Iranian Veterinary Surgery Association

Iranian Journal of Veterinary Surgery

Journal homepage: www.ivsajournals.com

Original Article

Evaluation Cardiac Structure and Function Changes Following Ovariohysterectomy by Echocardiographic Measurements in Immature Cats

Boshra Elyasi, Mohammad Nasarolahzade-Masouleh*, Alireza Jahandideh

Department of Clinical Science, Faculty of Specialized Veterinary Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran.

ARTICLE INFO

Article History:

Received 1 September 2022
Revised 25 October 2022
Accepted 19 November 2022
Online 19 November 2022

Keywords:

Cardiac output
Cat
Ejection fraction
Fractional shortening

ABSTRACT

The aim of this study was conducted to identify the short-term effects of ovariohysterectomy on the heart of immature cats using echocardiography. This longitudinal study was conducted on a sample consisting of 6 immature female DSH cats. After the selection of test items, echocardiography was performed on the cats before the ovariohysterectomy (D0) and ten days (D10), twenty days (D20), and thirty days (D30) after the ovariohysterectomy. Cardiac parameters, including fractional shortening (FS), ejection fraction (EF), cardiac output (CO), left atrial-to-aortic root diameter ratio (LA/Ao), and left ventricular wall thickness to interventricular septum ratio (LVWD/IVS) was measured. Results indicated that the average EF at D10 (71.83%), D20 (71.00%), and D30 (69.83%) was significantly reduced compared to D0 (77.66%). The average CO at D10 (1.68 l/min), D20 (1.51 l/min), and D30 (1.5 l/min) was significantly reduced compared to D0 (2.05 l/min). However, the average FS at D10 (40.54%), D20 (40.50%), and D30 (39.33%) reduced compared to D0 (45.00%); the reduction was not statistically significant. The average Ao/LA and LVPW/IVS remained unchanged during the study (without noticeable changes). Ovariohysterectomy negatively impacts cardiac function; accordingly, special care and follow-up during sterility are essential for maintaining cardiac health.

Introduction

Overpopulation of cats is one of the growing concerns of the current societies. Hence, scientific communities struggle to solve this problem by seeking non-destructive methods. Ovariohysterectomy (OHE) or spaying is one of the methods. This surgery removes the ovaries and uterus from the body. The reproductive glands (ovaries) are the origin and primary source of the known sex hormones (estrogen, progesterone, and testosterone), and their removal inevitably takes away the possibility of fertility.[1]

Alteration in the secretion of sex hormones can cause several impacts (either beneficial or non-beneficial) on various body organs. In particular, findings indicate that removing the reproductive organs of multiple animals through surgery can prevent several diseases, including uterine and breast tumors, pyometra, vaginal inflammation, and vaginal prolapse.[1,2] However, removing the mentioned organs

* Correspondence to: Mohammad Nasarolahzade-Masouleh, Department of Clinical Science, Faculty of Specialized Veterinary Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran, Email: mnmasouleh@srbiau.ac.ir

https://doi.org/10.30500/ivsa.2022.360154.1321

may also lead to an increased possibility of multiple organ dysfunctions, such as early closure of growth plates,[3] diabetes mellitus,[4] hypothyroidism,[5] and gastrointestinal lymphoma.[6] Infertility (or menopause) can lead to cardiovascular diseases.[7,8] These changes are probably caused by the loss of estrogen. Estrogen leads to promoting vasodilatation by regulating nitric oxide production. Therefore, with the loss of estrogen, it probably leads to vascular dysfunction. Also, due to increased expression of inflammatory cytokines, which may damage the cardiac function.[9] Early spaying also results in reduced lifetime exposure to endogenous estrogen, which may account for the increased incidence of cardiovascular disease in immature animals.[10]

Metabolic risk factors, mainly lipids, during infertility can increase the risk of cardiovascular diseases. In a number of studies, it has been determined that during menopause, the level of triglycerides and low-density lipoprotein-cholesterol (LDL-C) in the blood increases, while the level of high-density lipoprotein cholesterol (HDL-C) decreases, which is a potential development of cardiovascular diseases.[11,12]

Also, during this period, androgens increase, but sex hormone-binding globulin (SHBG) decrease, which can also have negative effects on the heart.[13] Androgens have proinflammatory and vasoconstrictive properties and lead to increased blood pressure and other vascular vascular impairment.[14] Androgens lead to an effect on the growth-promoting effect on muscle cells, which themselves can lead to enlarged cardiomyocytes and cardiac hypertrophy, thus leading to a change in the ejection fraction (EF).[15]

Despite the multitude of conducted human studies on hormonal changes due to menopause and cardiovascular diseases,[16-18] based on inquiries in valid scientific databases, there is no study available on impacts of OHE in animals, especially cats. Hence, the extent of the consequences caused by these types of actions on animals (especially cats) is not yet known. Accordingly, in this study, we tried to identify the cardiovascular changes caused by OHE in cats with an experimental research approach using echocardiography.

