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Comparison of Effectiveness Profile of Danazol and Gestrinone in Pelvic Endometriosis: A Community Based Observational Study in Wardha District-Eastern Maharashtra

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ABSTRACT:
BACKGROUND*: Endometriosis is the presence of functioning endometrial tissue outside the uterus and most commonly affects women in the reproductive age group. The present study was conducted to evaluate the effectiveness of Danazol and Gestrinone, steroidal androgenic drugs in the treatment of women with Pelvic Endometriosis in a District of Central India.*
METHODS*: From a period of January 2008 to March 2014 we got 282 women with laparoscopically confirmed diagnosis of Pelvic Endometriosis who were treated with either Danazol or Gestrinone. Out of which 154 were treated with Danazol and 128 were treated with Gestrinone.. Disease severity was measured by calculating the Total symptom severity score using the Biberoglu and Behrman scale at diagnosis and after 90 and 180 days of treatment. Effectiveness was assessed by mean changes in Total symptom severity score after 90 days and 180 days of treatment from the baseline for Danazol and Gestrinone and compared.*
RESULTS: *All demographic and baseline factors were comparable in Danazol and Gestrinone treated groups. Both Danazol and Gestrinone satisfactorily resolved Dysmenorhhoea, Dyspareunia, Pelvic Discomfort, Pelvic Induration and Pelvic Tenderness from baseline. No significant difference were noted in effectiveness endpoints between Danazol and Gestrinone treated groups regarding Total symptom severity score after 90 days and 180 days.*
CONCLUSION: *Both Danazol and Gestrinone demonstrated similar clinical effectiveness. But it was observed that Danazol is more commonly prescribed then Gestrinone but has more secondary and GI intolerant side effects. However Prospective interventional study is required to confirm the efficacy of the both drugs.*
KEY WORDS: *Pelvic Endometriosis, Danazol, Gestrinone, Effectiveness, Total symptom severity score, Biberoglu and Behrman scale.*

I. INTRODUCTION

The presence of functioning endometrium in sites other than uterine mucosa is termed as Endometriosis. These ectopic endometrial tissues may be found in the myometrium when it is known as endometriosis interna or Adenomyosis and when these tissues are found at the sites other than uterus it is referred to endometriosis externa.[1] Common sites of endometriosis are Ovary, Pouch of Douglas, Uterosacral ligament, Rectovaginal septum, Sigmoid colon and Abdominal scar following hysterectomy, caesarean section, tubectomy and myomectomy.[2]

During the last of few decades, the prevalence of Endometriosis has been increasing in terms of real and apparent. The real one is due to delayed marriage, postponement of first conception and adoption of small family norm. The apparent one is due to increased use of diagnostic laparoscopy as well as heightened awareness of this disease complex amongst the gynecologists.[2]

Endometriosis has an estimated apparent incidence of 40,000 new patients every year in Germany and world wide nearly 80 million women are affected by the disease.[3] The prevalence of endometriosis varies widely because of diagnostic difficulty.

Prevalence is higher among the infertile women (34-46%) as based on diagnostic laparoscopy and laparotomy. The morbidity spectrum includes chronic pelvic pain, dyspareunia, infertility and decreased quality of life. Malignancy is a rare event (1:150) and mostly manifests as endometroid carcinoma.[2]

However there is lack of data on Prevalence and Incidence of Endometriosis in different parts of India.

Many theories have been put forward to the armamentarium of the disease but no single theory can explain endometriosis at all sites. Genetic frame work and modulation in local cellular immunity may be implicated.[1]

In pelvic endometriosis, small black dots-powder burns or gunshot burns - are observed on uterosacral ligaments and pouch of Douglas. Other lesions manifest as flame-shaped, polypoidal, hemorrhagic and white patches.[4] About 25% of ladies suffering from endometriosis, have no symptoms. Moreover, symptoms are not related to the extent of the lesion.[3]

Severity of endometriosis and the degree of pelvic pain are not always proportional. Unlike primary dysmenorrhoea, the pain lasts for many days before and after menstruation.[4] Danazol and Gestrinone are two frequently used drugs for management of Pelvic Endometriosis.

