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ORIGINAL ARTICLE

Effect of Hormonal Supplementation on Pain Tolerance in Women, A Cross Sectional Study

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ABSTRACT

Background and Aim: Hormonal supplementation (Oestrogen and progesterone) significantly influence pain sensitivity in women. Neuropathic pain prevention and nociceptive actions are strongly affected by progesterone and oestrogen. The present study aimed to investigate the gonadal hormones on women's pain sensation.

Materials and Method: this case-control study was conducted on 46 females (study group) on the combined oral contraceptive pill (COCP) and 46 healthy males (control group) at the Department of Physiology, Lahore General Hospital, Lahore from November 2020 to July 2021. As a stimulus source, a cold pressor test was used. The participant's least dominant hands were placed in a water bath with a temperature between 0◦C and 2◦C and were instructed to notify when the pain was first sensation feel which represents the pain threshold of participants. Pain tolerance was referred to the duration from the initial threshold to a stage where pain severity increased beyond the participant's coping with pain. A visual analog scale was set to measure the unpleasantness and pain intensity. SPSS version 23 was used for data analysis. The Chi-square test was used, and p values less than 0.05 were considered significant.

Results: Pain tolerance and unpleasantness was not significantly differ in men and women taking combined oral contraceptive pill. However, women on combined oral contraceptive pill had significantly higher ($p<0.001$) pain tolerance on average scale. Average pain threshold had insignificant association with age. Comparing to naturally menstruating women the unpleasantness pain on average scale was less severe in women taking hormonal pills. The average pain intensity was considerably differ between women on COCP pills and normal women.

Conclusion: Our study suggests that gonadal hormone levels changes had a lower effect on experimental pain and unpleasantness in women. COCP influence the average pain reported by participants. Upon comparing normal and women on COCP pills, a significant increase in pain tolerance was observed in females on pill therapy. Women utilizing hormonal contraceptives should be kept under supervision for unpleasant and severe pain.

Keywords: Hormonal supplementation, Pain tolerance, Combined oral contraceptive pill

INTRODUCTION

Pain is an imperative sensation that primarily serves as body protection. Evidence suggested that pain varies in men and women. Therefore, variation in tolerance levels, pain threshold, and incidence of clinical pain conditions are described, and men are less vulnerable regarding conditions of chronic pain and sensitivity compared to women [1, 2]. The hormonal milieu is the possible explanation for the variance in pain experienced by men and women. The significant differences in men's and women's physiological changes are the hormones or sex steroids, occurrence, and absolute levels of women's cyclic fluctuation [3]. After puberty, these hormones are responsible for male and female embryological development and successful reproduction function. Pain symptoms variation observed between puberty and menopause along with symptoms of clinical variation among women plays a significant role in changes in pain experienced by women [4, 5].

Previous research has found no link between women's menstrual cycle and pain. Yet, there are some contradictory reports claiming that pain threshold and response are affected by cyclic sex hormones [6, 7]. Around puberty, the occurrence of sex hormones changes dramatically whereas clinical pain conditions due to sex differences begin to observe. Painful conditions development and age had no significant association in women initially [8, 9], but individual puberty varies significantly with timing. Few recent investigations found that instead of controlling chronological age, the pubertal development stage should be associated with pain [10]. In either sex, the chances of pubertal changes or development are increased by painful conditions experienced [11, 12]. There is a scarcity of data regarding pain in various aspects in women with normal menstruation versus women on COCP pills. The purpose of this study is to compare the effect of hormonal COCP on pain sensitivity response in women receiving COCP to that of naturally menstruating women.

METHODOLOGY

This case-control study was conducted on 46 females (study group) on the combined oral contraceptive pill (COCP) and 46 healthy males (control group) at the Department of Physiology, Lahore General Hospital, Lahore from November 2020 to July 2021. As a stimulus source, a cold pressor test was used. The participant's least dominant hands were placed in a water bath with a temperature between 0◦C and 2◦C and were instructed to notify when the pain was first sensation feel which represents the pain threshold of participants. Pain tolerance was referred to the duration from the initial threshold to a stage where pain severity increased beyond the participant's coping with pain. A visual analog scale was set to measure the unpleasantness and pain intensity. Women on combined oral contraceptive pill therapy were enquired about previous intake of the pill. All the participant's women were taking no COCP pills and had natural menstruation. Chronic disease participants and those who took analgesics 48 hours before the research start were excluded. Female with one hormones and were taking mini-pills were excluded. SPSS version 23 was used for data analysis. The Chi-square test was used, and p values less than 0.05 were considered significant.

