Original Research

Beyond Treatment: Understanding and Addressing Letrozole's Adverse Effects

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Abstract

Introduction: Letrozole, an aromatase inhibitor has been widely used in ovulation induction and in medical management of leiomyoma uterus.

Material and Methods: The study was conducted on 30 premenopausal women in the outpatient department of Obstetrics and Gynaecology with symptomatic fibroid uterus. All selected subjects were given tablet Letrozole 2.5 mg per day for 12 weeks, regardless of the day of the menstrual period. While on therapy, the women were called for follow up visits after 4 weeks,8 weeks and 12 weeks. On each visit patient underwent history taking for improvement or deterioration of symptoms, to ascertain compliance and document any adverse effects.

Results: Majority of patients (83.3%) did not experience any adverse effect of the drug. 13.3 % patients had nausea and hot flushes was present in only one patient.

Conclusion: Letrozole, an aromatase inhibitor is a promising medical management option for medical treatment of fibroids with minimal side effects.

Keywords: Letrozole, Aromatase Inhibitor, adverse effects

Introduction

Letrozole, an aromatase inhibitor has been widely used in ovulation induction and in medical management of leiomyoma uterus. Uterine myomas are the most common benign tumors of the uterus. The growth of these tumors is directly associated with the circulating Estrogen and Progesterone in the body, thereby the size increases in pregnancy and reduces in postmenopausal age group. The treatment of uterine myomas includes expectant management, medical management, and surgical procedures. Medical management and other therapeutic approaches using varied pharmacological agents have been tried in recent years. Gonadotropin releasing hormone analogues (GnRHa) have been used successfully to achieve hypoestrogenism both as a primary means of conservative therapy for myomas and as an adjunct to myomectomy.[1] Therapy with GnRH agonists have so far proven to be most effective medical treatment for leiomyoma. However, their effects are transient and the myomas return to pretherapy size within a few months of discontinuation of therapy.[2] Menopausal symptoms, osteoporosis and pelvic pain are some of the adverse effects of this therapy and a hormonal add back, if given, may negate the beneficial effects on myoma size.[3] Danazol administration has been tried after 6 months of GnRH therapy in an effort to prolong the therapeutic effects of GnRH. The bone mineral content that is substantially reduced during prolonged GnRHa treatment is reported to significantly improve with danazol, though a rebound of uterine volume due to its antiprogestrone effect is a possibility.[4] Progestational agents are thought to produce a hypoestrogenic effect by inhibiting gonadotropin secretion and suppressing ovarian function, apart from exerting a direct anti estrogenic effect at the cellular level. However recent evidence that the antiprogesterone, mifepristone, decreases myoma size raises concern about its mechanism.[5] Use of levonorgestrel IUD (LNG-IUD) has been reported to be associated with a significant reduction in total myoma volume, average uterine size and marked reduction in menstural blood loss, though bleeding disturbances may occur in about 68% women with its use.[6] Letrozole, a nonsteroidal aromatase inhibitor commonly used in anovulatory infertility in the follicular phase has been suggested to have potential therapeutic role in treatment of leiomyoma and endometriosis.[7] Aromatase, a member of cytochrome p 450 super family, is a microsomal enzyme that catalyses the conversion of androgens to estrogen. Letrozole is a potent (97-99% potency) and highly

specific, third generation aromatase inhibitor that was approved initially for use in postmenopausal women with breast cancer to block estrogen production.[8] Letrozole is rapidly and completely absorbed from the gastrointestinal tract and absorption is not affected by food. It is metabolized slowly to an inactive metabolite whose glucuronide conjugate is excreted renally, representing the major clearance pathway. A known hypersensitivity to letrozole is the only absolute contraindication present. Relative contraindication includes abnormal renal function, history suggestive of thromboembolism, abnormal vaginal bleeding and deranged lipid profile. Letrozole is generally well tolerated. The observed adverse reactions are mild or moderate in nature including hot flashes, night sweats, weight increase, nausea, vaginal bleeding & irritation, endometrial proliferation disorders etc.