Danazol is an oral androgenic agent that induces amenorrhoea through suppression of the hypothalamic-pituitary-ovarian (HPO) axis, accompanied by increased serum androgen concentrations and low serum estrogen levels. Poor tolerability represents the major drawback of danazol as a treatment for endometriosis: this agent has both androgenic and anabolic properties, leading to side effects, such as weight gain, edema, myalgia, acne, oily skin and hirsuitism.[5]

Gestrinone is a 19-nortestosterone derivative that has androgenic activity and is an antiprogesterone and antioestrogen. By interacting with hypothalamic and pituitary steroid receptors it decreases the secretion of luteinising hormone and follicle stimulating hormone. In three uncontrolled studies it was found that Gestrinone is an effective treatment for endometriosis. Main side effects reported were acne, hirsuitism, seborrhea and weight gain.[6]

The present study was conceived, designed and carried out to evaluate and compare the efficacy and pharmacovigilance profile of Danazol and Gestrinone in Pelvic endometriosis to recommend a rational treatment guideline for health care providers to treat the womenhood suffering from this ailment.

II. METHODS

Present study was a community based observational study. The research proposal was submitted to the Secretary Institutional Ethics Committee of Datta Meghe Institute of Medical Sciences. The proposal was approved by the I.E.C. with an assumption that the proposed work will be carried out in accordance with the ethical guidelines prescribed by Central Ethics Committee on Human Research (Ref. No. DMIMS (DU)/IEC/2012-13/830).Women aged > 18 years with laparoscopically confirmed diagnosis of Pelvic endometriosis and who were treated with either Danazol or Gestrinone were selected for the study. The aim of the present study was to compare the effectiveness of the Danazol and Gestrinone. Data were collected from all the health care centers coming under Wardha district as well as Acharya Vinoba Bhave Rural Hospital- a tertiary teaching hospital joined with Jawaharlal Nehru Medical College. Duration of the study was two years from October 2012 to September 2014. Data were collected from January 2008 to September 2014. Prospective and Retrospective study was done by Collection of Data of patients of Pelvic Endometriosis who attended Obstetrics and Gynecology O.P.D. and I.P.D. of Acharya Vinoba Bhave Rural Hospital, Sawangi (Meghe) and Health Centers of Wardha District. All those women who were less than 18 year of age, Pregnant, lactating, suffering from other types of endometriosis, treated surgically or treated by medicines other than Danazol or Gestrinone were excluded. Data were collected from case sheets of the patients, in depth discussion with Gynecologist, interview of the patients suffering from Pelvic endometriosis. Data were collected keeping in mind following aspects- age distribution of pelvic endometriosis, relation of pelvic endometriosis with marital status, evaluation of effectiveness of Danazol and Gestrinone. The primary effectiveness outcome was to evaluate change in Endometriosis related Pelvic pain with the help of Biberoglu and Behrman scale from baseline at Diagnosis to 90 days and 180 days after treatment in both the groups and to compare them. B and B scale is the scoring system established by Biberoglu and Behrman, is a subjective rating scale (+ = mild, ++ = moderate, +++ = severe) based on the patients self assessment of pain and the gynecological palpation of the attending physician. It is a physician completed questionnaire generally, based on patients interview referring to previous 4 weeks. Biberoglu and Behrman scale evaluates three cardinal symptoms reported by endometriosis patients which are dysmenorrhoea, dyspareunia and pelvic pain/ discomfort and two signs reported by Physician during gynecological examination are Pelvic tenderness, pelvic induration. Each symptom has four possible intensities 0 = None, 1 = mild, 2 = moderate, 3 = severe. The sum of three symptoms known as Pelvic symptom score and can be graded as mild = 1-3, moderate = 4-6, severe = 7-9.While two signs constitute physical symptom score. Sum of both- Pelvic and Physical symptom score is known as Total symptom severity score. Total symptom severity score graded as mild = 1-2, moderate = 3-5, severe = 6-10, very severe = 11-15. Evaluation of Total symptom severity score of all patients were done at diagnosis, after 90 days and after 180 days of treatment in both the Danazol and Gestrinone treated groups and compared. Data were presented in tabular form in excel format and analyzed using SPSS software version 17.0 from the statistics department of Jawaharlal Nehru Medical College, Sawangi (M), Wardha.

