THE GENDER PERSPECTIVE IN DRUG DESIGNING AND DEVELOPMENT PROCESSES- A REVIEW

Maj Neerja Masih *1
1 Department of Biotechnology, Isabella Thoburn College, Lucknow - 226007, India

Abstract:
It has long been assumed that females have the same response as males to the drugs in all the five phases of drug development processes namely drug discovery & development, preclinical trials, clinical trials, drug review and drug marketing. The fact is that the diseases exhibit the potential sex difference in its prevalence, diagnosis, severity and outcomes. Diseases like breast cancer, urinary tract infections affect men and women differently. The difference also exits in the manifestation of the diseases like cardiovascular disease and sexually transmitted diseases. The differences of the sex are further widened by the gender perspective. Gender is one of the fundamental determinants of health inequalities. There are differences in the physiology of the sexes that causes difference in the pharmacodynamics for specific drug which can be due to the circulating levels of endogenous hormones such as testosterone and estradiol. Women typically have a lower bodyweight than men, so when taking the same dose of a drug results in higher level of drug. Lyophilic agents may have a larger distribution in females owing to their higher body fat content. Women may experience different health issues due to cultural, social and economical factor and hence it becomes an issue related to gender bias. There is a need to examine the potential difference by sex at all the life stages at all the levels, like genetic and cellular level to organism level. Also, there is a need to take into consideration this sex difference in all the stages of the drug development, pre-clinical and clinical trial. It has been observed that while studying diseases prevalent in both the sexes only male animals were considered to be norm study population. It was assumed that female would have same response as males during the pre-clinical trials and that women will have same response as men from drugs in the clinical trials. The assumption of equality puts women at risk, not only reducing disease treatment efficacy but also risking exposure to unforeseen side effects. Women have been viewed as more expensive test subjects because of their more fluctuating hormone levels. It has to take the possible hormonal interaction into consideration during the pharmacodynamics, pharmacokinetics when it comes to determine the safety, efficacy and tolerance of new drugs. Although there have been lack of representation of women in clinical trials initially due to non availability of data that the potential sex differences exist but now guidelines, policies and organizations have been established to increase the quality of women’s health research. In 1993, the National Institute of Health Revitalization Act came into being to promote inclusion of women in clinical trials. The acceptance that sex differences should be considered while taking clinical decisions itself proves that there has been a major breakthrough, but a lot is to be done. The studies on cardiovascular disease pattern for males and females creates awareness and the governments are making policies and guidelines for the gender specificity in the drug designing and development processes and strict enforcement during the approval processes. There is along way to go.
1. Introduction

It's only in the past decade that all medical research has been carried out on men based on the assumption that both the sexes will react in the same way, with no regards for any differences that might exist between the sexes.

We are only beginning to understand the impact of an individual’s sex and their sex hormones on their health, the way they experience the diseases and the response to treatment. Also, the potential differences between two sexes is widened by the gender biases in the societies. The gender biases expose both the sexes to different environments due to the differences in the culture, economical status and educational awareness. The diseases differ in the prevalence and manifestation in both the sexes due to these gender biases. The poor health care and the poor nutritional status of women further enhance this gap. Women’s menstrual cycles and fluctuating hormone effect the studies and increases the cost of research which resulted in lack of inclusion of women as subjects in drug development procedures which takes place in five phases and chronologically are drug discovery & development, preclinical trials, clinical trials, drug review and drug marketing. The understanding of sex and gender lead to 1993 NIH Revitalization Act to ensure the efficacy of treatments for women would no longer be extrapolated from data derived from male participants but instead would be scientifically determined. The author is of the opinion that the acceptance and identification of the need for sex and gender specific research and having government policies is a major breakthrough but we have a long way to go.

The purpose of this review is to enhance our understanding of the different ways in which the metabolic processes differ by sex and gender and how it manifested differently.

