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Evaluation of Using Dienogest and N-Acetyl Cysteine on the Volume of Uterine Leiomyoma

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What is already known on this subject? AND

What does this study add?

Apart from surgical procedures, there are numerous hormonal and non-hormonal drugs for management of leiomyoma. One of the non-hormonal drugs is *N*-acetyl cysteine (NAC), but its use for this indication is poorly understood ***(Aghaamoo et al., 2021)***

This randomized controlled comparative clinical trial will assess the impact of Dienogest versus N-Acetyl Cysteine in management of women with uterine leiomyoma.

1.INTRODUCTION/ REVIEW

Leiomyoma is a relatively common benign tumor. It is the most common cause of abnormal uterine bleeding and pelvic pain ***(Ali et al., 2018).***

Leiomyoma originates from the smooth muscle of the uterus and its incidence is 4.5%–68.6%. In black women, the prevalence is doubled and they have higher numbers of leiomyoma and more severe symptoms than white women ***(Vercellini and Frattaruolo, 2017)***

Leiomyoma is symptomatic in patients and there are numerous clinical presentations, for instance, pressure on adjacent organs, infertility, abnormal uterine bleeding, and obstetric complications ***(Stewart et al., 2017)***

Leiomyoma is considered the most common cause of gynecologic surgery worldwide ***(Yuan et al., 2021)***

Recent research has succeeded in stemming the leiomyoma and found a multi-factorial inheritance pattern, but leiomyoma is still a matter of debate by experts and poses tremendous challenges ***(Ayakannu et al., 2019)***

More than 100 gene abnormalities are identified in leiomyoma, in the genes for estrogen receptors, progesterone receptors, growth factors, prolactin receptors, extracellular matrix, and collagens ***(Sogoyan et al., 2020)***

Apart from surgical procedures, there are numerous hormonal drugs for leiomyoma. Dienogest is a selective progestin that combines the pharmacologic properties of 19-norprogestins and progesterone derivatives, offering potent progestogenic effects without androgenic, mineral corticoid, or glucocorticoid activity ***(Caruso et al., 2019)***

Previous trials demonstrated that dienogest provides effective reductions in endometriosis-associated pelvic pain and laparoscopic measures of pathology ***(Taylor et al., 2021)***

Recently, the new progesterone 2 mg daily demonstrated equivalent efficacy to GnRHa (e.g., buserelin acetate and leuprolide acetate) for relieving the pain of endometriosis in two 24 week randomized studies ***(Marquardt et al., 2019)***

Because uterine myomas and endometriosis have many common features, these successful trials on endometriosis support that the use of dienogest inhibits myoma growth. While evaluating superiority of dienogest in women with endometriosis, significant shrinkage of myoma nodes was found coexisting with endometriosis over several months during an administration of dienogest ***(Pritts et al., 2015)***

One of the non-hormonal drugs suggested for management of leiomyoma is *N*-acetyl cysteine (NAC), but its use for this indication is poorly understood. NAC is a medication that was used to treat paracetamol overdose, and in chronic obstructive pulmonary disease ***(Aghaamoo et al., 2021)***

It can be prescribed intravenously, orally, or inhaled as a mist. However, in leiomyoma, NAC is based on a simple premise. It is an anti-oxidative drug that inhibits free oxidative radicals and consequently neutralizes the proliferation of the tumor cells ***(Izadi et al., 2014)***

Adverse effects have been reported for NAC, including stomatitis, nausea, vomiting, fever, rhinorrhea, drowsiness, fatigue, chest tightness, and bronchoconstriction. NAC-induced bronchospasm occurs clinically rarely and unpredictably, even in patients with asthma bronchitis or bronchitis that complicates bronchial asthma ***(Farris et al., 2019)***

Acquired hypersensitivity to NAC has been reported, also rarely. Sensitization reports in patients with patch testing have not been confirmed.