Materials and Methods

Animals and Surgery

This study was conducted on six healthy immature female DSH cats with an average weight of 2.70 kg and a mean age of 184 days. All the animals included in the study used the same food ration (commercial dry food) and passed a 12-hours starvation process before the surgery. In order to check the health of cats, biochemical factors included renal factor (blood urea nitrogen [BUN] and creatinine) and liver factor (alanine aminotransferase [ALT], alkaline phosphatase [ALP], and aspartate aminotransferase [AST]) and complete blood cell (CBC) were measured.

A standard OHE was conducted on the test subjects. They received ketamine (5.5 mg/kg, intravenous [IV]) and diazepam (0.28 mg/kg, IV) as pre-anesthetic agents, and ketamine (0.6 mg/kg IV) was injected for anesthesia. During the operation, the heart rate and respiratory rate of the animals were under constant monitoring.

Echocardiography

We removed the hair on the 4th and 5th intercostal spaces of test subjects to perform the echocardiography. Then the animals were placed on the echocardiography table in the appropriate lying-down situation. Then, using the ultrasonography device (Esaote Mylab 40 2011, Italy) with phased array probe (3.5 MHz) in standard right parasternal views to the short axis at the level of the papillary muscles and with motion modality and with diastole Teichezole technique, various parameters (including interventricular septum thickness during the systole, left ventricular internal diameter at the end of diastole, left ventricular internal diameter at the end of systole, left ventricular free wall diameter during the diastole, left ventricular free wall diameter during the systole, and heart rate) were measured. Then, using the following formulas, the device measured the cardiac output (CO), ejection fraction, and left ventricular fractional shortening (LVFS) values. Also, in the aortic root measurement level, the aortic root and left atrial diameters and their ratio (LA/Ao) were recorded. Then the left ventricular wall thickness to interventricular septum ratio (LVWD/IVS) was measured at the long axis of the 4-chamber view:

$$LVFS=\frac{LVIDd-LVIDs}{LVIDd}$$

$$FS=\frac{EDV-ESV}{EDV}$$

$$CO=HR\times SV$$

Measurement Days

The measurements were conducted in ten days intervals, before the injection (D0), ten days after the

surgery (D10), twenty days after the surgery (D20), and thirty days after the surgery (D30).

Statistical Analysis

First, we calculated the averages of the various parameters for data analysis. Then we used the Kolmogorov–Smirnov test to investigate the normality of data distribution. Next, we applied repeated measures ANOVA to compare the differences between the components during the time and applied Tukey's test for pair-wise comparison of the means (p-values less than 0.05 were statistically significant).

Results

The Normality Test of the Data

The normality test of the data distribution indicated calculated p-values of all data higher than 0.05, showing that the data distribution was normal. Accordingly, parametric statistical tests were applicable.

Changes in Cardiac Parameters with Motion Modality (M-Mode)

As can be seen in Figure 1, the average FS on day 10 (45.5%), day 20 (40.50%), and day 30 (39.44%) were reduced compared to the value before OHE (45%); however, the changes were not statistically significant ($p > 0.05$). The average EF compared to before the OHE (77.66%) was significantly reduced ($p = 0.001$) by day 10 (71.83). Also, this factor was significantly reduced ($p = 0.03$) until day 20 (71%). The average EF indicated a decline until day 30 (69.83%); however, this reduction was not statistically significant ($p = 0.09$). The average CO compared to the value before the OHE (2.05 l/min) was significantly reduced ($p = 0.01$) by day 10 (1.68 l/min). The changes on days 20 and 30 (1.51 l/min) were also statistically significant ($p = 0.03$ and 0.004, respectively) (Figures 1 and 2).

