

# Does pain perception vary across the reproductive life or with the use of HRT in postmenopausal women?

SHIKHA GAUTAM, NILIMA SHANKAR, O.P.TANDON, NEERJA GOEL

## ABSTRACT

**Background:** Recent clinical research has suggested that ovarian hormones may influence pain perception among women. Hormone replacement therapy (HRT) supplements exogenous ovarian hormones to postmenopausal women.

**Aims:** This study was designed to see whether the pain perception, which was induced by the cold pressor test, varied with the gonadal hormone fluctuations of the menstrual cycle, postmenopausal hormone depletion or HRT in postmenopausal women.

**Design:** This study included 90 adult female subjects from similar socio-economic backgrounds in 3 study groups, Group 1 (n=30): Pre-menopausal women in the age group of 30 to 45 years, Group 2 (n=30): Post-menopausal women in the age group of 45 to 55 years and Group 3 (n=30): Post-menopausal women in the age group of 45 to 55 years on HRT, who were on oral HRT.

**Methods:** The pain perception was assessed by the cold pressor test. Statistical Analysis: It was done by using SPSS-13 for Windows and one-way ANOVA, followed by Tukey's test at a 5% level of significance.

**Results:** The pain threshold and pain tolerance was significantly higher in post-menopausal women as compared to the pre-menopausal women in the proliferative phase. In pre-menopausal women, the pain threshold and pain tolerance was significantly higher in the secretory phase as compared to the proliferative phase. The pain threshold and pain tolerance were significantly lower in post-menopausal women who were on HRT as compared to the other post-menopausal women.

**Conclusion:** The present study provides evidence that the pain responses vary across the reproductive cycle and with the use of HRT in post-menopausal women.

**Key Words:** Pain perception, ovarian hormones, Hormone replacement therapy, Cold pressor test, Post-menopausal women, Pre-menopausal women

## INTRODUCTION

Pain is a key component of the body's normal defense mechanisms which protect the body from the potentially hostile external environment by initiating behavioural and reflex avoidance strategies [1]. Pain sensitivity is thought to be mediated by socio-cultural, psychological and biological factors. Sex differences in pain have been noted; women typically report more pain than men.

In women, the sex steroid hormones, oestrogen and progesterone, are known to be mostly involved in reproduction. However, recent research findings have made it clear that these hormones exert significant effects on various unrelated physiological, biochemical and psychological parameters of the body, other than the regulation of the reproductive system. The levels of these sex hormones, oestrogen and progesterone, vary in the different phases of the reproductive life of women. Animal and human research has also shown that the pain sensitivity changes during the menstrual cycle, which has been ascribed to hormonal variations. However, the nature of these menstrual cycle effects have remained unclear, as the studies gave inconclusive and contradictory results.

After menopause, the ovarian function declines and the levels of oestrogen and progesterone fall down. Hormone replacement therapy (HRT) supplements exogenous ovarian hormones to post-

menopausal women. Recent clinical research has suggested that exogenous hormone use may influence the prevalence and the severity of clinical pain among women. This study was designed to check whether the perception of pain, which was induced by the cold pressor test, varied with the gonadal hormone fluctuations of the menstrual cycle, post-menopausal hormone depletion or HRT in post-menopausal women.

## METHODS

The study was conducted in the Department of Physiology, University College of Medical Sciences (UCMS) and GTB Hospital, Delhi. The ethical committee of the institution cleared the project. The subjects of the study were informed about the project both in writing and in person and a written consent was obtained from all the subjects. The subjects were recruited from the OPD and the HRT clinic of the Department of Obstetrics and Gynaecology, UCMS and GTB hospital. The study included 90 adult female subjects from similar socioeconomic backgrounds. The post-menopausal subjects were recruited from the HRT clinic of the Department of Obstetrics and Gynaecology, GTB hospital. All the post-menopausal women who were included had cessation of menstruation at least one year before. The pre-menopausal women were recruited from the relatives of the post-menopausal women who attended the HRT clinic. Subjects who were on oral contraceptive pills and drugs that altered the cardiovascular

functions were also excluded from the study. All those women with a history of diabetes mellitus, hypertension, heart disease and a history of smoking and alcoholism were excluded. The subjects were divided into the following 3 groups.