Sensitivity has been confirmed by several inhalation therapists who have reported a history of skin eruption after repeated and prolonged contact with NAC ***(Timuroğlu et al., 2018)***

There is a consensus of opinion concerning the anti-oxidative effect of NAC, but it is difficult to assess its effectiveness in leiomyoma. Not only would using NAC avoid some of the adverse effects of hormonal drugs, but NAC is also cheaper than the hormonal alternatives. This spurs efforts to develop non-hormonal therapies in leiomyoma ***(Aghaamoo et al., 2021)***

Experts have suggested several hormonal drugs, according to steroid receptors identified in leiomyoma tissue. Given the majority of previous and current research that has been carried out in medical treatment for leiomyoma, oral non-hormonal drugs may be on track to overtake other treatment options. Evidence suggests that anti-oxidative mechanisms may lead to a reduction in leiomyoma volume. The administration of NAC as an anti-oxidant reduces oxidative stress by inhibiting free radicals and glutathione synthesis, but its protection is incomplete. As a result, it prevents the peroxidation of membrane lipids and prevents their release ***(Tahmasebi et al., 2020)***

The present study is a randomized control trial that aims to assess the impact of NAC versus Dienogest on the volume of uterine leiomyoma.

2.AIM / OBJECTIVES

This study aims to assess the effect of Dienogest and NAC on the volume of uterine leiomyoma in women previously diagnosed with leiomyoma.

Research hypothesis: In women with leiomyoma, the use of NAC as a non-hormonal drug in the treatment of leiomyoma of the uterus is more feasible and effective in the reduction of leiomyoma volume with no hormonal side effects compared with Dienogest.

Research question: In women with leiomyoma, is the use of NAC as a non-hormonal drug in the treatment of leiomyoma of the uterus more feasible and effective in the reduction of leiomyoma volume with no hormonal side effects compared with Dienogest?

3.METHODOLOGY:

Patients and Methods/ Subjects and Methods/ Material and Methods

Type of Study:

A Randomized Controlled Trial

Study Setting:

The study will be conducted at Ain Shams University Maternity Hospital (ASUMH) "outpatient gynaecology clinic"

Study duration:

After protocol approval till completing of required sample size

Study Population:

Women attending outpatient gynaecology clinic at Ain Shams University Maternity Hospital with the following criteria:

Inclusion criteria:

1. Age: 20-45 years.
2. Women with uterine leiomyoma (sub-mucous, sub-serous or intramural) based on transvaginal sonography criteria. Uterine fibroids most often appear as concentric, solid, hypoechoic masses. This appearance results from the prevailing muscle, which is observed at histologic examination. These solid masses absorb sound waves and therefore cause a variable amount of acoustic shadowing.

Exclusion criteria:

1. Pregnant or menopausal women.
2. History of malignancies, metabolic, hematologic, cardiac, thromboembolism, diabetes, renal or hepatic diseases.
3. History of hormonal drug use or treatment for leiomyoma in the past 3 months.

Sampling Method:

simple random sample

Sample Size:

The study will be conducted on 40 women; they will be subdivided into 2 equal groups.

Group (A): women will receive Dienogest, with brand name GYNOPROGEST, 2mg pills daily for 3 months (20 cases) ***(Ichigo et al., 2011)***

Group (B): women will receive NAC, with brand name GEMACYSTEINE, orally at a dose of 600 mg/day for 3 months (20 cases) ***(Aghaamoo et al., 2021)***

Sample size Justification:

Assuming an effect size of 1.0 reflecting the percentage change (reduction) in the volume of uterine leiomyoma, a sample of 12 patients in each group will be enough to detect such rate, if true, at 0.01 α error and 0.90 power of the test. We will increase the sample to 20 cases in each group to maximize the power of the study.

Randomization:

It will be done using computer generated randomization sheet.

Allocation and concealment:

It will be done by use of sealed opaque packages that will be given to a third person (nurse) who will assign the packages to study groups. Each woman will be invited to pull out a package. According to the number inside her package, women will be allocated to either group A or B according to a computer- generated random list.

Blinding:

The tablets will be enclosed in an opaque packages labelled according to a computer- generated random list. Each woman will be invited to pull out a package. The tablets will be administered anonymously with coding with no knowledge of the codes. Final assessment will be performed by another colleague who will have no information about the groups. Patients and assessor will be blinded to the groups.