Cardiac Parameters Variations with Brightness-Mode (B-Mode)

As can be seen in Figure 3, the average LA/Ao of day 10 after the surgery (1.41) has increased compared to the time before the surgery (1.25); however, the increase was not statistically significant ($p = 0.06$). The average related parameter on day 20 after the surgery (1.35) and day 30 after the surgery (1.28) was higher than before the surgery; yet, this difference was also not statistically significant ($p > 0.05$). The mean LVPW/IVS did not change during the study (Figures 3, 4, and 5).

Discussion

The heart is one of the vital body organs, and any disorder will inevitably affect the body's functions and may even lead to the organism's death.[19] The findings of this study and many previous medical types of research indicated that removal or dysfunction of reproductive organs (elective surgery and early or late menopause) are among the factor contributing to cardiac functional changes and failures. Accordingly, such factors can increase the possibility of cardiovascular diseases. Reviewing a number of the prior studies will provide evidence to verify the claim.

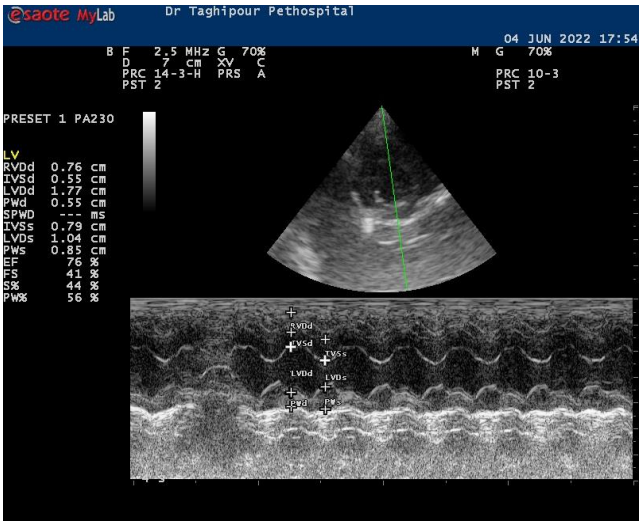

Figure 1. M-mode echocardiography of immature cat. Right parasternal short-axis at the level of the papillary muscles. EF = 76%, and FS = 41%.

Figure 2. Mean and standard deviation of FS (%), EF (%), and CO (l/min) before the ovariohysterectomy (D0), after ten days (D10), after twenty days (D20), and after thirty days (D30).

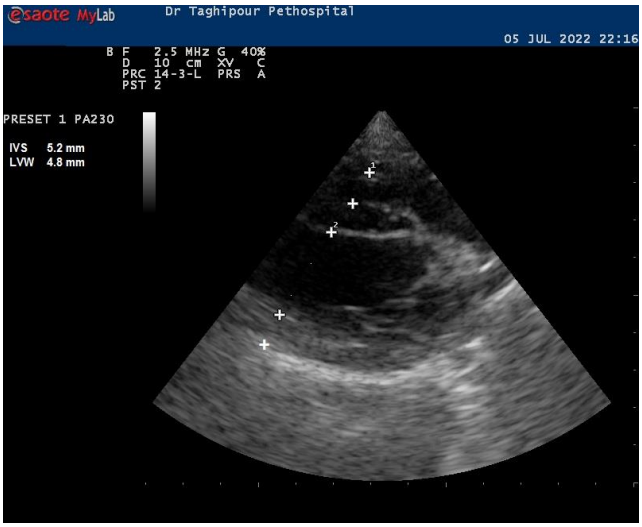

Figure 3. B-mode echocardiography of immature cat. Right parasternal short-axis at the level of the aortic root level. LA/Ao = 1.41.

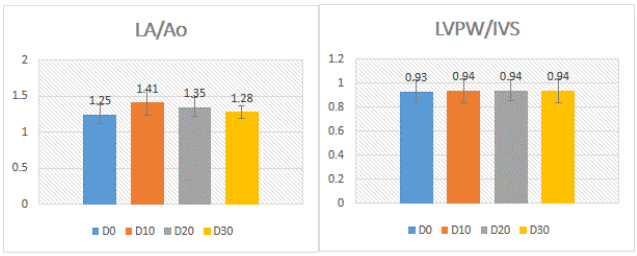

Figure 4. Mean and standard deviation of LA/Ao and LVPW/IVS before the ovariohysterectomy (D0), after then days (D10), after twenty days (D20), and after thirty days (D30).