Demographic and baseline characteristics were tabulated by descriptive statistics and results were described as **mean ± standard deviation**. Chi- square value and p value were calculated as test for significance for demographic variables. Differences in Total Symptom Severity Score (TSSS) from baseline to 90 days and 180 days within the group were assessed by **Student's paired 't' test.** Difference in Total Symptom Severity Score (TSSS) between the group were assessed by **Student's unpaired 't' test.**

III. OBSERVATIONS AND RESULTS

The present study comprised 282 (49.21%) out of total 573 cases of Pelvic Endometriosis as an inclusion criteria who were treated by either Danazol or Gestrinone. Out of 282 cases of pelvic endometriosis, 154 (54.60%) were treated by Danazol and 128 (45.39%) were treated by Gestrinone (Table No. 1)

Table-1 : Comparison of Danazol and Gestrinone Treated Patients

Sr. No.	Treatment	Number of Cases treated (n=282)	Percentage(%)
1	**Danazol**	**154**	**54.60**
2	**Gestrinone**	**128**	**45.39**

. 282 cases were divided into five groups viz. 18-25years, 26-33 years, 34-41 years,42-49 years and >50years. Among these five groups, Pelvic Endometriosis was found to be common in 26-33 years of age group, followed by 34-41 years, 18-25 years and 42-49 years of age group respectively.(Table No. 2).

Table-2 : Age Distribution of Patients of Pelvic Endometriosis

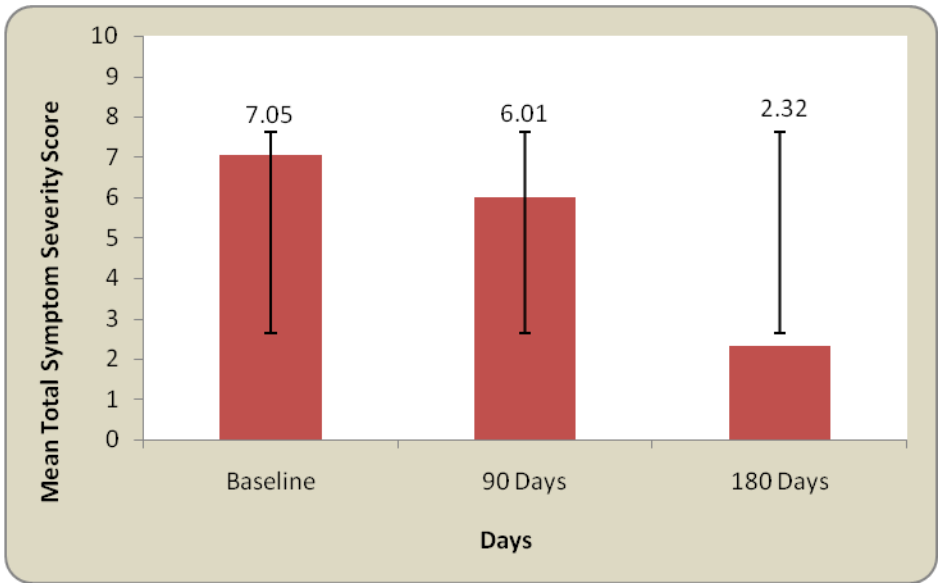
Sr. No.	Age Group (Yrs)	Danazol Group	Gestrinone Group	χ^2-value	p-value
1	18-25	26(16.88%)	18(14.06%)		
2	26-33	75(48.70%)	65(50.78%)		
3	34-41	43(27.92%)	40(31.25%)		
4	42-49	8(5.19%)	5(3.91%)		
5	≥50	2(1.30%)	0(0%)	**1.59**	**0.80 NS,p>0.05**
	Total	**154(100%)**	**128(100%)**		
	Mean Age	**31.33**	**31.10**		
	SD	**6.90**	**6.09**		
	Range	**19-55**	**21-48**		

Age range of the patient in Danazol group was 19-55 with mean age of 31.33 ± 6.90 SD while in Gestrinone group it was 21-48 with mean age 31.10 ± 6.09. Both the age groups were compared using Chi square($x^2 = 1.59$) and *p* value calculated ($p = 0.80$) and found non significant ($p = > 0.05$). So age groups in both treatment group was comparable. There was no statistically significant difference found and both the groups were comparable. ($p = > 0.05$)**.** Out of 154 in Danazol group 112 (72.73%) were married while 42 (27.27%) were unmarried while in Gestrinone group 99 (77.34%) were married and 29 (22.66%) were unmarried**.** It was found that in Danazol group out of 112 (33.93%) married women, 38 women were suffering from infertility while in Gestrinone group out of 99 married women, 26 (26.26 %) women were suffering from infertility**.** It was found that infertility in Danazol treated group was highest in 26-33(n=26) years of age group followed by 34-41(n=12) while in other age groups no infertile patients were found**.** While in Gestrinone treated group also number of infertility patients were seen maximum in the age group of 26-33(n=23) years and then in the 18-25 (n=2) years and 34-41 (n=1) years. The number of patient suffering from Infertility in both the age group was statistically significant with respect to total number of cases in the group and attributable to the Disease. In Danazol treated group 30 (19.48%), 123 (79.87%), 1 (0.65%) patients were suffering from moderate, severe, very severe disease**.** In Gestrinone treated group 128(100%) were suffering from severe disease**.**