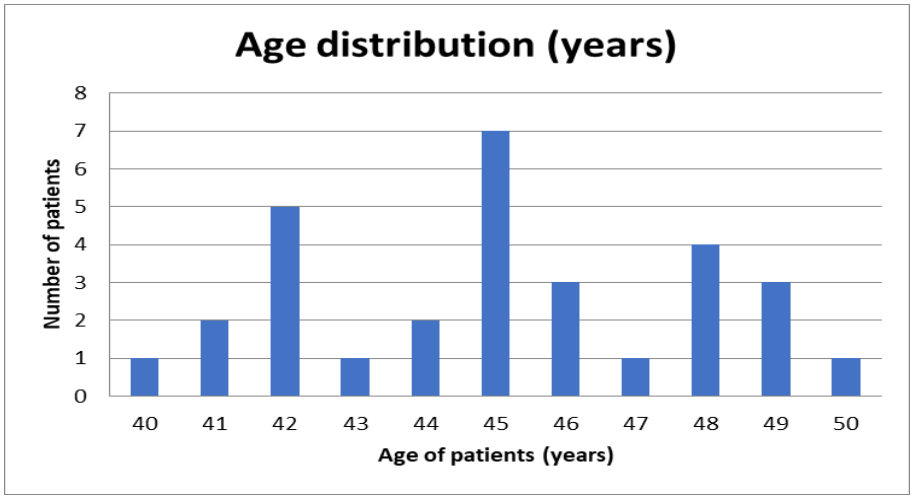
Material and Methods

The study was conducted on 30 premenopausal women in the outpatient department of Obstetrics and Gynaecology with symptomatic fibroid uterus. Women with impaired renal functions, pregnancy, oral administration of any type of estrogen and progesterone more recently than a month, previous hormonal or surgical treatment for leiomyomata or history of previous deep vein thrombosis were excluded from the study.

All selected subjects were given tablet Letrozole 2.5 mg per day for 12 weeks, regardless of the day of the menstrual period. While on therapy, the women were called for follow up visits after 4 weeks,8 weeks and 12 weeks. On each visit patient underwent history taking for improvement or deterioration of symptoms, to asertain compliance and document any adverse effects.

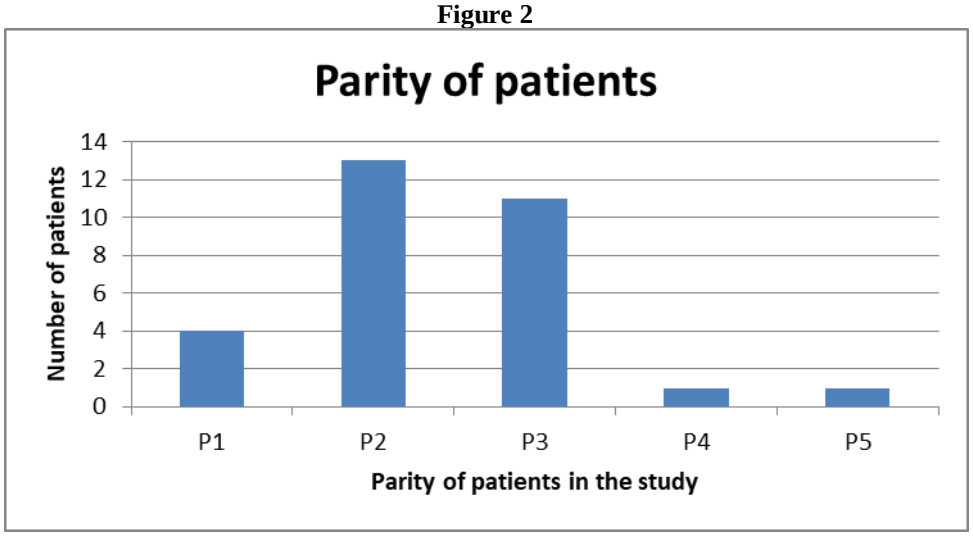
Results

It is evident from the Fig 1 that 7 patients (23.3%) out of 30 were 45 years of age. The mean age was 45.6 ± 0.54 years.