2. Diseases in Their Manifestation

Heart diseases and diseases across many other organ systems manifest differently in men and women. Disease symptoms are often reported differently by men and women, and the normal ranges for disease biomarkers can differ substantially by sex. (Katherine & Mager, 2016)

In the cardiovascular clinical trial women have been underrepresented and therefore the gender specific cardiologic evidence based medicines are not beneficial to them as much as to men. Many CVD risk factors are similar in men and women but their prevalence and the relative risk they confer on different CV conditions vary substantially by gender. (Westerman & Wenger, 2016; Gulati et al., 2012 & Regentstenier et al., 2015) For example systemic autoimmune disease, which are much more common in women are associated with accelerated atherosclerosis and increased CHD risk.
Among CVD risk factors the socio-cultural factors on heart disease exhibit some of the biggest difference between men and women. For example, the stress induced by the marital loss through divorce early in life is associated with a significant increase in a risk of CVD in woman’s life which is due to the negative effects of divorce on emotional well-being and socio-economic status. (Zang & Hayward, 2006). On the other hand, the relationship between marital loss and CVD in late midlife appears negligible for men. In addition, emerging data indicate that younger women may be particularly susceptible to mental stress induced myocardial ischemia. (Vaccarino et al., 2016 & Sullivan et al., 2018)

In many cases the initial presentation of IHD in women is acute myocardial infarction (MI) and sudden cardiac death (SCD). Although chest pain is the most common symptom of acute coronary syndromes (including MI and stable angina) in everyone, women with acute coronary syndromes are less likely than men to present with chest pain. Women are more likely to present with upper-back pain; pain in the neck, arm, and/or jaw; difficulty breathing; weakness; and a sense of fear (Pagidipati and Peterson, 2016). Compared with men, women have a significantly higher risk of mortality in the first year after an acute MI, especially women age < 55 years. Moreover, women who present with MI are less likely than men to receive fibrinolytic drugs, stents, and related therapies (Clayton & Arnegard, 2018).

3. Drug Designing and Development Processes

3.1. Phases of Drug Designing and Discovery

step 1. Drug discovery and development
a) Drug Discovery: The researcher discovers new drug through new insights into a disease process that allows researchers to design a product to stop or reverse the effects of the disease. Many tests are conducted of molecular compounds to find possible beneficial effects against any or a large no of diseases. (Gupta et al., 2012)
b) Drug Development: Once researchers identify a promising compound for development, the experiments are conducted to gather information on how is it absorbed, distributed, metabolised and excreted, potential benefits, mechanism of action, best dosage, mode of intake oral or through injection, its side effects and interaction with the other drugs and its efficacy as compared to other similar drugs. (Ravinder & Suresh, 2019)

Step 2: Preclinical Research
Before testing the drugs on people, researchers must find out whether it is toxic by in vitro and in vivo. These studies are carried out on cells in vitro and on animals in vivo. Every cell has a sex (Wizemann & Pardue, 2001). The animals used are generally males on the basis of the assumption that the females respond similarly and that managing female subjects has many complications and its not cost effective.

Step 3 Clinical Trials
While preclinical research answers basic questions about a drug’s safety, it is not a substitute for studies of ways the drug will interact with the human body. “Clinical research” refers to studies, or trials, that are done in people. The Investigational New Drug process begins before the clinical research begins. Researchers then design the clinical trials to answer specific research questions
by developing a protocol taking into consideration the subjects, size of the group, control group, drug dosage & collection, assessment review and analysis of the data.