In Danazol treated group baseline TSSS was 7.05 ± 1.87 SD while after 90 days it was 6.01± 1.45 SD and after 180 days it was 2.32 ± 0.52 SD. Students paired 't' test was applied to evaluate the efficacy of Danazol after 90 days and after 180 days of treatment and p value was calculated which was found to be significant (($p < 0.05$. It is clear from the TSSS score after 90 days and 180 days of treatment that Danazol is quite effective in decreasing total symptom severity score. In comparison to TSSS at 180 days, decrease in TSSS at 90 days from baseline is very less.

Table-3, Figure -1 : Change in Total Symptom Severity Score (Danazol Group)

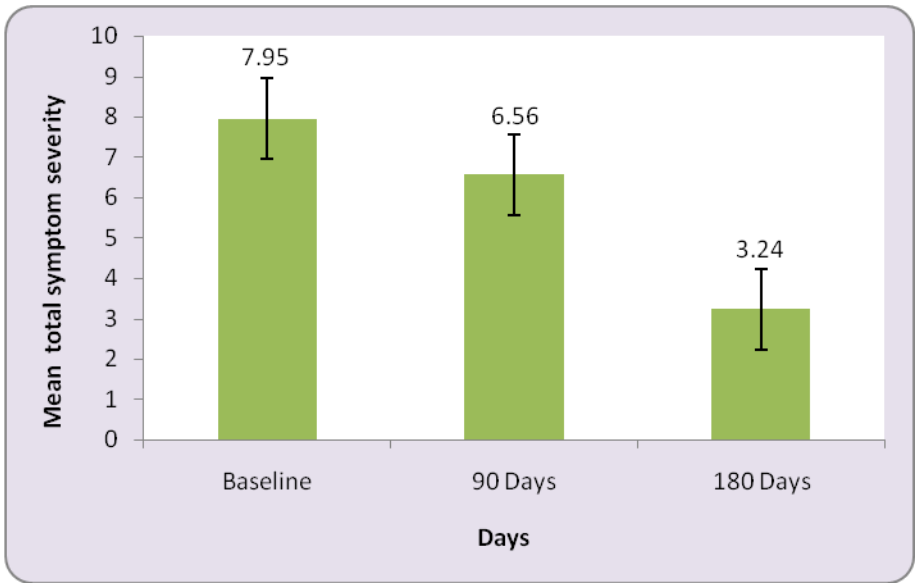
Day	Mean	N	Std. Deviation	Std. Error Mean
Baseline	7.05	154	1.87	0.15
90 Days	6.01	154	1.45	0.11
180 Days	2.32	154	0.52	0.04



In Gestrinone treated group, baseline TSSS was 7.95 ± 1.10 SD while after 90 days it was 6.56 ± 0.81 SD and after 180 days it was 3.24 ± 0.81 SD. Students paired 't' test was applied to evaluate efficacy of Gestrinone after 90 days and after 180 days of treatment and p value was calculated which was found to be significant.($p < 0.05$)**.** Gestrinone also is quite efficacious in decreasing TSSS after 90 days and 180 days of treatment from baseline. It was noted that TSSS in Gestrinone treated group was slightly higher(7.95 ± 1.10) at baseline compared to Danazol (7.05 ± 1.87).

