind to the uterus of the rabbit; US-FDA, in 2017 informed the manufacturer of this drug that more clinical trial are required in order to validated the oral usage of this drug as it was administered orally; the manufacturer has also considered working on the vaginal route of the administration of this medication. Ulipristal (UPA) helps to reduce the Uterine Fibroid by regulating the PCNA and the BCL 2 expression.

6. CONCLUSION

In this systematic article review, we've seen what fibroid is, its risk factors, etiology & prevalence, pathogenesis, complete anatomy of uterine fibroids; how to manage it and its possible treatments. It has been concluded that despite all the research and clinical research and trial been carried out for the past 40 years, no possible formulation has been discovered to treat uterine fibroids like other drugs cure certain illness which it's meant for. This is to say, aside Surgical method of removal of fibroids, there is no other means to completely terminate uterine fibroids. Even surgical method is not a permanent method to terminate it, as it can still occur again and multiply even after surgical removal; unless the uterus was completely removed

(hysterectomy) that the women can never conceive and become pregnant ever in her lifetime.

Conflict of interest

None declared

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