Clinical research is carried out in several phases:

- **Phase 1:** The purpose is to study the safety and dosage of the drug which is done on 20-100 healthy volunteers or people with the disease condition for several months. Approximately 70% of drugs move to the next phase.
- **Phase 2:** This study is carried out for 1-300 up to hundred people with disease for checking the efficacy and side effects of the drug. Approximately 33% of drugs move to the next phase.
- **Phase 3:** This study has 300-3000 volunteers who have the disease condition for the purpose of studying efficacy and monitoring of adverse reactions. (Kuhlmann, 1999)

### 3.2. The concept of Sex and Gender

It is important to define and use the terms ‘sex’ and ‘gender’ appropriately. Sex refers to a set of biological attributes in humans and animals. It is primarily associated with physical and physiological features including chromosomes, gene expression, hormone levels and reproductive/sexual anatomy. Gender refers to how people perceive themselves and others as well as how they act and interact. Gender refers to social behaviours, expectations, expressions and identities of men, women, and gender diverse people. Cultural norms pertaining to gender roles and sex-related behaviours fluctuate and change over time as well as across cultures. Gender impacts disease risk, diagnosis, and treatment. For example, men are often thought to be at an increases risk for cardiovascular disease (CVD), in part due to their gender-based propensity to engage in risk-taking behaviours such as smoking or alcohol consumption. Also, women who have taken on societal roles associates with the male gender have an increased disease prevalence linked with the pressures associated with these gender-defined roles. Using the term gender when referring to in vitro assays or animal studies in basic science research is incorrect, and instead the term sex should be used.

Till the last decade, the role of sex in scientific discovery, disease detection, diagnosis, and treatment has not been taken into account. The awareness about not only taking into account the sex of the subjects for clinical studies and the sex of the animals for pre-clinical studies but also to consider the sex of the cell for in vitro studies. Many of the intrinsic properties of the cell may appear hormone independent, cells also exhibit differential variations upon exposure to sex hormones. Female and male cells respond differently to chemical and microbial stressors, and yet the sex of the cell lines studied in vitro is often ignored and rarely reported. When sex is factored into disease risk, it is well established that premenopausal women are relatively protected from diseases associated with the metabolic syndrome, including cardiovascular disease (CVD), when compared to age-matched men (Collins et al., 2002; Ren and Kelly, 2009; Skafar et al., 1997; Yanes and Rexklhoff, 2011). This ‘sex advantage’ disappears after menopause, leading to the generally accepted conclusion that sex hormones, and in particular estrogens, protect against the metabolic syndrome. Low levels of estrogens are associated with increased CVD risk. Early atherosclerosis and a 2.6-fold increase in the risk of CVD (Kannel and Wilson, 1995) as well as increased CVD mortality (Cooper and Sandler, 1998; Jacobsen et al., 1997) compared to women experiencing later menopause. Jankowska et al. demonstrated that men with the lowest quintile of
estradiol (E2) (lowest 20%, <12.90 pg/mL) were found to have the highest death rates from congestive heart failure over a 3-year period, while men with E2 in the range of 20–30 pg/mL had the lowest rates (Jankowska et al., 2009). However, men with the higher E2 levels i.e R37.40 pg/mL also had a greater incidence of atherosclerosis (heart disease), diabetes, obesity, stroke, enlarged prostate, breast tissue growth, breast cancer, and other problems. Lower T levels in middle-aged and older men are associated with insulin resistance, the metabolic syndrome, and diabetes. Furthermore, lower T in older men predicts cardiovascular events, including stroke and transient ischemic attack, and is associated with higher CVD and overall mortality (Schwarcz and Frishman, 2010). Other differences seen between the sexes (weight, muscled mass, body fat, metabolic enzymes, and the plasma proteins) may also impact the pharmacokinetic parameters of a particular drug. (Miller, M 2001; Woosly R 1998; Beirele I et al. 1999) Women typically have a lower body weight than men, so when taking the same dose of a drug, results in a higher level of drug. (Woosely R, 1998)

The notion that there are biological differences between the sexes is most evident and comfortable when it is applied to the reproductive system. However, sex differences have been identified or suggested at many levels of biological organization, from biochemical to behavioral. (Wizemann & Pardue, 2001) Both hormones and sex chromosomes impact disease risk and prevalence (Arnold, 2009; Arnold and Chen, 2009).