Table-4, Figure-2 : Change in Total Symptom Severity Score (Gestrinone Group)

Day	Mean	N	Std. Deviation	Std. Error Mean
Baseline	7.95	128	1.10	0.09
90 Days	6.56	128	0.83	0.07
180 Days	3.24	128	0.81	0.07



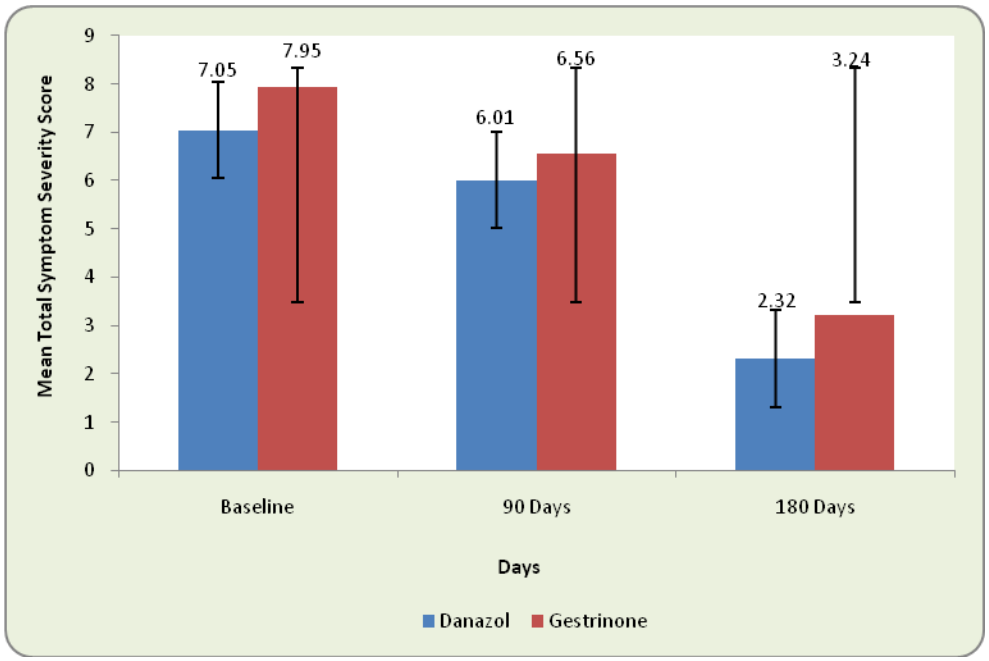
It may be inferred that both Danazol and Gestrinone are effective for the treatment of Pelvic endometriosis as both decrease Total symptom severity score at significant level after 90 days and 180 days of treatment.

For comparison of Efficacy of Danazol and Gestrinone Student's unpaired 't' test was applied. Unpaired 't' test was applied to evaluate the difference in TSSS from baseline to 180 days in both the groups. Danazol decreased TSSS from baseline (7.05 ± 1.87) to (2.32 ± 0.52) 180 days of treatment. The paired

difference was 4.72 ± 1.66**. While in Gestrinone group TSSS decreased from baseline (7.95 ±1.10) to (3.24 ± 0.81) 180 days of treatment. The paired difference was (4.71 ± 1.23).** Difference in TSSS from baseline to 90 days and 180 days in both the group is statistically significant but between group is not statistically significant.

Table No.- 5, Fig.-13 : Comparison of Overall TSS Score

	Group	N	Mean	Std. Deviation	Std. Error Mean
Baseline	Danazol	154	7.05	1.87	0.15
	Gestrinone	128	7.95	1.10	0.09
90 Days	Danazol	154	6.01	1.45	0.11
	Gestrinone	128	6.56	0.83	0.07
180 Days	Danazol	154	2.32	0.52	0.04
	Gestrinone	128	3.24	0.81	0.07



IV. DISCUSSION

Despite receiving very little mention in historical compendiums of disease, endometriosis has impacted lives of women for centuries. The disease remains even now as a chronic, costly illness requiring long-term, multidisciplinary treatment modules. Endometriosis may go undiagnosed for years, with no absolute cure and a high recurrence rate. Even now it continues to be a significant reproductive health concern with highly negative and far-reaching effects. The profound economic burden and significantly impaired quality of life of the sufferer, contribute to the urgent need for continued research and improvement in diagnostic and treatment modalities. Focus on better understanding of pathogenesis and pain mechanisms as well as linkage to certain morbidities for example, malignancies and autoimmune disorders is the need of time.

Although prevention remains elusive, increasingly sophisticated research efforts may lead to more timely intervention and appropriate, multifactorial treatments to restore quality of life, preserve or improve fertility, and lead to long-term effective management of this enigmatic disease. The present study was conceived, designed and carried out to evaluate the Efficacy and Pharmacovigilance profile of Danazol and Gestrinone in Pelvic Endometriosis. Indicators used to evaluate the efficacy were relief in Dysmenorrhoea, Dyspareunia, Pelvic Discomfort/Pain, Pelvic Induration and Pelvic Tenderness. It was found that management of women with endometriosis is complex and therapeutic strategies have to be tailored in accordance with patients age and complaints. Till date, medical therapy is mainly based upon endocrine treatment modalities including Danazol, Gestrinone, Progestogens and GnRh Analogues.