**Group 1 (n=30)** Pre-menopausal women in the age group of 30 to 45 years, who had a regular menstrual cycle. The cycle phase during which the subjects began their participation was determined randomly. The subjects in the Group1 were investigated twice:

**Group 1 A** In the proliferative phase of the menstrual cycle  
**Group 1 B** In the secretory phase of the menstrual cycle

**Group 2 (n=30)** Post-menopausal women in age group of 45 to 55 years, who had not yet been put on HRT. **Group 3 (n=30)** Post-menopausal women in age group of 45 to 55 years on HRT, who were on oral HRT for the last three months or more, in the form of a continuous combined regimen.(conjugated equine oestrogen 0.625mg and medroxyprogesterone acetate 2.5 mg daily).

The oestradiol levels were recorded in Group 3 (HRT group) and Group 2 (post-menopausal group). For the women in Group 1 (pre-menopausal women), the assessment was done in the late proliferative phase and in the mid-secretory phase. The oestradiol levels were not assessed for women who were in the pre-menopausal group because of financial limitations, as the test was not available in government hospitals.

**Experimental set up:** The subjects were familiarized with the laboratory and they were briefed about the test. A cold pressor test was used as the stimulus source to elicit pain. The subjects were asked to immerse their dominant hand up to the wrist in cold water of 4-6 degrees centigrade. The pain threshold was determined as the duration of the time between when the subjects first reported pain and the time of exposure to the painful stimulus. Pain tolerance was determined as the duration of the time until the subjects withdrew their hands from the test water because the pain was too intensive. Statistical Analysis All the results were obtained by using SPSS-13 for Windows and one-way ANOVA, followed by Tukey's test at a 5% level of significance.

## RESULTS

[Table/Fig 1] shows the average age and the oestradiol levels of the groups. The average age of Group 1 (pre-menopausal women) was less than that of Group 2 (post-menopausal women) and Group 3 (post-menopausal women on HRT). Both the groups of post-menopausal women were comparable in terms of age. The oestradiol level in Group 2 (post-menopausal women) was less as compared to that of Group 3 (post-menopausal women on HRT).

[Table/Fig 2] shows the pain perception of Group 2 (post-menopausal women), Group1A (pre-menopausal women in proliferative phase of menstrual cycle) and Group 1B (pre-menopausal women in secretory phase of menstrual cycle) and their intercomparison. The pain threshold and pain tolerance were significantly higher in Group 2 (post-menopausal women) as compared to Group1A (pre-menopausal women in the proliferative

phase), while no significant difference was found in the pain perception between Group 2 (post-menopausal women) and Group 1B (pre-menopausal women in secretory phase). The pain threshold and pain tolerance were significantly higher in Group1B (secretory phase) as compared to Group 1A (proliferative phase).

[Table/Fig 3] shows the comparison of the pain perception of Group 2 (post-menopausal women) and Group 3 (post-menopausal women on HRT). The pain threshold and pain tolerance was significantly lower in Group 3 (post-menopausal women on HRT) as compared to Group 2 (post-menopausal women).

## DISCUSSION

In this study, between the proliferative and the secretory phase of the menstrual cycle, higher values of pain threshold and pain tolerance were seen in the secretory phase. [Table/Fig 2]. This decrease in pain perception to the cold pressor test in the secretory phase could be due to a decrease in the level of oestrogen and an increase in the level of progesterone in the secretory phase. Similarly, a previous study on menstrual cycle and pain perception by using the cold pressor test found that the pain threshold was significantly higher during the second phase of the menstrual cycle [2]. In contrast, other researchers studied the nociceptive flexion reflex in women during the follicular and the luteal phase. A higher sensitivity to the pain stimuli was observed during the luteal phase of the menstrual cycle [3]. The results of a study by Fillingim et al which used thermal and ischaemic pain stimuli in pre-menopausal women indicated that women showed less ischaemic pain sensitivity during the midfollicular phase as compared to the ovulatory and the mid-to-late luteal phase, but that the thermal pain response did not vary significantly across the menstrual cycle phases [4].