The concept that there would be a sexual dimorphism in natural selection favoring a greater (or lesser) disease risk in one sex over the other may be explained with bio-anthropological, animal behavior, and evolutionary biology literatures (Arnold, 2010). In many past cultures, males were predominately the hunters, and some Y genes might have bestowed effects that were advantageous to their bio-anthropological roles. Additionally, gonadal hormones, which are critical for manifesting stereotypic sex differences associated with the evolution of a phenotype, may have been more adaptive in one sex than the other. Therefore, gathering more information about sex and gender in disease risk will indirectly provide information on the interactions between the X and Y genes, gonadal hormones, and their influence on phenotypic sex differences.

The gender bias in health care is largely a result of gender bias in the generation of knowledge. The real source of gender bias in the clinical practices may be due to errors in research resulting from a lack of gender awareness, leading to the erroneous view that men and women are similar in exposure to risks or in the natural history of a disease i.e. symptoms and signs of onset and course, response to treatment and prognosis and where the main consequence of gender bias in research and health care is the lack of valid results.

The arguments in favour of the systemic exclusion of women from clinical trials have been based on foetal risk during pregnancy, hormonal interactions due to the menstrual cycle of the concomitant use of exogenous hormones (hormonal contraceptives and hormonal replacement therapies HRT, difficulties in recruiting, and higher drop out rates. (Hers 1997 & Lipmann, 2006)

The irony is that these are the very reasons why women’s participation is necessary. under the false premise that men and women are same, medications have traditionally been tested on men and the knowledge obtained about efficacy and effectiveness has been extrapolated to women. following the tragedies related to the teratogenic effects of thalidomide and diethylstilbestrol in 1977, the
FDA issued the gender consideration for the clinical evaluation of drugs. (Merkaz and Junod 1994; NIH Guidelines 1994). Subsequently NIH Revitalisation Act was approved, making it a requirement that women be included in all the NIH funded CTs.

Clinical research also exhibits gender bias in other areas. One of these is in recruitment into clinical trials; (Soderstrom, 2001) another is the reporting of gender-related data. (Rochon et al. 1998). However, there is a dearth of gender-based clinical research from within India. Thus, it is pertinent to use studies from North America and Europe where these issues have been investigated.

It was in 1994 that the US National Institutes of Health (NIH) issued a guideline for the study and evaluation of gender differences in clinical trials to ensure that the safety and efficacy of drugs would be adequately investigated in the full range of patients who would use the therapy. (La Rose, 1993) Prior to this policy, women had been excluded from early studies of most drugs—mainly for safety reasons, but this prohibition meant there was little information about the effects of drugs in women. For example, women may have a different drug efficacy or side effect profile to men. (Ruiz V, 1997) It was reported in 2005 that eight out of ten prescription drugs were withdrawn from the US market because of women’s health issues. (Ruiz et al., 2007). This represents an enormous waste of research money as a consequence of neglecting gender research. The aims of the NIH guidance were to recruit enough women into studies to be able to allow valid analyses of differences in intervention effect, to evaluate the risks and benefits in women, and to provide opportunities for women to contribute to research through active participation in clinical trials while preventing exposure of a fetus to a toxic drug.

With the advent of gender medicine as a specialty that is developing across the world, a woman's reproductive status, menstrual cycle and contraceptive history has become significant in studying health, disease and pharmacology. (Holdcroft A, 2016)

Inequality between men and women has not been traditionally considered as the determinant of health care, it was Karachi who published on the first studies to indicate the importance of gender inequality as a social determinant of health, demonstrating the association between women’s social status and morbidity in both sexes according to geographical region in the same country. (Kawachi et al., 1999) A relationship has also been shown between women’s empowerment and their participation in the political economic and social life are associated with lower mortality are associated with child health and with lower mortality rates in men and women. (Varkey et al. 2010).