RESULT

Pain tolerance and unpleasantness was not significantly differ in men and women taking combined oral contraceptive pill. However, women on combined oral contraceptive pill had significantly higher ($p<0.001$) pain tolerance on average scale. Average pain threshold had insignificant association with age. Comparing to naturally menstruating women the unpleasantness pain on average scale

was less severe in women taking hormonal pills. The average pain intensity was considerably differ between women on COCP pills and normal women. Pain responses to the cold pressor test differed by group as shown in Table-I. Table-II compared of different pain parameters between groups. There is a significant difference in pain threshold and tolerance between women on the pill and women who menstruate naturally as shown in Figure-1. Figure-2 illustrate the significant difference in pain intensity and unpleasantness between women on COCP and women menstruating normally.

Table-1: Pain responses to the cold pressor test differed by group

Pain Parameters	Women on COCP	Women with natural menstruation
Pain threshold (time; sec)	9.72±3.54	8.45±3.9
Pain Tolerance (sec)	48.95±22.43	36.4±10.96
Pain Intensity (mm)	58.81±7.65	67.7±7.29
Pain Unpleasantness(mm)	54.3±5.86	66.7±8.3

Table-2: comparison of different pain parameters between groups

Pain Parameters	Women on COCP	Women with natural menstruation
Average Pain threshold (time; sec)	0.33	0.32
Average Pain Tolerance (sec)	0.08	0.00
Average Pain Intensity (mm)	0.02	0.54
Average Pain Unpleasantness(mm)	0.01	0.21

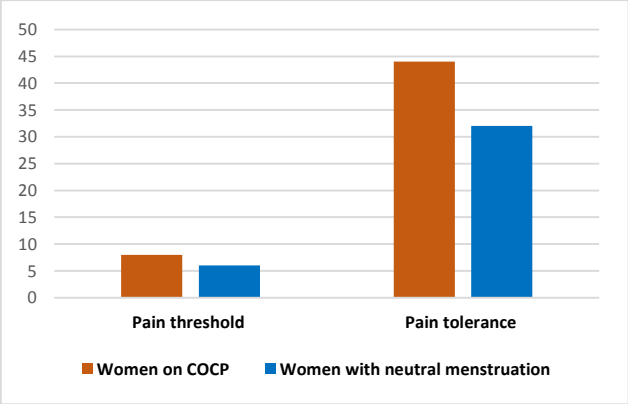

Figure-1: Difference in pain threshold and tolerance between women on the pill and women who menstruate naturally

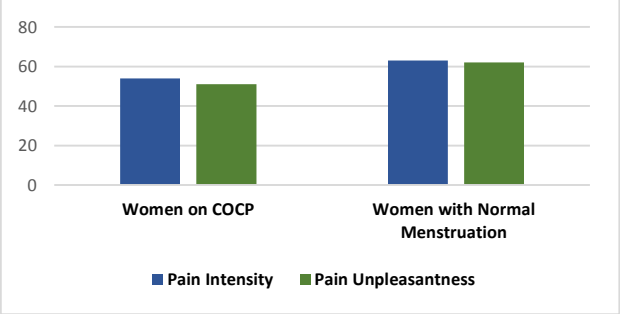

Figure-2: illustrate the significant difference in pain intensity and unpleasantness between women on COCP and women menstruating normally

DISCUSSION

The present study investigated the effects of the gonadal hormone on pain induced in different groups of hormonal milieus in different women. The gonadal hormones such as estrogen and progesterone different phases before and after substitution effects the menstrual cycle whereas treatment with Vitro fertilization might affects the levels of dichotomous hormonal [13]. A significant variation was reported in women taking COCP pills and women with normal menstruation. On the other hand, men and women who both took COCP pills had shown insignificant association. The threshold of average pain between the two groups is statistically insignificant. Naturally menstruating women found severely unpleasant pain compared to contraceptive users women. This could be explained by pain relief or coping with severe pain due to COCP pills therapy which potentially masks pain. The pill therapy females had a higher tolerance of average pain compared to women menstruating normally [14].