These substances are effective in terms of reduction in implant scores proven upon operation and relief of subjective symptoms. Therefore the treatment should be choiced on the basis of metabolic and general adverse effect profile of individual biomolecule.[7]

Steroidal therapy with Danazol, because of its satisfactory clinical efficacy, has traditionally been the standard treatment for endometriosis. Danazol is an isoxazol derivative of 17-alpha ethinyl testosterone which was introduced into the management of Endometriosis in 1971 by **Grenblatt et al.** They reported their effectiveness in treatment of Endometriosis and considered as the 'Gold Standard' for Endometriosis therapy.[8]

However, the androgenic and hypoestrogenic adverse effects like Weight gain, Edema, Acne, Hirsuitism, Seborrhea, Hot flushes : create a major concern about the safety and long term treatment of Endometriosis with Danazol. On the other hand, Gestrinone is an alternative to Danazol for the treatment of Endometriosis. [9,10]

Gestrinone is a synthetic trienic 19-norsteroid compound with potent anti-estradiol and antigonadotropin properties. The compound inhibits gonadotropin secretion and ovulation which prevents the occurrence of menstruation. Because of its marked inhibitory effects on ER and PR in the Endometrium and uterus it is quite comparable to other treatment methods of endometriosis.[9,10] While the efficacy of Gestrinone is comparable to Danazol for the treatment of Endometriosis, its pharmacovigilance profile also exhibits resemblance with Danazol. As per the information gathered, no such studies have yet been carried out in Wardha district or Vidarbha region of Maharashtra. In the present study it was found in our study that most common age group for Endometriosis in this region is 26-33 years(49.64%) followed by the age group 34-41years(29.43%), while **Abbas et al** [11] from Germany and **Dmowski WP et al** [12] have reported the most common age group for endometriosis 35-44years followed by 25-34year. This may be due to the delay in the diagnosis of disease or late presentation of disease in that particular region or may be disease asymptomatic in that age group to present too early or may be more patient in that study were infertile so presented late with infertility as presenting complain. The most justified answer to this may be the average delay between onset of clinical symptoms and surgically confirmed endometriosis. **Hadfield RM et al** [13] found in their study a delay of 3 years in women with infertility and 6years in women with pain in general.[13] In our study it was observed that out of 282 patients, 211 were married and 64(30.33%) of them were suffering from Infertility. Calculating the Chi-square value, x^2 was 55.25 ($p<0.05$) in Danazol group while x^2 was 78.45 ($p<0.05$) in Gestrinone group. In both the groups p values were significant showing infertility may be attributable to the disease. In our study, most patients who were infertile belonged to the age group of 26-33years contrary to the findings of **Dmowski WP et al** [12] **in Baltimore, USA** who noted the mean age 35 in women who present with infertility**.** This may be due to the tradition and concept of early marriage and early conception in Wardha district as well as in Maharashtra state compared to the western tradition where women get married late and prefer to conceive late because of their busy life schedule. The diagnosis of Pelvic endometriosis in infertile women becomes possible only when they note down their infertility. In our study it was found that 30.33 % of women with Endometriosis are suffering from infertility which is in consonance with the finding of **Counsellor VS** [14] who reported that about 25 to 50% of infertile women have endometriosis, while 30 to 50% of women with endometriosis are infertile. **Mahmood TA et al** [15] noted endometriosis associated infertility remains one of the most difficult situations in reproductive medicine because the prevalence of endometriosis in the infertile populations is estimated to be 20-40%. In our study, 7 cases out of 282 was found in post menopausal age group, constituting 2.48% which is in consonance with the findings of **Haas D et al** [16] they reported that endometriosis is frequently diagnosed in symptomatic post-menopausal women with an incidence of 2.55%. Efficacy outcome was assessed with change in TSSS from baseline to after 90days and 180 days of treatment with the help of Biberoglu and Behrman scale. The results of this study suggested that all the patients had significant decrease in endometriosis associated symptoms viz Pelvic pain, Dysmenorhhoea, Dyspareunia and signs Pelvic Tenderness and Pelvic induration after 3 months and 6 months of treatment with either Danazol or Gestrinone. It was found that in Danazol group after 90 days and 180 days of treatment, change in TSSS from baseline was 6.01 ± 1.45 and 2.32 ± 0.52 respectively.