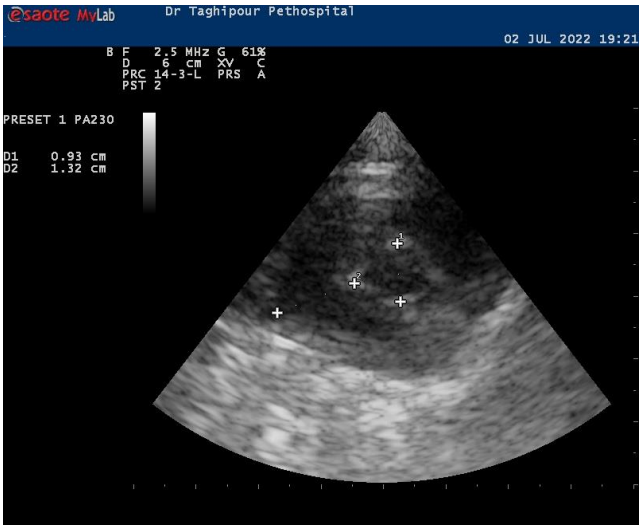

Figure 5. B-mode echocardiography of immature cat. Right parasternal Long-axis at the level of 4 chamber view. LVPW/IVS = 0.92.

Muka *et al*. (2016) compared the risk of developing cardiovascular diseases (CVDs) in young women (before menopause) and women older than 45 years (after menopause). They revealed that the risk of developing CVDs in women before menopause is higher than in those who have reached menopause.[20] Shen *et al*. (2019) also stated that for each 1-year delay in menopausal age, the rate of CVD notification reduced by 3 % [10]. Similar results were seen in other studies.[21,22]

Løkkegaard *et al*. (2006) also reported a statistically significant correlation between early menopause and the risk of coronary disease.[23] Dam *et al*. (2019) also reached a linear relationship between these two elements. They discovered that each year after menopause, the risk of developing cardiac diseases increases by 3 percent.[24] Reethega *et al*. (2018) also obtained similar results to this study.[25] Based on the results of longitudinal research on the human population, Khoudary *et al*. (2020) reported that due to causing dysfunction in coronary arteries, menopause increases the risk of developing cardiovascular diseases.[26] The results of some short-term studies suggested that early onset of menopause with ventricular dysfunction causes negative effects of the disease.[27-29] In another study, it was found that women who experience early natural menopause have a higher risk for developing heart failure.[30]

There are several mechanistic interpretations regarding the relationship between early infertility and the risk of cardiovascular diseases. Altered ovarian function may lead to long-term activation of the renin-angiotensin-aldosterone system, which impairs endothelial dysfunction, inflammation, and immune dysfunction, resulting in membrane damage.[31] Also, the beginning of sterility may be partially mediated via the transmembrane G protein-coupled estrogen receptor.[32] In addition, this change may become a biological mechanism, which itself can be damaged in the function of the organ.[33]

Zhoa *et al*. (2018) reported that decreased hormonal levels after menopause would increase the risk of cardiovascular diseases in the last years of patients' life.[34] Dosi *et al*. (2014) also indicated that the risk of cardiovascular diseases among women with reproductive system dysfunction is significantly higher. They also revealed that women with central obesity and abnormal lipid profile face an increased risk of developing CVDs.[35] In line with the mentioned studies, Ingelsson *et al*. (2011) also discovered that elective spaying increases the possibility of cardiac diseases in women. In short, the findings of this study, in line with previously mentioned research, indicated that early menopause, either by targeted elective spaying or through several other factors, would significantly increase the possibility of developing various

cardiovascular disorders.[36]

Abbas *et al*. (2018) also showed that the loss of sex hormones, whether due to natural or surgical menopause, both lead increase the risk for cardiovascular disease. In this study, both Carotid femoral pulse wave velocity (cfPWV) and Brachial Ankle Pulse wave velocity (baPWV) were significantly higher in surgical and natural menopause compared to women with Premenopausal group. But the results of this study of reveal that women with surgical menopause are associated with greater arterial stiffness when compared to women with natural menopause and premenopause.[37] Therefore, attention to the heart, especially during selective sterility, should be more than during natural sterility.

Considering the findings of this study, we can conclude that OHE can change the cardiac function of immature cats and endanger their health. Accordingly, after spaying these cats, preventing them from developing cardiovascular diseases through constant and accurate evaluations, controlling their nutrition, lifestyle management, and also replacing their sex hormones with injections is essential.

Acknowledgment

This article is based on a doctoral thesis in radiology and ultrasonography of Islamic Azad University, Science and Research Branch, Tehran, Iran. By this means, we deem it necessary to thank the university authorities. Also, we pay our respect and appreciate the efforts of Professor Ali Delavar, who helped us in analyzing the obtained data. The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

The authors of the article do not disclose any conflict of interest.