Numerous literature reported the existence of pain sensation with gender differences, however, in animals, pain sensitivity is experienced to be influenced by gonadal hormonal while elusive in human beings [15]. Pain sensitivity is affected slightly by hormonal changes in exceptional cases of cold pressor test where a rating of pain sensation is significantly affected. Insignificant changes with estradiol levels' extreme variations in pain tolerance were observed with poor outcomes [16].

The association of differences in hormonal states could be visualized with variation in pain sensitivity as reported by two different investigative studies [17, 18]. Another study by Davis et al, investigated the left masseter muscle skin heating applied during the lower and higher levels of estrogen and found insignificant differences in levels of progesterone [19]. Two different patterns of activation were seen regardless of insignificant pain rating differences. The participant's finger was immersed in hot water (painful) during higher and lower estrogen/progesterone phases [20].

Pain sensitivity in a cyclic variation of women could be observed with pain clinical conditions. A healthy woman with no difference in balloon distension from rectal sensitivity during the cycle whereas sensitivity increases during the menstrual phase in women with IBS. Women suffering from fibromyalgia, IC, and dysmenorrhea had significant variations in pain sensitivity [21].

Brain could be effected by steroid hormones in either ways activational and organizational. The organizational effect could be early neonate's life or observed during utero development. The exposure of steroid hormones during development of brain had shown variation in sexually dimorphic behaviours in different species that includes spatial learning, play pattern, maternal behavior, and sexual behavior [22]. Maternal circulation can gives these hormones either in endogenous or exogenous form, twin, and foetus. Brain neurotransmission modulated by steroids hormones in the brain, peripheral nerves, and spinal cord changes the receptor availability and specific brain area excitability [23].

The peripheral structure could also be affected by steroid hormones besides the nervous and reproductive systems. The peripheral structure could be blood vessels, bone, ligaments, and joint surfaces [24].

CONCLUSION

Our study suggests that gonadal hormone levels changes had a lower effect on experimental pain and unpleasantness in women. COCP influence the average pain reported by participants. Upon comparing normal and women on COCP pills, a significant increase in pain tolerance was observed in females on pill therapy. Women utilizing hormonal contraceptives should be kept under supervision for unpleasant and severe pain.

REFERENCES

1. Mokal SJ, Hirkani M, Gadkari V, Bhalerao A. Study of Pain Perception in Different Phases of Menstrual Cycle. Int J Med Res Prof. 2018;4(6):114–7.
2. Nastri, C.O.; Lara, L.A.; Ferriani, R.A.; Rosa, E.S.A.C.; Figueiredo, J.B.; Martins, W.P. Hormone therapy for sexual function in