There is a need for appropriate representation of women in clinical research in all steps of the drug designing and development processes and all phases of clinical trials. Early-phase trials typically aim to determine the recommended dose (or methodology) and the toxicity profile (or other risks) of an investigational drug (or intervention). It is critically important to have equitable representation in early-phase trials for drugs that are intended for both men and women, because in general, women are more likely than men to have adverse drug reactions. Pragmatic clinical trials, which typically follow the approval of a new drug, device, or procedure, are carried out in real-world clinical settings to investigate the effectiveness of an intervention in broad patient populations. Pragmatic trials are especially amenable to recruitment of older individuals, despite comorbidity and polypharmacy, making these late-phase trials particularly relevant to heart diseases that tend to affect women later in life than men. (Clayton & Arnegard, 2018).
4. Conclusion

In this review it has been discusses that the many differences in health and disease between men and women have their origins in factors ranging from biological (including genetic, molecular, and physiological factors) to psychosocial. The disease manifestation and symptoms differ in men and women and also in the responses of male and female cells towards the drugs during the in vitro studies. The sex-chromosomal complement influences many fundamental mechanisms of structure and function, which are apparent across preclinical research models, including cells in culture, isolated tissues, and animal models in all preclinical and translational research that precedes clinical trials, it is necessary to consider the possibility of sex differences, to investigate them when appropriate, and to report such results regardless of whether sex differences are present or absent. In fact, sex influences are so widespread across medical disciplines, and knowledge of them is so critical to scientific rigor and reproducibility, that the National Institutes of Health (NIH) expects sex as a biological variable to be factored into research designs, analyses, and reporting in NIH-funded vertebrate animal and human studies.

It has to take the possible hormonal interaction into consideration during the pharmacodynamics, pharmacokinetics when it comes to determine the safety, efficacy and tolerance of new drugs during during the peri-menopausal and post menopausal women. More women have died annually from Ischemic Heart Disorder, Myocardial Infarction and sudden cardiac arrest. More unbiased research is required to benefit women equally.

The studies on cardiovascular disease pattern for males and females creates awareness and the governments are making policies and guidelines for the gender specificity in the drug designing and development processes and strict enforcement during the approval processes. Recent studies also show that this Act doesn't seem to have improved gender balance enrolment or promoted the use of gender specific analysis in clinical trial published in an influential medical journal. Mandating disclosure when a study uses only male or female animals in the title should improve transparency and assist drugs and treatment approval processes. Also funding agencies can make it as an important eligibility criterion for funding.

References

[1] Arnold, A.P. Mouse Models for Evaluating Sex Chromosome Effects That Cause Sex Differences In Non-Gonadal Tissues. J. Neuroendocrinol. 21, 2009, 377–386.
[2] Arnold, A.P. Promoting The Understanding Of Sex Differences To Enhance Equity And Excellence In Biomedical Science. Biol. Sex Differ. 2010, 1.
[3] Arnold, A.P., And Burgoyne, P.S. Are XX and XY Brain Cells Intrinsically Different? Trends Endocrinol. Metab. 15, 2004, 6–11.
[4] Arnold, A.P., And Chen, X. What Does The ‘‘Four Core Genotypes’’ Mouse Model Tell Us About Sex Differences In The Brain And Other Tissues? Front. Neuroendocrinol. 30, 2009, 1–9.
[5] Beierle I, Meibohm B, Derendorf H. Gender Differences in Pharmacokinetics And Pharmacodynamics. Int J Clin Pharmacol Ther. 1999;37(11):529–547.
[6] Bekhouche, Y.H.R., Tyson, L.D., And Zahidi, S. The Global Gender Gap Report, 2015 (World Economic Forum).
[7] Bhatt A. Clinical Trials In India: Pangs Of Globalization. Indian J. Pharmacol. 36(4), 2004, 207 - 08.
Bozkurt B1, Khalaf S1. Heart Failure in Women. Methodist Debakey Cardiovasc J. 2017 Oct-Dec; 13(4):216-223.