Some other studies have documented no variation of pain perception in different phases of the menstrual cycle. Ring et al measured venipuncture and intravenous catheterization pain during the follicular and luteal phases of the menstrual cycle. Pain was also assessed in a group of men. The pain ratings were higher in women than in men. In women, the pain ratings did not differ between the follicular and the luteal phases [5]. Rebecca et al examined the pain sensitivity in men and in premenopausal women who were in different phases of the menstrual cycle, in response to the cold pressor, heat, and ischaemic pain. Women were more sensitive to cold pain, heat pain, and ischaemic pain than men, but the pain perception was not influenced by the menstrual cycle in women [6].

In our study, the values of both the pain threshold and pain

	Age (years) Mean ± SD	Estradiol (pg/ml) Mean ± SD
Group 1 (premenopausal women)	33.83 ± 2.44	Not Done
Group 2 (postmenopausal group)	51.03 ± 3.28	19.09 ± 2.71
Group 3 (HRT group)	52.53 ± 2.87	43.11 ± 2.24

[Table/Fig-1]: Showing the average age and estradiol levels of groups

Pain perception (in seconds)	Group 1A	Group 2	Tukey test (group 1A & 2) pvalue	Group 1B	Tukey test (group 1B & 2) pvalue	Tukey test (group 1A&1B) pvalue
	Mean ± SD	Mean ± SD		Mean ± SD		
Pain Threshold	28.13 ± 3.68	38.57 ± 9.72	0.007	36.47 ± 15.21	0.911	0.047
Pain Tolerance	47.43 ± 20.02	65.80 ± 13.92	0.002	65.57 ± 24.37	1.000	0.002

[Table/Fig-2]: Showing pain perception of Group 1A (pre-menopausal women in proliferative phase), Group 1B (pre-menopausal women in secretory phase), & Group 2 (post-menopausal women)

Pain perception (in seconds)	Group 2	Group 3	Tukey test (Group 2 & 3) p-value
	Mean $\pm$ SD	Mean $\pm$ SD	
Pain Threshold	38.57 $\pm$ 9.72	23.57 $\pm$ 9.38	< 0.001
Pain Tolerance	65.80 $\pm$ 13.92	35.0 $\pm$ 17.12	< 0.001

**[Table/Fig-3]:** Showing pain perception of Group 2 (post-menopausal women) and Group 3 (post-menopausal women on HRT)

tolerance were significantly more in postmenopausal women as compared to those in the pre-menopausal women who were in the proliferative phase of the menstrual cycle. The comparison of the post-menopausal women and the secretory phase was non-significant. [Table/Fig 2] This decrease in pain perception in post-menopausal women, where the gonadal hormones are at low levels as compared to the pre-menopausal women, indicates that the female gonadal hormones may be increasing the pain perception. In contrast, Mitchell et al who studied the changes in the levels of back pain and joint pain during the stages of menopausal transition and early postmenopause, found that post-menopausal women experienced a significant increase in back pain [7].

The post-menopausal women who were on HRT had significantly lower values of pain threshold and pain tolerance as compared to the postmenopausal women who were not on HRT. [Table/Fig 3] These findings on the post-menopausal women who were on HRT where the oestradiol levels were higher than in other post-menopausal women [Table/Fig 1], suggest that the female gonadal hormones increase pain perception. Some previous studies have also reported increased pain perception with HRT use. Macfarlane et al have found that amongst pre - and per-i menopausal women, the risk of chronic widespread pain was unrelated to the menstrual cycle or to the use of oral contraceptive pills. Amongst the post-menopausal women, an increased risk of chronic widespread pain was associated with HRT [8]. Fillingim et al examined the experimental thermal pain responses and the recent pain complaints in women who were on HRT, in women who were not on HRT and in men. The results indicated no group differences in the recent pain complaints or in self-reported health, but differences emerged for the measures of thermal pain perception. Specifically, the women on HRT showed lower pain thresholds and tolerances than the women who were not on HRT [9].