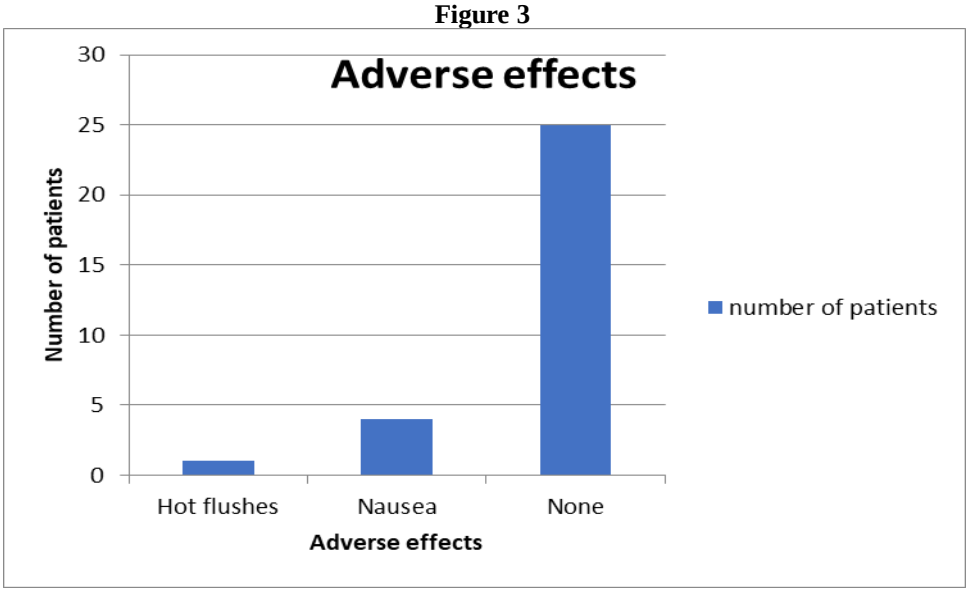
It is evident from Figure 2 that maximum number of patients enrolled in the study were para 2 (43.3%) and para 3

Figure 2



The adverse effects of the drug were seen in only 5 patients (16.6 %) in the study while the remaining 83.3% patients did not experience any side effect (Figure 3). Nausea was the main adverse effect seen followed by hot flushes and these were self-limiting. No therapy was required for these effects and no woman discontinued the therapy. The mean duration of appearance of these effects was 10 weeks after initiation of treatment, while the mean time of disappearance was 2 weeks of discontinuation of therapy.

Figure 3



Discussion

Majority of patients (83.3%) did not experience any adverse effect of the drug. 13.3 % patients had nausea and hot flushes was present in only one patient. Parsanezhad et al compared letrozole with triptorelin (GnRH agonist) and found that none of the patients given letrozole had hot flushes as compared to 96.3% patients on triptorelin.[9] Verma et al have stated that the most common side effect was irregular bleeding with anastrozole and joint pains with letrozole.[10] However, no patient in the present study complained of joint pains or irregular vaginal bleeding. The mean time of appearance of adverse effects after treatment initiation was 10 weeks, whereas the mean time symptoms subsided after treatment discontinuation was 2 weeks in the present study.

Conclusion

It may be concluded from the present study that aromatase inhibitor, Letrozole has a beneficial role in symptomatic premenopausal women with fibroids. The drug is fairly safe, with no major adverse effect and no participant discontinuing the treatment midway through therapy period. Thus, Letrozole is a promising option for management of premenopausal patients with fibroids. However, the need for larger trials cannot be understated.

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