Cambronero Saiz B, Ruiz Cantero MT, Papi Galvez N. Quality of Pharmaceutical Advertising and Gender Bias In Medical Journals (1998–2008): A Review Of The Scientific Literature. Gac Sanit. 2012;26: 469–76.

Clayton JA1, Arnegard ME1. Taking Cardiology Clinical Trials to The Next Level: A Call to Action. Clin Cardiol. 2018 Feb; 41(2):179-184. Doi: 10.1002/Clic.22907. Epub 2018 Feb 26.

Collins, P., Stevenson, J.C., And Mosca, L. Spotlight On Gender. Cardiovasc. Res. 53, 2002, 535–537.

Cooper, G.S., And Sandler, D.P. Age At Natural Menopause And Mortality. Ann. Epidemiol. 8, 1998, 229–235.

Dai, W., Li, Y., And Zheng, H. Estradiol/ Testosterone Imbalance: Impact On Coronary Heart Disease Risk Factors in Postmenopausal Women. Cardiology 121, 2012, 249–254.

Gulati M, Shaw LJ, Bairey Merz CN. Myocardial Ischemia In Women: Lessons From The NHLBI WISE Study. Clin Cardiol. 2012;35: 141–148.

Gupta V, C. Mohan Reddy, K. Pradeep Reddy, R. Ajay Kulkarni, H.G. Shivakumar. Process of Approval of New Drug in India with Emphasis on Clinical Trials. Volume 13, Issue 2, March – April 2012; Article-004 ISSN 0976 – 044X, International Journal of Pharmaceutical Sciences Review and Research.

Harris DJ, Douglas PS. Enrollment of Women in Cardiovascular Clinical Trials Funded by The National Heart, Lung, And Blood Institute. N Engl J Med 2000;343: 475-80

Hausmann, R., Tyson, Laura D., And Zahidi, S. The Global Gender Gap Report, 2012 (World Economic Forum).

Herz S. Don't Test, Do Sell: Legal Implications of Inclusion of Women In Clinical Drug Trials. Epilepsia. 1997;38(Suppl 4):S42–9.

Honorio S. Phases of Drug Development; Good Practices In Clinical Research. Available At: Www.Hstelearning.Mit.Edu. Accessed On Feb 26, 2019

Holdcroft A. Gender Bias in Research: How Does It Affect Evidence Based Medicine? Pharm Pract(Granada) 2016 Jan-Mar; 14(1): 708. Published Online 2016 Mar 15.

Izadnegahdar, M., Singer, J., Lee, M.K., Gao, M., Thompson, C.R., Kopec, J., And Humphries, K.H. Do Younger Women Fare Worse? Sex Differences in Acute Myocardial Infarction Hospitalization and Early Mortality Rates Over Ten Years. J. Womens Health 23, 2014, 10–17

Jacobsen, B.K., Nilssen, S., Heuch, I., And Kva’Le, G. (1997). Does Age at Natural Menopause Affect Mortality From Ischemic Heart Disease? J. Clin. Epi-Demiol. 50, 475–479.

Jankowska, E.A., Rozentropy, P., Ponikowska, B., Hartmann, O., Kustrzycka-Kratchowl, D., Re-Czuch, K., Nowak, J., Borodulin-Nadzieja, L., Po- Lonski, L., Banasiak, W., Et Al. Circulating Estradiol And Mortality In Men With Systolic Chronic Heart Failure. JAMA 301, 2009, 1892–1901.

Kannel, W.B., And Wilson, P.W. Risk Factors That Attenuate the Female Coronary Disease Advan- Tage. Arch. Intern. Med. 155, 1995, 57–61.

Katherine A. Liu and Natalie A Dipietro Mager. Women’s Involvement in Clinical Trials: Historical Perspective and Future Implications. 2016 March, 15, Pharm Pract.