References

1. Root Kustriz M. Determination the optimal age for gonadectomy of dogs and cats. *Journal of the American Veterinary Medical Association*. 2007; 231: 1665-1675.
2. Egenvall A, Bonnett BN, Ohagen P. Incidence of and survival after mammary tumors in a population of over 80.000 insured female dogs in sweden from 1995 to 2002. *Preventive Veterinary Medicine*. 2005; 69: 109-127.
3. Salmeri KR, Bloomberg MS, Scruggs SL, Shille V. Gonadectomy in immature dogs: effects on skeletal, physical, and behavioral development. *Journal of the American Veterinary Medical Association*. 1991; 1193–1203.
4. Marmor M. Willeberg P, Glickman LA, Priester W, Cypess RH, Hurvitz A. Epizootiologic patterns of diabetes mellitus in dogs. *American Journal of Veterinary Research*. 1982; 43: 465–470.
5. De Leo V, D'Antona D, Lanzetta D. Thyrotropin secretion before and after ovariectomy in premenopausal women. *Gynecological Endocrinology*. 1993; 7: 279–283.
6. Rissetto K, Villamil JA, Selting KA. Recent trands in feline intestinal neoplasia: an epidemiologic study of cases in the veterinary medical database from 1964 to 2004. *Journal of the American Animal Hospital Association*. 2011; 47: 28-36.
7. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: the Framingham study. *Annals of Internal Medicine*. 1976; 85: 447-452.
8. Gordon T, Kannel WB, Hjortland MC, McNamara PM. Menopause and coronary heart disease: the Framingham study. *Annals of Internal Medicine*. 1978; 89: 157-161.
9. Knowlton A, Lee A. Estrogen and the cardiovascular system. *Pharmacology and Therapeutics*. 2012; 135: 54-70.
10. Shen L, Song L, Liu B, Li H, Zheng X, Zhang L, Yuan J, Liang Y, Wang Y. Effects of early age at natural menopause on coronary heart disease and stroke in Chinese women. *International Journal of Cardiology*. 2017; 241: 6-11.
11. Matthews KA, Kuller LH, Sutton-Tyrrell K, Chang Y-F. Changes in cardiovascular risk factors during the perimenopause and postmenopause and carotid artery atherosclerosis in healthy women. *Stroke*. 2001; 32: 1104-1111.
12. Matthews KA, Wing RR, Kuller LH, Meilahn EN, Plantinga P. Influence of the perimenopause on cardiovascular risk factors and symptoms of middle-aged healthy women. *Archives of Internal Medicine*. 1994; 154: 2349-2355.
13. Sutton-Tyrrell K, Wildman RP, Matthews KA, Chae C, Lasley BL, Brockwell S, Pasternak RC, Lloyd-Jones D, Sowers MF, Torréns JI. Sex hormone–binding globulin and the free androgen index are related to cardiovascular risk factors in multiethnic premenopausal and perimenopausal women enrolled in the Study of Women Across the Nation (SWAN). *Circulation*. 2005; 111: 1242-1249.
14. Oskui PM, French WJ, Herring MJ, Mayeda GS, Burstein S, Kloner RA. Testosterone and the cardiovascular system: a comprehensive review of the clinical literature. *Journal of the American Heart Association*. 2013; 2(6): 272.
15. Subramanya V, Zhao DI, Ouyang P, Lima JA, Vaidya D, Ndumele CE, Bluemke DA, Shah SJ, Guallar E, Nwabuo

CC, Allison MA. Sex hormone levels and change in left ventricular structure among men and post-menopausal women: the Multi-Ethnic Study of Atherosclerosis (MESA). *Maturitas*. 2018; 108: 37-44.