Other researchers have found no association between the female sex hormones, HRT and pain perception. France et al examined pain coping, HRT, and laboratory and clinical pain in men, in post-menopausal women who were receiving HRT and in post-

menopausal women who were not receiving HRT. They found no significant group differences in the arthritis pain, electro-cutaneous pain, or in the nociceptive flexion reflex threshold [10]. The reasons for the inconsistent findings of previous researches concerning the female sex hormones and pain could be because of the methodological differences like the timing of the experimental session in the menstrual cycle and the nature of the pain stimuli which were chosen to elicit the pain response.

## CONCLUSION

The present study provides evidence that pain responses vary across the reproductive cycle and with the use of HRT in women; and that these differences are related to the differences in the hormone levels. However, the limitation of this study was the small population size. Also, the hormone levels of the pre-menopausal group could not be assessed due to financial limitations. Further research, including measurements of the plasma hormone levels during different phases of the reproductive cycle in a larger population are needed to clarify the role which is played by the female sex hormones in pain perception.

## REFERENCES

- [1] Woolf CJ. Somatic pain – pathogenesis and prevention. *Br J Anaesth* 1995;75:169-76.
- [2] Hellstorm B, Lundberg U. Pain perception to the cold pressor test during the menstrual cycle in relation to the estrogen levels and a comparison with men. *Integr Physiol Behav Sci* 2000;35:132-41.
- [3] Tassorelli C, Sandrini G, Cecchini AP, Nappi RE, Sances G, Martignoni E. Changes in the nociceptive flexion reflex threshold across the menstrual cycle in healthy women. *Psychosom Med* 2002;64:621-26.
- [4] Fillingim RB, Maixner W, Girdler SS, Light KC, Harris MB, Sheps DS, et al. Ischaemic, but not thermal pain sensitivity varies across the menstrual cycle. *Psychosom Med* 1997;59:512-20.
- [5] Ring C, Veldhuijzen van Zanten JJ, Kavussanu M. Effects of sex, phase of the menstrual cycle and gonadal hormones on pain in healthy humans. *Biol Psychol* 2009 ;3:189-91.
- [6] Klatzkin RR, Mechlin B, Girdler SS. The menstrual cycle phase does not influence the gender differences in the experimental pain sensitivity. *Eur J Pain* 2010;14:77.
- [7] Mitchell ES, Woods NF. Pain symptoms during the menopausal transition and in early postmenopause. *Climacteric* 2010;13:467-78.
- [8] Macfarlane TV, Blinkhorn A, Worthington HV, Davies RM, Macfarlane GJ. Sex hormonal factors and chronic widespread pain: a population study among women. *Rheumatology*. 2002;41:454-57.
- [9] Fillingim RB, Edwards RR. The association of hormone replacement therapy with the experimental pain responses in post-menopausal women. *Pain* 2001;92:229-34.
- [10] France CR, Keefe FJ, Emery CF, Affleck G, France JL, Waters S, et al. Laboratory pain perception and clinical pain in post-menopausal women and in age matched men with osteoarthritis: relationship to pain coping and hormonal status. *Pain* 2004;112:274-81 .

### AUTHOR(S):

1. Dr. Shikha Gautam,
2. Dr. Nilima Shankar,
3. Dr. O.P.Tandon,
4. Dr. Neerja Goel,

### PARTICULARS OF CONTRIBUTORS:

1. Corresponding Author,
2. Professor, Dept of Physiology,
3. Professor, Dept of Physiology,
4. Professor, Dept of Gynaecology & Obstetrics, UCMS & GTB Hospital, Dilshad Garden, Delhi – 110095, India.

### NAME, ADDRESS, TELEPHONE, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Shikha Gautam,  
Senior Demonstrator, Dept of Physiology  
UCMS & GTB Hospital,  
Dilshad Garden, Delhi – 110095, India.  
Phone: 09810557315  
E-mail: drshikhagautam@yahoo.co.in,

### DECLARATION ON COMPETING INTERESTS:

No competing Interests.

Date of Submission: **Nov 08, 2011**  
Date of Peer Review: **Dec 06, 2011**  
Date of Acceptance: **Dec 28, 2011**  
Date of Publishing: **May 01, 2012**