Kawachi I, Kennedy B, Gupta V, Prothow-Stith D. Women's Status and The Health of Women and Men. Soc Sci Med. 1999;48:21–32.

Kuhlmann J, Alternative Strategies in Drug Development: Clinical Pharmacological Aspects. Int. J. Clin. Pharmacol. Ther. 37(12), 1999, 575-83.

Lachman L, Liberman HA, Kanig JL, The Theory and Practice of Industrial Pharmacy, Varghese Publishing House, 3rd Edition 1987. 856-82.

Larosa J, Pinn VW. Gender Bias in Biomedical Research. J Am Med Womens Assoc. 1993; 48:145–51.
Lippman A. The Inclusion of Women In Clinical Trials: Are We Asking The Right Questions? Women and Health Protection. 2006. Available From: Http://Www.Whp-Apsf.Ca/Pdf/Clinicaltrialsen.Pdf#Sthash.Nfpovx0l.Dpuf

Merkatz RB, Junod SW. Historical Background of Changes In FDA Policy On The Study And Evaluation Of Drugs In Women. Acad Med. 1994; 69:703–7.

Miller M. Gender Differences in The Toxicity of Pharmaceuticals - The Food And Drug Administration’s Perspective. Int J Toxicol. 2001; 20(3):149–152.

Schwarcz, M.D., And Frishman, W.H. Testosterone and Coronary Artery Disease. Cardiol. Rev. 18, 2010, 251–257.

Skafar, D.F., Xu, R., Morales, J., Rami, J. And Sowers, JR. Clinical Review 91: Female Sex Hormones and Cardiovascular Disease In Women. J. Clin. Endocrinol. Metab. 82, 1997, 3913–3918.

Sozzi, F.B., Danzi, G.B., Foco, L., Ferlini, M., Tu, Bao, M., Galli, M., Celli, P. And Mannucci, P.M. Myocardial Infarction in The Young: A Sex-Based Comparison. Coron. Artery Dis. 2007, 432–437.

Soderstrom M. Why Researchers Excluded Women from Their Trial Populations. Lakartidningen 2001;98: 1524–8.
[49] Varkey P, Kureshi S, Lesnick T. Empowerment of Women and Its Association with The Health of The Community. J Womens Health. 2010; 19:71–6.

[50] Weisz D, Gusmano MK, Rodwin VG. Gender and The Treatment of Heart Disease In Older Persons In The United States, France, And England: A Comparative, Population-Based View Of A Clinical Phenomenon. Gend Med. 2004;1: 29-40

[51] Westerman S1, Wenger NK2. Women And Heart Disease, The Under-recognized Burden: Sex Differences, Biases, And Unmet Clinical And Research Challenges. Clin Sci (Lond). 2016 Apr;130(8):551-63. Doi: 10.1042/CS20150586.

[52] Wizemann TM And Pardue ML. Understanding The Biology Of Sex And Gender Differences, Exploring The Biological Contributions To Human Health; Does Sex Matter? National Academic Press (US) 2001,2 Every Cell Has a Sex.

[53] Woosley R. From Benchside to Bedside: Role of Gender-Based Therapeutics In The Clinical Care Of Women. J Womens Health. 1998;7(1):21–23.

[54] Westerman S, Wenger NK. Women and Heart Disease, The Under-Recognized Burden: Sex Differences, Biases, And Unmet Clinical And Research Challenges. Clin Sci (Lond). 2016;130: 551–563.

[55] Yanes, L.L., And Reckelhoff, J.F. Postmenopausal Hypertension. Am. J. Hypertens. 24, 2011, 740–749.

[56] Zhang Z, Hayward MD. Gender, The Marital Life Course, And Cardio- Vascular Disease In Late Midlife. J Marriage Fam. 2006; 68: 639–657

*Corresponding author.

E-mail address: neerjamasih@yahoo.com