Ethical and Safety Consideration:

This study will be done after approval of the Ethical Committee of the Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University. Informed consent will be taken from all participants before recruitment in the study,

and after explaining the purpose and procedures of the study. The investigator will obtain the written, signed informed consent of each subject prior to performing any study specific procedures on the subject. The investigator will retain the original signed informed consent form. All data will be collected confidentially. All cases will be counseled about the side effects associated with study medications. The study will be based on the investigator self-funding.

Study procedures and interventions:

1. After approval of study protocol, women will be enrolled into the study according to inclusion and exclusion criteria.
2. Eligible patients will be randomized using a computer-generated sequence 1:1 either to
3. **Intervention:**
   - Group (A): women will receive Dienogest, with brand name GYNOPROGEST, 2mg pills daily for 3 months (20 cases) ***(Ichigo et al., 2011)***
   - Group (B): women will receive NAC, with brand name GEMACYSTEINE, orally at a dose of 600 mg/day for 3 months (20 cases) ***(Aghaamoo et al., 2021)***
4. **Methodology:** All cases will be subjected to:
   - **Full history taking:** with special emphasis to age, parity, BMI, age of menarche, obstetric history, drug history as well as presence of any medical disease.
   - **Full general examination:** for pallor, fatigue.
   - **Abdominal examination:** to assess the leiomyoma size, surface, contour and consistency.
   - **Bimanual vaginal examination(for uterus <12 weeks):** to confirm its uterine origin.
   - **Vaginal Ultrasound examination with the addition of a transabdominal approach if needed** to diagnose and assess the leiomyoma (size and number).

Ultrasound will be done using the same machine.

The principal investigator will hold regular meetings with the research team to assess data and adverse events.

Serious adverse events will be reported to the research ethics committee, Faculty of medicine, Ain Shams university within 24 hours.

Outcomes:

- **Primary outcome:**

  Leiomyoma volume: Size of myoma will be measured at three diameters of myomas (transverse, vertical and anterior–posterior). These measurements will be repeated after 3 months of therapy by the same sonographer.

- **Secondary outcomes:**
  - **Dysmenorrhea:** according to the visual analog scale (VAS) is a validated, subjective measure for acute and chronic pain. The scale is composed of 0 (no pain at all) to 10 (worst imaginable pain).
  - **Heavy menstrual bleeding (HMB).**

  1.Actual blood loss per menstrual period: according to PBAC score is seen in Figure 1,also defined by FIGO System is seen in Figure 2 according to frequency, duration, regularity and flow volume.

  2.using the measurement of hemoglobin.

Pads		
1 point	For each lightly stained pad	
5 points	For each moderately stained pad	
20 points	For each completely saturated pad	
Tampons		
1 point	For each lightly stained tampon	
5 points	For each moderately stained tampon	
10 points	For each completely saturated tampon	
Clots/Flooding		
1 point	For each small clot	
5 points	For each large clot	
5 points	For each episode of flooding	

FIGURE 1 The PBAC scoring system; pictorial blood loss assessment chart (PBAC) semi objective assessment blood loss has variable accuracy 80% -90% sensitivity but variable specificity and PPV &NPV 60% (score >100 = HMB) (**Magnay et al., 2020)**

Parameter	Normal	Abnormal	☑
Frequency	Absent (no bleeding) = amenorrhea		☐
	Infrequent (>38 days)		☐
	Normal (≥24 to ≤38 days)		☐
	Frequent (<24 days)		☐
Duration	Normal (≤8 days)		☐
	Prolonged (>8 days)		☐
Regularity	Normal or "Regular" (shortest to longest cycle variation: ≤7-9 days)*		☐
	Irregular (shortest to longest cycle variation: ≥8-10 days)*		☐
Flow Volume (patient determined)	Light		☐
	Normal		☐
	Heavy		☐

Intermenstrual Bleeding (IMB) Bleeding between cyclically regular onset of menses	None		☐
	Random		☐
	Cyclic (Predictable)	Early Cycle	☐
		Mid Cycle	☐
		Late Cycle	☐

Unscheduled Bleeding on Progestin ± Estrogen Gonadal Steroids (birth control pills, rings, patches or injections)	Not Applicable (not on gonadal steroid medication)	☐
	None (on gonadal steroid medication)	☐
	Present	☐

FIGURE 2 The FIGO AUB System ***(Munro et al., 2018)***

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