16. Xing D, Nozell S, Chen YF, Hage F, Oparil S. Estrogen and mechanisms of vascar protection. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2009; 29(3): 289–295.
17. Deschamps AM, Murphy E, Sun J. Estrogen receptor activation and cardioprotection in ischemia reperfusion injury. *Trends in Cardiovascular Medicine*. 2010; 20(3): 73–78.
18. Korzick D, Lancaster T. Age-related differences in cardiac ischemia–reperfusion injury: effects of estrogen deficiency. Pflugers *Archiv European Journal of Physiology*. 2013; 465(5): 669–685.
19. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR. on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation*. 2019; 139: 56–528.
20. Muka, C Oliver-Williams, S Kunutsor. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiology*. 2016; 767-776.
21. Zhu D, Chung HF, Dobson AJ, Pandeya N, Giles GG, Bruinsma F, Brunner EJ, Kuh D, Hardy R, Avis NE, Gold EB. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. *The Lancet Public Health.* 2019; 4(11): 553-564.
22. De Kat AC, Dam V, Onland-Moret NC, Eijkemans MJ, Broekmans FJ, Van Der Schouw YT. Unraveling the associations of age and menopause with cardiovascular risk factors in a large population-based study. *BMC Medicine*. 2017; 15(1): 1.
23. Løkkegaard E, Jovanovic Z, Heitmann BL, Keiding N, Ottesen B, Pedersen AT. The association between early menopause and risk of ischaemic heart disease: influence of hormone therapy. *Maturitas*, 2006; 53(2): 226-233.
24. Dam V, Van Der Schouw YT, Onland-Moret NC, Groenwold RH, Peters SA, Burgess S, Butterworth A. Association of menopausal characteristics and risk of coronary heart disease: a pan-European case–cohort analysis. *International Journal of Epidemiology*. 2019; 48(4): 1275-1285.
25. Reethega L, Devi RG, Priya AJ. A survey on prevalence of heart diseases in women after menopause. *Drug Invention Today*. 2018; 10.
26. Khoudary SR, Aggarwal B, Beckie TM, Hodis HN, Johnson AE, Langer RD. American Heart Association Prevention Science Committee of the Council on Epidemiology and Prevention; and Council on Cardiovascular and Stroke Nursing. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. *Circulation*. 2020; 142(25): 506-532.
27. Duzenli MA, Ozdemir K, Sokmen A, Gezginc K, Soylu A, Celik C, Altunkeser BB, Tokac M. The effects of hormone replacement therapy on myocardial performance in early postmenopausal women. *Climacteric*. 2010; 13: 157–170.
28. Duzenli MA, Ozdemir K, Sokmen A, Soylu A, Aygul N, Gezginc K, Tokac M. Effects of menopause on the myocardial velocities and myocardial performance index. *Circulation Journal*. 2007; 71: 1728–1733.
29. Kaur M, Singh H, Ahuja GK. Cardiac performance in relation to age of onset of menopause. *The Journal of the Indian Medical Association*. 2011; 109: 234–237.
30. Rahman I, Åkesson A, Wolk A. Relationship between age at natural menopause and risk of heart failure. *Menopause*. 2015; 22(1): 12-16.
31. Ruiz-Ortega M, Lorenzo O, Rupérez M, Esteban V, Suzuki Y, Mezzano S, Plaza JJ, Egido J. Role of the renin-angiotensin system in vascular diseases: expanding the field. *Hypertension*. 2001; 38(6): 1382-1387.
32. Zhao Z, Wang H, Jessup JA, Lindsey SH, Chappell MC, Groban L. Role of estrogen in diastolic dysfunction. *American Journal of Physiology-Heart and Circulatory Physiology*. 2014; 306(5): H628-H640.
33. Rocca WA, Shuster LT, Grossardt BR, Maraganore DM, Gostout BS, Geda YE, Melton III LJ. Long-term effects of bilateral oophorectomy on brain aging: unanswered questions from the Mayo Clinic Cohort Study of Oophorectomy and Aging. *Women's Health*. 2009; 5(1): 39-48.
34. Zhoa Di, Guallar E, Ouyang P, Subramanya V, Vaidya D, Ndumele CE, Lima JA, Allison MA, Shah SJ, Bertoni AG, Budoff MJ, Post WS, Erin B. Endogenous Sex hormones and incident cardiovascular disease in post-menopausal women. *Journal of the American College of Cardiology*. 2018; 71: 2555-2566.
35. Dosi R, Bhatt N, Shah P, Patell R. Cardiovascular disease and menopause. *Journal of Clinical and Diagnostic Research*. 2014; 8(2): 62.
36. Ingelsson E, Lundholm C, Johansson AL, Altman D. Hysterectomy and risk of cardiovascular disease: a population-based cohort study. *European Heart Journal.* 2011; 32(6), 745-750.
37. Abbas SZ, Sangawan V, Das A, Pandey AK. Assessment of cardiovascular risk in natural and surgical menopause. *Indian Journal of Endocrinology and Metabolism*. 2018; 22(2) :223-228.