In Gestrinone group after 90days and 180 days of treatment, change in TSSS from baseline was 6.56 ± 0.83 and 3.24 ± 0.81 respectively. In both the groups, improvements in TSSS from baseline to 90 days and 180 days were statistically significant in almost all the 5 items used to evaluate the symptoms. However regarding the net change in TSSS, no statistically significant difference was noted after 180 days (Danazol = 4.72 ± 1.66 SD and Gestrinone = 4.71 ± 1.23 SD). Both Danazol and Gestrinone satisfactorily resolved Dysmenorhhoea, Dyspareunia, Pelvic Discomfort / Pain, Pelvic Tenderness and Pelvic Induration. As difference in TSSS from baseline to after 180days was not statistically significant between the groups, both the drugs are equally effective for the treatment of Endometriosis. It is in agreement with the previous finding of **Fedele L et al** [9]**,** who conducted a clinical trial for comparison of Danazol and Gestrinone in 39 patients of Endometriosis and found that there was no significant difference between the two groups in reduction of disease extent and both the drugs decreases disease severity equally. **Ruiz V et al** [17] found in his comparative trial of Danazol and Gestrinone in 80 patients with Endometriosis that improvement of symptoms and favorable follow-up were similar with both treatments**.** Both the drugs are equally effective with respect to outcome**.**

Pharmacological management of endometriosis must be set within the framework of long-term therapeutic strategies. As the available drugs are not curative, treatments will need to be administered for years or until women desire a pregnancy. The various therapies studied have shown similar efficacy. Consequently, based on a more favourable profile in terms of safety, tolerability and cost, combined oral contraceptives and progestins should be considered as the first-line option, both as an alternative to surgery and as a postoperative adjuvant measure.

Gonadotrophin-releasing hormone analogues, danazol and gestrinone should be used when progestins and oral contraceptives fail, are not tolerated or are contra-indicated. Future therapies for endometriosis must compare favourably with existing drugs before hypothesizing their implementation in current practice. Medical treatment is not indicated in women seeking conception because reproductive prognosis is not ameliorated.[18] In particular, combined oral contraceptives, danazol, gonadotropin-releasing hormone (GnRH) analogues and progestins have been extensively used in clinical practice. Novel agents that will hopefully improve the therapeutic potential include aromatase inhibitors, immunomodulators, anti-inflammatory agents, steroids receptor modulators and GnRH antagonists. It is still early for enthusiasm as there is limited knowledge about their short- and long-term adverse effects.[19]

Despite some agents show efficacy in relieving pain, all differ in their adverse effects, making it difficult to achieve a balance between efficacy and safety. Efficacy has been demonstrated with danazol or GnRH analogues; however, treatment is limited to 6 months because of significant metabolic adverse effects. Alternatives for longer-term management of symptoms include add-back therapy with GnRH analogues, COCs or progestins. Newer options for treatment of endometriosis include depot medroxyprogesterone acetate subcutaneous injection, as well as several agents under investigation that may prove to have therapeutic potential.[20]

But in the present circumstances the treatment should be tailored according to the patients age, health status profile, tolerability and quality of life of the patient. Besides academic and research domain, this study has its own social concerns. These findings may be utilized for health education, health motivation and health promotion of the women of community for early diagnosis and management of Pelvic endometriosis...

V. CONCLUSION

Pelvic Endometriosis is common in 26-33 years of age group followed by 34-41years of age group in Wardha district Most common presenting complaints are Dysmenorhhoea and Pelvic pain Approximately 30% of women with Pelvic Endometriosis present with infertility. 30-50% of women with infertility have Pelvic Endometriosis. Most common age group of Pelvic Endometriosis to present with infertility is 26-33 years in Wardha district. Laparoscopy is the confirmatory method for diagnosis of Pelvic Endometriosis. Danazol is the most commonly used Hormonal therapy for the Medical treatment of Pelvic Endometriosis in Wardha district. Gestrinone is an alternative for the Hormonal medical management of Pelvic Endometriosis in Wardha district. Danazol and Gestrinone are equally effective in reducing the severity of Pelvic endometriosis. Danazol produces more Gastrointestinal intolerance and secondary adverse effects compared to Gestrinone. Gestrinone produces more Androgenic and Anabolic adverse effects compared to Danazol.

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