perimenopausal and postmenopausal women. Cochrane Database Syst. Rev. 2019.
3. Corona, G.; Rastrelli, G.; Morgentaler, A.; Sforza, A.; Mannucci, E.; Maggi, M. Meta-analysis of Results of Testosterone Therapy on Sexual Function Based on International Index of Erectile Function Scores. Eur. Urol. 2017, 72, 1000–1011.
4. Cepeda, M.S.; Zhu, V.; Vorsanger, G.; Eichenbaum, G. Effect of Opioids on Testosterone Levels: Cross-Sectional Study using NHANES. Pain Med. 2018, 16, 2235–2242.
5. Wersocki, E.; Bedson, J.; Chen, Y.; LeResche, L.; Dunn, K.M. Comprehensive systematic review of long-term opioids in women with chronic noncancer pain and associated reproductive dysfunction (hypothalamic–pituitary–gonadal axis disruption). Pain 2016, 158, 8–16.
6. Aminilari, M.; Manjoo, P.; Craigie, S.; Couban, R.; Wang, L.; Busse, J.W. Hormone Replacement Therapy and Opioid Tapering for Opioid-Induced Hypogonadism Among Patients with Chronic Noncancer Pain: A Systematic Review. Pain Med. 2018, 20, 301–313.
7. Hochberg, U.; Ojeda, A.; Brill, S.; Perez, J. An Internet-Based Survey to Assess Clinicians' Knowledge and Attitudes Towards Opioid-Induced Hypogonadism. Pain Pr. 2018, 19, 176–182.
8. Lin, T.-C.; Ho, S.-T.; Ger, L.-P.; Liou, H.-H.; Hwang, S.-L. Gender difference in long-term use of opioids among Taiwan officially registered patients with chronic noncancer pain. Medicine 2018, 97, e10805.
9. Taiwan Food and Drug Administration. Physician Guidelines on Clinical Use of Narcotics in Chronic Noncancer Pain. (in Chinsese, Amended on 4 December 2018). Available online: https://www.fda.gov.tw/tc/lawContent.aspx?cid=183&id=3086 (accessed on 30 November 2020).
10. Dowell, D.; Haegerich, T.M.; Chou, R. CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. JAMA 2016, 315, 1624–1645. [Google Scholar] [CrossRef]
11. Opioid Dose Equivalence. Faculty of Pain Medicine, ANZCA—March 2019. Available online: https://www.anzca.edu.au/getattachment/6892fb13-47fc-446b-a7a2-11cdfe1c9902/PM01-(Appendix-2)-Opioid-Dose-Equivalence-Calculation-of-Oral-Morphine-Equivalent-Daily-Dose-(oMEDD).aspx (accessed on 30 November 2020).
12. Guy, G.P.; Zhang, K. Opioid Prescribing by Specialty and Volume in the U.S. Am. J. Prev. Med. 2018, 55, e153–e155.
13. Lin, T.-C.; Ger, L.-P.; Pergolizzi, J.V.; Raffa, R.B.; Wang, J.-O.; Ho, S.-T. Knowledge, Attitude and Practice Survey of Prescribing Opioids for Chronic Noncancer Pain in Taiwan—Comparison of Pain and Non-Pain Physicians. Pain Med. 2016, 20, 2397–2410.
14. Hsu, Y.-C.; Lin, S.-L.; Sung, C.-S.; Ger, L.-P.; Liou, H.-H.; Lin, T.-C.; Ho, S.-T. Knowledge, attitude, and barriers regarding prescribing long-term opioids among Taiwan physicians treating officially registered patients with chronic noncancer pain. J. Chin. Med. Assoc. 2020, 84, 227–232.
15. Haack, M.; Simpson, N.; Sethna, N.; Kaur, S.; Mullington, J. Sleep deficiency and chronic pain: Potential underlying mechanisms and clinical implications. Neuropsychopharmacology 2019, 45, 205–216.
16. Oliva, E.M.; Bowe, T.; Manhapra, A.; Kertesz, S.; Hah, J.M.; Henderson, P.; Robinson, A.; Paik, M.; Sandbrink, F.; Gordon, A.J.; et al. Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans: Observational evaluation. BMJ 2020, 368, m283.
17. Decaroli, M.C.; Rochira, V. Aging and sex hormones in males. Virulence 2016, 8, 545–570.
18. De Vries, F.; Bruin, M.; Lobatto, D.J.; Dekkers, O.M.; Schoones, J.W.; Van Furth, W.R.; Pereira, A.M.; Karavitaki, N.; Biermasz, N.R.; Najafabadi, A.H.Z. Opioids and Their Endocrine Effects: A Systematic Review and Meta-analysis. J. Clin. Endocrinol. Metab. 2019, 105, 1020–1029.
19. Davis, S.R.; Baber, R.; Panay, N.; Bitzer, J.; Perez, S.C.; Islam, R.M.; Kaunitz, A.M.; Kingsberg, S.A.; Lambrinoudaki, I.; Liu, J.; et al. Global Consensus Position Statement on the Use of Testosterone Therapy for Women. J. Clin. Endocrinol. Metab. 2019, 104, 4660–4666
20. Beggs S, Kwok CHT, et al. Microglial P2X4R-evoked pain hypersensitivity is sexually dimorphic in rats. Pain. 2018;159(9):1752–63.
21. DiSabato DJ, Quan N, Godbout JP. Neuroinflammation: the devil is in the details. J Neurochem. 2016;139(Suppl):2136–53.
22. Sorge RE, Totsch SK. Sex differences in pain. J Neurosci Res. 2017;95(6):1271–81.
23. Doyle HH, Murphy AZ. Sex differences in innate immunity and its impact on opioid pharmacology. J Neurosci Res. 2017;95(1–2):487–99.
24. Doyle HH, Murphy AZ. Sex-dependent influences of morphine and its metabolites on pain sensitivity in the rat. Physiol Behav. 2018;18732–41.